disorders. Improved approaches are needed. Provided are methods, uses and articles of manufacture that meet such needs.

Summary

[0005] Provided herein are methods of treating a subject having or suspected of having a disease or condition that is a relapsed or refractory large B cell lymphoma (r/r LBCL). In some of any of the provided examples, the method involves administering to the subject a dose of $CD4^+$ and $CD8^+$ T cells, wherein T cells of each dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein: the dose of T cells comprises between at or about 1 x 10^7 CAR-expressing T cells and at or about 2 x 10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 $CD4^+$ T cells expressing the CAR to $CD8^+$ T cells expressing the CAR; and the administration comprises administering a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising $CD8^+$ T cells and a second composition comprising $CD4^+$ T cells.

[0005a] In one aspect, the present disclosure refers to the use of a dose of CD4+ and CD8+ T cells, wherein T cells of each dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, for the manufacture of a medicament for treatment of a subject having or suspected of having a disease or condition that is a relapsed or refractory large B cell lymphoma (r/r LBCL), wherein: at or immediately prior to the time of the administration of the dose of cells, the subject is or has been identified as being ineligible for both a high-dose chemotherapy and a hematopoietic stem cell transplantation (HSCT); the dose of T cells comprises between 1 x 10^7 viable CAR-expressing T cells and 2 x 10^8 viable CAR-expressing T cells, inclusive.

[0006] Also provided herein are methods of treating a subject having or suspected of having a disease or condition, the method containing administering to the subject a dose of $CD4^+$ and $CD8^+$ T cells, each of the $CD4^+$ and the $CD8^+$ T cells, individually, containing receptor that specifically binds to an antigen, e.g., target antigen, expressed by the disease or condition or a cell or tissue thereof and/or that is associated with the disease or condition, wherein the administration includes administering a plurality of separate compositions, the plurality of separate compositions containing a first composition containing $CD8^+$ T cells and a second composition containing $CD4^+$ T cells.

[0007] Also provided herein are methods of treating a subject having or suspected of having a disease or condition that is a B cell malignancy, the method comprising administering to the subject a dose of $CD4^+$ and $CD8^+$ T cells, wherein T cells of each dose comprises a recombinant receptor that specifically binds to an antigen, e.g., target antigen, expressed by the disease or condition or a cell or tissue thereof and/or that is associated with the disease or condition, wherein the administration comprises administering a plurality of separate compositions, the plurality of separate compositions comprising a first composition comprising $CD8^+$ T cells and a second composition comprising $CD4^+$ T cells.

[0008] Also provided herein are methods of treating a subject having or suspected of having a disease or condition that is a large B cell lymphoma, the method comprising administering to the subject a dose of $CD4^+$ and $CD8^+$ T cells, wherein T cells of each dose comprises a recombinant receptor that specifically binds to an antigen, e.g., target antigen, expressed by the disease or condition or a cell or tissue thereof and/or that is associated with the disease or condition, wherein the administration comprises administering a plurality of separate compositions, the plurality of separate compositions

higher than grade 2, wherein the administration includes administering a plurality of separate compositions, the plurality of separate compositions containing a first composition containing $CD8^+$ T cells and a second containing comprising $CD4^+$ T cells.

[0013] In some of any of the provided examples, the method includes administering, to a subject that has a disease or condition that is a lymphoma, a dose of T cells containing T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen, e.g., target antigen, expressed by the lymphoma, wherein the lymphoma in the subject is associated with or involves central nervous system (CNS) involvement; and the dose of T cells contains $CD4^+$ and $CD8^+$ T cells, wherein T cells of each dose comprises a receptor that specifically binds to an antigen, e.g., target antigen, expressed by the disease or condition or a cell or tissue thereof and/or that is associated with the disease or condition, wherein the administration includes administering a plurality of separate compositions, the plurality of separate compositions containing a first composition containing $CD8^+$ T cells and a second composition containing $CD4^+$ T cells. In some of any of the provided examples, at or prior to the time of administration of the dose of cells, the subject comprises a brain lesion, such as a temporal lobe brain lesion. In some of any such examples, the lymphoma is a B cell malignancy. In some of any such examples, the lymphoma is non-Hodgkin lymphoma (NHL) or a large B cell lymphoma.

[0014] Provided herein is a method of treatment involving (a) selecting a subject that has a follicular lymphoma (FL) for treatment; (b) administering to the subject a dose of T cells comprising T cells expressing a recombinant receptor that specifically binds to an antigen, e.g., target antigen, expressed by FL or a cell or tissue thereof and/or that is associated with FL.

[0015] In some of any of the provided examples, the large B cell lymphoma is selected from an aggressive non-Hodgkin lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), optionally DLBCL NOS (de novo or transformed from indolent), high-grade B-cell lymphoma (HGBCL), double/triple hit lymphoma, primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), transformed follicular lymphoma (tFL), and/or follicular lymphoma (FL), optionally follicular lymphoma Grade 3B (FL3B). In some of any examples, the large B cell lymphoma is a Diffuse Large B-Cell Lymphoma (DLBCL). In some of any examples, the DLBCL is a DLBCL NOS, a de novo DLBCL or a DLBCL transformed from indolent lymphoma. In some of any examples, the DLBCL is a de novo DLBCL. In some of any examples, the DLBCL is a DLBCL transformed from indolent lymphomas other than FL. In some of any examples, the DLBCL is a DLBCL transformed from marginal zone lymphoma (tMZL) or a DLBCL transformed from chronic lymphocytic leukemia (tCLL; Richter's). In some of any examples, the large B cell lymphoma is a high-grade B cell lymphoma (HGBCL). In some of any examples, the HGBCL has MYC and BCL2 and/or BCL6 rearrangements. In some of any examples, the HGBCL has a DLBCL histology. In some of any examples, the large B cell lymphoma is a double/triple hit lymphoma. In some of any examples, the large B cell lymphoma is primary mediastinal B-cell lymphoma (PMBCL). In some of any examples, the large B

provided examples, the T cells are autologous to the subject. In some of any of the provided examples, the subject is a human subject.

