acceptance parameters rely on readouts of the composition of TILs (*e.g.*, CD28, CD8, or CD4 positivity) and on fold expansion and viability of the REP product.

[0004] Current TIL manufacturing and treatment processes are limited by length, cost, sterility concerns, and other factors described herein such that the potential to treat patients which are refractory to anti-PD1 and as such have been severely limited. There is an urgent need to provide TIL manufacturing processes and therapies based on such processes that are 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

[0005] 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.

[0006] 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, including from multiple tumor fragments or biopsies;

(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.

[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: (a) a first population of TILs is obtained and/or received from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for a sample to be obtained that contains a mixture of tumor and TIL cells from a NSCLC tumor in a patient, including from multiple tumor fragments or biopsies; (b) the tumor fragments are contacted with a first cell culture medium; (c) an initial expansion of the first population of TILs is performed in the first cell culture medium to obtain a second population of TILs, wherein the first cell culture medium comprises IL-2; (d) a rapid expansion of the second population of TILs is performed 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) the third population of TILs is harvested; and (f) 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 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: (a) one or more tumors is resected from a patient, the one or more tumors comprising a first population of TILs; (b) the one or more tumor is fragmented into tumor fragments; (c) the tumor fragments are contacted with a first cell culture medium; (d) an initial expansion of the first population of TILs is performed in the first cell culture medium to obtain a second population of TILs, wherein the first cell culture medium comprises IL-2; (e) a rapid expansion of the second population of TILs is performed 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) the third population of TILs is harvested; and (g) 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 yet another aspect, the present disclosure refers to a use of expanded tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, and wherein: (a) 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 obtained from the subject into multiple tumor fragments; (b) the tumor fragments are added into a closed system; (c) a first

expansion is performed 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) a second expansion is performed 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 third population of TILs is a therapeutic 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) the therapeutic population of TILs obtained from step (d) is harvested, wherein the transition from step (d) to step (e) occurs without opening the system; and (f) the harvested TIL population from step (e) is transferred to an infusion bag, wherein the transfer from step (e) to (f) occurs without opening the system; (g) the infusion bag comprising the harvested TIL population from step (f) is cryopreserved 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. 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").

[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.

[0015] In some examples, the refractory NSCLC has low expression of PD-L1.

[0016] 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.

[0017] 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.

[0018] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0019] 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

[0020] 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.

[0021] 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.

[0022] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[0023] 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.

[0024] 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.

[0025] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[0026] In some examples, 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 from clone: RMP1-14; and 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.

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

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

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

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

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

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

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

[0034] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0035] In some examples, the initial expansion is performed over a period of 21 days or less.

[0036] In some examples, the initial expansion is performed over a period of 14 days or less.

[0037] In some examples, 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.

[0038] 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.

[0039] 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.

[0040] In some examples, the initial expansion is performed using a gas permeable container.

[0041] In some examples, the rapid expansion is performed using a gas permeable container.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] In some examples, the invention 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 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 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.

[0049] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0050] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0051] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0052] 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.

[0053] 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.

[0054] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0055] In some examples, the refractory NSCLC has low expression of PD-L1.

[0056] 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.

[0057] 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.

[0058] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0059] 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

[0060] 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.

[0061] 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.

[0062] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[0063] 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.

[0064] 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.

[0065] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[0066] In some examples, 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 from clone: RMP1-14; and 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.

[0067] In some examples, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[0068] In some examples, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[0069] In some examples, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

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

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

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

[0073] In some examples, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[0074] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0075] In some examples, the initial expansion is performed over a period of 21 days or less.

[0076] In some examples, the initial expansion is performed over a period of 14 days or less.

[0077] In some examples, 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.

[0078] 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.

[0079] 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.

[0080] In some examples, the initial expansion is performed using a gas permeable container.

[0081] In some examples, the rapid expansion is performed using a gas permeable container.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] In some examples, the invention 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 one or more tumors resected from a subject by processing the one or more tumors 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.

[0089] 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 embodiments, '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").

[0090] In some examples, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0091] In some examples, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0092] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0093] 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.

[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 been previously treated a chemotherapeutic agent.

[0095] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0096] In some examples, the refractory NSCLC has low expression of PD-L1.

[0097] 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.

[0098] 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.

[0099] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[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 low expression of PD-L1.

[00101] 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.

[00102] 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.

[00103] In some examples, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[00104] 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.

[00105] 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.

[00106] In some examples, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[00107] In some examples, 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 from clone: RMP1-14; and 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.

