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) 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 sample that contains a mixture of tumor and TIL cells from a NSCLC tumor in a 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 first cell culture medium comprises IL-2; (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 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; (e) harvesting the third population of TILs; and (f) 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. 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

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

(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.

[0006] In some examples, "obtaining" indicates the TILs employed in the method and/or process can be derived directly from the sample (including from a surgical resection, needle biopsy, core biopsy, small biopsy, or other sample) as part of the method and/or process steps. In some examples, "receiving" indicates the TILs employed in the method and/or process can be derived indirectly from the sample (including from a surgical resection, needle biopsy, core biopsy, small biopsy, or other sample) and then employed in the method and/or process, (for example, where step (a) begins will TILs that have already been derived from the sample by a separate process not included in part (a), such TILs could be refered to as "received").

[0007] In some examples, the first population of TILs comprises a multilesional sampling method.

[0008] 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.

[0009] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0010] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0011] 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.

[0012] 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.

[0013] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0014] In some examples, the refractory NSCLC has low expression of PD-L1.

[0015] In some examples, 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.

[0016] In some examples, 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.

[0017] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0018] In some examples, 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

[0019] In some examples, 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.

[0020] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0021] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[0022] In some examples, 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.

[0023] In some examples, 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.

[0024] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[0025] In some examples, the refractory NSCLC is refractory to an anti-PD-1 antibody or an anti-PD-L1 selected from the group consisting of nivolumab, pembrolizumab, ipilimumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[0026] In some examples, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[0027] In some examples, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[0028] In some examples, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

[0029] In some examples, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[0030] In some examples, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[0031] In some examples, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[0032] In some examples, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[0033] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0034] In some examples, the initial expansion is performed over a period of 21 days or less.

[0035] In some examples, the initial expansion is performed over a period of 14 days or less.

[0036] In some examples, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[0037] In some examples, 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.

[0038] In some examples, the initial expansion is performed using a gas permeable container.

[0039] In some examples, the rapid expansion is performed using a gas permeable container.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[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 fortreating non-small cell lung carcinoma (NSCLC), wherein the use comprises: (a) that 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 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 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 (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

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

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

[0047] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0048] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0049] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0050] 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.

[0051] 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.

[0052] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0053] In some examples, the refractory NSCLC has low expression of PD-L1.

[0054] In some examples, 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.

[0055] In some examples, 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.

[0056] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0057] In some examples, 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

[0058] In some examples, 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.

[0059] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0060] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[0061] In some examples, 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.

[0062] In some examples, 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.

[0063] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[0064] In some examples, the refractory NSCLC is refractory to an anti-PD-1 or an 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, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[0065] In some examples, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[0066] In some examples, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[0067] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.

[0068] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[0069] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[0070] In some examples, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[0071] In some examples, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[0072] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0073] In some examples, the initial expansion is performed over a period of 21 days or less.

[0074] In some examples, the initial expansion is performed over a period of 14 days or less.

[0075] In some examples, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[0076] In some examples, 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.

[0077] In some examples, the initial expansion is performed using a gas permeable container.

[0078] In some examples, the rapid expansion is performed using a gas permeable container.

[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 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 3-14 days to obtain the second 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 7-14 days to obtain the third 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 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

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

[0086] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0087] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0088] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0089] 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.

[0090] 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.

[0091] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0092] In some examples, the refractory NSCLC has low expression of PD-L1.

[0093] In some examples, 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.

[0094] In some examples, 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.

[0095] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0096] In some examples, 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.

[0097] In some examples, 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.

[0098] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0099] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[00100] In some examples, 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.

[00101] In some examples, 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.

[00102] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[00103] In some examples, the refractory NSCLC is refractory to an anti-PD-1 or an 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, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[00104] In some examples, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[00105] In some examples, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[00106] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.

[00107] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[00108] In some examples, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[00109] In some examples, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[00110] In some examples, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[00111] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[00112] In some examples, the initial expansion is performed over a period of 21 days or less.

[00113] In some examples, the initial expansion is performed over a period of 14 days or less.

[00114] In some examples, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[00115] In some examples, 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.

[00116] In some examples, the initial expansion is performed using a gas permeable container.

[00117] In some examples, the rapid expansion is performed using a gas permeable container.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] In some examples, the NSCLC is refractory to a combination treatment comprising an anti-PD-1 and chemotherapeutic agent.

[00125] In some examples, 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, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[00126] In some examples, the antiPD-1 is pembrolizumab.

