

DESCRIPTION

METHODS AND COMPOSITIONS FOR TUSC2 IMMUNOTHERAPY

[0001] This application claims the benefit of United States Provisional Patent Application No. 62/407,329, filed October 12, 2016, the entirety of which is incorporated herein by reference.

5

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The present embodiments provided herein relate generally to the fields of molecular biology, immunology and cancer therapy.

2. Description of Related Art

10

[0003] As the molecular and genetic mechanisms of oncogenesis become better elucidated, the focus of cancer therapy has shifted from the tissue to the genetic level (Bishop, 1991). Mutations in two major classes of genes, oncogenes and tumor suppressor genes (TSGs), play central roles in the oncogenic process. TSGs appear to require homozygous deletion or mutation for inactivation, and restoration of TSG expression is feasible in human tumors (Lowe *et al.*, 2004; Roth, 2006).
15 Homozygous deletions in the 3p21.3 region in lung cancer cell lines and primary lung tumors have led to the identification of multiple genes with tumor suppressor activity from this region (Lerman *et al.*, 2000). These deletions have led to the development of targeted anti-cancer therapies. However, it remains unclear how the efficacy of such therapies could be enhanced.

SUMMARY

20

[0004] In one aspect, the present disclosure refers to the use of a TUSC2 therapy in the manufacture of a medicament for combination therapy of a lung cancer, wherein the subject has been or is being treated with at least one immune checkpoint inhibitor. In another aspect, the present disclosure refers to the use of a TUSC2 therapeutic and an immune checkpoint inhibitor in the manufacture of a combination therapy for use in treating a lung cancer. In one example, there is
25 described a method of treating a subject having a cancer comprising administering a tumor suppressor therapy (*e.g.*, a TUSC2 therapy) in conjunction with an immune checkpoint inhibitor. Thus, a method is disclosed for treating a subject having a cancer, wherein the subject is being treated with (or was previously administered) at least one immune checkpoint inhibitor, the method comprising administering a tumor suppressor therapy, such as a TUSC2 therapy, to the subject. For example, a
30 subject to be treated with a TUSC2 therapy can be a subject who was administered an immune checkpoint inhibitor less than one hour, 6 hours, 12 hours, 1 day, 3 days, one week or two weeks before administration of the TUSC2 therapy. As used herein, a TUSC2 therapy can be any

type of therapy that provides or causes expression of a TUSC2 polypeptide in a cancer cell (see, *e.g.*, U.S. Patent No. 7,902,441, incorporated herein by reference). For example, a TUSC2 therapy may comprise delivery of a TUSC2 polypeptide or TUSC2 expression vector to cancer cell. A therapy may, for instance, be delivered via nanoparticles, or in the case of nucleic acid expression vectors, through the use of a viral vector.

[0005] In certain examples, a method is disclosed for treating a subject having a cancer, comprising administering to the subject a TUSC2 therapy in conjunction with at least one immune checkpoint inhibitor. For instance, the TUSC2 therapy can be administered, before, after or essentially concomitantly with the at least one immune checkpoint inhibitor. Thus, in some examples, a composition is disclosed comprising a TUSC2 therapeutic and an immune checkpoint inhibitor in a therapeutically effective amount to treat a cancer.

[0006] In some examples, the at least one checkpoint inhibitor is selected from an inhibitor of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, BTLA, B7H3, B7H4, TIM3, KIR, or A2aR. In certain examples, the at least one immune checkpoint inhibitor is a human programmed cell death 1 (PD-1) axis-binding antagonist. In some examples, the PD-1 axis-binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDL1-binding antagonist and a PDL2-binding antagonist. In certain examples, the PD-1 axis-binding antagonist is a PD-1-binding antagonist. In some examples, the PD-1-binding antagonist inhibits the binding of PD-1 to PDL1 and/or PDL2. In particular examples, the PD-1-binding antagonist is a monoclonal antibody or antigen binding fragment thereof. In specific examples, the PD-1-binding antagonist is nivolumab, pembrolizumab, pidilizumab, KEYTRUDA®, AMP-514, REGN2810, CT-011, BMS 936559, MPDL3280A or AMP-224. In some examples, the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody. In particular examples, the anti-CTLA-4 antibody is tremelimumab, YERVOY®, or ipilimumab. In certain examples, the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody. In some examples, the anti-KIR antibody is lirilumab. In certain examples, the subject has been or is being administered more than one immune checkpoint inhibitors, such as an anti-PD1 antibody and an anti-CTLA4 antibody.