[0087] Also provided herein are articles of manufacture containing a composition containing genetically engineered cells expressing a recombinant receptor. In some of any such examples, the articles of manufacture also contains instructions for administering a dose of the cells in accord with any of the methods provided herein.

[0088] Provided herein are methods of assessing the risk of developing a toxicity after administration of a cell therapy containing: (a) assessing one or more parameters in a subject, wherein the one or more parameters is selected from the level, amount or concentration of LDH, ferritin or C-reactive protein (CRP) in a biological sample from the subject, or is a sum of product dimensions (SPD) of a tumor in the subject; wherein the subject is a candidate for treatment with the cell therapy, said cell therapy containing a dose of genetically engineered cells expressing a recombinant receptor; and wherein the assessing is carried out prior to administering the cell therapy and/or said biological sample or tumor does not contain the recombinant receptor and/or said engineered cells; and (b) identifying if the subject is as at risk of toxicity wherein the subject is at risk of toxicity if the one or more parameters is above a threshold level and the subject is not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein: (i) the parameter is a sum of product dimensions (SPD), and the threshold level is above at or about 30 cm^2, 40 cm^2, 50 cm^2, 60 cm^2 or 70 cm^2; (ii) the parameter is LDH, and the threshold level is above at or about 300 units per liter, 400 units per liter, 500 units per liter or 600 units per liter; (iii) the parameter is ferritin, and the threshold level is above at or about 1000 nanograms per milliliter, 2000 nanograms per milliliter, 3000 nanograms per milliliter, 4000 nanograms per milliliter, 5000 nanograms per milliliter, 6000 nanograms per milliliter, 7000 nanograms per milliliter or 8000 nanograms per milliliter; and/or (iv) the parameter is CRP, and the threshold level is above at or about 5 milligrams per liter, 10 milligrams per liter, 15 milligrams per liter, 20 milligrams per liter, 25 milligrams per liter, 30 milligrams per liter, 40 milligrams per liter or 50 milligrams per liter.

[0089] Also provided are methods of identifying a subject, the method containing: (a) assessing one or more parameters in a subject, wherein the one or more parameters is selected from the level, amount or concentration of LDH, ferritin or C-reactive protein (CRP) in a biological sample from the subject, or is a sum of product dimensions (SPD) of a tumor in the subject; wherein the subject is a candidate for treatment with the cell therapy, said cell therapy containing a dose of genetically engineered cells expressing a recombinant receptor; and wherein the assessing is carried out prior to administering the cell therapy and/or said biological sample or tumor does not contain the recombinant receptor and/or said engineered cells; and (b) identifying a subject who has a risk of developing a toxicity after administration of a cell therapy, wherein the subject is at risk of toxicity if the one or more parameters is above a threshold level and the subject is not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein:(i) the parameter is a sum of product dimensions (SPD), and the threshold level

is above at or about 30 cm^2, 40 cm^2, 50 cm^2, 60 cm^2 or 70 cm^2; (ii) the parameter is LDH, and the threshold level is above at or about 300 units per liter, 400 units per liter, 500 units per liter or 600 units per liter; (iii) the parameter is ferritin, and the threshold level is above at or about 1000 nanograms per milliliter, 2000 nanograms per milliliter, 3000 nanograms per milliliter, 4000 nanograms per milliliter, 5000 nanograms per milliliter, 6000 nanograms per milliliter, 7000 nanograms per milliliter or 8000 nanograms per milliliter; and/or (iv) the parameter is CRP, and the threshold level is above at or about 5 milligrams per liter, 10 milligrams per liter, 15 milligrams per liter, 20 milligrams per liter, 25 milligrams per liter, 30 milligrams per liter, 40 milligrams per liter or 50 milligrams per liter.

[0090] Also provided herein are methods of treatment, containing: (a) assessing one or more parameters in a subject, wherein the one or more parameters is selected from the level, amount or concentration of LDH, ferritin or C-reactive protein (CRP) in a biological sample from the subject, or is a sum of product dimensions (SPD) of a tumor in the subject; wherein the subject is a candidate for treatment with the cell therapy, said cell therapy containing a dose of genetically engineered cells expressing a recombinant receptor; and wherein the assessing is carried out prior to administering the cell therapy and/or said biological sample or tumor does not contain the recombinant receptor and/or said engineered cells; and (b) identifying if the subject is as at risk of toxicity wherein the subject is at risk of toxicity if the one or more parameters is above a threshold level and the subject is not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein: (i) the parameter is a sum of product dimensions (SPD), and the threshold level is above at or about 30 cm^2, 40 cm^2, 50 cm^2, 60 cm^2 or 70 cm^2; (ii) the parameter is LDH, and the threshold level is above at or about 300 units per liter, 400 units per liter, 500 units per liter or 600 units per liter; (iii) the parameter is ferritin, and the threshold level is above at or about 1000 nanograms per milliliter, 2000 nanograms per milliliter, 3000 nanograms per milliliter, 4000 nanograms per milliliter, 5000 nanograms per milliliter, 6000 nanograms per milliliter, 7000 nanograms per milliliter or 8000 nanograms per milliliter; and/or (iv) the parameter is CRP, and the threshold level is above at or about 5 milligrams per liter, 10 milligrams per liter, 15 milligrams per liter, 20 milligrams per liter, 25 milligrams per liter, 30 milligrams per liter, 40 milligrams per liter or 50 milligrams per liter; and (c) following or based on the results of the assessment, administering to the subject the cell therapy. In some of any such examples, the methods also involve administering an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity.

