Field

[0003] The present disclosure relates in some aspects to adoptive cell therapy involving the administration of doses of cells for treating subjects with disease and conditions such as certain B cell malignancies, and related methods, compositions, uses and articles of manufacture. The cells generally express recombinant receptors such as chimeric antigen receptors (CARs). In some embodiments, the disease or condition is a non-Hodgkin lymphoma (NHL), such as relapsed or refractory NHL or specific NHL subtype; in some embodiments, the subject is of a specific group or subset of NHL subjects, such as heavily pretreated or poor-prognosis subjects.

Background

[0004] Various immunotherapy and/or cell therapy methods are available for treating diseases and conditions. For example, adoptive cell therapies (including those involving the administration of cells expressing chimeric receptors specific for a disease or disorder of interest, such as chimeric antigen receptors (CARs) and/or other recombinant antigen receptors, as well as other adoptive immune cell and adoptive T cell therapies) can be beneficial in the treatment of cancer or other diseases or disorders. Improved approaches are needed. Provided are methods and uses that meet such needs.

Summary

[0005] Provided herein are methods, uses, compositions, formulations and articles of manufacture for treating subjects having or suspected of having a disease or condition, such as a cancer or tumor, optionally a B cell malignancy such as NHL or ALL or CLL or a subtype thereof. The methods and other examples generally relate to administering to the subject T cells, generally engineered T cells, such as those expressing or containing a recombinant receptor such as a chimeric antigen receptor (CAR) or TCR.

[0005a] In one aspect, the present disclosure refers to use of a first composition comprising CD4+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy with a dose of $CD4^+$ T cells and $CD8^+$ T cells, wherein: the medicament is to be administered with a second composition comprising CD8+ T cells; each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same the dose of the CD4+ T cells

and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD4^+$ T cells and the second composition comprising the $CD8^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1 x 10^7 and 2 x 10^8 total CAR-expressing T cells, inclusive; and (ii) a defined ratio of CAR-expressing CD4+ cells to CAR-expressing CD8+ cells that is between 1:3 and 3:1.

[0005b] In another aspect, the present disclosure refers to use of a first composition comprising CD8+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy with a dose of $CD4^+$ T cells and $CD8^+$ T cells, wherein: the medicament is to be administered with a second composition comprising CD4+ T cells; each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same; the dose of the CD4+ T cells and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD8^+$ T cells and the second composition comprising the $CD4^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1 x 10^7 and 2 x 10^8 total CAR-expressing T cells, inclusive; and (ii) a defined ratio of CAR-expressing CD4+ cells to CAR-expressing CD8+ cells that is between 1:3 and 3:1.

[0006] In some examples, the dose of cells or cells administered in connection with any examples of the provided methods, compositions, articles of manufacture and uses, contains $CD4^+$ T cells or a subtype or phenotype thereof (such as engineered or recombinant receptor-expressing $CD4^+$ T cells) and/or $CD8^+$ T cells or a subtype thereof (such as an engineered or recombinant receptor-expressing $CD4^+$ cells). In some examples, the $CD8^+$ cells or subtype or phenotype are present at a particular dose or amount or number; in some examples the $CD4^+$ cells or subtype or phenotype are present at a particular dose or amount or number. In

[0021a] In another example, the present disclosure refers to an article of manufacture comprising (1) a vial comprising a composition comprising a plurality of $CD4^+$ T cells expressing a recombinant receptor, and (2) instructions for administering to a subject having a disease or condition: a unit dose of cells of the composition, the unit dose comprising all or a portion of the plurality of $CD4^+$ T cells, and a unit dose of a composition comprising $CD8^+$ T cells expressing a recombinant receptor, wherein the vial does not comprise the unit dose of the composition comprising CD8+ T cells expressing the recombinant receptor.