[0007] In certain examples, administration of a TUSC2 therapy comprises administration of a TUSC2 expression vector, such a DNA plasmid encoding TUSC2. An expression vector for use according to the embodiments disclosed herein will generally comprise control elements for the expression of the TUSC2 coding sequence. For example, a

vector can comprise a promoter and enhancer element that are effective for expression in cancer cell of interest. In certain examples, for instance, TUSC2 expression is disclosed by a CMV promoter or recombinant version thereof, such as the CMV promoter construct described in U.S. Patent Publication No. 20070092968, incorporated herein by reference. In certain examples, a
5 vector disclosed herein comprises a modified CMV promoter. In certain examples, a vector disclosed herein comprises a mini-CMV promoter. Additional expression control elements can be included such as, for example, an intron, a drug response element, a RNA stabilizing or destabilizing sequence, a cellular localization signal, a polyadenylation signal sequence and/or an optimized translation start codon. Plasmid DNA vectors may also comprise sequences that help
10 facilitate DNA production, such as, a bacterial origin of replication and/or a drug resistance marker. In certain specific examples, the TUSC2 expression vector is the pLJ143/KGB2/FUS1 plasmid.

[0008] Methods for delivery of an expression vector to cells (*e.g.*, *in vivo* delivery) are well known in the art and include, without limitation, nanoparticles (*e.g.*, liposome
15 nanoparticles), lipid conjugates and viral vectors. In certain examples, a TUSC2 expression vector is administered in a nanoparticle, such as N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTAP):cholesterol liposome nanoparticle. A skilled artisan will recognize that various properties of liposomes can be adjusted to optimize vector delivery. For example, the liposomes may be adjusted to have a certain size range and/or a particular ratio of
20 DNA to lipid; DNA to cholesterol; or lipid to cholesterol. For instance, in the case of a DOTAP:cholesterol liposome, the DOTAP:cholesterol ratio can be defined as between about 1.5:1 and 1:1.5, such as about 10:9. In further examples, a TUSC2 expression vector is provided in a liposome nanoparticle, wherein the nanoparticles comprise an average particle size of between about 50 and about 500 nm (*e.g.*, 200-500 nm). In still further examples, a TUSC2-
25 nanoparticle formulation can be defined by their optical density (OD), such as having OD₄₀₀ of between about 0.65 and 0.95.

[0009] In still further examples, a TUSC2 therapy can comprise administration of a TUSC2 polypeptide. Methods for administration of TUSC2 polypeptide are described for example in U.S. Publication Nos. 20060251726 and 20090023207, incorporated herein by
30 reference. A TUSC2 polypeptide may be modified to enhance its activity and/or ability to enter cancer cells. For instance, the polypeptide can be modified with a lipid moiety (*e.g.*, myristoylated). In certain examples a TUSC2 is provided as a nanoparticle (*e.g.*, a lipid-based

nanoparticle) such as, a superparamagnetic nanoparticle, a nanoshell, a semiconductor nanocrystal, a quantum dot, a polymer-based nanoparticle, a silicon-based nanoparticle, a silica-based nanoparticle, a metal-based nanoparticle, a fullerene or a nanotube.

5 [0010] A TUSC2 therapy and/or an immune checkpoint inhibitor according to the embodiments disclosed herein is typically formulated in a pharmaceutically acceptable carrier. A therapy according to the examples may be delivered, for example, intravenously, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, intramuscularly, intraperitoneally, subcutaneously, subconjunctival, 10 intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularly, orally, topically, locally, via inhalation (*e.g.* aerosol inhalation), by injection or by infusion, and the route of delivery can depend upon the type of cancer to be treated. For example, a TUSC2 expression vector complexed with DOTAP:cholesterol liposome can be administer via intravenous infusion. In certain specific examples, a TUSC2 therapy is administered intravenously in a dose of from 15 about 0.01 mg/kg to about 0.10 mg/kg, such as a dose of about 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08 0.09 or 0.10 mg/kg. In further examples, a TUSC2 therapy, can be administer two or more times (*e.g.*, 3, 4, 5, 6, 7, 8, 9 or 10 times). The timing between doses of such a therapy can be varied and can include, without limitation, about 1, 2 or 3 days, about 1, 2, or 3 weeks or 1 month or more between doses.

