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: 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 dose of T cells is to be administered to the subject as 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.

[0005b] In one aspect, the present disclosure refers to 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 use in the treatment of a subject suspected or having a disease or condition that is a relapsed or refractory large B cell lymphoma (r/r LBCL), wherein: the dose of T cells comprises between at or about 1 x 107 CAR-expressing T cells and at or about 2 x 108 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 dose of T cells is to be administered to the subject as 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.

[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

comprising a first composition comprising $CD8^+$ T cells and a second composition comprising $CD4^+$ T cells.

[0009] Provided herein are methods of treating a subject having or suspected of having a disease or condition that is a non-Hodgkin lymphoma (NHL) or a large B cell lymphoma, the method including administering to the subject 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 NHL or large B cell lymphoma, wherein: the dose of T cells contains 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; and the dose of T cells contains $CD4^+$ and $CD8^+$ T cells, each of the $CD4^+$ and the $CD8^+$ T cells, individually, containing 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 comprising $CD8^+$ T cells and a second composition containing $CD4^+$ T cells.

[0010] In some of any of the provided examples, the dose of T cells comprises a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio is approximately 1:1 or is between approximately 1:3 and approximately 3:1.

[0011] Provided herein are methods of treating a subject having a disease or condition that is a non-Hodgkin lymphoma (NHL) or a large B cell lymphoma, the methods including administering to the subject a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen, e.g., target antigen, expressed by the NHL or large B cell lymphoma, the dose of T cells containing a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio is approximately or is 1:1, wherein the administration includes administering a plurality of separate compositions, the plurality of separate compositions containing a first composition comprising $CD8^+$ T cells and a second composition containing $CD4^+$ T cells.

[0012] Also provided herein are methods of treating a subject having a disease or condition that is a non-Hodgkin lymphoma (NHL) or a large B cell lymphoma, including administering to the subject a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen, e.g., target antigen, expressed by the NHL or large B cell lymphoma, wherein: the dose of T cells contains between at or about 5 x 10^7 recombinant receptor-expressing T cells and at or about 1.5 x 10^8 recombinant receptor-expressing T cells, inclusive, said dose containing a defined ratio of $CD4^+$ cells expressing the recombinant receptor to $CD8^+$ cells expressing the recombinant receptor and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio is approximately or is 1:1; and the method results in (1) a complete response (CR) in at least 35%, at least 40% or at least 50% of subjects treated and/or objective response (OR) in at least 50%, at least 60% or at least 70% of subjects treated and (2) results in no more than 50% of subjects exhibiting a cytokine release syndrome (CRS) higher than grade 2 and/or a neurotoxicity

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.

[0014a] In one aspect, the present disclosure refers to the use of a dose of T cells comprising T cells expressing a recombinant receptor that specifically binds to an antigen expressed by follicular lymphoma (FL) or a cell or tissue thereof and/or that is associated with FL for the manufacture of a medicament for treatment of a subject having a FL, wherein: (a) the subject is selected for treatment as having a follicular lymphoma (FL); and (b) the subject is to be administered the dose of T cells.

[0014b] In one aspect, the present disclosure refers to a dose of T cells comprising T cells expressing a recombinant receptor that specifically binds to an antigen expressed by follicular lymphoma (FL) or a cell or tissue thereof and/or that is associated with FL for use in the treatment of a subject that has a FL, wherein the subject is selected for treatment and is to be administered the dose of T cells.

[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

cell lymphoma is mantle cell lymphoma (MCL). In some of any examples, the large B cell lymphoma is not a primary central nervous system lymphoma (PCNSL). In some of any examples, the large B cell lymphoma is a transformed follicular lymphoma (tFL). In some of any examples, the large B cell lymphoma is follicular lymphoma (FL). In some of any examples, 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. In some of any examples, the large B cell lymphoma is follicular lymphoma grade 3B (FL3B).

[0016] In some of any examples, 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. In some of any examples, greater than at or about 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. In some of any examples, the dose of T cells comprises a defined ratio of $CD4^+$ cells expressing the receptor to $CD8^+$ cells expressing the receptor and/or of $CD4^+$ T cells to $CD8^+$ T cells, which ratio is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any examples, the defined ratio is or is approximately 1:1. In some of any examples, the dose of T cells comprises 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 FL or a cell or tissue thereof and/or that is associated with FL, 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.

[0017] In some of any of the provided examples, the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out no more than 48 hours apart. In some of any of the provided examples, 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. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out between at or about 0 and at or about 48 hours, between at or about 0 and at or about 36 hours, between at or about 0 and at or about 24 hours, between at or about 0 and at or about 12 hours, between at or about 0 and at or about 6 hours, between at or about 0 and at or about 2 hours, between at or about 0 and at or about 1 hours, between at or about 0 and at or about 30 minutes, between at or about 30 minutes and at or about 48 hours, between at or about 30 minutes and at or about 36 hours, between at or about 30 minutes and at or about 24 hours, between at or about 30 minutes and at or about 12 hours, between at or about 30 minutes and at or about 6 hours, between at or about 30 minutes and at or about 4 hours,

between at or about 30 minutes and at or about 2 hours, between at or about 30 minutes and at or about 1 hour, between at or about 1 hours and at or about 48 hours, between at or about 1 hour and at or about 36 hours, between at or about 1 hour and at or about 24 hours, between at or about 1 hour and at or about 12 hours, between at or about 1 hour and at or about 6 hours, between at or about 1 hour and at or about 4 hours, between at or about 1 hour and at or about 2 hours, between at or about 2 hours and at or about 48 hours, between at or about 2 hours and at or about 36 hours, between at or about 2 hours and at or about 24 hours, between at or about 2 hours and at or about 12 hours, between at or about 2 hours and at or about 6 hours, between at or about 2 hours and at or about 4 hours, between at or about 4 hours and at or about 48 hours, between at or about 4 hours and at or about 36 hours, between at or about 4 hours and at or about 24 hours, between at or about 4 hours and at or about 12 hours, between at or about 4 hours and at or about 6 hours, between at or about 6 hours and at or about 48 hours, between at or about 6 hours and at or about 36 hours, between at or about 6 hours and at or about 24 hours, between at or about 6 hours and at or about 12 hours, between at or about 12 hours and at or about 48 hours, between at or about 12 hours and at or about 36 hours, between at or about 12 hours and at or about 24 hours, between at or about 24 hours and at or about 48 hours, between at or about 24 hours and at or about 36 hours or between at or about 36 hours and at or about 48 hours.

[0018] In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out on the same day, are carried out between about 0 and about 12 hours apart, between about 0 and about 6 hours apart or between about 0 to 2 hours apart; or the initiation of administration of the first composition and the initiation of administration of the second composition are carried out between about 1 minute and about 1 hour apart or between about 5 minutes and about 30 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 2 hours, no more than 1 hour, no more than 30 minutes, no more than 15 minutes, no more than 10 minutes or no more than 5 minutes apart.

[0019] In some of any of the provided examples, the receptor contained by the $CD4^+$ T cells and/or the receptor contained by the $CD8^+$ T cells includes 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 a recombinant receptor that is the same.

[0020] In some of any of the provided examples, the dose of $CD4^+$ and $CD8^+$ T cells contains a defined ratio of $CD4^+$ cells expressing a recombinant receptor to $CD8^+$ cells expressing a recombinant receptor and/or of $CD4^+$ cells to $CD8^+$ cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and/or the $CD4^+$ T cells containing the receptor in the one of the first and second compositions and the $CD8^+$ T cells containing the receptor in the other of the first and second compositions are present at a defined ratio that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and/or the $CD4^+$ T cells containing the receptor and the $CD8^+$ T cells containing the receptor administered in the first and second compositions are present at a defined ratio, which ratio

is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any of the provided examples, the defined ratio is or is approximately 1:1.

[0021] In some of any of the provided examples, the dose of $CD4^+$ and $CD8^+$ T cells contains: between at or about 1 x 10^7 and at or about 2 x 10^8 total recombinant receptor-expressing T cells, inclusive; between at or about 2.5 x 10^7 and at or about 1.5 x 10^8 total recombinant receptor-expressing T cells, inclusive; between at or about 5 x 10^7 and at or about 1 x 10^8 total recombinant receptor-expressing T cells, inclusive; at or about 5 x 10^7 total recombinant receptor-expressing T cells; at or about 1 x 10^8 total recombinant receptor-expressing T cells; or at or about 1.5 x 10^8 total recombinant receptor-expressing T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 5 x 10^7 total recombinant receptor-expressing T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 1 x 10^8 total recombinant receptor-expressing T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 1.5 x 10^8 total recombinant receptor-expressing T cells.

[0022] In some of any of the provided examples, the dose of $CD4^+$ and $CD8^+$ T cells contains: between at or about 1 x 10^7 and at or about 1 x 10^8 recombinant receptor-expressing $CD8^+$ T cells, inclusive; between at or about 1.25 x 10^7 and at or about 7.5 x 10^7 recombinant receptor-expressing $CD8^+$ T cells, inclusive; between at or about 2.5 x 10^7 and at or about 5 x 10^7 recombinant receptor-expressing $CD8^+$ T cells, inclusive; at or about 2.5 x 10^7 recombinant receptor-expressing $CD8^+$ T cells; at or about 5 x 10^7 recombinant receptor-expressing $CD8^+$ T cells; or at or about 7.5 x 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 x 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 x 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 x 10^7 recombinant receptor-expressing $CD8^+$ T cells.

[0023] In some of any of the provided examples, the recombinant receptor specifically binds to an antigen associated with the disease or condition or expressed in cells of the environment of a lesion associated with the disease or condition.

[0024] In some of any of the provided examples, the disease or condition is a cancer. In some of any such examples, the disease or condition is a B cell malignancy. In some of any such examples, the disease or condition is a myeloma, a leukemia or a lymphoma. In some of any of the provided examples, the disease or condition is a B cell malignancy and/or is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphoblastic leukemia (CLL), non-Hodgkin lymphoma (NHL), or a large B cell lymphoma. In some of any of the provided examples, the disease or condition is a large B cell lymphoma. In some of any of the provided examples, the disease or condition, such as the large B cell lymphoma, is a Diffuse Large B-Cell Lymphoma (DLBCL). In some of any of the provided examples, the DLBCL is a DLBCL, not otherwise specified (NOS), a de novo DLBCL or a DLBCL

transformed from indolent lymphoma. In some of any of the provided examples, the DLBCL is a de novo DLBCL. In some of any of the provided examples, the DLBCL is a DLBCL transformed from follicular lymphoma (tFL). In some of any of the provided 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 of the provided examples, the disease or condition is primary mediastinal B-cell lymphoma (PMBCL) or a follicular lymphoma (FL), such as follicular lymphoma grade 3B (FL3B). In some of any examples, the disease or condition is follicular lymphoma (FL). In some of any of the provided examples, the NHL or the large B cell lymphoma is selected from the group consisting of aggressive NHL, diffuse large B cell lymphoma (DLBCL), NOS (de novo or transformed from indolent), primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), and/or follicular lymphoma (FL), such as follicular lymphoma Grade 3B (FL3B). In some of any examples, the disease or condition is follicular lymphoma (FL). In some of any examples, 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. In some of any examples, the disease or condition is mantle cell lymphoma (MCL).

[0025] In some of any such examples, the target antigen is a B cell antigen. In some of any of the provided examples, the antigen is CD19.

[0026] In some of any examples, 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, three, four or more prior therapy for the disease or condition other than another dose of cells expressing the CAR.

[0027] In some of any examples, the prior therapy comprises an anthracycline and a CD20-targeted agent. In some of any examples, the one or more CD20-targeted agent comprises rituximab. In some of any examples, the one or more CD20-targeted agent comprises R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin) and prednisone).

[0028] In some of any examples, the prior therapy comprises an allogeneic or an autologous hematopoietic stem cell transplantation (HSCT). In some of any examples, the subject has relapsed within 1 year or less than 1 year after receiving the HSCT.

[0029] In some of any examples, the subject has not achieved complete remission (CR) in response to the prior therapy.

[0030] In some of any examples, at or prior to the administration of the dose of cells, the subject has been identified as having an aggressive disease or high-risk disease or as having poor prognosis.

[0031] In some of any examples, at or prior to the administration of the dose of cells, the subject has been identified as having a chemorefractory disease or having a persistent or relapsed disease following chemotherapy. In some of any examples, at or prior to the administration of the dose of

cells, the subject has been identified as having a chemorefractory lymphoma, optionally a chemorefractory DLBCL.

[0032] In some of any examples, at or prior to the administration of the dose of cells, the subject has been identified as having a lymphoma associated with or involving central nervous system (CNS) involvement or a secondary CNS lymphoma. In some of any examples: at or prior to administration of the dose of cells, 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 at least 70%, at least 80%, at least 90% or at least 95% of subjects treated according to the method who, at or prior to the administration of 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.

[0033] In some of any examples, the subject is age 65 years or older. In some of any examples, among the subjects treated, greater than at or about 35%, greater than at or about 40%, greater than at or about 45% or greater than at or about 50%, or any value between any of the foregoing, are aged 65 years or older. In some of any examples the subject is age 70 years or older.

[0034] In some of any examples, at or prior to the administration of the dose of cells, the subject is or has been identified as having an impaired cardiac function, optionally with a left ventricular ejection fraction (LVEF) of less than at or about 50%. In some of any examples, at or prior to the administration of the dose of cells, the subject is or has been identified as having an impaired renal function, optionally with a calculated creatinine clearance of less than at or about 60 mL/min. In some of any examples, at or prior to the administration of the dose of cells, the subject is or has been identified as having an impaired pulmonary function, optionally with a diffusing capacity of the lungs for carbon monoxide (DLCO) of at or about 60% or less. In some of any examples, at or prior to the administration of the dose of cells, the subject is or has been identified as having an impaired hepatic function, optionally with an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than at or about twice the upper limit of normal (ULN).

[0035] In some of any examples, at or prior to the administration of the dose of cells, 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. In some of any examples, at or prior to the administration of the dose of cells, the subject has received a bridging chemotherapy for disease control after a prior therapy. In some of any examples, 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.

[0036] In some of any examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2. In some of any examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance

Status (ECOG PS) of 0 or 1. In some of any examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2.

[0037] In some of any examples, prior to the administration of the dose of cells, the subject is or has been identified as having a sum of product dimensions (SPD) of a tumor in the subject that is at or about 50 cm^2 or greater.

[0038] In some of any of the provided examples, the recombinant receptor is a chimeric antigen receptor (CAR). In some of any of the provided examples, the CAR contains an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling domain containing a CD3-zeta (CD3ζ) chain and a costimulatory signaling region that is a signaling domain of CD28 or 4-1BB.

[0039] In some of any of the provided examples, the T cells are primary T cells obtained from a subject. In some of any of the provided examples, the T cells are autologous to the subject.

[0040] In some of any of the provided examples, 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.

[0041] In some of any of the provided examples, at least 35%, at least 40% or at least 50% of subjects treated according to the method 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 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 treated according to the method 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.

[0042] In some of any of the provided examples, the cells are autologous to the subject, and no minimum absolute lymphocyte count (ALC) for apheresis is required and/or specified for production of the therapy; and/or the cells are produced by a process which, for at least 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100% of subjects having the disease or condition or of the selected population of subjects, is capable of generating a cell product for administration according to the method.

[0043] In some of any of the provided examples, greater than or greater than about 50%, about 60%, about 70%, or about 80% of the subjects treated according to the method 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.

[0044] In some of any of the provided examples, 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 treated according to the method 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 treated with the method 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 treated with the method 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 treated according to the method 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 treated with the method and achieving an OR remain in response or survive for at or greater than 3 months and/or at or greater than 6 months.

[0045] In some of any of the provided examples, at or prior to administration of the dose of cells, the subject is or has been identified as having a lymphoma associated with or involving central nervous system (CNS) involvement; and/or at least 70%, at least 80%, at least 90% or at least 95% of subjects treated according to the method who, at or prior to the administration of the dose of cells exhibited or were identified to exhibit a lymphoma with CNS involvement, achieved a resolution of the CNS disease.

[0046] In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out no more than 48 hours apart. In some of any of the provided examples, 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.

[0047] In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out between at or about 0 and at or about 48 hours, between at or about 0 and at or about 36 hours, between at or about 0 and at or about 24 hours, between at or about 0 and at or about 12 hours, between at or about 0 and at or about 6 hours, between at

or about 0 and at or about 2 hours, between at or about 0 and at or about 1 hours, between at or about 0 and at or about 30 minutes, between at or about 30 minutes and at or about 48 hours, between at or about 30 minutes and at or about 36 hours, between at or about 30 minutes and at or about 24 hours, between at or about 30 minutes and at or about 12 hours, between at or about 30 minutes and at or about 6 hours, between at or about 30 minutes and at or about 4 hours, between at or about 30 minutes and at or about 2 hours, between at or about 30 minutes and at or about 1 hour, between at or about 1 hours and at or about 48 hours, between at or about 1 hour and at or about 36 hours, between at or about 1 hour and at or about 24 hours, between at or about 1 hour and at or about 12 hours, between at or about 1 hour and at or about 6 hours, between at or about 1 hour and at or about 4 hours, between at or about 1 hour and at or about 2 hours, between at or about 2 hours and at or about 48 hours, between at or about 2 hours and at or about 36 hours, between at or about 2 hours and at or about 24 hours, between at or about 2 hours and at or about 12 hours, between at or about 2 hours and at or about 6 hours, between at or about 2 hours and at or about 4 hours, between at or about 4 hours and at or about 48 hours, between at or about 4 hours and at or about 36 hours, between at or about 4 hours and at or about 24 hours, between at or about 4 hours and at or about 12 hours, between at or about 4 hours and at or about 6 hours, between at or about 6 hours and at or about 48 hours, between at or about 6 hours and at or about 36 hours, between at or about 6 hours and at or about 24 hours, between at or about 6 hours and at or about 12 hours, between at or about 12 hours and at or about 48 hours, between at or about 12 hours and at or about 36 hours, between at or about 12 hours and at or about 24 hours, between at or about 24 hours and at or about 48 hours, between at or about 24 hours and at or about 36 hours or between at or about 36 hours and at or about 48 hours.

[0048] In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out on the same day, are carried out between about 0 and about 12 hours apart, between about 0 and about 6 hours apart or between about 0 to 2 hours apart; or the initiation of administration of the first composition and the initiation of administration of the second composition are carried out between about 1 minute and about 1 hour apart or between about 5 minutes and about 30 minutes apart.

[0049] In some of any of the provided examples, the first composition and second composition are administered no more than 2 hours, no more than 1 hour, no more than 30 minutes, no more than 15 minutes, no more than 10 minutes or no more than 5 minutes apart.

[0050] In some of any of the provided examples, the receptor comprised by the $CD4^+$ T cells and/or the receptor comprised by the $CD8^+$ T cells comprises 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 a recombinant receptor that is the same.

[0051] In some of any of the provided examples, the lymphoma is a B cell malignancy. In some of any of the provided examples, the lymphoma is non-Hodgkin lymphoma (NHL).

[0052] In some of any of the provided examples, at least 35%, at least 40% or at least 50% of subjects treated according to the method 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 treated according to the method 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 or greater than about 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 treated according to the method.

[0053] In some of any of the provided examples, greater than or greater than about 30%, 35%, 40%, or 50% of the subjects treated according to the method do not exhibit any grade of cytokine release syndrome (CRS) or neurotoxicity; and/or at least at or about 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of subjects treated according to the method 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 treated according to the method is at or after the median peak of, or median time to resolution of, CRS in subjects treated according to the method and/or the median onset of neurotoxicity among subjects treated according to the method is greater than at or about 8, 9, 10, or 11 days.

[0054] In some of any examples, greater than or greater than about 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% of the subjects treated according to the method exhibit an improvement of 10 points or greater in European Organization for Research and Treatment Core Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30) in global health status at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment. In some of any examples, greater than or greater than about 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% of the subjects treated according to the method exhibit an improvement of 10 points or greater in EORTC QLQ-C30 in physical functioning at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment. In some of any examples, greater than or greater than about 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% of the subjects treated according to the method exhibit an improvement of 10 points or greater in EORTC QLQ-C30 in fatigue at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment. In some of any examples, greater than or greater than about 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% of the subjects treated according to the

method exhibit an improvement of 10 points or greater in EORTC QLQ-C30 in pain at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment. In some of any examples, greater than or greater than about 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% of the subjects treated according to the method exhibit an improvement of 10 points or greater in EORTC QLQ-C30 in pain at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment.

[0055] In some of any examples, the mean 5-level EuroQol-5D (EQ-5D-5L) score among subjects treated according to the method is the same or greater at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment. In some of any examples, the mean EuroQol global visual analog scale (EQ-VAS) score among subjects treated according to the method is the same or greater at months 6 or month 12 after administration compared to the score prior to treatment or at month 1 after treatment.

[0056] In some of any of the provided examples, prior to initiation of administration of the dose of cells, the subject has not been administered an agent or treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity following administration of the dose of cells.

[0057] In some of any of the provided examples, the agent is or comprises an anti-IL-6 antibody, anti-IL-6 receptor antibody or a steroid. In some of any of the provided examples, the agent is or comprises tocilizumab, siltuximab, dexamethasone or methylprednisolone.

[0058] In some of any of the provided examples, the administration and any follow up is 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 admitted to the hospital or to an overnight stay at a hospital and/or is 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.

[0059] In some of any of the provided examples, the NHL is selected from the group consisting of aggressive NHL, diffuse large B cell lymphoma (DLBCL), NOS (de novo or transformed from indolent), primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), and/or follicular lymphoma (FL), such as follicular lymphoma Grade 3B (FL3B). In some of any examples, the subject has follicular lymphoma (FL). In some of any of the provided examples, the NHL is a DLBCL. In some of any of the provided examples, the DLBCL is a DLBCL, not otherwise specified (NOS), a de novo DLBCL or a DLBCL transformed from indolent lymphoma. In some of any of the provided examples, the DLBCL is a de novo DLBCL. In some of any of the provided examples, the DLBCL is a DLBCL transformed from follicular lymphoma (tFL). In some of any of the provided 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 of the provided

examples, the NHL is primary mediastinal B-cell lymphoma (PMBCL) or a follicular lymphoma (FL), such as follicular lymphoma grade 3B (FL3B). In some of any examples, the subject has follicular lymphoma (FL).

[0060] In some of any of the provided examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0, 1 or 2. In some of any examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

[0061] In some of any of the provided examples, 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, one or more prior therapies for the disease or condition, such as a large B cell lymphoma or an NHL. In some examples, the one, two or three prior therapies are other than another dose of cells expressing the CAR.

[0062] In some of any examples, 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, one prior therapy for the disease or condition other than another dose of cells expressing the CAR. In some of any examples, 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 therapy for the disease or condition other than another dose of cells expressing the CAR. In some of any examples, 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 a high-dose chemotherapy. In some of any examples, 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 a hematopoietic stem cell transplantation (HSCT). In some of any examples, 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).

[0063] In some of any examples, the subject has a relapsed/refractory NHL, and 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), 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.In some of any examples, at or prior to the administration of the dose of cells: the subject has or has been identified as having a relapsed or refractory large B cell lymphoma; and/or 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 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 cell dose is carried out via outpatient delivery.

[0064] In some of any of the provided examples, at or prior to the administration of the dose of cells: the subject is or has been identified as having a double/triple hit lymphoma; and/or the subject is or has been identified as having a chemorefractory lymphoma, such as a chemorefractory DLBCL; and/or the subject has not achieved complete remission (CR) in response to a prior therapy; and/or the subject has relapsed within 1 year or less than 1 year after receiving an autologous stem cell transplant (ASCT).

[0065] In some of any examples, at or prior to the administration of the dose of cells, the subject has a positron emission tomography (PET)-positive disease.

[0066] In some of any examples, 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. In some of any examples, the one or more CD20-targeted agent comprises rituximab. In some of any examples, the one or more CD20-targeted agent comprises R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin) and prednisone).

[0067] In some of any of the provided example, prior to administration of the dose of cells, identifying or selecting a subject for the administration of the dose of cells that has: a double/triple hit lymphoma; a chemorefractory lymphoma, such as a chemorefractory DLBCL; not achieved complete remission (CR) in response to a prior therapy for treating the disease or disorder, such as the malignancy, such as the NHL or large B cell lymphoma; and/or 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.

[0068] In some of any examples, prior to administration of the dose of cells, the provided examples involve identifying or selecting for the administration of the dose of cells a subject that has a follicular lymphoma (FL), such a FL that 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.

[0069] In some of any examples, at or prior to the administration of the dose of cells, 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.

[0070] In some of any examples, at or prior to the administration of the dose of cells: the subject has or has been identified as having a relapsed or refractory large B cell lymphoma; and/or 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 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.

[0071] In some of any examples, the administration of the cell dose is carried out via outpatient delivery.

[0072] In some of any examples, at or prior to the administration of the dose of cells: the subject has or has been identified as having a relapsed or refractory large B cell lymphoma; and/or 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 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 cell dose is carried out via outpatient delivery.

[0073] In some of any examples, prior to administration of the dose of cells, identifying or selecting for the administration of the dose of cells a subject that has a relapsed/refractory NHL; that is or has been identified as being ineligible for both a high-dose chemotherapy and a hematopoietic stem cell transplantation (HSCT); and that 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.

[0074] In some of any examples, prior to administration of the dose of cells, identifying or selecting for the administration of the dose of cells a subject that is or has: age 70 years or older; and/or an ECOG performance status of 2; and/or an impaired pulmonary function, optionally with a diffusing capacity of the lungs for carbon monoxide (DLCO) of at or about 60% or less; and/or an impaired cardiac function, optionally with a left ventricular ejection fraction (LVEF) of less than at or about 50%; and/or an impaired renal function, optionally with a calculated creatinine clearance of less than at or about 60 mL/min; and/or an impaired hepatic function, optionally with an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than at or about twice the upper limit of normal (ULN).

[0075] In some of any examples, prior to administration of the dose of cells that is carried out via carried out via outpatient delivery, identifying or selecting for the administration of the dose of cells a subject that is or has: a relapsed or refractory large B cell lymphoma; and/or an anthracycline and one or more CD20-targeted agent; and/or relapsed or refractory disease after two or more lines of therapy or after autologous HSCT; and/or an ECOG performance status of 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.

[0076] In some of any examples, prior to the administration, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide. In some of any examples, the methods also involveimmediately prior to the administration of a dose of the cells, administering a lymphodepleting therapy to the subject comprising the administration of fludarabine and/or cyclophosphamide.

[0077] In some of any examples, the administration of the cell dose and/or the lymphodepleting therapy is carried out via outpatient delivery. In some of any examples, the administration of the cell dose and/or the lymphodepleting therapy is carried out in a non-tertiary care center. In some of any examples, after the administration of a dose of the cells, the subject is monitored in an outpatient setting, optionally via contacting by telephone and/or a visit by a healthcare professional.

[0078] In some of any of the provided examples, the methods further include administering to the subject an additional therapeutic agent or therapy. In some examples, the additional agent or therapy is a therapy other than a cell therapy, such as other than CAR^+ T cell therapy.

[0079] In some of any of the provided examples, the CAR comprises an extracellular antigen-binding domain specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which, in some cases, is a 4-1BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which, in some cases, is a CD3zeta; the CAR comprises, in order, an extracellular antigen-binding domain specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule; or the CAR comprises an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling domain comprising a CD3-zeta (CD3ζ) chain and a costimulatory signaling region that is a signaling domain of CD28 or 4-1BB.

[0080] In some of any of the provided examples, the antigen-binding domain is an scFv. In some of any such examples, 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 or binds to the same epitope as or competes for binding with any of the foregoing, and, in some cases, wherein the scFv comprises, in order, a V_H, a linker, which in some cases, comprising SEQ ID NO: 24, and a V_L, and/or the scFv comprises a flexible linker and/or comprises the amino acid sequence set forth as SEQ ID NO: 43.

[0081] In some of any of the provided examples, the costimulatory signaling region is a signaling domain of CD28 or 4-1BB. In some of any such examples, the costimulatory signaling region is a signaling domain of 4-1BB. In some of any such examples, 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.

[0082] In some of any of the provided examples, the primary signaling domain is a CD3zeta signaling domain. In some of any such examples, 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.

In some of any of the provided examples, the CAR further comprises a spacer between the transmembrane domain and the scFv. In some of any such examples, the spacer is a polypeptide spacer that comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof, in some cases, an IgG4 hinge, or a modified version thereof.

[0083] In some of any such examples, the spacer is about 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region. In some of any such examples, the spacer is at or about 12 amino acids in length. In some of any such examples, 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 X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

[0084] In some of any of the provided examples, the CAR contains an scFv specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which, in some cases, is or contains a 4-1BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which, in some cases, is or contains a CD3zeta signaling domain and, in some cases, further contains a spacer between the transmembrane domain and the scFv; the CAR contains, in order, an scFv specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which, in some cases, is or comprises a 4-1BB signaling domain, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which, in some cases, is a CD3zeta signaling domain; or the CAR contains, in order, an scFv specific for the antigen, a spacer, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which, in some cases, is a 4-1BB signaling domain, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which, in some cases, is or contains a CD3zeta signaling domain; and wherein: the spacer is a polypeptide spacer that (a) contains or consists of all or a portion of an immunoglobulin hinge or a modified version thereof or contains about 15 amino acids or less, and does not contain a CD28 extracellular region or a CD8 extracellular region, (b) contains or consists of all or a portion of an immunoglobulin hinge, which, in some cases, is an IgG4 hinge, or a modified version thereof and/or contains about 15 amino acids or less, and does not contain a CD28 extracellular region or a CD8 extracellular region, or (c) is at or about 12 amino acids in length and/or contains or consists of all or a portion of an immunoglobulin hinge, which, in some cases, is an IgG4, or a modified version thereof; or

(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) contains or consists of the formula X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine; and/or the costimulatory domain contains 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; and/or the primary signaling domain includes 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/or the scFv contains 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 or binds to the same epitope as or competes for binding with any of the foregoing, and in some cases wherein the scFv contains, in order, a V_H, a linker, which, in some cases, includes SEQ ID NO: 24, and a V_L, and/or the scFv contains a flexible linker and/or contains the amino acid sequence set forth as SEQ ID NO: 24.

[0085] In some of any of the provided examples, the antigen is a B cell antigen. In some of any such examples, the antigen is CD19. In some of any of the provided examples, prior to the administration, the subject has been preconditioned with a lymphodepleting therapy including the administration of fludarabine and/or cyclophosphamide. In some of any of the provided examples, immediately prior to the administration, administering a lymphodepleting therapy to the subject including the administration of fludarabine and/or cyclophosphamide. In some of any of the provided examples, the administration of the cell dose and/or the lymphodepleting therapy is carried out via outpatient delivery; 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 admitted to the hospital or to an overnight stay at a hospital and/or is 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.

[0086] In some of any of the provided examples, the dose of cells is administered parenterally. In some of any such examples, the dose of cells is administered intravenously. In some of any of the provided examples, the T cells are primary T cells obtained from a subject. In some of any of the

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.

[0087a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition comprising genetically engineered cells expressing a recombinant receptor; and optionally instructions for administering a dose of the cells in accord with the use or dose disclosed 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.

[0088a] In one aspect, the present disclosure refers to a method of assessing the risk of developing a toxicity after administration of a cell therapy, wherein: (a) one or more parameters is assessed 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 comprising a dose of genetically engineered cells expressing a recombinant receptor; and wherein the subject is assessed prior to administration of the cell therapy to the subject and/or said biological sample or tumor does not comprise the recombinant receptor and/or said engineered cells; and (b) the subject is identified 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 identified as not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein: (i) 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 (ii) 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.

[0090a] In one aspect, the present disclosure refers to the use of a cell therapy for the manufacture of a medicament for treatment of a disease or condition, wherein: (a) one or more parameters is assessed 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 a cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and wherein the subject is assessed prior to administration of cell therapy to the subject and/or said biological sample or tumor does not comprise the recombinant receptor and/or said engineered cells; and (b) the subject is identified 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 identified as not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein: (i) 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 (ii) 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, the subject is to be administered the cell therapy, and, optionally, 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.

[0093a] In one aspect, the present disclosure refers to a method of assessing the risk of developing a toxicity after administration of a cell therapy, wherein: (a) 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 comprising the genetically engineered cells is assessed; and (b) if the subject is identified as at risk of toxicity wherein the subject is at risk of toxicity if the peak concentration of genetically engineered cells is above a threshold level and the subject is identified as 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.

[0095a] In one aspect, the present disclosure refers to the use of a cell therapy for the manufacture of a medicament for treatment of a disease or condition, wherein: (a) 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 comprising the genetically engineered cells is assessed; and (b) the subject is identified as at risk of toxicity wherein the subject is at risk of toxicity if the peak concentration of genetically engineered cells is above a threshold level and the subject is identified as 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, the subject is to be administered the cell therapy, and, optionally, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity.

[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,

sarilumab, olokizumab (CDP6038), elsilimomab, ALD518/BMS-945429, sirukumab (CNTO 136), CPSI-2634, ARGX-109, FE301 and FM101. In some of any of the provided examples, the agent or other treatment is tocilizumab. In some of any of the provided examples, the agent or other treatment is or contains one or more steroids. In some of any of the provided examples, the steroid is dexamethasone or methylprednisolone. In some of any of the provided examples, the steroid is dexamethasone. In some of any of the provided examples, the agent or other treatment contains administration of a vasopressor. In some of any of the provided examples, the agent or other treatment includes intubation. In some of any of the provided examples, the agent or other treatment includes dialysis.

[0100] In some of any of the provided examples, the recombinant receptor specifically binds to an antigen (e.g., target antigen) associated with the disease or condition or expressed in cells of the environment of a lesion associated with the disease or condition. In some of any such examples, the antigen is a B cell antigen. In some of any such examples, the antigen is CD19. In some of any of the provided examples, the disease or condition is a cancer. In some of any of the provided examples, the disease or condition is a myeloma, a leukemia or a lymphoma. In some of any of the provided examples, the disease or condition is a B cell malignancy and/or is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphoblastic leukemia (CLL), non-Hodgkin lymphoma (NHL), or a large B cell lymphoma. In some of any such examples, the disease or condition is a large B cell lymphoma.In some of any of the provided examples, the disease or condition, such as the large B cell lymphoma, is a Diffuse Large B-Cell Lymphoma (DLBCL). In some of any of the provided examples, the DLBCL is a DLBCL, not otherwise specified (NOS), a de novo DLBCL or a DLBCL transformed from indolent lymphoma. In some of any of the provided examples, the DLBCL is a de novo DLBCL. In some of any of the provided examples, the DLBCL is a DLBCL transformed from follicular lymphoma (tFL). In some of any of the provided 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 of the provided examples, the disease or condition is primary mediastinal B-cell lymphoma (PMBCL) or a follicular lymphoma (FL), such as follicular lymphoma grade 3B (FL3B). In some of any examples, the disease or condition is follicular lymphoma (FL). In some of any examples, the disease or condition is follicular lymphoma (FL). In some of any examples, 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. In some of any examples, the disease or condition is mantle cell lymphoma (MCL).

[0101] In some of any of the provided examples, the recombinant receptor is a chimeric antigen receptor (CAR). In some of any of the provided examples, the engineered cells comprise T cells, such as $CD4^+$ T cells and/or $CD8^+$ T cells. In some of any of the provided examples, the cell therapy includes administering a dose of $CD4^+$ and $CD8^+$ T cells to a subject, 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.

[0102] In some of any of the provided examples, the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out no more than 48 hours apart. In some of any of the provided examples, 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.

[0103] In some of any of the provided examples, the receptor contained by the $CD4^+$ T cells and/or the receptor contained by the $CD8^+$ T cells includes 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 a recombinant receptor that is the same.

[0104] In some of any of the provided examples, the dose of $CD4^+$ and $CD8^+$ T cells contains a defined ratio of $CD4^+$ cells expressing a recombinant receptor to $CD8^+$ cells expressing a recombinant receptor and/or of $CD4^+$ cells to $CD8^+$ cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and/or the $CD4^+$ T cells containing the receptor in the one of the first and second compositions and the $CD8^+$ T cells containing the receptor in the other of the first and second compositions are present at a defined ratio that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and/or the $CD4^+$ T cells containing the receptor and the $CD8^+$ T cells containing the receptor administered in the first and second compositions are present at a defined ratio, which ratio is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any of the provided examples, the defined ratio is or is approximately 1:1.

[0105] 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 2×10^8 total recombinant receptor-expressing T cells, inclusive; between at or about 2.5×10^7 and at or about 1.5×10^8 total recombinant receptor-expressing T cells, inclusive; between at or about 5×10^7 and at or about 1×10^8 total recombinant receptor-expressing T cells, inclusive; at or about 5×10^7 total recombinant receptor-expressing T cells; at or about 1×10^8 total recombinant receptor-expressing T cells; or at or about 1.5×10^8 total recombinant receptor-expressing T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 5×10^7 total recombinant receptor-expressing T cells. In some of any such examples, the dose of $CD4^+$ and $CD8^+$ T cells comprises at or about 1×10^8 total recombinant receptor-expressing T cells. In

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

[0108a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition comprising genetically engineered cells expressing a recombinant receptor and optionally an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity; and instructions for assessing the risk of developing a toxicity, identifying a subject or treating a subject in accord with the use disclosed herein or method disclosed herein.

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:

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 dose of T cells is to be administered to the subject as 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.