[0021b] In another example, the present disclosure refers to an article of manufacture comprising (1) a vial comprising a composition comprising a plurality of $CD8^+$ T cells expressing a recombinant receptor, and (2) instructions for administering to a subject having a disease or condition: a unit dose of cells of the composition, the unit dose comprising all or a portion of the plurality of $CD8^+$ T cells, and a unit dose of a composition comprising $CD4^+$ T cells expressing a recombinant receptor, wherein the vial does not comprise the unit dose of the composition comprising CD4+ T cells expressing the recombinant receptor.

[0022] In some of any of the examples, the CAR comprises, in order, the CAR includes an scFv specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is or comprises a 4-1BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is or comprises a CD3zeta signaling domain and optionally further includes a spacer between the transmembrane domain and the scFv;

[0023] In some of any of the examples, the CAR includes, in order, an scFv specific for the antigen, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is or comprises a 4-1BB signaling domain, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is a CD3zeta signaling domain.

[0024] In some of any of the examples, the CAR comprises or consists of, in order, an scFv specific for the antigen, a spacer, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is a 4-1BB signaling domain, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is or comprises a CD3zeta signaling domain.

[0025] In some examples, 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

$CD8^+$ T cells and/or $CD4^+$ T cells, expressing a chimeric antigen receptor (CAR) that specifically binds to a target antigen expressed by the NHL.

[0047] In some examples, the dose of T cells comprises between at or about 5 x 10^7 CAR-expressing T cells and 1 x 10^8 CAR-expressing T cells, inclusive; and the NHL comprises diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B and wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0 or 1.

[0047a] In another example, the present disclosure refers to use of a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for treatment of a non-Hodgkin lymphoma (NHL) in a subject, wherein: the CAR specifically binds to a target antigen expressed by the NHL; the dose of T cells comprises between at or about 2.5 x 10^7 CAR-expressing T cells and 2 x 10^8 CAR-expressing T cells, inclusive; and the NHL comprises diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma) or follicular lymphoma Grade 3B, and wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0 or 1.

[0048] In some examples of any of the provided examples, the methods further comprise identifying, or the article of manufacture includes information specifying, treatment of a subject having diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B having an ECOG status of 0 or 1. In some examples of any of the provided examples, the dose of T cells and/or the cells administered 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 optionally is approximately 1:1 or is between approximately 1:3 and approximately 3:1.

[0049] In some examples, the examples are for treating a subject having non-Hodgkin lymphoma (NHL) and involve administering to the subject a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) that specifically binds to a target antigen expressed by the NHL. In some examples, the dose of T cells includes 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 in some examples is approximately or is 1:1. In some examples, the NHL comprises diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (not otherwise specificed) (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B.

[0049a] In another example, the present disclosure refers to use of a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for treatment of a non-Hodgkin lymphoma (NHL) in a subject, wherein: the CAR specifically binds to a target antigen expressed by the NHL; 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 or is 1:1; and the NHL comprises diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma) or follicular lymphoma Grade 3B.

[0050] In particular examples of any of the provided examples, the subject is or has been identified as or is specified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0, 1 or 2. In certain examples of any of the provided examples, the subject is or has been identified as or is specified as having an ECOG status of 0 or 1.

[0051] In some examples of any of the provided examples, the methods and/or uses and/or administration of cells according to the articles of manufacture, achieve certain outcomes and/or are associated with certain reduced risks of toxicity, e.g., in the population of subjects treated according to the methods or according to information provided in the article of manufacture. In some examples,: at least 35%, at least 40% or at least 50% of subjects treated according to the method achieve a complete response (CR) and/or a durable 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) and/or a durable OR. In particular examples of any of the provided methods, the response is durable for greater than 3 months or greater than 6 months. In some 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, optionally relapse within 12 months, following administration of an autologous stem cell transplant (ASCT), achieved an OR, optionally wherein the OR is durable for at or greater than 3 months or at or greater than 6 months. In certain examples of any of the provided methods, greater than or greater than about 50% of the subjects treated according to the method do not exhibit a grade 3 or greater cytokine release syndrome (CRS) or a grade 3 or greater neurotoxicity. In some examples, such subjects do not exhibit early onset CRS and/or neurotoxicity.

