appropriate for use in treating patients for whom very few or no viable treatment options remain. The present invention meets this need by providing a shortened manufacturing process for use in generating TILs which can then be employed in the treatment of non-small cell lung carcinoma (NSCLC) patients whom are refractory to anti-PD-1 treatment.

SUMMARY

[0004] The present disclosure provides improved and/or shortened methods for expanding TILs and producing therapeutic populations of TILs for use in treatment of non-small cell lung carcinoma (NSCLC) patients whom are refractory to anti-PD-1 treatment.

[0005] In one aspect, the present disclosure refers to the use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating non-small cell lung carcinoma (NSCLC), wherein the use comprises: (a) providing a first population of TILs which is to be obtained and/or received from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a tumor sample that contains a mixture of tumor cells and TILs ~~cells~~ from ~~a NSCLC tumor in~~ a NSCLC patient; (b) contacting the first population of TILs with a first cell culture medium; (c) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, OKT-3, and antigen presenting cells (APCs) and further wherein the initial expansion is performed during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days; (d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs~~.~~, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion, wherein the second cell culture medium comprises IL-2, OKT-3 ~~(anti-CD3 antibody)~~, and ~~optionally~~ irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed ~~over a period of 14 days or less~~during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days, 9 days, 10 days or 11 days; (e) harvesting the third population of TILs; and (f) ~~that~~ providing a therapeutically effective portion of the third population of TILs ~~is to be administered~~for administration to ~~a patient with~~ the NSCLC patient~~.~~, wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody. The present disclosure provides a method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) obtaining and/or receiving a first population of TILs from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample that contains a mixture of tumor and TIL cells from a NSCLC tumor in a patient;

(c) contacting the tumor fragments with a first cell culture medium;

(d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs

[0046] In another aspect, the present disclosure refers to the use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating non-small cell lung carcinoma (NSCLC), wherein the use comprises: (a) ~~that~~ providing a tumor ~~is to be~~ resected from a patient, the tumor comprising a first population of TILs; (b) fragmenting the tumor into tumor fragments; (c) contacting the tumor fragments with a first cell culture medium; (d) performing an initial expansion of the first population of TILs ~~comprised in the tumor fragments of (c)~~ in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, wherein the first cell culture medium comprises IL-2, OKT-3, and antigen presenting cells (APCs) and further wherein the initial expansion is performed during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days; (e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion,~~;~~ wherein the second cell culture medium comprises IL-2, OKT-3 ~~(anti-CD3 antibody)~~, and ~~optionally~~ irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed ~~over a period of 14 days or less~~during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days, 9 days, 10 days or 11 days; (f) harvesting the third population of TILs; and (g) that a therapeutically effective portion of the third population of TILs is to be administered to a patient with the NSCLC; wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody. In some examples, the disclosure provides a method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient, the tumor comprising a first population of TILs;

(b) fragmenting the tumor into tumor fragments;

(c) contacting the tumor fragments with a first cell culture medium;

(d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2;

(e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and optionally irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed over a period of 14 days or less;

(f) harvesting the third population of TILs; and

[0079] In some examples, the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0080] In some examples, the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0081] In some examples, the method further comprises the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

[0082] In some examples, the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m^2/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days.

[0083] In some examples, the method further comprises the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.

[0084] In some examples, the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

[0085] In another aspect, the present disclosure refers to the use of expanded tumor infiltrating lymphocytes in the manufacture of a medicament for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the non-small cell lung carcinoma is refractory to treatment with an anti-PD-1 antibody, the use comprises: (a) ~~obtaining and/or receiving~~providing a first population of TILs obtained and/or received from a tumor resected from a subject by processing a tumor sample obtained from the subject into multiple tumor fragments; (b) adding the tumor fragments into a closed system; (c) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2 to produce a second population of TILs, wherein the first expansion is performed in a closed container providing a first gas-permeable surface area, wherein the first expansion is performed for ~~about~~ during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 ~~3-14~~ days to obtain the second population of TILs, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, and wherein the transition from step (b) to step (c) occurs without opening the system; (d) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the second expansion is performed for ~~about~~ during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days,7 days or 8 days, 9 days, 10 days or 11 ~~-14~~ days to obtain the third population of TILs, wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (c) to step (d) occurs without opening the system; (e) harvesting therapeutic population of TILs obtained from step (d), wherein the transition from step (d) to step (e) occurs without opening the system; ~~and~~ (f) transferring the harvested TIL population from step (e) to an infusion bag, wherein the transfer from step (e) to (f) occurs

without opening the system; (g) cryopreserving the infusion bag comprising the harvested TIL population from step (f) using a cryopreservation process; and (h) providing a therapeutically effective dosage of the third population of TILs from the infusion bag in step (g) is to be administered to the subject. In some examples, the disclosure provides a method for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, the method comprising administering expanded tumor infiltrating lymphocytes (TILs) comprising:

(a) obtaining and/or receiving a first population of TILs from a tumor resected from a subject by processing a tumor sample obtained from the subject into multiple tumor fragments;

(b) adding the tumor fragments into a closed system;

(c) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2 to produce a second population of TILs, wherein the first expansion is performed in a closed container providing a first gas-permeable surface area, wherein the first expansion is performed for about 3-11 days to obtain the second population of TILs, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, and wherein the transition from step (b) to step (c) occurs without opening the system;

(d) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the second expansion is performed for about 7-11 days to obtain the third population of TILs, wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (c) to step (d) occurs without opening the system;

(e) harvesting therapeutic population of TILs obtained from step (d), wherein the transition from step (d) to step (e) occurs without opening the system; and

(f) transferring the harvested TIL population from step (e) to an infusion bag, wherein the transfer from step (e) to (f) occurs without opening the system;

(g) cryopreserving the infusion bag comprising the harvested TIL population from step (f) using a cryopreservation process; and

WHAT IS CLAIMED IS:

1. Use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating non-small cell lung carcinoma (NSCLC), wherein the use comprises:

(a) providing a first population of TILs which is to be obtained and/or received from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a tumor sample that contains a mixture of tumor cells and TILs ~~cells~~ from ~~a NSCLC tumor in~~ a NSCLC patient;

(b) contacting the first population of TILs with a first cell culture medium;

(c) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, OKT-3, and antigen presenting cells (APCs) and further wherein the initial expansion is performed during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs~~;~~, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion, wherein the second cell culture medium comprises IL-2, OKT-3 ~~(anti-CD3 antibody)~~, and ~~optionally~~ irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed ~~over a period of 14 days or less~~during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days, 9 days, 10 days or 11 days;

(e) harvesting the third population of TILs; and

(f) ~~that~~ providing a therapeutically effective portion of the third population of TILs ~~is to be administered~~for administration to ~~a patient with~~ the NSCLC patient~~;~~, wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

2. The use of Claim 1, wherein ~~the obtaining~~ the first population of TILs ~~comprises~~ is obtained using a multilesional sampling method.

3. The use of Claim 1, wherein the refractory NSCLC:

i) has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody; ~~or the refractory NSCLC~~

ii) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody;

iii) ~~, wherein optionally the refractory NSCLC~~ has been treated with a chemotherapeutic agent; ~~or~~

iv) ~~wherein the refractory NSCLC~~ has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent; ~~.~~

~~4. The use of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent or the refractory NSCLC~~

v) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent~~, ~~; or

vi) ~~wherein optionally the refractory NSCLC~~ has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

~~5~~4. The use of Claim 1, wherein the refractory NSCLC has low expression of ~~–~~PD-L1~~, ~~.

5. The use of Claim 4, wherein ~~optionally~~ the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody. ~~and has low expression of PD-L1 or~~

6. The use of Claim 4, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody ~~and has low expression of PD-L1,~~.

7. The use of Claim 4, ~~optionally~~ wherein the refractory NSCLC has been treated with a chemotherapeutic agent. ~~and has low expression of PD-L1 or~~

8. The use of Claim 4, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent ~~and has low expression of PD-L1~~.

~~6~~9. The use of Claim 1, wherein the refractory NSCLC ~~has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and~~ has bulky disease at baseline.

10. The use of Claim 9, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

11. The use of Claim 9, ~~or~~ wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody ~~and has bulky disease at baseline.,~~

12. The use of Claim 9, wherein ~~optionally~~ the refractory NSCLC has been treated with a chemotherapeutic agent.

13. The use of Claim 9, wherein ~~and has bulky disease at baseline or~~ the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent. ~~and has bulky disease at baseline,~~

14. The use of any one of Claims 1 to 13, ~~optionally~~ wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

~~7~~15. The use of any one of Claims 1 to 14~~Claim 1~~, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies and/or wherein the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, any anti-PD-1 antibody disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, and avelumab~~, and fragments, derivatives, variants, as well as biosimilars thereof~~, wherein ~~optionally~~ the refractory NSCLC is refractory to pembrolizumab ~~or a biosimilar thereof~~, nivolumab ~~or a biosimilar thereof~~, an anti-CLTA-4 antibody, such as ipilimumab ~~or a biosimilar thereof~~ or an anti-CLTA-4 antibody, such as ipilimumab ~~or a biosimilar thereof~~ and pembrolizumab ~~or a biosimilar thereof~~, ~~optionally~~ wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab ~~or a biosimilar thereof~~ and nivolumab ~~or a biosimilar thereof~~.