2. 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 use in the treatment of a subject suspected or having a disease or condition that is a relapsed or refractory large B cell lymphoma (r/r LBCL), wherein:

the dose of T cells comprises between at or about 1 x 107 CAR-expressing T cells and at or about 2 x 108 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 dose of T cells is to be administered to the subject as 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.

3. The use of claim 1 or the dose of claim 2, wherein 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 lymphoma), 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).

4. The use or dose of 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 3 or the dose of claim 2 or claim 3, wherein the large B cell lymphoma is a high-grade B cell lymphoma (HGBCL), optionally wherein

(a) the HGBCL has MYC and BCL2 and/or BCL6 rearrangements; and/or

(b) the HGBCL has a DLBCL histology.

6. The use of claim 1 or claim 3 or the dose of claim 2 or claim 3, 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).

7. Use of a dose of T cells comprising T cells expressing a recombinant receptor that specifically binds to an antigen expressed by follicular lymphoma (FL) or a cell or tissue thereof and/or that is associated with FL for the manufacture of a medicament for treatment of a subject having a FL, wherein:

(a) the subject is selected for treatment as having a follicular lymphoma (FL); and

(b) the subject is to be administered the dose of T cells.

8. A dose of T cells comprising T cells expressing a recombinant receptor that specifically binds to an antigen expressed by follicular lymphoma (FL) or a cell or tissue thereof and/or that is associated with FL for use in the treatment of a subject that has a FL, wherein the subject is selected for treatment and is to be administered the dose of T cells.

9. The use of claim 7 or the dose of claim 8, wherein the dose of T cells comprises a dose of $CD4^+$ and $CD8^+$ T cells, wherein T cells of each dose comprises a recombinant receptor that specifically binds to an antigen expressed by FL or a cell or tissue thereof and/or that is associated with FL, wherein the dose of T cells is to be administered to the subject as 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.

10. The use of claim 7 or claim 9 or the dose of claim 8 or claim 9, wherein the recombinant receptor is a chimeric antigen receptor (CAR).

11. The use of any of claims 7, 9, and 10 or the dose of any of claims 8-10, wherein the antigen is CD19.

12. The use of any of claims 5-7 and 9-11 or the dose of any of claims 5-6 and 8-11, wherein:

(a) 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; and/or

(b) the FL is follicular lymphoma grade 3B (FL3B).

13. The use of any of claims 1, 3-7, and 9-12 or the dose of any of claims 2-6 and 8-12, 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 or dose of claim 13, wherein the prior therapy comprises an anthracycline and one or more CD20-targeted agent, optionally

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).

15. The use or dose of claim 13 or claim 14, 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.

16. The use or dose of any of claims 13-15, wherein the prior therapy comprises an allogeneic or an autologous hematopoietic stem cell transplantation (HSCT), optionally

wherein the subject has relapsed within 1 year or less than 1 year after receiving the HSCT.

17. The use or dose of any of claims 13-16, wherein the subject has not achieved complete remission (CR) in response to the prior therapy.

18. The use of any of claims 1, 3-7, and 9-17 or the dose of any of claims 2-6 and 8-17, 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, optionally a chemorefractory DLBCL; 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 treated according to the use or dose who, at or prior to the administration of 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.

19. The use of any of claims 1, 3-7, and 9-18 or the dose of any of claims 2-6 and 8-18, wherein:

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

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

20. The use of any of claims 1, 3-7, and 9-19 or the dose of any of claims 2-6 and 8-19, 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, optionally with a left ventricular ejection fraction (LVEF) of less than at or about 50%;

(b) the subject is or has been identified as having an impaired renal function, optionally with a calculated creatinine clearance of less than at or about 60 mL/min;

(c) the subject is or has been identified as having an impaired pulmonary function, optionally with a diffusing capacity of the lungs for carbon monoxide (DLCO) of at or about 60% or less;

(d) the subject is or has been identified as having an impaired hepatic function, optionally with an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than at or about twice the upper limit of normal (ULN);

(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;

(g) the subject is or has been identified as being ineligible for a high-dose chemotherapy;

(h) the subject is or has been identified as being ineligible for a hematopoietic stem cell transplantation (HSCT); and/or

(i) 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,

optionally

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.

21. The use of any of claims 1, 3-7, and 9-20 or the dose of any of claims 2-6 and 8-20, wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2, optionally an ECOG PS of 0 or 1.

22. The use of any of claims 1, 3-7, and 9-21 or the dose of any of claims 2-6 and 8-21, 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 at or about 50 cm^2 or greater; or

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

23. The use of any of claims 1, 3-7, and 9-22 or the dose of any of claims 2-6 and 8-22, 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:

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

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

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

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.

24. The use of any of claims 1, 3-7, and 9-22 or the dose of any of claims 2-6 and 8-22, 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, optionally with a diffusing capacity of the lungs for carbon monoxide (DLCO) of at or about 60% or less; and/or

an impaired cardiac function, optionally with a left ventricular ejection fraction (LVEF) of less than at or about 50%; and/or

an impaired renal function, optionally with a calculated creatinine clearance of less than at or about 60 mL/min; and/or

an impaired hepatic function, optionally with an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than at or about twice the upper limit of normal (ULN).

25. The use of any of claims 1, 3-7, and 9-22 or the dose of any of claims 2-6 and 8-22, 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, optionally the NHL;

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.

26. The use of any one of claims 1, 3-7, and 9-25 or the dose of any of claims 2-6 and 8-25, 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, optionally wherein greater than at or about 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.

27. The use of any of claims 1, 3-7, and 10-26 or the dose of any of claims 2-6, 8, and 10-26, wherein the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition, optionally

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.

28. The use of any of claims 1, 3-7, and 9-27 or the dose of any of claims 2-6 and 8-27, 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.

29. The use of any of claims 1, 3-7, and 9-28 or the dose of any of claims 2-6 and 8-28, wherein the dose of $CD4^+$ and $CD8^+$ T cells comprises:

(a) between at or about 2.5×10^7 and at or about 1.5×10^8 total recombinant receptor-expressing T cells, inclusive;

between at or about 5×10^7 and at or about 1×10^8 total recombinant receptor-expressing T cells, inclusive;

at or about 5×10^7 total recombinant receptor-expressing T cells;

at or about 1×10^8 total recombinant receptor-expressing T cells; or

at or about 1.5×10^8 total recombinant receptor-expressing T cells; or

(b) 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.

30. The use of any of claims 1, 3-7, and 9-29 or the dose of any of claims 2-6 and 8-29, wherein, prior to the administration, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

31. The use or dose of claim 30, wherein the administration of the dose of cells and/or the lymphodepleting therapy is carried out via outpatient delivery.