20 [0011] In yet a further example, there is disclosed a method for treating a subject having a cancer, comprising administering a TUSC2 therapy to the subject in conjunction at least one immune checkpoint inhibitor and/or in conjunction with one or more anti-inflammatory agent. For example, the anti-inflammatory agent may be administered before, after or during a TUSC2 therapy. In a further example, more than one anti-inflammatory agent is administered, such as 25 administration of an antihistamine and a corticosteroid. Thus, in certain specific examples the anti-inflammatory for use in conjunction with a TUSC2 therapy is diphenhydramine and/or dexamethasone.

[0012] In further examples, a method disclosed herein further comprises administering a further anticancer therapy. The further anticancer therapy may be, without limitation, a surgical 30 therapy, chemotherapy (*e.g.*, administration of a protein kinase inhibitor or a EGFR-targeted therapy), radiation therapy, cryotherapy, hyperthermia treatment, phototherapy, radioablation therapy, hormonal therapy, immunotherapy, small molecule

therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy or a biological therapies such as monoclonal antibodies, siRNA, antisense oligonucleotides, ribozymes or gene therapy. Without limitation the biological therapy may be a gene therapy, such as tumor suppressor gene therapy, a cell death protein gene therapy, a cell cycle regulator gene therapy, a cytokine gene therapy, a toxin gene therapy, an immunogene therapy, a suicide gene therapy, a prodrug gene therapy, an anti-cellular proliferation gene therapy, an enzyme gene therapy, or an anti-angiogenic factor gene therapy.

[0013] Thus, in yet a further example disclosed herein are compositions, therapies, and methods for treating a subject having a cancer, comprising administering to the subject a TUSC2 therapy (*e.g.*, a TUSC2 polypeptide or a TUSC2 expression vector) in conjunction with an immune checkpoint inhibitor and a further anticancer agent, such as a chemotherapeutic. For example, the chemotherapeutic can be a protein kinase inhibitor, such as a Src or Akt kinase inhibitor. In some examples, the chemotherapeutic is an epidermal growth factor receptor (EGFR) inhibitor.

[0014] Thus, in certain examples, a method is disclosed for treating a subject having a cancer, comprising administering to the subject a TUSC2 therapy in conjunction with at least one immune checkpoint inhibitor and, optionally, a protein kinase inhibitor. For instance, the TUSC2 therapy and or the immune checkpoint inhibitor can be administered, before, after or essentially concomitantly with the protein kinase inhibitor. Thus, in some examples, a composition is disclosed comprising a TUSC2 therapeutic, an immune checkpoint inhibitor and a protein kinase inhibitor in a therapeutically effective amount to treat a cancer. Protein kinase inhibitors for use according to the embodiments include, without limitation, EGFR, VEGFR, AKT, Erb1, Erb2, ErbB, Syk, Bcr-Abl, JAK, Src, GSK-3, PI3K, Ras, Raf, MAPK, MAPKK, mTOR, c-Kit, eph receptor or BRAF inhibitors. For example, the protein kinase inhibitor can be Afatinib, Axitinib, Bevacizumab, Bosutinib, Cetuximab, Crizotinib, Dasatinib, Erlotinib, Fostamatinib, Gefitinib, Imatinib, Lapatinib, Lenvatinib, Mubritinib, Nilotinib, Panitumumab, Pazopanib, Pegaptanib, Ranibizumab, Ruxolitinib, Saracatinib, Sorafenib, Sunitinib, Trastuzumab, Vandetanib, AP23451, Vemurafenib, CAL101, PX-866, LY294002, rapamycin, temsirolimus, everolimus, ridaforolimus, Alvocidib, Genistein, Selumetinib, AZD-6244, Vatalanib, P1446A-05, AG-024322, ZD1839, P276-00, GW572016, or a mixture thereof. In certain examples, the protein kinase inhibitor is an AKT inhibitor (*e.g.*, MK-2206, GSK690693, A-443654, VQD-002, Miltefosine or Perifosine).