~~8~~16. The use of any one of Claims 1 to 15~~Claim 1~~, wherein the refractory NSCLC is refractory to durvalumab ~~or a biosimilar thereof~~, atezolizumab, ~~or a biosimilar thereof~~ or avelumab ~~or a biosimilar thereof~~.

~~9~~17. The use of any one of Claims 1 to ~~8~~16, wherein the initial expansion is performed for 1 to 8 days and the second expansion is performed for 1 to 9 days~~wherein the initial expansion is performed over a period of 21 days or less or a period of 14 days or less~~.

18. The use of any one of Claims 1 to 17, wherein the initial expansion is performed for 8 days and the second expansion is performed for 7 to 9 days.

~~10~~19. The use of any one of Claims 1 to 19, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium, wherein optionally the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

~~11~~20. The method of any one of Claims 1 to ~~10~~19, wherein the initial expansion is performed using a gas permeable container and/or the rapid expansion is performed using a gas permeable container.

~~12~~21. The use of any one of Claims 1 to 20~~11~~, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof and/or wherein the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

~~13~~22. The use of any one of Claims 1 to ~~12~~21, wherein the ~~method further comprises the step of treating the patient~~ patient is to be treated with a non-myeloablative lymphodepletion regimen prior to ~~administering~~ administration of the third population of TILs to the patient, wherein optionally the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m~~-~~^{2}/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days.

~~14~~23. The use of any one of Claims 1 to ~~13~~22, further comprises the step wherein the patient is to be treated with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient, wherein optionally the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, ~~or a biosimilar or variant thereof,~~ administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

~~15~~24. Use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating non-small cell lung carcinoma (NSCLC), wherein the use comprises:

(a) ~~that~~ providing a tumor ~~is to be~~ resected from a patient, the tumor comprising a first population of TILs;

(b) fragmenting the tumor into tumor fragments;

(c) contacting the tumor fragments with a first cell culture medium;

(d) performing an initial expansion of the first population of TILs ~~comprised in the tumor fragments of (c)~~ in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of

TILs, wherein the first cell culture medium comprises IL-2, wherein the first cell culture medium comprises IL-2, OKT-3, and antigen presenting cells (APCs) and further wherein the initial expansion is performed during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days;

(e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion,~~;~~ wherein the second cell culture medium comprises IL-2, OKT-3 ~~(anti-CD3 antibody)~~, and ~~optionally~~ irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed ~~over a period of 14 days or less~~during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 days, 9 days, 10 days or 11 days;

(f) harvesting the third population of TILs; and

(g) that a therapeutically effective portion of the third population of TILs is to be administered to a patient with the NSCLC;

~~_____~~ ~~———~~wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

~~16~~25. The use of Claim ~~15~~24, wherein the tumor is to be resected from one or more tumor sites. ~~and/or the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody, wherein optionally the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and/or the refractory NSCLC has been treated with a chemotherapeutic agent, optionally wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent or the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.~~

~~17~~26. The use of Claim 24 or 25, wherein the refractory NSCLC:

i) has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody;

ii) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody;

iii) has been treated with a chemotherapeutic agent;

iv) has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent;

v) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent; or

vi) has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

~~17. The use of Claim 16, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and/or wherein the refractory NSCLC has low expression of PD-L1, wherein optionally the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1 or the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1, optionally wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1 or the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1.~~

~~18~~27. The use of Claim 26, wherein the refractory NSCLC has low expression of PD-L1.

28. The use of Claim 27, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

29. The use of Claim 27, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

30. The use of Claim 27, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

31. The use of Claim 27, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

~~18. The use of Claim 15, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline or wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline, wherein optionally the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline, or the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline, optionally wherein said bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.~~

32. The use of Claim 26, wherein the refractory NSCLC has bulky disease at baseline.

33. The use of Claim 32, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

34. The use of Claim 32, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

35. The use of Claim 32, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

36. The use of Claim 32, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

37. The use of any one of Claims 26 to 36, wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

~~19~~38. The use of any one of Claims 26 to 37~~Claim 15~~, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies and/or the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, any anti-PD-1 antibody disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, and avelumab, ~~and fragments, derivatives, variants, as well as biosimilars thereof,~~ wherein ~~optionally~~ the refractory NSCLC is refractory to pembrolizumab ~~or a biosimilar thereof~~; nivolumab ~~or a biosimilar thereof~~; anti-CLTA-4 antibody, such as ipilimumab ~~or a biosimilar thereof~~; anti-CLTA-4 antibody, such as ipilimumab ~~or a~~