[00108] In some examples, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

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

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

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

[00112] In some examples, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[00113] In some examples, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[00114] In some examples, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[00115] In some examples, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[00116] In some examples, the initial expansion is performed over a period of 21 days or less.

[00117] In some examples, the initial expansion is performed over a period of 14 days or less.

[00118] In some examples, the initial expansion is performed over a period of about 3-11 days and the second expansion is performed over a period of about 7-11 days.

[00119] In some examples, 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.

[00120] 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.

[00121] 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.

[00122] In some examples, the initial expansion is performed using a gas permeable container.

[00123] In some examples, the rapid expansion is performed using a gas permeable container.

[00124] 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.

[00125] 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.

[00126] 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.

[00127] 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.

[00128] 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.

[00129] 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.

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:

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

   (b) the tumor fragments are contacted with a first cell culture medium;

   (c) an initial expansion of the first population of TILs is performed in the first cell culture medium to obtain a second population of TILs, wherein the first cell culture medium comprises IL-2;

   (d) a rapid expansion of the second population of TILs is performed 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) the third population of TILs is harvested; and

   (f) 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.

4. 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.

5. The use of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

6. 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.

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 and has been previously treated a chemotherapeutic agent.
8. The use of Claims 5 to 7, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
9. The use of Claim 1, wherein the refractory NSCLC has low expression of PD-L1.
10. 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 low expression of PD-L1.
11. 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 low expression of PD-L1.
12. The use of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.
13. The use of Claim 1, 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.
14. 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.
15. 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 bulky disease at baseline.
16. The use of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.
17. The use of Claim 1, wherein 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.
18. The use of Claims 14 to 17, 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. 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.

20. 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, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

21. The use of Claim 1, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

22. The use of Claim 1, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

23. The use of Claim 1, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

24. The use of Claim 1, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

25. The use of Claim 1, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

26. The use of Claim 1, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

27. The use of Claim 1, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

28. The use of Claim 1, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

29. The use of any one of Claims 1 to 28, wherein the initial expansion is performed over a period of 21 days or less.

30. The use of any one of Claims 1 to 29, wherein the initial expansion is performed over a period of 14 days or less.

31. The use of any one of Claims 1 to 30, 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.

32. The use of any one of Claims 1 to 31, 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.

33. The use of any one of Claims 1 to 32, 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.

34. The use of any one of Claims 1 to 33, wherein the initial expansion is performed using a gas permeable container.

35. The use of any one of Claims 1 to 34, wherein the rapid expansion is performed using a gas permeable container.

36. The use of any one of Claims 1 to 35, 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.

37. The use of any one of Claims 1 to 36, 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.

38. The use of any one of Claims 1 to 37, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the therapeutically effective portion of the third population of TILs to the patient.

39. The use of Claim 38, 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.

40. The use of any one of Claims 1 to 39, further comprising the step of treating the patient with an IL-2 regimen starting on the day after administration of the therapeutically effective portion of the third population of TILs to the patient.

41. The use of Claim 40, 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.

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

(a) one or more tumors is resected from a patient, the one or more tumors comprising a

first population of TILs;

(b) the one or more tumor is fragmented into tumor fragments;

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

(d) an initial expansion of the first population of TILs is performed in the first cell culture medium to obtain a second population of TILs, wherein the first cell culture medium comprises IL-2;

(e) a rapid expansion of the second population of TILs is performed 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) the third population of TILs is harvested; and

(g) 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.

43. The use of Claim 42, wherein the tumor is resected from one or more tumor sites.

44. The use of Claim 42, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.

45. The use of Claim 42, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

46. The use of Claim 42, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

47. The use of Claim 42, 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.

48. The use of Claim 42, 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 a chemotherapeutic agent.

49. The use of Claims 46 to 48, wherein the refractory NSCLC has been treated with a

chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

50. The use of Claim 42, wherein the refractory NSCLC has low expression of PD-L1.

51. The use of Claim 42, wherein 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.

52. The use of Claim 42, 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.

53. The use of Claim 42, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

54. The use of Claim 42, 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.

55. The use of Claim 42, 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.

56. The use of Claim 42, 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.

57. The use of Claim 42, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

58. The use of Claim 42, wherein 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.

59. The use of Claims 55 to 58, 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.

60. The use of Claim 42, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

61. The use of Claim 42, 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, avelumab, and

fragments, derivatives, variants, as well as biosimilars thereof.