[0091] In some of any of the provided examples, the parameter in the provided methods is SPD, and the threshold level is 50 cm^2. In some of any of the provided examples, the parameter in the provided methods is LDH, and the threshold level is 500 units per liter. In some of any of the provided examples, the one or more parameter in the provided methods is SPD and LDH, and the threshold level for SPD is 50 cm^2 and the threshold level for LDH is 500 units per liter. In some of any of the provided examples, the parameter in the provided methods is ferritin, and the threshold level is 5000

nanograms per milliliter. In some of any of the provided examples, the parameter in the provided methods is CRP, and the threshold level is 10 milligrams per liter. In some of any of the provided examples, the one or more parameter in the methods is ferritin and CRP, and the threshold level for ferritin is 5000 nanograms per milliliter and the threshold level for CRP is 10 milligrams per liter.

[0092] In some of any of the provided examples, the biologic sample in the provided methods is a blood or plasma sample. In some of any of the provided examples, the SPD in the provided methods is measured based on CT and/or MRI imaging or other imaging of the body. In some of any of the provided examples, the level, amount or concentration of one or more analyte and/or the SPD is measured prior to treatment, prior to apheresis, or prior to cell product manufacturing.

[0093] Also provided herein are methods of assessing the risk of developing a toxicity after administration of a cell therapy, the method containing: (a) assessing the peak concentration of genetically engineered cells expressing a recombinant receptor in a biological sample from a subject that has been previously administered a cell therapy containing the genetically engineered cells; and (b) identifying if the subject is as at risk of toxicity wherein the subject is at risk of toxicity if the one or more parameters, such as the peak concentration of genetically engineered cells, is above a threshold level and the subject is not at risk of toxicity if the peak concentration of genetically engineered cells is at or below a threshold level, wherein: the threshold level is above at or about 300 cells per microliter, 400 cells per microliter, 500 cells per microliter, 600 cells per microliter, 700 cells per microliter, 800 cells per microliter, 900 cells per microliter or 1000 cells per microliter.

[0094] Also provided herein are methods of identifying a subject, the method containing: (a) assessing the peak concentration of genetically engineered cells expressing a recombinant receptor in a biological sample from a subject that has been previously administered a cell therapy containing the genetically engineered cells; and (b) identifying a subject who has a risk of developing a toxicity after administration of a cell therapy, wherein the subject is at risk of toxicity if the one or more parameters, such as the peak concentration of genetically engineered cells, is above a threshold level and the subject is not at risk of toxicity if the peak concentration of genetically engineered cells is at or below a threshold level, wherein: the threshold level is above at or about 300 cells per microliter, 400 cells per microliter, 500 cells per microliter, 600 cells per microliter, 700 cells per microliter, 800 cells per microliter, 900 cells per microliter or 1000 cells per microliter.

[0095] Also provided herein are methods of treatment, containing: (a) assessing the peak concentration of genetically engineered cells expressing a recombinant receptor in a biological sample from a subject that has been previously administered a cell therapy containing the genetically engineered cells; and (b) identifying if the subject is as at risk of toxicity wherein the subject is at risk of toxicity if the one or more parameters, such as the peak concentration of genetically engineered cells, is above a threshold level and the subject is not at risk of toxicity if the peak concentration of genetically engineered cells is at or below a threshold level, wherein: the threshold level is above at or about 300 cells per

microliter, 400 cells per microliter, 500 cells per microliter, 600 cells per microliter, 700 cells per microliter, 800 cells per microliter, 900 cells per microliter or 1000 cells per microliter; and (c) following or based on the results of the assessment, administering to the subject the cell therapy. In some of any such examples, the methods also involve administering an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity. In some of any of the provided examples, the threshold level in the provided methods is 500 cells per microliter.

[0096] Also provided herein are methods further containing monitoring the subject for symptoms of toxicity if the subject is administered a cell therapy and is identified as having a risk of developing a toxicity.

[0097] In some of any of the provided examples, the toxicity is neurotoxicity or CRS. In some of any of the provided examples, the toxicity is a grade 1 or higher neurotoxicity or CRS. In some of any of the provided examples, the toxicity is a severe neurotoxicity or is a grade 2 or higher neurotoxicity, a grade 3 or higher neurotoxicity, or a grade 4 or higher neurotoxicity. In some of any of the provided examples, the toxicity is a grade 1 or higher neurotoxicity. In some of any of the provided examples, the toxicity is a severe neurotoxicity or a grade 3 or higher neurotoxicity. In some of any of the provided examples, the toxicity is a severe CRS or is a grade 2 or higher CRS, a grade 3 or higher CRS, or a grade 4 or higher CRS. In some of any of the provided examples, the toxicity is a grade 1 or higher CRS. In some of any of the provided examples, the toxicity is a severe CRS or a grade 3 or higher CRS.

