performed over a period of 14 days or less;

(f) harvesting the third population of TILs; and

(g) administering a therapeutically effective portion of the third population of TILs to a patient with the NSCLC;

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

[0007] In one aspect, the present disclosure refers to a use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of medication for treating non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, comprising the steps of: (a) providing a first population of TILs is obtained and/or received from one or more tumors resected from a subject by processing the one or more tumors intomultiple tumor fragments; (b) adding the tumor fragments into a closed system; (c) performing a firstexpansion 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 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 (anti-CD3 antibody), and antigen-presenting cells (APCs) to produce a third population of TILs, wherein the second expansion is performed for 7 to 11 days to obtain the third 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 the third 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 population of TILs 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) wherein a therapeutically effective amount of the third population of TILs is to be administered from the infusion bag in step (g) to the subject. In another aspect, the present disclosure refers to a

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 NSCLC is refractory to treatment with an anti-PD-1 antibody, the method comprising the steps of: (a) one or more tumors is resected from a patient, the one or more tumors comprising a first population of TILs; (b) fragmenting the one or more tumors 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 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 second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and antigen-presenting cells (APCs); and wherein the rapid expansion is performed over a period of 14 days or less; (f) harvesting the third population of TILs ; and (g) wherein a therapeutically effective portion of the third population of TILs is to be administered to a patient with the NSCLC.

[0008] In some examples, obtaining the first population of TILs comprises a multilesional sampling method.

[0009] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.

[0010] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0011] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0012] In some examples, 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.

[0013] In some examples, 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.

[0014] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

WHAT IS CLAIMED IS:

1. Use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of medication for treating non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, comprising the steps of:

   (a) providing a first population of TILs obtained and/or received from one or more tumors resected from a subject by processing the one or more tumors 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 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 (anti-CD3 antibody), and antigen-presenting cells (APCs) to produce a third population of TILs, wherein the second expansion is performed for 7 to 11 days to obtain the third 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 the third 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 population of TILs 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) wherein a therapeutically effective amount of the third population of TILs is to be administered from the infusion bag in step (g) to the subject

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2. The use of Claim 1, wherein the tumor sample is derived from a multilesional sampling method.
3. The use of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.
4. The use of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.
5. 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 with a chemotherapeutic agent.
6. The use of claim 5, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
7. 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.
8. 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 been previously treated with a chemotherapeutic agent.
9. The use of Claim 8, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
10. The use of Claims 1 to 9, wherein the refractory NSCLC has low expression of PD-L1.
11. The use of Claims 1 to 10, wherein the refractory NSCLC has bulky disease at baseline.
12. The use of claim 11, 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.
13. The use of Claim 1, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.
14. The use of Claim 1, wherein the refractory NSCLC is refractory to an anti-PD-1 antibody selected from the group consisting of nivolumab, pembrolizumab, ipilimumab, JS001,

TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 antibody from clone: RMP1-14; and an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, and avelumab.

15. The use of Claim 1, wherein the refractory NSCLC is refractory to ipilimumab and pembrolizumab, or to ipilimumab and nivolumab.

16. The use of any one of Claims 1 to 15, wherein the first expansion is performed over a period of about 11 days and the second expansion is performed over a period of about 11 days.

17. The use of any one of Claims 1 to 16, wherein 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.

18. The use of any one of Claims 1 to 17, wherein the first expansion and/or the second expansion is performed using a gas permeable container.

19. The use of any one of Claims 1 to 18, wherein the first cell culture medium 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.

20. The use of any one of Claims 1 to 19, further that the patient is to be treated with a non-myeloablative lymphodepletion regimen prior to administering the therapeutically effective amount of the third population of TILs to the subject.

21. The use of Claim 20, wherein 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.

22. The use of any one of Claims 1 to 21, further comprising that the subject is to be treated with an IL-2 regimen starting on the day after administration of the therapeutically effective portion of the third population of TILs to the subject.

23. The use of Claim 22, wherein the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, , which is to be administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

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 NSCLC is refractory to treatment with an anti-PD-1 antibody, the method comprising the steps of:

(a) resecting one or more tumors from a patient, the one or more tumors comprising a first population of TILs;

(b) fragmenting the one or more tumors 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 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 second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and antigen-presenting cells (APCs); and wherein the rapid expansion is performed over a period of 14 days or less;

(f) harvesting the third population of TILs; and

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

25. The use of Claim 24, wherein the tumor is resected from one or more tumor sites.

26. The use of Claim 24, wherein the refractory NSCLC has been previously treated or has not 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 been treated with a chemotherapeutic agent.

27. The use of Claim 24, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

28. 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.

29. The use of claims 24 to 28, wherein the refractory NSCLC has low expression of PD-L1.

30. The use of claims 24 to 28, wherein the refractory NSCLC has bulky disease at baseline.

31. The use of claim 30, 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 24, wherein the refractory NSCLC is refractory to at least two prior

systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

33. The use of Claim 24, wherein the refractory NSCLC is refractory to an anti-PD-1 antibody selected from the group consisting of nivolumab, pembrolizumab, ipilimumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 antibody from clone: RMP1-14; and an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, and avelumab.

34. The use of Claim 24, wherein the refractory NSCLC is refractory to (i) ipilimumab and pembrolizumab or (ii) ipilimumab and nivolumab.

35. The use of any one of Claims 24 to 34, wherein the initial expansion is performed over a period of 21 days or less.

36. The use of any one of Claims 24 to 35, wherein the initial expansion is performed over a period of 14 days or less.

37. The use of any one of Claims 24 to 36, wherein the initial expansion is performed over a period of about 11 days and the rapid expansion is performed over a period of about 11 days.

38. The use of any one of Claims 24 to 37, wherein 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.

39. The use of any one of Claims 24 to 38, wherein the initial expansion and/or the rapid expansion is performed using a gas permeable container.

40. The use of any one of Claims 24 to 39, wherein the first cell culture medium and/or 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.

41. The use of any one of Claims 24 to 40, further comprising that the patient is to be treated with a non-myeloablative lymphodepletion regimen prior to administration of the therapeutically effective portion of the third population of TILs to the patient.

42. The use of Claim 41, wherein the non-myeloablative lymphodepletion regimen comprises that a cyclophosphamide is to be administered 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.

43. The use of any one of Claims 24 to 42, further comprising that the patient is to be treated

with an IL-2 regimen starting on the day after administration of therapeutically effective portion of the third population of TILs to the patient.

44. The use of Claim 43, wherein 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.