~~biosimilar thereof~~ and pembrolizumab ~~or a biosimilar thereof~~; anti-CLTA-4 antibody, such as ipilimumab ~~or a biosimilar thereof~~ and nivolumab ~~or a biosimilar thereof~~; durvalumab ~~or a biosimilar thereof~~; atezolizumab ~~or a biosimilar thereof~~; or avelumab ~~or a biosimilar thereof~~.

~~20~~39. The use of any one of Claims ~~15~~ 26 to ~~19~~38, wherein the initial expansion is performed ~~over~~ for 1 to 8 days and the second expansion is performed for 1 to 9 days~~a period of 21 days or less or the initial expansion is performed over a period of 14 days or less~~.

40. The use of any one of Claims 26 to 39, wherein the initial expansion is performed for 8 days and the second expansion is performed for 7 to 9 days.

~~21~~41. The use of any one of Claims ~~15~~ 26 to ~~20~~40, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium, wherein optionally the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

~~22~~42. The use of any one of Claims ~~15~~ 26 to ~~21~~41, wherein the initial expansion is performed using a gas permeable container and/or the rapid expansion is performed using a gas permeable container.

~~23~~43. The use of any one of Claims ~~15~~ 26 to ~~22~~42, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof and/or the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL- 21, and combinations thereof.

~~24~~44. The use of any one of Claims ~~15~~ 26 to ~~23~~43, further comprises the step wherein the patient is to be treated with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient and/or further comprising the step wherein the patient is to be treated with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient, wherein optionally the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m~~-~~^{2}/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days and/or the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin~~, or a biosimilar or variant thereof~~, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

~~25~~45. Use of expanded tumor infiltrating lymphocytes in the manufacture of a medicament

for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the non-small cell lung carcinoma is refractory to treatment with an anti-PD-1 antibody, the use comprises:

(a) ~~obtaining and/or receiving~~providing a first population of TILs obtained and/or received from a tumor resected from a subject by processing a tumor sample obtained from the subject into multiple tumor fragments;

(b) adding the tumor fragments into a closed system;

(c) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2 to produce a second population of TILs, wherein the first expansion is performed in a closed container providing a first gas-permeable surface area, wherein the first expansion is performed for ~~about~~ during a period of up to or at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or 8 ~~3-14~~ days to obtain the second population of TILs, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, and wherein the transition from step (b) to step (c) occurs without opening the system;

(d) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the second expansion is performed for ~~about~~ during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days,7 days or 8 days, 9 days, 10 days or 11 ~~7-14~~ days to obtain the third population of TILs, wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (c) to step (d) occurs without opening the system;

(e) harvesting therapeutic population of TILs obtained from step (d), wherein the transition from step (d) to step (e) occurs without opening the system; ~~and~~

(f) transferring the harvested TIL population from step (e) to an infusion bag, wherein the transfer from step (e) to (f) occurs without opening the system;

(g) cryopreserving the infusion bag comprising the harvested TIL population from step (f) using a cryopreservation process; and

(h) providing a therapeutically effective dosage of the third population of TILs from the infusion bag in step (g) is to be administered to the subject.

~~26~~46. The use of Claim ~~25~~45, wherein the tumor sample is derived from a multilesional sampling method. ~~and/or the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody, wherein optionally the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and/or the refractory NSCLC has been treated with a chemotherapeutic agent, optionally wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent or the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.~~

47. The use of Claim 45 or 46, wherein the refractory NSCLC:

i) has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody;

ii) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody;

iii) has been treated with a chemotherapeutic agent;

iv) has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent;

v) has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent; or

vi) has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

~~27. The use of Claim 25, wherein the refractory NSCLC has low expression of PD-L1, wherein optionally the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1 or wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1, optionally wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1 or the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1.~~

~~28~~48. The use of Claim 47, wherein the refractory NSCLC has low expression of -PD-L1.

49. The use of Claim 48, wherein the refractory NSCLC has been previously treated with

an anti-PD-1 and/or anti-PD-L1 antibody.