[0015] EGFR-targeted therapies for use in accordance with the embodiments include, but are not limited to, inhibitors of EGFR/ErbB1/HER, ErbB2/Neu/HER2, ErbB3/HER3, and/or ErbB4/HER4. A wide range of such inhibitors are known and include, without limitation, tyrosine kinase inhibitors active against the receptor(s) and EGFR-binding antibodies or aptamers. For instance, the EGFR inhibitor can be gefitinib, erlotinib, cetuximab, matuzumab, panitumumab, AEE788; CI-1033, HKI-272, HKI-357 or EKB-569. In certain examples, the compositions and therapies disclosed herein are administered systemically or locally. In one example, the compositions and therapies disclosed herein are administered systemically. In certain examples, an EGFR inhibitor is administered to a patient before, after or essentially concomitantly with a TUSC2 therapy. For example, the therapies may be co-administered, such as by co-administration in an intravenous infusion. In certain embodiments, TUSC2 and EGFR inhibitors can be administered in any amount effective to treat cancers. In certain examples, the compositions, therapies, and methods disclosed herein comprise administering TUSC2 and EGFR inhibitors in lower doses than either composition administered alone. In certain examples, the compositions, therapies, and methods comprise administering TUSC2 and EGFR inhibitors in lower doses that reduce side effects. In certain examples, the compositions, therapies, and methods comprise administering a TUSC2 therapy, an immune checkpoint inhibitor and EGFR inhibitors in doses effective to provide additive, cooperative, or synergistic effect than that provided by either composition administered alone. In certain examples, cancers for treatment with such therapies can be any of those described herein, such as lung cancers (*e.g.*, non-small cell lung cancer). In certain preferred examples, a cancer for treatment with a combination therapy is an EGFR-expressing cancer. In certain examples, the EGFR-expressing cancer comprises at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% tumor cells expressing EGFR.

[0016] In yet still a further example disclosed herein is a method for treating a subject having a cancer, wherein it was previously determined that the cancer expresses an EGFR, the method comprising administering to the subject a TUSC2 therapy in conjunction with an immune checkpoint inhibitor and an EGFR inhibitor. In certain examples, disclosed herein is a method for treating a subject having a cancer comprising the step of determining whether the cancer expresses an EGFR, and administering to the subject a TUSC2, an immune checkpoint inhibitor and an EGFR inhibitor. Methods for assessing the EGFR-expression status of a cancer have been described, for example in U.S. Patent Publ. No.

20110052570, incorporated herein by reference. In certain examples, the EGFR-expressing cancer can be a cancer that expresses a mutant EGFR, such as a cancer expressing an EGFR having a L858R and/or T790M mutation. In certain examples, the compositions and therapies disclosed herein are administered to the patient that have an EGFR-expressing cancer that
5 comprises at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% tumor cells expressing EGFR. In still further examples, the subject for treatment has a cancer that was previously determined to express an EGFR and in which at least 10% of the cells of the cancer are apoptotic. In certain examples, the methods disclosed herein further comprise determining whether at least 10%, 15%, 20%,
10 25%, 30%, 35%, 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of the cells of the EGFR-expressing cancer are apoptotic.

[0017] In certain examples, a cancer for treatment or assessment may present as a tumor, such as primary or metastatic tumor. A cancer may be an early stage cancer, or may be a metastatic or late stage cancer. In certain examples, the cancer is an oral cancer, oropharyngeal
15 cancer, nasopharyngeal cancer, respiratory cancer, a urogenital cancer, a gastrointestinal cancer, a central or peripheral nervous system tissue cancer, an endocrine or neuroendocrine cancer, a hematopoietic cancer, a glioma, a sarcoma, a carcinoma, a lymphoma, a melanoma, a fibroma, a meningioma, brain cancer, oropharyngeal cancer, nasopharyngeal cancer, renal cancer, biliary cancer, prostatic cancer, pheochromocytoma, pancreatic islet cell cancer, a Li-Fraumeni tumor, thyroid cancer, parathyroid cancer, pituitary tumors, adrenal gland tumors, osteogenic sarcoma
20 tumors, multiple neuroendocrine type I and type II tumors, breast cancer, lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)), head & neck cancer, prostate cancer, esophageal cancer, tracheal cancer, skin cancer brain cancer, liver cancer, bladder cancer, stomach cancer, pancreatic cancer, ovarian cancer, uterine cancer, cervical cancer, testicular
25 cancer, colon cancer, rectal cancer or skin cancer. In further examples, a cancer may be defined as a cancer that is resistant to one or more anticancer therapy, such a chemotherapy resistant cancer. For example, the cancer may be a cancer that is resistant to a platinum-based chemotherapeutic, such as cisplatin.

