IV. BRIEF SUMMARY

[0004a] In one aspect, the present disclosure relates to use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating an endometrial cancer in a subject, wherein the endometrial cancer is relapsed or refractory to at least one prior therapy, and wherein the population of TILs is produced by a method comprising:

(a) adding a tumor sample from the endometrial cancer into a closed system, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from the subject;

(b) 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 (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising 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 (b) to step (c) occurs without opening the system;

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

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

(f) optionally cryopreserving the infusion bag comprising the harvested TIL population from step (e) using a cryopreservation process.

[0004b] In another aspect, the present disclosure relates to a method of expanding tumor infiltrating lymphocytes (TILs) comprising:

(a) adding a tumor sample from an endometrial cancer in a subject into a closed system, wherein the endometrial cancer is relapsed or refractory to at least one prior therapy, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from the subject;

(b) 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 (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising 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 (b) to step (c) occurs without opening the system;

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

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

(f) optionally cryopreserving the infusion bag comprising the harvested TIL population from step (e) using a cryopreservation process.

[0004c] In another aspect, the present disclosure relates to a therapeutic population of tumor infiltrating lymphocytes (TILs) produced by a method comprising:

(a) adding a tumor sample into a closed system, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from a subject having endometrial cancer, and wherein the endometrial cancer is relapsed or refractory to at least one prior therapy;

(b) 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 a first period of about 3 to 14 days to obtain the second population of TILs, and wherein the transition from step (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising IL-2, OKT-3, and antigen presenting cells (APCs) to produce a third population of TILs, wherein the second expansion is performed for a second period of about 7 to 14 days to obtain the third population of TILs, wherein the third population of TILs is the 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 (b) to step (c) occurs without opening the system;

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

(e) transferring the harvested therapeutic population of TILs from step (d) to an infusion bag, wherein the transfer from step (d) to (e) occurs without opening the system; and

(f) optionally cryopreserving the infusion bag comprising the harvested therapeutic population of TILs from step (e) using a cryopreservation process.

[0005] In an embodiment, the invention provides methods and compositions for the treatment of endometrial cancer using tumor infiltrating lymphocyte therapies. In an embodiment, the invention provides methods and compositions for the treatment of uterine cancer using tumor infiltrating lymphocyte therapies.

[0006] In an embodiment, the invention provides methods and compositions for the treatment of endometrial cancer using tumor infiltrating lymphocyte therapies, wherein the endometrial cancer is resected and processed to prepare tumor infiltrating lymphocytes.

[0007] Embodiments disclosed herein provide a method of treating a subject with endometrial cancer, the method comprising administering expanded tumor infiltrating lymphocytes (TILs) comprising:

(a) adding a tumor digest or tumor fragments from an endometrial cancer into a closed system, wherein the tumor digest or tumor fragments comprise a first population of TILs and are obtained from a tumor that was resected from the subject;
(b) 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, and wherein the transition from step (b) to step (c) occurs without opening the system;
(c) performing a second expansion by supplementing additional cell culture medium comprising 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 second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (b) to step (c) occurs without opening the system;
(d) harvesting the third population of TILs obtained from step (c), wherein the transition from step (c) to step (d) occurs without opening the system;
(e) transferring the harvested third TIL population from step (d) to an infusion bag, wherein the transfer from step (d) to (e) occurs without opening the system;
(f) cryopreserving the infusion bag comprising the harvested TIL population from step (e) using a cryopreservation process; and
(g) administering a therapeutically effective dosage of the third population of TILs from the infusion bag in step (f) to the subject.

[0008] In some embodiments, the endometrial cancer is metastatic or unresectable. In some embodiments, the subject was refractory to or progressed following prior treatment with a PD-1 or

CLAIMS

What is claimed is:

1. Use of a population of tumor infiltrating lymphocytes (TILs) in the manufacture of a medicament for treating an endometrial cancer in a subject, wherein the endometrial cancer is relapsed or refractory to at least one prior therapy, and wherein the population of TILs is produced by a method comprising:

(a) adding a tumor sample from the endometrial cancer into a closed system, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from the subject;

(b) 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 (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising 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 (b) to step (c) occurs without opening the system;

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

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

(f) optionally cryopreserving the infusion bag comprising the harvested TIL population from step (e) using a cryopreservation process.