[0098] Also provided herein are methods of treatment, wherein if the subject is identified as having a risk of developing a toxicity, administering to the subject: (a) (1) an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity and (2) the cell therapy, wherein administration of the agent is to be administered (i) prior to, (ii) within one, two, or three days of, (iii) concurrently with and/or (iv) at first fever following, the initiation of administration of the cell therapy to the subject; and/or (b) a cell therapy at a reduced dose or at a dose that is not associated with risk of developing toxicity or severe toxicity, or is not associated with a risk of developing a toxicity or severe toxicity in a majority of subjects, and/or a majority of subjects having a disease or condition that the subject has or is suspected of having, following administration of the cell therapy; and/or (c) administering to the subject a cell therapy in an inpatient setting and/or with admission to the hospital for one or more days. In some of any such examples, the cell therapy is otherwise to be administered to subjects on an outpatient basis or without admission to the hospital for one or more days.

[0099] In some of any of the provided examples the agent or other treatment is an anti-IL-6 antibody or an anti-IL-6 receptor antibody. In some of any of the provided examples, the agent or other treatment is or contains an agent selected from among tocilizumab, siltuximab, clazakizumab,

some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 1.5×10^8 total recombinant receptor-expressing T cells.

[0106] In some of any of the provided examples, the dose of $CD4^+$ and $CD8^+$ T cells contains: between at or about 1×10^7 and at or about 1×10^8 recombinant receptor-expressing $CD8^+$ T cells, inclusive; between at or about 1.25×10^7 and at or about 7.5×10^7 recombinant receptor-expressing $CD8^+$ T cells, inclusive; between at or about 2.5×10^7 and at or about 5×10^7 recombinant receptor-expressing $CD8^+$ T cells, inclusive; at or about 2.5×10^7 recombinant receptor-expressing $CD8^+$ T cells; at or about 5×10^7 recombinant receptor-expressing $CD8^+$ T cells; or at or about 7.5×10^7 recombinant receptor-expressing $CD8^+$ T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 2.5×10^7 recombinant receptor-expressing $CD8^+$ T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 5×10^7 recombinant receptor-expressing $CD8^+$ T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 7.5×10^7 recombinant receptor-expressing $CD8^+$ T cells.

[0107] In some of any of the provided examples, the T cells are primary T cells obtained from a subject or are autologous to the subject.

[0108] Provided herein are articles of manufacture containing a composition including genetically engineered cells expressing a recombinant receptor; and instructions for assessing the risk of developing a toxicity, identifying a subject or treating a subject in accord with any of the methods provided herein. In some of any such examples, the articles of manufacture also contain an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity

Brief Description of the Drawings

[0109] **FIG. 1** shows the percentage of subjects who experienced laboratory abnormalities and treatment-emergent adverse events (TEAEs) that occurred in ≥20% of subjects. *: One Grade 5 AE of multi-organ failure unrelated to study treatment and due to progression of lymphoma; †: One Grade 5 AE of diffuse alveolar damage, investigator assessed as related to fludarabine, cyclophosphamide, and CAR T cell therapy, occurred on day 23 in a subject who refused mechanical ventilation for progressive respiratory failure while neutropenic on growth factors and broad spectrum antibiotics and antifungals

[0110] **FIG. 2** is a Kaplan meier curve depicting observed time to onset of CRS and neurotoxicity.

[0111] **FIG. 3A** and **FIG. 3B** depict 3 month objective response rates (ORR) among subgroups of treated subjects.

[0112] **FIG. 4A** and **FIG. 4B** show the duration of response (CR/PR, CR or PR) and overall survival in the full and core cohort of subjects.

[0113] **FIG. 5A** shows the pharmacokinetics of the CAR^+ T cells in peripheral blood at various time points post-treatment at different dose levels. **FIG. 5B** shows the pharmacokinetics of the CAR^+ T cells

CLAIMS

1. Use of a dose of CD4+ and CD8+ T cells, wherein T cells of each dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, for the manufacture of a medicament for treatment of a subject having or suspected of having a disease or condition that is a relapsed or refractory large B cell lymphoma (r/r LBCL), wherein:

at or immediately prior to the time of the administration of the dose of cells, the subject is or has been identified as being ineligible for both a high-dose chemotherapy and a hematopoietic stem cell transplantation (HSCT);

the dose of T cells comprises between 1 x 10^7 viable CAR-expressing T cells and 2 x 10^8 viable CAR-expressing T cells, inclusive.

2. The use of claim 1, wherein the large B cell lymphoma is selected from an aggressive non-Hodgkin lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), double/triple hit lymphoma, primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), transformed follicular lymphoma (tFL), or follicular lymphoma (FL).

3. The use of claim 2, wherein the large B cell lymphoma is DLBCL and the DLBCL is DLBCL NOS (de novo or transformed from indolent lymphoma).

4. The use of claim 2 or claim 3, wherein the DLBCL is:

(a) a DLBCL transformed from an indolent lymphoma other than FL; or

(b) a DLBCL transformed from marginal zone lymphoma (tMZL) or a DLBCL transformed from chronic lymphocytic leukemia (tCLL; Richter's).