[00127] In some examples, the chemotherapeutic agent(s) is a platinum doublet chemotherapeutic agent.

[00128] In some examples, the platinum doublet therapy comprises:

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

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

[00129] In some examples, the chemotherapeutic agent is in combination with pemetrexed.

[00130] In some examples, the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, and cisplatin.

[00131] In some examples, the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, cisplatin, nivolumab, and ipilimumab.

BRIEF DESCRIPTION OF THE DRAWINGS

[00132] **Figure 1:** Exemplary Process 2A chart providing an overview of Steps A through F.

[00133] **Figure 2:** Process Flow Chart of Process 2A.

[00134] Figure 3: Shows a diagram of an embodiment of a cryopreserved TIL exemplary manufacturing process (~22 days).

[00135] Figure 4: Shows a diagram of an embodiment of process 2A, a 22-day process for TIL manufacturing.

[00136] Figure 5: Comparison table of Steps A through F from exemplary embodiments of process 1C and process 2A.

[00137] Figure 6: Detailed comparison of an embodiment of process 1C and an embodiment of process 2A.

[00138] Figure 7: Exemplary GEN 3 type process for NSCLC tumors.

[00139] Figure 8A-8B: A) Shows a comparison between the 2A process (approximately 22-day process) and an embodiment of the Gen 3 process for TIL manufacturing (approximately 14-days to 16-days process). **B)** Exemplary Process Gen3 chart providing an overview of Steps A through F (approximately 14-days to 16-days process). **C)** Chart providing three exemplary Gen 3 processes with an overview of Steps A through F (approximately 14-days to 16-days process) for each of the three process variations.

[00140] Figure 9: Provides an experimental flow chart for comparability between GEN 2 (process 2A) versus GEN 3.

[00141] Figure 10A-10C: A) L4054 - Phenotypic characterization on TIL product on Gen 2 and Gen 3 process. **B)** L4055-Phenotypic characterization on TIL product on Gen 2 and Gen 3 process. **C)** M1085T-Phenotypic characterization on TIL product on Gen 2 and Gen 3 process.

[00142] Figure 11A-11C: **A)** L4054 – Memory markers analysis on TIL product from the Gen 2 and Gen 3 processes. **B)** L4055 – Memory markers analysis on TIL product from the

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) 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 sample that contains a mixture of tumor and TIL cells from a NSCLC tumor in a 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 first cell culture medium comprises IL-2;

(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 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;

(e) harvesting the third population of TILs; and

(f) 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.

2. The use of Claim 1, wherein the obtaining the first population of TILs comprises 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 or the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody, wherein optionally the refractory NSCLC has been treated with a chemotherapeutic agent or 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 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, wherein optionally the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

5. The use of Claim 1, 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.

6. 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 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 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. 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 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, 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. The use of 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. The use of any one of Claims 1 to 8, wherein the initial expansion is performed over a period of 21 days or less or a period of 14 days or less.

10. The use of any one of Claims 1 to 9, 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. The method of any one of Claims 1 to 10, wherein the initial expansion is performed using a gas permeable container and/or the rapid expansion is performed using a gas permeable container.

12. The use of any one of Claims 1 to 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. The use of any one of Claims 1 to 12, wherein 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, 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. The use of any one of Claims 1 to 13, 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. Use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament fortreating non-small cell lung carcinoma (NSCLC), wherein the use comprises:

(a) that 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 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 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

(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. The use of Claim 15, wherein the tumor is 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. 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. 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.

19. The use of 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, 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. The use of any one of Claims 15 to 19, 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.

21. The use of any one of Claims 15 to 20, 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. The use of any one of Claims 15 to 21, wherein the initial expansion is performed using a gas permeable container and/or the rapid expansion is performed using a gas permeable container.

23. The use of any one of Claims 15 to 22, 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. The use of any one of Claims 15 to 23, 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. 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 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 3-14 days to obtain the second 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 7-14 days to obtain the third 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) 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. The use of Claim 25, 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.

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. 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.

29. The use of Claim 25, 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, 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; an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof; an 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.

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.

31. The use of any one of Claims 25 to 30, 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.

32. The use of any one of Claims 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. The use of any one of Claims 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. The use of any one of Claims 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 the third population of TILs to the patient and/or wherein 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, 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.

35. The use according to Claim 25, 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.

36. The use according to Claim 35, wherein the chemotherapeutic agent is a platinum doublet chemotherapeutic agent(s), 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. The use according to Claim 35 or 36, wherein the chemotherapeutic agent(s) is in combination with pemetrexed, 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.