[0052] Provided herein are methods of assessing likelihood of a response to a cell therapy, the methods involving: assessing the level, amount or concentration of one or more analyte in a biological sample, wherein the one or more analyte is selected from ferritin, LDH, CXCL10, G-CSF, and IL-10, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and comparing, individually, the level, amount or concentration of the analyte in the sample to a threshold level, thereby determining a likelihood that a subject will achieve a response to the cell therapy. In some examples, the methods also involve administering the cell therapy to the subject if the subject is likely to achieve a response.

[0052a] In another example, the present disclosure refers to a method of assessing likelihood of a response to a cell therapy, the method comprising: (a) assessing the level, amount or concentration of one or more analyte in a biological sample, wherein the one or more analyte is selected from ferritin, LDH, CXCL10, G-CSF, and IL-10, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and (b) comparing, individually, the level, amount or concentration of the analyte in the sample to a threshold level, thereby determining a likelihood that a subject will achieve a response to the cell therapy.

[0053] Provided herein are methods of selecting a subject for treatment, the methods involving: assessing the level, amount or concentration of one or more analyte in a biological

[0057] In some examples, the threshold level is within 25%, within 20%, within 15%, within 10% or within 5% and/or is within a standard deviation above the median or mean level, amount or concentration of the analyte in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group went on to exhibit stable disease (SD) and/or progressive disease (PD) after administration of a recombinant-receptor-expressing therapeutic cell composition for treating the same disease or condition.

[0058] In some examples, the response comprises objective response. In some examples, the objective response comprises complete response (CR) or partial response (PR).

[0059] Provided herein are methods of assessing likelihood of a durable response to a cell therapy, the methods involving: assessing the level, amount or concentration of one or more analyte in a biological sample, wherein the one or more analyte is selected from LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and comparing, individually, the level, amount or concentration of the analyte in the sample to a threshold level, thereby determining a likelihood that a subject will achieve a durable response to the cell therapy.

[0059a] In another example, the present disclosure refers to a method of assessing likelihood of a durable response to a cell therapy, the method comprising: (a) assessing the level, amount or concentration of one or more analyte in a biological sample, wherein the one or more analyte is selected from LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and (b) comparing, individually, the level, amount or concentration of the analyte in the sample to a

response to the cell therapy by comparing, individually, the level, amount or concentration of the analyte in the sample to a threshold level. In some examples, the methods also involve administering the cell therapy to the subject selected for treatment.

[0061a] In another example, the present disclosure refers to a method of selecting a subject for treatment, the method comprising: (a) assessing the level, amount or concentration of one or more analyte in a biological sample, wherein the one or more analyte is selected from LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and (b) selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a durable response to the cell therapy by comparing, individually, the level, amount or concentration of the analyte in the sample to a threshold level.

[0062] Provided herein are methods of treatment, the methods involving: selecting a subject who is likely to respond to treatment with a cell therapy based on the results of determining a likelihood that a subject will achieve a durable response to the cell therapy by comparing, individually, the level, amount or concentration of one or more analyte in a biological sample to a threshold level, wherein the one or more analyte is selected from LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β, wherein: the biological sample is from a subject that is a candidate for treatment with the cell therapy, said cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and administering the cell therapy to a subject selected for treatment.

[0063] In some examples, the subject is likely to achieve a durable response if the level, amount or concentration one or more of the analyte is below a threshold level and the subject is not likely to achieve a durable response if the level, amount or concentration one or more of the analyte is above a threshold level.

[0064] In some examples, the threshold level is within 25%, within 20%, within 15%, within 10% or within 5% and/or is within a standard deviation below the median or mean level, amount or concentration, or is or is about the median or mean level, amount or concentration, of the analyte in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group went on to achieve a durable response after administration of a recombinant-receptor-expressing therapeutic cell composition for treating the same disease or condition.