32. The use of any of claims 1, 3-7, and 9-31 or the dose of any of claims 2-6 and 8-31, wherein:

the administration and any follow up is 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 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.

33. The use of any of claims 1, 3-7, and 9-32 or the dose of any of claims 2-6 and 8-32, 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.

34. The use of any of claims 1, 3-7, and 9-33 or the dose of any of claims 2-6 and 8-33, 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, optionally

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.

35. The use of any of claims 1, 3-7, and 9-34 or the dose of any of claims 2-6 and 8-34, 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 carried out via outpatient delivery.

36. The use of any of claims 1, 3-7, and 9-35 or the dose of any of claims 2-6 and 8-35, 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 treated according to the use or 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 treated according to the use or 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.

37. The use or dose of claim 36, 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 treated according to the use or 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 treated with the use or 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 treated with the use or 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 treated according to the use or 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 treated with the use or dose and achieving an OR remain in response or survive for at or greater than 3 months and/or at or greater than 6 months.

38. The use of any of claims 1, 3-7, and 37 or the dose of any of claims 2-6 and 8-37, wherein:

at least 35%, at least 40% or at least 50% of subjects treated according to the use or 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 treated according to the use or 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 or greater than about 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 treated according to the use or dose.

39. The use of any of claim 1, 3-7, and 9-38 or the dose of any of claims 2-6 and 8-38, wherein

greater than or greater than about 50%, about 60%, about 70%, or about 80% of the subjects treated according to the use or 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, optionally wherein:

greater than or greater than about 30%, 35%, 40%, or 50% of the subjects treated according to

the use or dose do not exhibit any grade of cytokine release syndrome (CRS) or neurotoxicity; and/or

at least at or about 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of subjects treated according to the use or 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 treated according to the use or dose is at or after the median peak of, or median time to resolution of, CRS in subjects treated according to the use or dose and/or the median onset of neurotoxicity among subjects treated according to the use or dose is greater than at or about 8, 9, 10, or 11 days.

40. The use of any of claims 1, 3-7, and 9-39 or the dose of any of claims 2-6 and 8-39, wherein:

at least 50% of subjects treated according to the use or dose achieve a complete response (CR);

at least 70% of the subjects treated according to the use or dose achieve objective response (OR);

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

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

41. The use of any of claims 1, 3-7, and 9-40 or the dose of any of claims 2-6 and 8-40, 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, optionally wherein the antigen-binding domain is an scFv, further optionally 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 or binds to the same epitope as or competes for binding with any of the foregoing, and optionally wherein the scFv comprises, in order, a V_H, a linker, optionally comprising SEQ ID NO: 24, and a V_L, and/or the scFv comprises a flexible linker and/or comprises the amino acid sequence set forth as SEQ ID NO: 43; and/or

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

42. The use or dose of claim 41, wherein the CAR further comprises a spacer between the transmembrane domain and the scFv, optionally 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, optionally an IgG4 hinge, or a modified version thereof;

(b) the spacer is at or about 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 X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

43. The use or dose of claim 42, 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 about 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, optionally an IgG4 hinge, or a modified version thereof and/or comprises about 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region, (c) is at or about 12 amino acids in length and/or comprises or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4, or a modified version thereof; (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, optionally wherein the scFv comprises, in order, a V_H, a linker, and a V_L, and/or the scFv comprises the amino acid sequence set forth as SEQ ID NO: 43.

44. The use or dose of claim 42, 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.

45. An article of manufacture comprising a composition comprising genetically engineered cells expressing a recombinant receptor; and optionally instructions for administering a dose of the cells in accord with the use or dose of any of claims 1-44.

46. A method of assessing the risk of developing a toxicity after administration of a cell therapy, wherein:

(a) one or more parameters is assessed 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 comprising a dose of genetically engineered cells expressing a recombinant receptor; and

wherein the subject is assessed prior to administration of the cell therapy to the subject and/or said biological sample or tumor does not comprise the recombinant receptor and/or said engineered cells; and

(b) the subject is identified 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 identified as not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein:

(i) 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

(ii) 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.

47. Use of a cell therapy for the manufacture of a medicament for treatment of a disease or condition, wherein:

(a) one or more parameters is assessed 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 a cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and

wherein the subject is assessed prior to administration of cell therapy to the subject and/or said biological sample or tumor does not comprise the recombinant receptor and/or said engineered cells; and

(b) the subject is identified 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 identified as not at risk of toxicity if the one or more parameters is at or below a threshold level, wherein:

(i) 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

(ii) 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, the subject is to be administered the cell therapy, and, optionally, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity.

48. A method of assessing the risk of developing a toxicity after administration of a cell therapy, wherein:

(a) 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 comprising the genetically engineered cells is assessed; and

(b) if the subject is identified as at risk of toxicity wherein the subject is at risk of toxicity if the peak concentration of genetically engineered cells is above a threshold level and the subject is identified as 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.

49. Use of a cell therapy for the manufacture of a medicament for treatment of a disease or condition, wherein:

(a) 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 comprising the genetically engineered cells is assessed; and

(b) the subject is identified as at risk of toxicity wherein the subject is at risk of toxicity if the peak concentration of genetically engineered cells is above a threshold level and the subject is identified as 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, the subject is to be administered the cell therapy, and, optionally, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity.

50. The use of claim 47 or claim 49 or the method of claim 46 or claim 48, wherein the subject is monitored for symptoms of toxicity if the subject is administered a cell therapy and is identified as having a risk of developing a toxicity; and/or

the toxicity is neurotoxicity or cytokine release syndrome (CRS), optionally

wherein 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 or

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.

51. The use of claim 47 or claim 49 or the method of claim 46 or claim 48, wherein if the subject is identified as having a risk of developing a toxicity, the subject is to be administered:

(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 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) a cell therapy in an inpatient setting and/or with admission to the hospital for one or more days, optionally wherein 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,

optionally wherein the agent or other treatment is an anti-IL-6 antibody or an anti-IL-6 receptor antibody and/or

wherein the agent or other treatment is or comprises one or more steroids.

52. An article of manufacture comprising a composition comprising genetically engineered cells expressing a recombinant receptor and optionally an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity; and instructions for assessing the risk of developing a toxicity, identifying a subject or treating a subject in accord with the use of any of claims 47 and 49-51 or method of any of claims 46, 48, and 50-51.