5. The use of claim 1 or claim 2, wherein the large B cell lymphoma is a high-grade B cell lymphoma (HGBCL).

6. The use of claim 5, wherein (a) the HGBCL has MYC and BCL2 and/or BCL6 rearrangements; and/or (b) the HGBCL has a DLBCL histology.

7. The use of claim 1 or claim 2, wherein:

(a) the large B cell lymphoma is a double/triple hit lymphoma;(b) the large B cell lymphoma is primary mediastinal B-cell lymphoma (PMBCL);(c) the large B cell lymphoma is mantle cell lymphoma (MCL);(d) the large B cell lymphoma is not a primary central nervous system lymphoma (PCNSL);(e)

the large B cell lymphoma is a transformed follicular lymphoma (tFL); or(f) the large B cell lymphoma is follicular lymphoma (FL).

8. The use of claim 1 or claim 2, wherein the large B cell lymphoma is follicular lymphoma (FL).

9. The use of claim 2 or claim 8, wherein the FL is follicular lymphoma Grade 3B (FL3B).

10. The use of claim 2, claim 8 or claim 9, wherein:
the FL is associated with co-expression of CD10, BCL6 and BCL2 within the follicles, and/or t(14;18)/(q32;q21) (IGH-BCL2) and/or BCL6 rearrangements.

11. The use of any of claims 1-10, wherein the administration comprises administration of a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising CD8+ T cells and a second composition comprising CD4+ T cells.

12. The use of any of claims 1-11, wherein the dose of T cells comprises a ratio of 1:1 CD4+ T cells expressing the CAR to CD8+ T cells expressing the CAR.

13. The use of any of claims 1-12, wherein, at or immediately prior to the time of the administration of the dose of cells, the subject has relapsed following remission after treatment with, or become refractory to, two or more prior therapies, three or more prior therapies, or four or more prior therapies for the disease or condition other than another dose of cells expressing the CAR.

14. The use of claim 13, wherein the prior therapy comprises an anthracycline and one or more CD20-targeted agent.

15. The use of claim 14, wherein (i) the one or more CD20-targeted agent comprises rituximab; and/or (ii) the one or more CD20-targeted agent comprises R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin) and prednisone).

16. The use of any of claims 13-15, wherein, if the prior therapy is a prior CD19-targeted therapy, a biological sample obtained from the subject after the prior CD19-targeted therapy comprises a cell expressing CD19.

17. The use of any of claims 13-16, wherein the prior therapy comprises an allogeneic or an autologous hematopoietic stem cell transplantation (HSCT).

18. The use of claim 17, wherein the subject has relapsed within 1 year or less than 1 year after receiving the HSCT.

19. The use of any of claims 13-18, wherein the subject has not achieved complete remission (CR) in response to the prior therapy.

20. The use of any of claims 1-19, wherein,

(a) at or prior to the administration of the dose of cells:

(i) the subject has been identified as having an aggressive disease or high-risk disease or as having poor prognosis;

(ii) the subject has been identified as having a chemorefractory disease or having a persistent or relapsed disease following chemotherapy;

(iii) the subject has been identified as having a chemorefractory lymphoma, and/or

(iv) the subject is or has been identified as having a lymphoma associated with or involving central nervous system (CNS) involvement or a secondary CNS lymphoma; and/or

(b) at least 70%, at least 80%, at least 90% or at least 95% of subjects to be administered the dose of cells exhibited or were identified to exhibit a lymphoma with CNS involvement or a secondary CNS lymphoma, achieved a resolution of the CNS disease.

21. The use of claim 20, wherein the chemorefractory lymphoma is a chemorefractory DLBCL.

22. The use of any of claims 1-21, wherein:

(a) the subject is age 65 years or older; and/or

(b) among the subjects treated, greater than 35%, greater than 40%, greater than 45% or greater than 50%, or any value between any of the foregoing, are aged 65 years or older.

23. The use of any of claims 1-22, wherein, at or prior to the administration of the dose of cells:

(a) the subject is or has been identified as having an impaired cardiac function;

(b) the subject is or has been identified as having an impaired renal function;

(c) the subject is or has been identified as having an impaired pulmonary function;

(d) the subject is or has been identified as having an impaired hepatic function;

(e) the subject has received a bridging chemotherapy between the time of leukapheresis to produce the dose of $CD4^+$ and $CD8^+$ T cells and the administration of the dose of $CD4^+$ and $CD8^+$ T cells;

(f) the subject has received a bridging chemotherapy for disease control after a prior therapy; and/or

(g) the subject is or has been identified as being ineligible for both a high-dose chemotherapy and a hematopoietic stem cell transplantation (HSCT), and the subject has relapsed following remission after treatment with, or become refractory to, one prior therapy for the disease or condition other than another dose of cells expressing the CAR.

24. The use of claim 23, wherein the impaired cardiac function comprises a left ventricular ejection fraction (LVEF) of less than 50%, and/or the impaired renal function comprises a calculated creatinine clearance of less than 60 mL/min, and/or the impaired pulmonary function comprises a diffusing capacity of the lungs for carbon monoxide (DLCO) of 60% or less, and/or the impaired hepatic function comprises an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than twice the upper limit of normal (ULN).