[0065] In some examples, the threshold level is within 25%, within 20%, within 15%, within 11% or within 5% and/or is within a standard deviation above the median or mean level, amount or concentration of the analyte in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group did not achieve a durable response after administration of a recombinant-receptor-expressing therapeutic cell composition for treating the same disease or condition.

[0066] In some examples, the durable response comprises a complete response (CR) or partial response (PR) that is durable for at or greater than 3 months, 4 months, 5 months, or 6 months.

[0067] In some examples, the durable response comprises a CR or PR that is durable for at least 3 months.

[0068] Provided herein are methods of assessing the risk of developing a toxicity after administration of a cell therapy, the methods involving assessing the level, amount or concentration of one or more analyte in a biological sample from a subject or a volumetric measure of tumor burden in a subject, wherein the one or more analyte is selected from LDH, Ferritin, C-reactive protein (CRP), D-dimer (fibrin degradation product), IL-6, IL-8, IL-10, IL-15, IL-16 TNF-α, IFN-α2, MCP-1, MIP-1α and MIP-1β, wherein: the subject is a candidate for treatment with the cell therapy, said cell therapy optionally comprising a dose or composition of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and comparing, individually, the level, amount or concentration of the analyte in the sample or the volumetric measure of tumor burden to a threshold level, thereby determining a risk of developing a toxicity after administration of the cell therapy.

[0068a] In another example, the present disclosure refers to amethod of assessing the risk of developing a toxicity after administration of a cell therapy, the method comprising: (a) assessing the level, amount or concentration of one or more analyte in a biological sample from a subject or a volumetric measure of tumor burden in a subject, wherein the one or more analyte is selected from LDH, Ferritin, C-reactive protein (CRP), D-dimer (fibrin degradation product), IL-6, IL-8, IL-10, IL-15, IL-16 TNF-α, IFN-α2, MCP-1, MIP-1α and MIP-1β, wherein: the subject is a candidate for treatment with the cell therapy, said cell therapy optionally comprising a dose or composition of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and (b) comparing, individually, the level, amount or concentration of the analyte in the sample or the volumetric measure of tumor burden to a threshold level, thereby determining a risk of developing a toxicity after administration of the cell therapy.

[0069] Provided herein are methods of identifying a subject, the methods involving assessing the level, amount or concentration of one or more analyte in a biological sample from a subject or a volumetric measure of tumor burden in a subject, wherein the one or more analyte is selected from LDH, Ferritin, C-reactive protein (CRP), D-dimer (fibrin degradation product), IL-6, IL-8, IL-10, IL-15, IL-16 TNF-α, IFN-α2, MCP-1, MIP-1α and MIP-1β, wherein: the subject is a candidate for treatment with the cell therapy, said cell therapy optionally comprising a dose or composition of genetically engineered cells expressing a recombinant receptor; and the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the recombinant receptor and/or said engineered cells; and identifying a subject who has a risk of developing a toxicity after administration of a cell therapy based by comparing, individually, the level, amount or concentration of the analyte in the sample or the volumetric measure of tumor burden to a threshold level.

[0070] Provided herein are methods of treatment, comprising assessing the level, amount or concentration of one or more analyte in a biological sample from a subject or a volumetric

at or greater than 9 months; and/or wherein at least 60%, 70%, 80%, 90%, or 95% of subjects treated with the method who achieve a CR by one month and/or by three 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 nine 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) optionally wherein the OR is durable, or is durable in 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 wherein at least 60%, 70%, 80%, 90%, or 95% of subjects treated with the method and achieving an OR remain in response or surviving for greater at or greater than 3 months and/or at or greater than 6 months.

[0098] In some 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.

[0099] Provided herein are methods of treating a subject, the method involving administering, to a subject that has a lymphoma a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) that specifically binds to a target antigen expressed by the lymphoma, wherein the lymphoma in the subject is associated with or involves central nervous system (CNS) involvement. In some examples, at or prior to the time of administration of the dose of cells, the subject comprises a brain lesion, optionally a temporal lobe brain lesion. In some examples, the lymphoma is a B cell malignancy. In some examples, the lymphoma is non-Hodgkin lymphoma (NHL).