62. The use of Claim 42, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

63. The use of Claim 42, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

64. The use of Claim 42, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

65. The use of Claim 42, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

66. The use of Claim 42, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

67. The use of Claim 42, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

68. The use of Claim 42, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

69. The use of Claim 42, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

70. The use of any one of Claims 42 to 69, wherein the initial expansion is performed over a period of 21 days or less.

71. The use of any one of Claims 42 to 70, wherein the initial expansion is performed over a period of 14 days or less.

72. The use of any one of Claims 42 to 71, 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.

73. The use of any one of Claims 42 to 72, 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.

74. The use of any one of Claims 42 to 73, 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.

75. The use of any one of Claims 42 to 74, wherein the initial expansion is performed using a gas permeable container.

76. The use of any one of Claims 42 to 75, wherein the rapid expansion is performed using a gas permeable container.

77. The use of any one of Claims 42 to 76, 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.

78. The use of any one of Claims 42 to 77, 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.

79. The use of any one of Claims 42 to 78, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the therapeutically effeictve portion of the third population of TILs to the patient.

80. The use of Claim 79, 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.

81. The use of any one of Claims 42 to 80, further comprising the step of treating the patient with an IL-2 regimen starting on the day after administration of therapeutically effeictve portion of the the third population of TILs to the patient.

82. The use of Claim 81, 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.

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

    (a) 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 obtained from the subject into multiple tumor fragments;

    (b) the tumor fragments are added into a closed system;

    (c) a first expansion is performed 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) a second expansion is performed 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 third population of TILs is a therapeutic 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) the therapeutic population of TILs obtained from step (d) is harvested, wherein the transition from step (d) to step (e) occurs without opening the system; and

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

(g) the infusion bag comprising the harvested TIL population from step (f) is cryopreserved 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.

84. The use of Claim 83, wherein the tumor sample is derived from a multilesional sampling method.

85. The use of Claim 83, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

86. The use of Claim 83, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

87. The use of Claim 83, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

88. The use of Claim 83, 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.

89. The use of Claim 83, 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 a chemotherapeutic agent.

90. The use of Claims 87 to 89, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

91. The use of Claim 83, wherein the refractory NSCLC has low expression of PD-L1.

92. The use of Claim 83, wherein 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.

93. The use of Claim 83, 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.

94. The use of Claim 83, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

95. The use of Claim 83, 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.

96. The use of Claim 83, 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.

97. The use of Claim 83, 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.

98. The use of Claim 83, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

99. The use of Claim 83, wherein 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.

100. The use of Claims 96 to 99, 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.

101. The use of Claim 83, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

102. The use of Claim 83, 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, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

103. The use of Claim 83, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

104. The use of Claim 83, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

105. The use of Claim 83, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

106. The use of Claim 83, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

107. The use of Claim 83, wherein the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

108. The use of Claim 83, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

109. The use of Claim 83, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

110. The use of Claim 83, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

111. The use of any one of Claims 83 to 110, wherein the initial expansion is performed over a period of 21 days or less.

112. The use of any one of Claims 83 to 111, wherein the initial expansion is performed over a period of 14 days or less.

113. The use of any one of Claims 83 to 112, wherein the initial expansion is performed over a period of about 3-11 days and the second expansion is performed over a period of about 7-11 days.

114. The use of any one of Claims 83 to 113, 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.

115. The use of any one of Claims 83 to 114, 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.

116. The use of any one of Claims 83 to 115, 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 cell culture medium in step (d).

117. The use of any one of Claims 83 to 116, wherein the initial expansion is performed using a gas permeable container.

118. The use of any one of Claims 83 to 117, wherein the rapid expansion is performed using a gas permeable container.

119. The use of any one of Claims 83 to 118, 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.

120. The use of any one of Claims 83 to 119, wherein the cell culture medium in step (d) further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

121. The use of any one of Claims 83 to 120, further comprising the step of treating the subject with a non-myeloablative lymphodepletion regimen prior to administering the therapeutically effective dosage of the third population of TILs to the subject.

122. The use of Claim 121, 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.

123. The use of any one of Claims 83 to 122, further comprising the step of treating the subject with an IL-2 regimen starting on the day after administration of the therapeutically effective dosage of the third population of TILs to the subject.

124. The use of Claim 123, 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.

125. The use of any one of the preceding claims, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs.

126. The use of any one of the preceding claims, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs.

127. The use of any one of the preceding claims, wherein the third population of TILs is a a therapeutic population of TILs comprising an increase subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs.