THERAPEUTIC METHODS AND COMPOSITIONS FOR TREATING NON-SMALL CELL LUNG CANCER

BACKGROUND OF THE INVENTION

[0001] Lung cancer is a disease which consists of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas, derived from epithelial cells. Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004. Common treatments for lung cancer include palliative care, surgery, chemotherapy, radiation therapy (radiotherapy) and target therapy.

[0002] The main types of lung cancer are *small cell lung cancer* (SCLC) and *non-small cell lung cancer* (NSCLC). Small cell lung cancer (SCLC) is a fast-growing type of lung cancer. It spreads much more quickly than non-small cell lung cancer. There are three different types of small cell lung cancer: small cell carcinoma (oat cell cancer), mixed small cell/large cell carcinoma and combined small cell carcinoma. Most small cell lung cancers are the oat cell type. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. There are three forms of NSCLC: adenocarcinomas, squamous cell carcinomas and large cell carcinomas. Also there are several other types that occur less frequently, and all types can occur in unusual histologic variants and as mixed cell-type combinations. Adenocarcinomas are often found in an outer area of the lung. Squamous cell carcinomas are usually found in the center of the lung by an air tube (bronchus). Large cell carcinomas can occur in any part of the lung. They tend to grow and spread faster than the other two types. Sometimes the phrase "non-small-cell lung cancer" ("not otherwise specified", or NOS) is used generically, usually when a more specific diagnosis cannot be made. This is most often the case when a pathologist examines a small amount of malignant cells or tissue in a cytology or biopsy specimen.

[0003] As a class, NSCLCs are relatively insensitive to chemotherapy, compared to small cell carcinoma. When possible, they are primarily treated by surgical resection with curative intent, although chemotherapy is increasingly being used both pre-operatively (neoadjuvant chemotherapy) and post-operatively (adjuvant chemotherapy).

SUMMARY

[0004] In one aspect the present invention refers to a composition suitable for treating non-small cell lung cancer in a subject comprising an extract or powder of a herbal mixture, and an anti-cancer agent, wherein said herbal mixture comprises all of the genus Astragalus, Cimicifuga Foetida Rhizoma, Ophiopogon Radix, Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus-Red, and Zingiber Officinale Radix wherein each genus comprises at least one species of said genus. Also provided herein are compositions for treating non-small cell lung cancer in a subject comprising an extract or powder of a herbal mixture, and an anti-cancer agent, wherein said herbal mixture comprises a component of at least one species from each of the genus *Astragalus, Cimicifuga Foetida Rhizoma, Ophiopogon Radix, Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus*

Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus, and Zingiber Officinale Radix.

[0005] In another aspect, the present invention refers to use of a therapeutically effective amount of an extract or powder of a herbal mixture, in the manufacture of a medicament for treating non-small cell lung cancer in a subject, wherein said herbal mixture comprises all of the genus Astragalus, Cimicifuga Foetida Rhizoma, Ophiopogon Radix, Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus-Red, and Zingiber Officinale Radix wherein each genus comprises at least on species of said genus. In one example, there are described methods for treating non-small cell lung cancer in a subject comprising administering an extract or powder of a herbal mixture, optionally with an anti-cancer agent to a subject, wherein said herbal mixture comprises a component of at least one species from each of the genus *Astragalus, Cimicifuga Foetida Rhizoma, Ophiopogon Radix, Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus, and Zingiber Officinale Radix.*

INCORPORATION BY REFERENCE

[0006] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0008] FIG. 1A-C show illustrative results of cell line cytotoxicity study of the combination therapy of Composition **3** with cisplatin or gefitinib. (2A) Combination treatment of cisplatin and Composition **3** in CL141 lung cancer cells at 48 hrs. Combination treatment of gefitinib and Composition **3** in (2B) CL141 and (2C) CL97 lung cancer cells at 72 hrs. (t-test, *: p value<0.05; **: p value<0.01; ***: p value<0.001 compared with different dosages of Composition 3 at the same dosage of cisplatin or gefitinib. $^{\#}$: p value<0.05; $^{\#\#}$: p value<0.01; $^{\#\#\#}$: p value<0.001 compared different treatments with vehicle control.)

WHAT IS CLAIMED IS:

1. A composition suitable for treating non-small cell lung cancer in a subject comprising an extract or powder of a herbal mixture, and an anti-cancer agent, wherein said herbal mixture comprises all of the genus *Astragalus*, *Cimicifuga Foetida Rhizoma*, *Ophiopogon Radix*, *Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus-Red, and Zingiber Officinale Radix* wherein each genus comprises at least one species of said genus.

2. The composition of claim 1, wherein the anti-cancer agent is selected from the group consisting of estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, nitrogen mustards, nitroso ureas, angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling pathway, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, agents that interfere with receptor tyrosine kinases (RTKs), integrin blockers, NSAIDs, PPAR agonists, inhibitors of inherent multidrug resistance (MDR), anti-emetic agents, agents useful in the treatment of anemia, agents useful in the treatment of neutropenia, immunologic-enhancing drugs, biphosphonates, aromatase inhibitors, agents inducing terminal differentiation of neoplastic cells, γ-secretase inhibitors, and cancer vaccines.

