

currently no second-line treatment for inoperable, aggressive, advanced, locally advanced, metastatic, or malignant PEComas. Accordingly, these subsets of PEComas remain very difficult to treat. The prognosis for patients within these patient subsets is poor, with a median survival estimated to be 12-17 months following diagnosis of advanced disease. Furthermore, for example, the 5-year survival rate of metastatic uterine PEComa is approximately 16%. *See*, Khaja, F. et al., *Case Reports in Medicine*, 2013:1-4 (2013).

[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, the present disclosure refers to use of an effective amount of a composition comprising nanoparticles comprising sirolimus and an albumin for the preparation of a medicament for the treatment of a malignant perivascular epithelioid cell tumor (PEComa) in an individual.

[0007] The present application in some examples provides a method of treating an epithelioid tumor in an individual, wherein the method comprises administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor and an albumin. In some examples, the epithelioid tumor is a perivascular epithelioid cell tumor (PEComa). In some examples, the PEComa is selected from the group consisting of a pulmonary clear cell 'sugar' tumor, a PEComa not otherwise specified (PEComa-NOS), angiomyolipoma, and lymphangioleiomyomatosis. In some examples, the epithelioid tumor is malignant. In some examples, the epithelioid tumor is locally advanced. In some examples, the epithelioid tumor is metastatic.

[0008] In some examples according to any of the use or methods described above, the mTOR inhibitor is a limus drug, such as sirolimus.

[0009] In some examples according to any of the use or methods described above, the effective amount of the mTOR inhibitor in the nanoparticle composition is about 10 mg/m² to about 100 mg/m² (including, for example, about 45- 100 mg/m², about 75-100 mg/m², or about 45, 50, 75, or 100 mg/m²). In some examples, the nanoparticle composition is administered weekly. In some examples, the nanoparticle composition is administered 2 out of every 3 weeks. In some examples, the nanoparticle composition is administered 3 out of 4 weeks. In some examples, the nanoparticle composition is administered on days 1 and 8 of a 21-day cycle. In some examples, the nanoparticle composition is administered on days 1, 8, and 15 of a 28-day cycle.

[0010] In some examples according to any of the use or methods described above, the nanoparticle composition is administered intravenously, intraarterially, intraperitoneally,

intravesicularly, subcutaneously, intrathecally, intrapulmonarily, intramuscularly, intratracheally, intraocularly, transdermally, orally, intraportally, intrahepatically, hepatic arterial infusion, or by inhalation. In some examples, the nanoparticle composition is administered intravenously. In some examples, the nanoparticle composition is administered subcutaneously.

[0011] In some examples according to any of the use or methods described above, the nanoparticles in the composition have an average diameter of no greater than about 150 nm, such as no greater than about 120 nm.

[0012] In some examples according to any of the use or methods described above, the mTOR inhibitor in the nanoparticles is associated (e.g., coated) with the albumin.

[0013] In some examples according to any of the use or methods described above, the individual is human.

[0014] In some examples according to any of the use or methods described above, the individual is selected for treatment based on a level (e.g., a high level) of a melanocytic marker (including, for example, HMB45, MelanA, and microphthalmia transcription factor) and a smooth muscle marker (including, for example, smooth muscle actin, pan-muscle actin, h-caldesmon, and calponin). In some examples, the level of the melanocytic marker and the smooth muscle marker is determined by immunohistochemistry.

[0015] In some examples according to any of the use or methods described above, the individual is selected for treatment based on the mutation status of a gene selected from the group consisting of TSC1, TSC2, TFE3, RHEB, MTOR, AKT, PIK3CA, and PTEN. In some examples, the individual is selected for treatment if the individual has a mutation in the gene, e.g., as determined by gene sequencing. In some examples, the gene sequencing is based on sequencing of a circulating or a cell-free DNA in a blood sample. In some examples, the gene sequencing is based on sequencing of DNA in a tumor sample.

[0016] In some examples according to any of the use or methods described above, the individual is selected for treatment based on the phosphorylation status of a protein selected from the group consisting of AKT, S6, S6K, and 4EBP1. In some examples, the individual is selected for treatment if the protein in the individual is phosphorylated. In some examples, the individual is selected for treatment if the protein in the individual is not phosphorylated. In some examples, the phosphorylation status of the protein is determined by immunohistochemistry.

[0017] In some examples according to any of the use or methods described above, the individual is selected for treatment based on a level of a proliferation marker or an apoptosis marker, such as, the proliferation marker, Ki-67, or the apoptosis marker, PARP or a fragment thereof. In some examples, the individual is selected for treatment based on the level of the proliferation marker and the apoptosis marker, e.g., as determined by immunohistochemistry.

[0018] In some examples according to any of the use or methods described above, the individual has not been previously treated with an mTOR inhibitor.

[0019] In some examples according to any of the use or methods described above, the individual has previously been treated with chemotherapy, radiation, or surgery.

[0020] These and other examples and advantages of the present 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 examples described herein may be combined to form other examples of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention provides methods and compositions for treating epithelioid cell tumors, such as perivascular epithelioid cell tumors (PEComas), in an individual in need thereof comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor (hereinafter also referred to as “mTOR nanoparticle composition”) and an albumin. In some embodiments, the composition comprises a limus drug and an albumin (hereinafter also referred to as “limus nanoparticle composition”).