2. The use of claim 1, wherein the endometrial cancer is

i) metastatic or unresectable;

ii) microsatellite instability high (MSI-H);

iii) mismatch repair deficient (dMMR);

iv) microsatellite stable (MSS);

v) mismatch repair proficient (pMMR);

vi) characterized by MLH-1 promoter hypermethylation;

vii) characterized by high mutation rates due to mismatch repair; and/or

viii) characterized by high mutation rates due to mismatch repair resulting from a defect in the MLH-1, MSH2, MSH6, or PMS2 genes.

3. The use of claim 1 or 2, wherein the at least one prior therapy comprises chemotherapy, radiation therapy, immunotherapy, or a combination thereof.

4. The use of claim 3, wherein the immunotherapy comprises a PD-1 or PD-L1 inhibitor.

5. The use according to according to any one of claims 1-4, wherein the medicament further comprises a PD-1 or PD-L1 inhibitor.

6. The use of claim 4 or 5, wherein the anti-PD-1 or anti-PD-L1 antibody comprises one or more of dostarlimab, nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-l from clone: RMP1-14, an anti-PD-l antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, or biosimilars thereof.

7. The use according to any one of claims 1-6, wherein the subject is further subject to

i) a non-myeloablative lymphodepletion regimen prior to the use of TILs; and/or

ii) an IL-2 regimen starting on the same day as or the day after administration of the therapeutic population of TILs.

8. A method of expanding tumor infiltrating lymphocytes (TILs) comprising:

(a) adding a tumor sample from an endometrial cancer in a subject into a closed system, wherein the endometrial cancer is relapsed or refractory to at least one prior therapy, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from the subject;

(b) 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 (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising 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 (b) to step (c) occurs without opening the system;

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

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

(f) optionally cryopreserving the infusion bag comprising the harvested TIL population from step (e) using a cryopreservation process.

9. The method of claim 8, wherein the endometrial cancer is

i) metastatic or unresectable;

ii) microsatellite instability high (MSI-H);

iii) mismatch repair deficient (dMMR);

iv) microsatellite stable (MSS);

v) mismatch repair proficient (pMMR);

vi) characterized by MLH-1 promoter hypermethylation;

vii) characterized by high mutation rates due to mismatch repair; and/or

viii) characterized by high mutation rates due to mismatch repair resulting from a defect in the MLH-1, MSH2, MSH6, or PMS2 genes.

10. The method of claim 8 or 9, wherein the at least one prior therapy comprises chemotherapy, radiation therapy, immunotherapy, or a combination thereof.

11. The method of claim 10, wherein the immunotherapy comprises a PD-1 or PD-L1 inhibitor.

12. The method of claim 11, wherein the anti-PD-1 or anti-PD-L1 antibody comprises one or more of dostarlimab, nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-l from clone: RMP1-14, an anti-PD-l antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, or biosimilars thereof.

13. A therapeutic population of tumor infiltrating lymphocytes (TILs) produced by a method comprising:

(a) adding a tumor sample into a closed system, wherein the tumor sample comprises a first population of TILs and are obtained from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample from a subject having endometrial cancer, and wherein the endometrial cancer is relapsed or refractory to at least one prior therapy;

(b) 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 a first period of about 3 to 14 days to obtain the second population of TILs, and wherein the transition from step (a) to step (b) occurs without opening the system;

(c) performing a second expansion by culturing the second population of TILs in a cell culture medium comprising IL-2, OKT-3, and antigen presenting cells (APCs) to produce a third population of TILs, wherein the second expansion is performed for a second period of about 7 to 14 days to obtain the third population of TILs, wherein the third population of TILs is the 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 (b) to step (c) occurs without opening the system;

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

(e) transferring the harvested therapeutic population of TILs from step (d) to an infusion bag, wherein the transfer from step (d) to (e) occurs without opening the system; and

(f) optionally cryopreserving the infusion bag comprising the harvested therapeutic population of TILs from step (e) using a cryopreservation process.

14. The use according to any one of claims 1-7 or the method according to any one of claims 8-12 or the therapeutic composition of claim 13, wherein at least a portion of the third population of TILs is gene-edited.

15. The use according to any one of claims 1-7 or the method according to any one of claims 8-12 or the therapeutic composition of claim 13, wherein the harvested third TIL population

i) exhibits an increased subpopulation of CD8+ cells relative to the first and/or second population of TILs; and/or

ii) provides for increased efficacy, increased interferon-gamma production, and/or increased polyclonality.