[0099a] In another example, the present disclosure refers to use of a dose of T cells comprising T cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for treatment of a lymphoma in a subject, wherein the CAR- specifically binds to a target antigen expressed by the lymphoma and the lymphoma in the subject is associated with or involves central nervous system (CNS) involvement.

[0100] In some of any such 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 and/or achieve reduction in or clearance of CNS disease, optionally wherein the CR or remission or reduction or clearance of the CNS disease is durable, or is durable in at least 60%, 70%, 80%, 90%, or 95% of subjects achieving the 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 or other reduction of CNS disease by one month and/or by three months remain in response, remain in remission, e.g., in CR, or remain showing signs of the reduction or

first dose of the T cells and a consecutive dose of the T cells, wherein one or both of the first dose and the second dose comprises administration of the plurality of compositions of T cells. In certain examples of any of the provided methods, the consecutive dose is administered at a point in time that is at least or more than about 7 days or 14 days after and less than about 28 days after initiation of the administration of the first dose of cells.

[0118] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of cells is to be administered to a subject having or identified to have non-Hodgkin lymphoma (NHL), the NHL selected from diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B, wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0 or 1; and the dose of T cells to be administered comprises between at or about 5 x 10^7 CAR-expressing T cells and 1 x 10^8 CAR-expressing T cells, inclusive. In some examples of any of the provided articles of manufacture, the instructions specify administering the dose of T cells at 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 optionally is approximately 1:1 or is between approximately 1:3 and approximately 3:1.

[0118a] In another aspect, the present disclosure refers to an article of manufacture comprising one or more dose of a cell therapy, each dose comprising a first composition comprising one of CD4+ T cells or CD8+ T cells and a second composition comprising the other of the CD4+ or CD8+ T cells, wherein the dose comprises CD4+ T cells and CD8+ T cells expressing the same CAR that specifically binds to CD19, and instructions for administering the cell therapy, wherein the instructions specify:

(i) the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and
(ii) the dose of cells is to be administered to a subject having or identified to have a non-Hodgkin lymphoma (NHL); the dose of cells to be administered comprises between 1 x 10^7 CAR-expressing T cells and 2 x 10^8 CAR-expressing T cells, inclusive; and the dose of cells is to be administered at 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 optionally is 1:1 or is between 1:3 and 3:1.

[0119] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of T cells is to be administered at 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; and the dose of cells is to be administered to a subject having or identified to have non-Hodgkin lymphoma (NHL), the NHL selected from diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B.

[0120] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of cells is to be administered to a subject having or identified to have non-Hodgkin

[0126] In some examples of any of the provided articles of manufacture, the instructions specify the first composition and second composition are to be administered at 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 optionally is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In certain examples of any of the provided articles of manufacture, the defined ratio is or is approximately 1:1. In particular examples of any of the provided articles of manufacture, the composition further comprises a cryoprotectant and/or the article further includes instructions for thawing the composition prior to administration to the subject.

[0127] In some examples of any of the provided articles of manufacture, the instructions specify administering the composition comprising the $CD4^+$ T cells and the composition comprising the $CD8^+$ T cells 0 to 12 hours apart, 0 to 6 hours apart or 0 to 2 hours apart. In certain examples of any of the provided articles of manufacture, the instructions specify administering the composition comprising the $CD4^+$ T cells and the composition comprising the $CD8^+$ T cells 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. In particular examples of any of the provided articles of manufacture, the instructions specify administering the composition comprising the $CD4^+$ T cells prior to administering the composition comprising the $CD8^+$ cells. In some examples of any of the provided articles of manufacture, the instructions specify administering the composition comprising the $CD8^+$ T cells prior to administering the composition comprising the $CD4^+$ cells.