25. The use of claim 23 or claim 24, wherein the bridging chemotherapy is selected from among one or more of: Rituximab-gemcitabine plus oxaliplatin, Dexamethasone, radiotherapy, Rituximab, Prednisone, BR, Lenalidomide, gemcitabine plus oxaliplatin, Brentuximab vedotin, Ibrutinib, Bendamustine, and/or Gemcitabine + rituximab.

26. The use of any of claims 1-25, wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2.

27. The use of claim 26, wherein the subject is or has been identified as having an ECOG PS of 0 or 1.

28. The use of any of claims 1-27, wherein, prior to the administration of the dose of cells:

(a) the subject is or has been identified as having a sum of product dimensions (SPD) of a tumor in the subject that is greater than 50 cm^2; or

(b) the subject has a positron emission tomography (PET)-positive disease.

29. The use of any of claims 1-28, wherein prior to administration of the dose of cells, a subject is identified or selected for the administration of the dose of cells if the subject has:

a relapsed or refractory large B cell lymphoma; and/or

been treated with an anthracycline and one or more CD20-targeted agent; and/or

a relapsed or refractory disease after two or more lines of therapy or after autologous HSCT; and/or

an ECOG performance status of 0, 1 or 2; and/or

received a prior CD19-targeted therapy, and a biological sample obtained from the subject after the prior CD19-targeted therapy comprises a cell expressing CD19.

30. The use of any of claims 1-29, wherein prior to administration of the dose of cells, a subject is identified or selected for the administration of the dose of cells if the subject has or is:

age 70 years or older; and/or

an ECOG performance status of 2; and/or

an impaired pulmonary function, and/or

an impaired cardiac function, and/or

an impaired renal function, and/or

an impaired hepatic function.

31. The use of claim 30, wherein the impaired pulmonary function comprises a diffusing capacity of the lungs for carbon monoxide (DLCO) of 60% or less; and/or the impaired cardiac function comprises a left ventricular ejection fraction (LVEF) of less than 50%; and/or the impaired hepatic function comprises a calculated creatinine clearance of less than 60 mL/min; and/or the impaired hepatic function comprises an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than twice the upper limit of normal (ULN).

32. The use of any of claims 1-31, wherein prior to administration of the dose of cells, a subject is identified or selected for the administration of the dose of cells if the subject has:

a double/triple hit lymphoma;

a chemorefractory lymphoma, optionally a chemorefractory DLBCL;

not achieved complete remission (CR) in response to a prior therapy for treating the malignancy;

has relapsed within 1 year or less than 1 year after receiving an autologous stem cell transplant (ASCT); and/or

has a lymphoma associated with or involving central nervous system (CNS) involvement.

33. The use of claim 32, wherein the malignancy is the NHL.

34. The use of any one of claims 1-33, wherein the dose of T cells is enriched for CD3+ T cells, CD4+ T cells, CD8+ T cells or CD4+ T cells and CD8+ T cells.

35. The use of claim 34, wherein greater than 70%, 75%, 80%, 85%, 90%, 95% or 98% of the cells in the dose of T cells are CD3+ T cells, CD4+ T cells, CD8+ T cells or CD4+ T cells and CD8+ T cells.

36. The use of any of claims 11-35, wherein the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition.

37. The use of claim 36, wherein (i) the administration of the first composition and the administration of the second composition are carried out no more than 48 hours apart; and/or (ii) the administration of the first composition and the administration of the second composition are carried out no more than 36 hours apart, no more than 24 hours apart, no more than 12 hours apart, no more than 6 hours apart, no more than 4 hours apart, no more than 2 hours apart, no more than 1 hour apart or no more than 30 minutes apart.

38. The use of any of claims 1-37, wherein the recombinant receptor comprised by the $CD4^+$ T cells and/or the recombinant receptor comprised by the $CD8^+$ T cells is a recombinant receptor that is the same and/or wherein the $CD4^+$ T cells and/or the $CD8^+$ T cells are genetically engineered to express the recombinant receptor that is the same.

39. The use of any of claims 1-38, wherein the dose of $CD4^+$ and $CD8^+$ T cells comprises:
(a) between 2.5×10^7 and 1.5×10^8 viable CAR-expressing T cells, inclusive;
between 5×10^7 and 1×10^8 viable CAR-expressing T cells, inclusive;
5×10^7 viable CAR-expressing T cells;
1×10^8 viable CAR-expressing T cells; or
1.5×10^8 viable CAR-expressing T cells; or
(b) between 1.25×10^7 and 7.5×10^7 viable CAR-expressing $CD8^+$ T cells, inclusive;
between 2.5×10^7 and 5×10^7 viable CAR-expressing $CD8^+$ T cells, inclusive;
2.5×10^7 viable CAR-expressing $CD8^+$ T cells;
5×10^7 viable CAR-expressing $CD8^+$ T cells; or
7.5×10^7 viable CAR-expressing $CD8^+$ T cells.

40. The use of any of claims 1-39, wherein, prior to the administration, the subject has been

preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

41. The use of claim 40, wherein the administration of the dose of cells and/or the lymphodepleting therapy is to be carried out via outpatient delivery.