[0018] In some examples, administering the TUSC2 therapy and at least one immune
30 checkpoint inhibitor results in an increase of NK and/or CD8⁺ T cell density in the tumor. In specific examples, the CD8⁺ T cell density increases by at least 3-fold, such as 4-, 5, 6, 7-, 8-, 9- or 10-fold. In some examples, administering the TUSC2 therapy and at

least one immune checkpoint inhibitor results in CcL3, CcL4, CcL21a, and/or CcL19 serum levels.

5 [0019] In still further examples herein is a kit comprising a TUSC2 therapeutic and at least one immune checkpoint inhibitor. For example, in some examples, a kit disclosed herein comprises a TUSC2 therapeutic, at least one immune checkpoint inhibitor and a reagent for testing a subject to determine their response for the TUSC2 therapeutic and/or the immune checkpoint inhibitor. For example, the reagent for testing a subject to determine their response for the TUSC2 therapeutic can be a reagent for determining the level of apoptosis in cancer cells of the subject. In further examples, a kit further comprises one or more anti-inflammatory agents or a kinase inhibitor. In still further examples the kit may comprise one more additional components including, but not limited to, a pharmaceutically acceptable dilution agent, a syringe, an infusion bag, an infusion line, and/or a set of instruction for use of the kit.

15 [0020] It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein. Likewise, aspects of the present embodiments discussed in the context of a method for treating a subject are equally applicable to a method of predicting response in a subject and *vice versa*.

[0021] The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

20 [0022] As used herein, “essentially free,” in terms of a specified component, is used herein to mean that none of the specified component has been purposefully formulated into a composition and/or is present only as a contaminant or in trace amounts. The total amount of the specified component resulting from any unintended contamination of a composition is therefore well below 0.01%. Most preferred is a composition in which no amount of the specified component can be detected with standard analytical methods.

[0023] As used herein in the specification and claims, “a” or “an” may mean one or more. As used herein in the specification and claims, when used in conjunction with the word “comprising”, the words “a” or “an” may mean one or more than one. As used herein, in the specification and claim, “another” or “a further” may mean at least a second or more.

30

CLAIMS

What Is Claimed Is:

1. Use of a TUSC2 therapy in the manufacture of a medicament for combination therapy of a lung cancer, wherein the subject has been or is being treated with at least one immune checkpoint inhibitor.
2. The use of claim 1, further comprising at least one immune checkpoint inhibitor to be administered to the subject.
3. The use of claim 2, wherein the at least one immune checkpoint inhibitor is to be administered to the subject before the TUSC2 therapy.
4. The use of claim 2, wherein the at least one immune checkpoint inhibitor is to be administered to the subject after or concomitantly with the TUSC2 therapy.
5. The use of claim 1, wherein the subject had been administered the at least one immune checkpoint inhibitor no more than two weeks before the TUSC2 therapy.
6. The use of claim 1, wherein the at least one immune checkpoint inhibitor comprises an anti-PD1 agent.
7. The use of claim 6, wherein the anti-PD1 agent comprises an anti-PD1 antibody, anti-PDL1 antibody, or an anti-PDL2 antibody.
8. The use of claim 6, wherein the anti-PD1 agent is nivolumab, pembrolizumab, pidilizumab, AMP-514, REGN2810, CT-011, BMS 936559, MPDL3280A or AMP-224.
9. The use of claim 1, wherein the at least one immune checkpoint inhibitor is selected from an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a human programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1), programmed death-ligand 2 (PD-L2), lymphocyte activation gene-3 (LAG-3), B and T lymphocyte attenuator (BTLA), B7 Homolog 3 (B7H3), B7 Homolog 4 (B7H4), T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), anti-killer-cell immunoglobulin-like receptor (KIR), or adenosine A2A receptor (A2aR).
10. The use of claim 1, wherein the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody.