[0128] Provided herein are articles of manufacture comprising one or more reagent capable of detecting one or more analytes, and instructions for using the reagent to assay a biological sample from a subject that is a candidate for treatment, optionally with a cell therapy, said cell therapy optionally comprising a dose or composition of genetically engineered cells expressing a recombinant receptor, wherein the one or more analytes is selected from LDH, ferritin, CRP, IL-6, IL-7, IL-8, IL-10, IL-15, IL-16, TNF-alpha, IFN-gamma, MCP-1, MIP-1beta, eotaxin, G-CSF, IL-1Ralpha, IL-1Rbeta, IP-10, perforin, and D-dimer (fibrin degradation product).

[0128a] In another example, the present disclosure refers to an article of manufacture comprising one or more reagent capable of detecting one or more analytes, and instructions for using the reagent to assay a biological sample from a subject that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose or composition of genetically engineered

cells expressing a recombinant receptor, wherein the one or more analytes is selected from: (i) ferritin, LDH, CXCL10, G-CSF and IL-10; (ii) LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β; or (iii) LDH, Ferritin, C-reactive protein (CRP), D-dimer (fibrin degradation product), IL-6, IL-8, IL-10, IL-15, IL-16 TNF-α, IFN-α2, MCP-1, MIP-1α and MIP-1β.

[0128b] In another example, the present disclosure refers to an article of manufacture comprising: a cell therapy comprising a dose of genetically engineered cells expressing a recombinant receptor, and instructions for administering the cell therapy following or based on the results of an assessment, in a biological sample of the level, or amount or concentration of one or more analyte in the biological sample, the biological sample obtained from the subject prior to administration of the cell therapy and/or the biological sample not comprising the recombinant receptor and/or the engineered cells, wherein the one or more analytes is selected from: (i) ferritin, LDH, CXCL10, G-CSF and IL-10; (ii) LDH, ferritin, CRP, D-dimer, SAA-1, IL-6, IL-10, IL-15, IL-16, TNF-α, IFN-γ, MIP-1α, CXCL-10, IL-8, MCP-1 and MIP-1β; or (iii) LDH, Ferritin, C-reactive protein (CRP), D-dimer (fibrin degradation product), IL-6, IL-8, IL-10, IL-15, IL-16 TNF-α, IFN-α2, MCP-1, MIP-1α and MIP-1β.

[0129] Particular examples of any of the provided articles of manufacture further comprise the cell therapy and/or further comprising instructions for use with, prior to and/or in connection with treatment with the cell therapy. Certain examples of any of the provided articles of manufacture further comprise one or more agents or treatments for treating,

CLAIMS

1. Use of a first composition comprising CD4+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy with a dose of $CD4^+$ T cells and $CD8^+$ T cells, wherein:

the medicament is to be administered with a second composition comprising CD8+ T cells;

each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same;the dose of the CD4+ T cells and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD4^+$ T cells and the second composition comprising the $CD8^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and

the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1×10^7 and 2×10^8 total CAR-expressing T cells, inclusive; and (ii) a defined ratio of CAR-expressing CD4+ cells to CAR-expressing CD8+ cells that is between 1:3 and 3:1.

2. Use of a first composition comprising CD8+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy with a dose of $CD4^+$ T cells and $CD8^+$ T cells, wherein:

the medicament is to be administered with a second composition comprising CD4+ T cells;

each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same;

the dose of the CD4+ T cells and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD8^+$ T cells and the second composition comprising the $CD4^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and

the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1 x 10^7 and 2 x 10^8 total CAR-expressing T cells, inclusive; and (ii) a defined ratio of CAR-expressing CD4+ cells to CAR-expressing CD8+ cells that is between 1:3 and 3:1.

3. The use of claim 1 or claim 2, wherein

the first composition and the second composition are to be administered between 1 minute and 1 hour apart or between 5 minutes and 30 minutes apart.

4. The use of any of claims 1-3, wherein the first composition and the second composition are to be 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.

5. The use of any of claims 1-4, wherein the composition comprising the CD8+ T cells is to be administered prior to the composition comprising the CD4+ T cells.