42. The use of any of claims 1-41, wherein:

the administration and any follow up is to be carried out on an outpatient basis and/or without requiring admission to or an overnight stay at a hospital; and

if the subject exhibits a sustained fever or a fever that is or has not been reduced or not reduced by more than 1ºC after treatment with an antipyretic, the subject is to be admitted to the hospital or to an overnight stay at a hospital and/or is to be administered an agent or treatment for the treatment or prevention or reduction or attenuation of a neurotoxicity and/or a cytokine release syndrome or risk thereof.

43. The use of any of claims 1-42, wherein prior to initiation of administration of the dose of cells, the subject has not been administered an agent or treatment for the treatment or prevention or reduction or attenuation of a neurotoxicity and/or a cytokine release syndrome or risk thereof.

44. The use of any of claims 1-43, wherein the subject is to be administered an agent or treatment for the treatment or prevention or reduction or attenuation of a neurotoxicity and/or a cytokine release syndrome or risk thereof.

45. The use of claim 44, wherein the agent is or comprises an anti-IL-6 antibody, anti-IL-6 receptor antibody or a steroid and/or the agent is or comprises tocilizumab, siltuximab, dexamethasone or methylprednisolone.

46. The use of any of claims 1-45, wherein, at or prior to the administration of the dose of cells:

the subject is or has been treated with an anthracycline and one or more CD20-targeted agent; and/or

the subject is or has relapsed or refractory disease after two or more lines of therapy or after autologous HSCT; and/or

the subject is or has been identified as having an ECOG performance status of 0, 1 or 2; and/or

if the subject has received a prior CD19-targeted therapy, a biological sample obtained from the

subject after the prior CD19-targeted therapy comprises a cell expressing CD19; and

the administration of the dose of cells is to be carried out via outpatient delivery.

47. The use of any of claims 1-46, wherein:

(a) at least 40%, at least 50%, at least 60%, at least 70% of the subjects who, at or prior to the administration of the dose of cells had or were identified to have a double/triple hit lymphoma or relapse following administration of an autologous stem cell transplant (ASCT), achieved an OR or an OR that is durable for at or greater than 3 months or at or greater than 6 months; and/or

(b) at least 35%, at least 40% or at least 50% of subjects to be administered the dose achieve a complete response (CR);

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving a CR exhibit a CR that is durable for at or greater than 3 months or at or greater than 6 months; and/or

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving a CR by one month and/or by 3 months remain in response, remain in CR, and/or survive or survive without progression, for at or greater than 3 months and/or at or greater than 6 months and/or at greater than 9 months after achieving the CR; and/or

at least 50%, at least 60% or at least 70% of the subjects to be administered the dose achieve objective response (OR);

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving an OR exhibit an OR that is durable for at or greater than 3 months or at or greater than 6 months; and/or

at least 35%, at least 40%, or at least 50% of subjects achieving an OR remain in response or survive for at or greater than 3 months and/or at or greater than 6 months after achieving the OR; and/or

at least 40%, at least 50%, at least 60%, at least 70% of the subjects who, at or prior to the administration of the dose of cells had or were identified to have a double/triple hit lymphoma or relapse, following administration of an autologous stem cell transplant (ASCT), achieved an OR, or an OR that is durable for at or greater than 3 months or at or greater than 6 months.

48. The use of claim 47, wherein:

the CR or the OR is durable for greater than 3 months or greater than 6 months; and/or

at least 20%, at least 25%, at least 35%, at least 40% or at least 50% of subjects to be administered the dose achieve a CR that is durable for greater than 3 months or greater than 6 months; and/or

at least 60%, 70%, 80%, 90%, or 95% of subjects to be administered the dose and who achieve a CR, remain in CR or remain in response or remain surviving for at or greater than 3 months or at or greater than 6 months or at or greater than 9 months; and/or

at least 60%, 70%, 80%, 90%, or 95% of subjects to be administered the dose who achieve a CR by one month and/or by 3 months remain in response, remain in CR, and/or survive or survive without progression, for greater at or greater than 3 months and/or at or greater than 6 months and/or at greater than 9 months; and/or

at least 50%, at least 60% or at least 70% of the subjects to be administered the dose achieve objective response (OR);

at least 60%, 70%, 80%, 90%, or 95% of subjects achieve an OR that is durable for at or greater than 3 months or at or greater than 6 months; and/or

at least at least 35%, at least 40%, or at least 50% of subjects to be administered the dose achieve an OR remain in response or survive for at or greater than 3 months and/or at or greater than 6 months.

49. The use of any of claims 1-48, wherein:

at least 35%, at least 40% or at least 50% of subjects to be administered the dose achieve a complete response (CR) or remission of CNS disease;

at least 60%, 70%, 80%, 90%, or 95% of subjects who achieve a CR remain in CR for at or greater than 3 months or at or greater than 6 months; and/or

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving a CR or remission of CNS disease by one month and/or by 3 months remain in response, remain in CR, and/or survive or survive without progression, for greater at or greater than 3 months and/or at or greater than 6 months and/or at greater than 9 months; and/or

at least 50%, at least 60% or at least 70% of the subjects to be administered the dose achieve objective response (OR) or remission of CNS disease;

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving the OR, for at or greater than 3 months or at or greater than 6 months; and/or

at least 60%, 70%, 80%, 90%, or 95% of subjects achieving OR or remission of CNS disease remain in response or survive for at or greater than 3 months and/or at or greater than 6 months; and/or

the brain lesion is reduced in size or volume by greater than 25%, 50%, 75% or more; and/or

reduction or remission or clearance of CNS disease is achieved in at least 35%, at least 40% or at least 50% of subjects to be administered the dose.