3. The composition of claim 1, wherein the anti-cancer agent is a cytotoxic agent.

4. The composition of claim 3, wherein the cytotoxic agent is selected from the group consisting of afatinib, erlotinib, osimertinib (AZD9291), AZD3759, gefitinib, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine-(chloro)platinum(II)]-tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3′-deamino-3′-morpholino-13-deoxo-10-hydroxycaminomycin,

annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin.

5. The composition of claim 1, wherein the anti-cancer agent is selected from the group consisting of gemcitabine, idarubicin/cytarabine, etopside phosphate, gleevac, temozolomide, bortezomib, letrozole, cetuximab, bevacizumab, nab-paclitaxel, docetaxel, erlotinib, pemetrexed, pemetrexed/carboplatin, paxlitaxel/carboplatin, letrozole/cyclophsphamide, temsirolimus,, bevacizumab/temsirolimus, lpilimumab, RAD001, Pazopanib, FOLFIRI, BKM120, GSK1120212, PF-05212384/irinotecan, AZD2171, PF-04691502, cyclophosphamide, cisplatin, cytarabine/daunorubcin, tersirolimus, erlotinib/temsirolimus, capecitabine, tamoxifen, bortezomib, trastuzumab, docetaxel/capecitabine, trastuzumab/tipifarnib, tipifarnib/gemcitabline, tootecan, or combinations thereof.

6. The composition of claim 2, wherein said agent that interfere with receptor tyrosine kinases (RTKs) is selected from the group consisting of afatinib, erlotinib, osimertinib (AZD9291), AZD3759, gefitinib.

7. The composition of claim 1, wherein the anti-cancer agent is cisplatin or gefitinib.

8. The composition of claim 1, wherein said composition improves the efficacy of cisplatin-based chemotherapy.

9. The composition of claim 1, wherein said composition increases the production of IL-1 β expression.

10. The composition of claim 1, wherein said composition increases the production of TNF-α expression.

11. The composition of claim 1, wherein said composition inhibits angiogenesis, or ABCG2.

12. The composition of claim 1, wherein said composition reduces phosphor-EGFR mediated signaling or prevents lipolysis, or overcome gefitinib resistance.

13. Use of a therapeutically effective amount of an extract or powder of a herbal mixture, in the manufacture of a medicament for treating non-small cell lung cancer in a subject, wherein said herbal mixture comprises all of the genus *Astragalus*, *Cimicifuga Foetida Rhizoma*, *Ophiopogon Radix*, *Atractylodes Lancea Rhizoma, Panax Ginseng-Red, Atractylodes Rhizoma-White, Massa Medicata Fermentata, Citrus Reticulata-Viride, Citrus Reticulata, Glycyrrhiza Radix, Schisandra Fructus, Angelica Sinensis Radix, Phellodendron*

Cortex, Alisma Rhizoma, Pueraria Radix, Ziziphus Fructus-Red, and Zingiber Officinale Radix wherein each genus comprises at least one species of said genus.

14. The use of claim 13, wherein said non-small cell lung cancer is adenocarcinomas.

15. The use of claim 13, wherein said non-small cell lung cancer is large cell carcinomas.

16. The use of claim 13, wherein said method decreases non small cell lung cancer tumor growth rate.

17. The use of claim 13, wherein said method reduces non small cell lung cancer tumor size or tumor volume.

18. The use of claim 13, wherein the medicament further comprises an anti-cancer agent selected from the group consisting of afatinib, erlotinib, osimertinib (AZD9291), AZD3759, gefitinib, gemcitabine, idarubicin/cytarabine, etopside phosphate, gleevac, temozolomide, bortezomib, letrozole, cetuximab, bevacizumab, nab-paclitaxel, docetaxel, erlotinib, pemetrexed, pemetrexed/carboplatin, paxlitaxel/carboplatin, letrozole/cyclophsphamide, temsirolimus,, bevacizumab/temsirolimus, lpilimumab, RAD001, Pazopanib, FOLFIRI, BKM120, GSK1120212, PF-05212384/irinotecan, AZD2171, PF-04691502, cyclophosphamide, cisplatin, cytarabine/daunorubcin, tersirolimus, erlotinib/temsirolimus, capecitabine, tamoxifen, bortezomib, trastuzumab, docetaxel/capecitabine, trastuzumab/tipifarnib, tipifarnib/gemcitabline, tootecan, or combinations thereof.

19. The use of claim 18, wherein the anti-cancer agent is cisplatin or gefitinib.

20. The use of claim 18, wherein said extract or powder of herbal mixture, and said anti-cancer agent are to be administered separately, simultaneously or sequentially.

21. The use of claim 18, wherein said extract or powder of herbal mixture, and/or said anti-cancer agent are to be administered orally, parenterally intravenously or by injection.