[0022] In some embodiments, there is provided a method of treating a PEComa in an individual in need thereof, comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising a limus drug and an albumin. In some embodiments, the limus drug is sirolimus. In some embodiments, the albumin is human albumin (such as human serum albumin). In some embodiments, the nanoparticles comprise sirolimus associated (e.g., coated) with albumin. In some embodiments, the average particle size of the nanoparticles in the nanoparticle composition is no more than about 150 nm (such as no greater than about 120 nm). In some embodiments, the composition comprises the albumin stabilized nanoparticle formulation of sirolimus. In some embodiments, the composition is *Nab*-sirolimus.

[0023] In some embodiments, there is provided a method of treating a PEComa in an individual, comprising administering to the individual an effective amount of a composition

CLAIMS

What is claimed is:

1. Use of an effective amount of a composition comprising nanoparticles comprising sirolimus and an albumin for the preparation of a medicament for the treatment of a malignant perivascular epithelioid cell tumor (PEComa) in an individual, wherein the medicament is prepared for intravenous administration.
2. The use of claim 1, wherein the malignant PEComa is selected from the group consisting of a pulmonary clear cell 'sugar' tumor, and a PEComa not otherwise specified (PEComa-NOS).
3. The use of claim 1 or 2, wherein the malignant PEComa is locally advanced.
4. The use of any one of claims 1-3, wherein the malignant PEComa is metastatic.
5. The use of any one of claims 1-4, wherein the malignant PEComa is recurrent.
6. The use of any one of claims 1-5, wherein the effective amount of sirolimus in the nanoparticle composition is 10 mg/m² to 150 mg/m².
7. The use of any one of claims 1-6, wherein the effective amount of sirolimus in the nanoparticle composition is about 100 mg/m².

8. The use of any one of claims 1-7, wherein the effective amount of sirolimus in the nanoparticle composition is about 75 mg/m².
9. The use of any one of claims 1-8, wherein the effective amount of sirolimus in the nanoparticle composition is about 56 mg/m².
10. The use of any one of claims 1-9, wherein the nanoparticle composition is prepared to be administered weekly.
11. The use of claim 1-10, wherein the nanoparticle composition is prepared to be administered weekly, 2 out of every 3 weeks.
12. The use of any one of claims 1-11, wherein the nanoparticles in the composition have an average diameter of no greater than 150 nm.
13. The use of any one of claims 1-12, wherein the nanoparticles in the composition have an average diameter of no greater than 120 nm.
14. The use of any one of claims 1-13, wherein the sirolimus in the nanoparticles is associated with the albumin.
15. The use of any one of claims 1-14, wherein the weight ratio of albumin and sirolimus in the nanoparticle composition is 1:1 to 9:1.

16. The use of any one of claims 1-15, wherein the weight ratio of albumin and sirolimus in the nanoparticle composition is about 9:1.
17. The use of any one of claims 1-16, wherein the albumin is human albumin.
18. The use of any one of claims 1-17, wherein the albumin is human serum albumin.
19. The use of any one of claims 1-18, wherein the individual is human.
20. The use of any one of claims 1-19, wherein the individual has a positive presence of a melanocytic marker and a smooth muscle marker.
21. The use of claim 20, wherein the melanocytic marker is selected from the group consisting of HMB45, MelanA, and microphthalmia transcription factor.
22. The use of claim 20 or 21, wherein the smooth muscle marker is selected from the group consisting of smooth muscle actin, pan-muscle actin, h-caldesmon, and calponin.
23. The use of any one of claims 20-22, wherein the level of the melanocytic marker and the smooth muscle marker is determined by immunohistochemistry.
24. The use of any one of claims 1-23, wherein the individual is selected for treatment based on the mutation status of a gene selected from the group consisting of TSC1, TSC2, TFE3, RHEB, MTOR, AKT, PIK3CA, and PTEN.
25. The use of claim 24, wherein the individual is selected for treatment if the individual has a mutation in the gene.

26. The use of claim 25, wherein the mutation status of the gene is determined by gene sequencing.
27. The use of claim 26, wherein the gene sequencing is based on sequencing of a circulating or a cell-free DNA in a blood sample.
28. The use of claim 27, wherein the gene sequencing is based on sequencing of DNA in a tumor sample.
29. The use of any one of claims 1-28, wherein the individual is selected for treatment based on the phosphorylation status of a protein selected from the group consisting of AKT, S6, S6K, and 4EBP1.
30. The use of claim 29, wherein the individual is selected for treatment if the protein in the individual is phosphorylated.
31. The use of claim 30, wherein the individual is selected for treatment if the protein in the individual is not phosphorylated.
32. The use of any one of claims 29-31, wherein the phosphorylation status of the protein is determined by immunohistochemistry.
33. The use of any one of claims 1-32, wherein the individual is selected for treatment based on a level of a proliferation marker or an apoptosis marker.
34. The use of claim 33, wherein the proliferation marker is Ki-67.
35. The use of claim 33, wherein the apoptosis marker is PARP or a fragment thereof.
36. The use of any one of claims 33-35, wherein the individual is selected for treatment based on the level of the proliferation marker and the apoptosis marker.

37. The use of any one of claims 33-36, wherein the level of the proliferation marker and the apoptosis marker is determined by immunohistochemistry.
38. The use of any one of claims 1-37, wherein the individual has not been previously treated with an mTOR inhibitor.
39. The use of any one of claims 1-38, wherein the individual has previously been treated with chemotherapy, radiation, or surgery.