6. The use of any of claims 1-5, wherein the defined ratio is 1:1.

7. The use of any of claims 1-6, wherein the T cells are autologous to the subject.

8. The use of any of claims 1-7, wherein the subject is or has been identified as having an ECOG status of 0 or 1.

9. The use of any of claims 1-8, wherein

the dose of T cells comprises between 5 x 10^7 CAR-expressing T cells and 1.5 x 10^8 CAR-expressing T cells, inclusive.

10. The use of any of claims 1-9, wherein the B cell malignancy is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), or Diffuse Large B-Cell Lymphoma (DLBCL).

11. The use of claim 10, wherein the B cell malignancy is a non-Hodgkin lymphoma (NHL).

12. The use of any of claims 1-11, wherein prior to initiation of administration of the dose of T 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 T cells.

13. The use of any of claims 1-12, wherein:

administration of the dose of T cells 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 by more than 1ºC after treatment with an antipyretic, the subject is to be admitted to a hospital or to an overnight stay at a hospital and/or is to be administered an agent or treatment for the treatment, prevention, reduction or attenuation of a neurotoxicity and/or a cytokine release syndrome or risk thereof.

14. The use of any of claims 11-13, wherein the NHL is selected from the group consisting of aggressive NHL, diffuse large B cell lymphoma (DLBCL), NOS (de novo and transformed from indolent), primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), and/or follicular lymphoma Grade 3B (FL3B).

15. The use of any of claims 11-14, wherein, at or immediately prior to 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 NHL.

16. The use of any of claims 1-15, wherein, at or prior to administration of the dose of T 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, or 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).

17. The use of any of claims 1-16, wherein:

the CAR comprises an scFv specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, a cytoplasmic signaling domain that comprises a CD3zeta signaling domain and a spacer between the transmembrane domain and the scFv.

18. The use of claim 17, wherein the costimulatory molecule is or comprises a 4-1BB.

19. The use of claim 17 or claim 18, wherein the spacer consists of all or a portion of an immunoglobulin hinge and is 15 amino acids or fewer in length.

20. The use of any of claims 17-19, wherein the spacer consists of 12 amino acids in length.

21. The use of any of claims 17-20, wherein the spacer consists of the sequence set forth in SEQ ID NO:1.

22. The use of any of claims 1-21, wherein the CAR comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO:35), a CDRL2 sequence of SRLHSGV (SEQ ID NO:36), a CDRL3 sequence of GNTLPYTFG (SEQ ID NO:37); a CDRH1 sequence of DYGVS (SEQ ID NO:38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO:39), and a CDRH3 sequence of YAMDYWG (SEQ ID NO:40).

23. The use of any of claims 1-22, wherein the CAR comprises the V_H sequence set forth in SEQ ID NO:41 and the V_L sequence set forth in SEQ ID NO:42.

24. The use of any of claims 1-23, wherein the CAR comprises the sequence set forth in SEQ ID NO:43.

25. The use of any of claims 1-24, wherein, prior to administration of the dose of T cells, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

26. The use of any of claims 1-25, wherein the dose of T cells comprises 1 x 10^8 CAR-expressing cells.

27. An article of manufacture comprising one or more dose of a cell therapy, each dose comprising a first composition comprising one of CD4+ T cells or CD8+ T cells and a second composition comprising the other of the CD4+ or CD8+ T cells, wherein the dose comprises CD4+ T cells and CD8+ T cells expressing the same CAR that specifically binds to CD19, and instructions for administering the cell therapy, wherein the instructions specify:

(i) the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and

(ii) the dose of cells is to be administered to a subject having or identified to have a non-Hodgkin lymphoma (NHL); the dose of cells to be administered comprises between 1 x 10^7 CAR-expressing T cells and 2 x 10^8 CAR-expressing T cells, inclusive; and the dose of cells is to be administered at 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 optionally is 1:1 or is between 1:3 and 3:1.