50. The use of Claim 48, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

51. The use of Claim 48, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

52. The use of Claim 48, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

~~28. The use of Claim 25, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline or wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline, wherein optionally the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline and/or the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline, optionally wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.~~

53. The use of Claim 47, wherein the refractory NSCLC has bulky disease at baseline.

54. The use of Claim 53, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

55. The use of Claim 53, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

56. The use of Claim 53, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

57. The use of Claim 53, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

58. The use of any one of Claims 47 to 57, wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

2959. The use of ~~Claim 25~~any of Claims 47 to 58, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

60. The use of any of Claims 47 to 59, ~~and/or~~ wherein the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, any anti-PD-1 antibody disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, and avelumab~~, and fragments, derivatives, variants, as well as biosimilars thereof~~.

61. The use of Claim 60, wherein ~~optionally~~ the refractory NSCLC is refractory to:

i) pembrolizumab ~~or a biosimilar thereof~~;

ii) nivolumab ~~or a biosimilar thereof~~;

iii) ~~an anti-CLTA-4 antibody, such as~~ ipilimumab ~~or a biosimilar thereof~~;

iv) ~~an anti-CLTA-4 antibody, such as~~ ipilimumab ~~or a biosimilar thereof~~ and pembrolizumab ~~or a biosimilar thereof~~;

v) ~~an anti-CLTA-4 antibody, such as~~ ipilimumab ~~or a biosimilar thereof~~ and nivolumab ~~or a biosimilar thereof~~;

vi) durvalumab ~~or a biosimilar thereof~~;

vii) atezolizumab ~~or a biosimilar thereof~~; or

viiii) avelumab ~~or a biosimilar thereof~~.

~~30. The use of any one of Claims 25 to 29, wherein the initial expansion is performed over a period of 21 days or less or the initial expansion is performed over a period of 14 days or less.~~

3162. The use of any one of Claims ~~25 to 30~~45 to 61, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium

63. The use of 62, wherein ~~optionally~~ the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

3264. The use of any one of Claims 45 to 63~~25 to 31~~, wherein the initial expansion is

performed using a gas permeable container and/or the rapid expansion is performed using a gas permeable container.

~~33~~65. The use of any one of Claims 45 to 64~~25 to 32~~, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof and/or the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL- 21, and combinations thereof.

~~34~~66. The use of any one of Claims 45 to 65~~25 to 33~~, ~~wherein the method further comprises the step~~ wherein the patient is to be treated with a non-myeloablative lymphodepletion regimen prior to ~~administering~~ administration of the third population of TILs to the patient and/or wherein the patient is to be further treated ~~method further comprises the step of treating the patient~~ with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.

67. The use of Claim ~~51~~66, wherein ~~optionally~~ the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m^2/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days and/or the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin~~, or a biosimilar or variant thereof~~, which is to be administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

~~35~~68. The use according to ~~Claim 25~~any one of Claims 45 to 67~~, wherein the NSCLC is refractory to a combination treatment or therapy comprising an anti-PD-1 and a chemotherapeutic agent~~, wherein ~~optionally~~ the anti-PD-1 or the anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, any anti-PD-1 antibody disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab~~, and fragments, derivatives, variants, as well as biosimilars thereof~~ or the anti-PD-1 is pembrolizumab.

69. The use of any one of Claims 45 to 68, wherein the initial expansion is performed for 1 to 8 days and the second expansion is performed for 1 to 9 days.

70. The use of any one of Claims 45 to 69, wherein the initial expansion is performed for 8 days and the second expansion is performed for 7 to 9 days.

~~36~~71. The use according to ~~Claim 35~~any one of Claims 3, 8, 13, 26, 31, 36, 47, 52, or 57, wherein the chemotherapeutic agent is a platinum doublet chemotherapeutic agent(s).

72. The use according to Claim 71, ~~optionally~~ wherein the platinum doublet therapy comprises:

(a) first chemotherapeutic agent selected from the group consisting of cisplatin and carboplatin,

(b) and a second chemotherapeutic agent selected from the group consisting of vinorelbine, gemcitabine and a taxane ~~(including for example, paclitaxel, docetaxel or nab-paclitaxel)~~.

~~37~~73. The use according to any one of Claims 71 to 72~~35 or 36~~, wherein the chemotherapeutic agent(s) is in combination with pemetrexed.

74. The use according to Claim 73, wherein ~~optionally~~ the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, and cisplatin or the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, cisplatin, nivolumab, and ipilimumab.

~~38. The use according to any one of Claims 1 to 24, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion.~~

~~39. The use according to any one of Claims 1 to 24 or 38, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs.~~

~~40. The use according to any one of Claims 25 to 37, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, optionally wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs.~~