SUMMARY

[0005a] In one aspect of the present disclosure, there is provided a use of a combination of:

(i) an agent that selectively blocks CD47 binding to SIRPα, selected from: an antibody that binds to CD47; an antibody that binds to SIRPα; and a soluble high affinity SIRPα polypeptide or a combination thereof; and

(ii) an antibody that specifically binds to one or more cell-surface antigens on lung cancer cells wherein the one or more cell-surface antigens on lung cancer cells are selected from CD24, CD166, CD56, CD326, CD298, CD29, CD63, CD9, CD164, CD99, CD45, CD59, CD57, CD165, and EpCAM,

in the manufacture of a medicament for treating an individual with small cell lung cancer (SCLC), wherein the medicament is to be administered in a dose effective to increase depletion of the SCLC cells.

[0006] Methods and compositions are also provided for the treatment of lung cancer with a targeted therapy. In some embodiments, the lung cancer is small cell lung cancer. In some embodiments, the therapy is targeted at one or more cell-surface antigens, including CD24, CD166, CD56, CD326, CD298, CD29, CD63, CD9, CD164, CD99, CD46, CD59, CD57, CD165, EpCAM, *etc.* In some embodiments the targeted therapy comprises administering to an individual suffering from lung cancer a therapeutic dose of an antibody that specifically binds to a cell surface marker selected from CD24, CD166, CD56, CD326, CD298, CD29, CD63, CD9, CD164, CD99, CD46, CD59, CD57, CD165 and EpCAM.

[0007] In some embodiments the targeted therapy is combined with a CD47 blocking agent. Cancer cells evade macrophage surveillance by upregulation of CD47 expression. Administration of agents that mask the CD47 protein, *e.g.* antibodies or small molecules that bind to CD47 or SIRPα and prevent interaction between CD47 and SIRPα, are administered to a patient, which increases the clearance of cancer cells via phagocytosis. The agent that blocks CD47 is combined with monoclonal antibodies directed against one or more lung cancer cell markers, which compositions can be synergistic in enhancing phagocytosis and elimination of cancer cells as compared to the use of single agents.

[0008] Specific reagent combinations of interest for therapy include anti-CD47 and anti-CD56; anti-CD47 and anti-CD44, anti-CD47 and anti-CD99, anti-CD47 and anti-EpCAM. In some such embodiments the anti-CD47 reagent is a high affinity SIRPα polypeptide, which can be provided in the form of a monomer or a multimer, e.g. as a fusion protein with an IgG Fc polypeptide.

[0009] In other embodiments, the therapy provides for a multispecific antibody that targets CD47 and a second cancer cell marker, including multispecific antibodies that target CD47 and CD56; CD47 and CD44, CD47 and EpCAM, *etc.* Compositions of such multispecific antibodies are also provided, where the multispecific antibody is desirably

treatment or for no treatment at all, even though a cure with aggressive therapy might technically be possible.

[0075] SCLC of any stage is typically initially responsive to treatment, but responses are usually short-lived. Chemotherapy, with or without radiation therapy, is given depending on the stage of disease. In many patients, chemotherapy prolongs survival and improves quality of life enough to warrant its use. Surgery generally plays no role in treatment of SCLC, although it may be curative in the rare patient who has a small focal tumor without spread (such as a solitary pulmonary nodule) who underwent surgical resection before the tumor was identified as SCLC. Chemotherapy regimens of etoposide and a platinum compound (either cisplatin or carboplatin) are commonly used, as are other drugs, such as irinotecan, topotecan, vinca alkaloids (vinblastine, vincristine, vinorelbine), alkylating agents (cyclophosphamide, ifosfamide), doxorubicin, taxanes (docetaxel, paclitaxel), and gemcitabine. When disease is confined to a hemithorax, radiation therapy further improves clinical outcomes; such response to radiation therapy was the basis for the definition of limited-stage disease. The use of cranial radiation to prevent brain metastases is also advocated in certain cases; micrometastases are common in SCLC, and chemotherapy has less ability to cross the blood-brain barrier.

[0076] In extensive-stage disease, treatment is based on chemotherapy rather than radiation therapy, although radiation therapy is often used as palliative treatment for metastases to bone or brain. In patients with an excellent response to chemotherapy, prophylactic brain irradiation is sometimes used as in limited-stage SCLC to prevent growth of SCLC in the brain.

[0077] Treatment for NSCLC typically involves assessment of eligibility for surgery followed by choice of surgery, chemotherapy, radiation therapy, or a combination of modalities as appropriate, depending on tumor type and stage.

Treatment of Cancer

[0078] The invention provides methods for reducing growth of lung cancer cells through the introduction of an effective dose of a targeted therapeutic agent directed to a lung cancer cell surface marker, including without limitation CD24, CD166, CD56, CD326, CD298, CD29, CD63, CD9, CD164, CD99, CD46, CD59, CD57, CD165, EpCAM, *etc.* In some embodiments the marker is one of CD56, CD44, CD99 and EpCAM. In preferred embodiments the targeted therapeutic agent is combined with a CD47 blocking agent, e.g. soluble SIRPα monomer or multimer, an anti-CD47 antibody, small molecule, etc. In certain embodiments the cancer is SCLC. By blocking the activity of CD47, the downregulation of phagocytosis that is found with certain tumor cells is prevented.

[0079] "Reducing growth of cancer cells" includes, but is not limited to, reducing proliferation of cancer cells, and reducing the incidence of a non-cancerous cell becoming a

WHAT IS CLAIMED IS:

1. Use of a combination of:

(i) an agent that selectively blocks CD47 binding to SIRPα, selected from: an antibody that binds to CD47; and antibody that binds to SIRPα; and a soluble high affinity SIRPα polypeptide or a combination thereof; and

(ii) an antibody that specifically binds to one or more cell-surface antigens on lung cancer cells wherein the one or more cell-surface antigens on lung cancer cells are selected from CD24, CD166, CD56, CD326, CD298, CD29, CD63, CD9, CD164, CD99, CD46, CD59, CD57, CD165, and EpCAM,

in the manufacture of a medicament for treating an individual with small cell lung cancer (SCLC), wherein the medicament is to be administered in a dose effective to increase depletion of the SCLC cells.

2. The use of claim 1, wherein the agent that selectively blocks CD47 binding to SIRPα is an antibody.

3. The use of claim 2, wherein the antibody specifically binds to CD47.

4. The use of claim 2, wherein the antibody specifically binds to SIRPα.

5. The use of claim 1, wherein the agent that selectively blocks CD47 binding to SIRPα is a soluble SIRPα polypeptide.

6. The use of claim 1, wherein the agent that selectively blocks CD47 binding to SIRPα is a soluble CD47 polypeptide.

7. The use of claim 1, wherein the combination of agents is to be administered simultaneously.

8. The use of claim 1, wherein the combination of agents is to be administered sequentially.

9. The use of claim 1, wherein the combination of agents is to be administered in overlapping dosing regimens.

10. The use of claim 1, wherein the individual is a human.

11. The use of Claim 1, wherein said marker is selected from CD99, CD44 and EpCAM.

12. The use of claim 1, wherein the combination of agents provides for a synergistic effect.

13. The use of claim 3 wherein the antibody is 5F9-G4.