50. The use of any of claim 1-49, wherein

greater than 50%, 60%, 70%, or 80% of the subjects to be administered the dose do not exhibit a grade 3 or greater cytokine release syndrome (CRS) and/or do not exhibit a grade 3 or greater neurotoxicity and/or greater than 40% or 50% or 55% do not exhibit any neurotoxicity or CRS.

51. The use of claim 50, wherein:

greater than 30%, 35%, 40%, or 50% of the subjects to be administered the dose do not exhibit any grade of cytokine release syndrome (CRS) or neurotoxicity; and/or

at least 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of subjects to be administered the dose do not exhibit onset of CRS earlier than 3 days following initiation of the administration and/or do not exhibit onset of neurotoxicity earlier than 5 days following initiation of the administration; and/or

the median onset of neurotoxicity among subjects to be administered the dose is at or after the median peak of, or median time to resolution of, CRS in subjects to be administered the dose and/or the median onset of neurotoxicity among subjects to be administered the dose is greater than 8, 9, 10, or 11 days.

52. The use of any of claims 1-51, wherein:

at least 50% of subjects to be administered the dose achieve a complete response (CR);

at least 70% of the subjects to be administered the dose achieve objective response (OR);

greater than 50% of the subjects to be administered the dose do not exhibit any grade of cytokine release syndrome (CRS) or neurotoxicity; and

greater than 80% of the subjects to be administered the dose do not exhibit a grade 3 or greater cytokine release syndrome (CRS) and/or do not exhibit a grade 3 or greater neurotoxicity.

53. The use of any of claims 1-52, wherein the CAR comprises an extracellular antigen-binding domain specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a 4-1BB, and a cytoplasmic signaling domain derived from a CD3zeta.

54. The use of claim 53, wherein the antigen-binding domain is an scFv.

55. The use of claim 54, wherein;

a) the scFv comprises an amino acid sequence of RASQDISKYLN (SEQ ID NO: 35), an amino acid sequence of SRLHSGV (SEQ ID NO: 36), and/or an amino acid sequence of GNTLPYTFG (SEQ ID NO: 37) and/or an amino acid sequence of DYGVS (SEQ ID NO: 38), an amino acid sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and/or an amino acid sequence of YAMDYWG (SEQ ID NO: 40) or wherein the scFv comprises a variable heavy chain region of FMC63 and a variable light chain region of FMC63 and/or a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63, and/or

(b) the scFv comprises a variable heavy chain region of FMC63 and a variable light chain region of FMC63.

56. The use of claim 54 or 55, wherein the scFv comprises in order, a VH, a linker, and a VL.

57. The use of claim 56, wherein the linker comprises SEQ ID NO: 24.

58. The use of claim 56, wherein the linker is a flexible linker and or comprises the amino acid sequence set forth as SEQ ID NO:43.

59. The use of any of claims 53-58, wherein the CAR further comprises a spacer between the transmembrane domain and the scFv.

60. The use of claim 59, wherein:

(a) the spacer is a polypeptide spacer that comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof,

(b) the spacer is 12 amino acids in length; and/or

(c) the spacer has or consists of the sequence of SEQ ID NO: 1, a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto; and/or the spacer comprises or consists of the formula X1PPX2P, where X1 is glycine, cysteine or arginine and X2 is cysteine or threonine.

61. The use of claim 59, wherein the immunoglobulin hinge or modified version thereof is an IgG4 hinge, or a modified version thereof.

62. The use of any of claims 59-61, wherein:

the spacer is a polypeptide spacer that: (a) comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof or comprises 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region, (b) comprises or consists of all or a portion of an immunoglobulin hinge, and/or comprises 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region, (c) is 12 amino acids in length and/or comprises or consists of all or a portion of an immunoglobulin hinge, (d) has or consists of the sequence of SEQ ID NO: 1, a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ

ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto, or (e) comprises or consists of the formula X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine;

the costimulatory domain comprises SEQ ID NO: 12 or a variant thereof having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto;

the primary signaling domain comprises SEQ ID NO: 13, 14 or 15 having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto; and

the scFv comprises an amino acid sequence of RASQDISKYLN (SEQ ID NO: 35), an amino acid sequence of SRLHSGV (SEQ ID NO: 36), an amino acid sequence of GNTLPYTFG (SEQ ID NO: 37), an amino acid sequence of DYGVS (SEQ ID NO: 38), an amino acid sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and an amino acid sequence of YAMDYWG (SEQ ID NO: 40) or wherein the scFv comprises a variable heavy chain region of FMC63 and a variable light chain region of FMC63 and/or a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63.

63. The use of claim 62, wherein the immunoglobulin hinge is an IgG4 hinge, or a modified version thereof.

64. The use of claim 62 or claim 63, wherein the scFv comprises, in order, a VH, a linker, and a VL, and/or the scFv comprises the amino acid sequence set forth as SEQ ID NO: 43.

65. The use of any of claims 59-61, wherein:

the spacer is a polypeptide spacer that comprises the sequence of SEQ ID NO: 1;

the costimulatory domain comprises SEQ ID NO: 12;

the primary signaling domain comprises SEQ ID NO: 13, 14 or 15; and

the antigen binding domain comprises an scFv that comprises a variable heavy chain region of FMC63 and a variable light chain region of FMC63.