11. The use of claim 10, wherein the anti-CTLA-4 antibody is tremelimumab, or ipilimumab.
12. The use of claim 1, wherein the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody.
- 5 13. The use of claim 12, wherein the anti-KIR antibody is lirilumab.
14. The use of claim 1, wherein the subject has been or is to be treated with two immune checkpoint inhibitors.
- 10 15. The use of claim 14, wherein the two immune checkpoint inhibitors are an anti-PD1 antibody and an anti-CTL4 antibody.
- 15 16. The use of claim 1, wherein the TUSC2 therapy comprises a TUSC2 expression vector to be administered.
17. The use of claim 16, wherein the TUSC2 expression vector is plasmid DNA.
18. The use of claim 17, wherein the plasmid is pLJ143/KGB2/FUS1.
19. The use of claim 16, wherein the TUSC2 expression vector is provided in a liposome.
- 20 20. The use of claim 19, wherein the liposome is a N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTAP):cholesterol liposome.
21. The use of claim 20, wherein the DOTAP:cholesterol ratio is between 1.5:1 and 1:1.5.
22. The use of claim 20, wherein the DOTAP:cholesterol ratio is about 10:9.
23. The use of claim 20, wherein the TUSC2 expression vector and DOTAP:cholesterol liposome are to be administered in a dose of from 0.01 mg/kg to 0.10 mg/kg.
- 25 24. The use of claim 1, wherein the TUSC2 therapy is to be administered two or more times.
25. The use of claim 1, further comprising an anti-inflammatory agent to be administered.
26. The use of claim 1, wherein the TUSC2 therapy comprises a TUSC2 polypeptide to be administered.
27. The use of claim 26, wherein the TUSC2 polypeptide is myristoylated.

28. The use of claim 26, wherein the TUSC2 polypeptide is comprised in a nanoparticle.
29. The use of claim 28, wherein the nanoparticle is a lipid-based nanoparticle, a superparamagnetic nanoparticle, a nanoshell, a semiconductor nanocrystal, a quantum dot, a polymer-based nanoparticle, a silicon-based nanoparticle, a silica-based nanoparticle, a metal-based nanoparticle, a fullerene or a nanotube.
30. The use of claim 1, further comprising a further anti-cancer therapy to be administered to the subject.
31. The use of claim 30, wherein the further anti-cancer therapy is chemotherapy, radiotherapy, gene therapy, surgery, hormonal therapy, anti-angiogenic therapy or cytokine therapy.
32. The use of claim 31, wherein the further anti-cancer therapy is an EGFR inhibitor.
33. The use of claim 1, wherein the lung cancer is a non-small cell lung cancer.
34. The use of claim 1, wherein the cancer is a metastatic lung cancer.
35. The use of claim 1, wherein the cancer is resistant to a least a first chemotherapy.
36. The use of claim 35, wherein the cancer is resistant to a platinum-based chemotherapy.
37. The use of claim 2, wherein the TUSC2 therapy and at least one immune checkpoint inhibitor to be administered results in an increase of NK and/or CD8⁺ T cell density in the tumor.
38. The use of claim 37, wherein the CD8⁺ T cell density increases by at least 3-fold.
39. The use of claim 2, wherein the TUSC2 therapy and at least one immune checkpoint inhibitor to be administered results in CcL3, CcL4, CcL21a, and/or CcL19 serum levels.
40. Use of a TUSC2 therapeutic and an immune checkpoint inhibitor in the manufacture of a combination therapy for use in treating a lung cancer.
41. The use of claims 40, wherein the immune checkpoint inhibitor is an anti-PD1 antibody.
42. The use of claim 32, wherein the EGFR inhibitor is a tyrosine kinase inhibitor.

43. The use of claim 32, wherein the EGFR inhibitor is an EGFR binding antibody or aptamer.
44. The use of claim 32, wherein the EGFR inhibitor is gefitinib, erlotinib, cetuximab, matuzumab, panitumumab, AEE788; CI-1033, HKI-272, HKI-357 or EKB-569.