lymph nodes. CLL is considered incurable. Patients eventually relapse or become refractory to available therapies. B cell receptor antagonists have shown improved outcomes for patients with relapsed/refractory CLL, however complete remission rates remain low, and patients who progress on or after therapy have poor outcomes. Effective therapies for patients with CLL and SLL who have failed B cell receptor antagonist therapy 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 CLL, SLL, 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.

[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 some examples, the $CD8^+$ cells or subtype or phenotype thereof and the $CD4^+$ cells or subtype or phenotype thereof, are present in the article or composition or combination, or are administered in the methods, at a defined ratio, such as at or about 1:1, or between at or about 1:3 and at or about 3:1. In some examples, the dose or administration contains or is of a particular amount or number of one population of the cells and the ratio is a defined ratio or is a naturally-occurring ratio, such as in the blood of the subject from which the cells are derived or ratio that occurs without selection or control for a particular ratio.

[0007] In some examples, the $CD4^+$ T cells (or subset thereof) and the $CD8^+$ T cells (or subset thereof), individually, contain a receptor that specifically binds to a target antigen expressed by the disease or condition, or a cell or tissue thereof, and/or that is associated with the disease or condition.

[0008] In some examples, the method of treating a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), comprises administering to the subject a dose of engineered T cells comprising $CD4^+$ and $CD8^+$ T cells, the $CD4^+$ and the $CD8^+$ T cells comprising a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to a Bruton's Tyrosine Kinase inhibitor (BTKi), venetoclax or BTKi and venetoclax. In particular examples, the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to treatment with a BTKi and venetoclax. In some examples, the BTKi is ibrutinib.

[0009] In some examples, the method of treating a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) comprises administering to the subject a dose of engineered T cells comprising CD4+ and CD8+ T cells, the CD4+ and the CD8+ T cells, comprising a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to ibrutinib and/or venetoclax. In particular examples, the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to treatment with ibrutinib and venetoclax.

[0010] In some examples, the dose of engineered T cells is enriched for CD4+ and CD8+ primary human T cells.

[0011] In some examples, the dose of engineered T cells comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR, optionally wherein the ratio is between approximately 1:3 and approximately 3:1. In some examples, the dose of engineered T cells comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells.

[0012] In some examples, the administration comprises administering a plurality of separate compositions, wherein the plurality of separate compositions comprising a first composition comprising one of the $CD4^+$ T cells and the $CD8^+$ T cells and a second composition comprising the other of the $CD4^+$ T cells and the $CD8^+$ T cells. In certain examples of any of the provided methods, the receptor contained by the $CD4^+$ T cells and/or the receptor contained by the $CD8^+$ T cells comprises T cells having a recombinant receptor, and/or wherein the $CD4^+$ T cells and/or the $CD8^+$ T cells are genetically engineered to express the receptor.

[0013] In some examples, the method comprises treating a subject having or suspected of having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), the method comprising administering to the subject a dose of engineered T cells comprising CD4+ and CD8+ T cells, the CD4+ and CD8+ T cells, comprising a CAR that specifically binds CD19, wherein the administration comprises administering a plurality of separate compositions, the plurality of separate compositions comprising a first composition comprising one of the CD4+ T cells and the CD8+ T cells and a second composition comprising the other of the CD4+ T cells and the CD8+ T cells.

[0013a] In one aspect, the present disclosure refers to the use of a dose of engineered T cells comprising $CD4^+$ and $CD8^+$ T cells, the $CD4^+$ and the $CD8^+$ T cells comprising a chimeric antigen receptor (CAR) that specifically binds to CD19, for the manufacture of a medicament for treatment of a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), wherein: (a) the dose of engineered T cells (i) is enriched for CD4+ and CD8+ primary human T cells; (ii) comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR; and (iii) comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing

cells; (b) the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to a Bruton's Tyrosine Kinase inhibitor (BTKi) and venetoclax; or (c) the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising one of the CD4+ T cells and the CD8+ T cells and a second composition comprising the other of the CD4+ T cells and the CD8+ T cells.

[0013b] In one aspect, the present disclosure refers to a dose of engineered T cells comprising $CD4^+$ and $CD8^+$ T cells, the $CD4^+$ and the $CD8^+$ T cells comprising a chimeric antigen receptor (CAR) that specifically binds to CD19 for use in the treatment of a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), wherein: (a) the dose of engineered T cells: (i) is enriched for CD4+ and CD8+ primary human T cells; (ii) comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR, and (iii) comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells; (b) the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to a Bruton's Tyrosine Kinase inhibitor (BTKi) and venetoclax; or (c) the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising one of the $CD4^+$ T cells and the $CD8^+$ T cells and a second composition comprising the other of the CD4+ T cells and the $CD8^+$ T cells.

[0014] In some examples, the dose of $CD4^+$ and $CD8^+$ engineered T cells comprises a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR is between approximately 1:3 and approximately 3:1. In some examples, the dose of engineered T cells comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells. In some examples, the dose of engineered T cells is enriched for CD4+ and CD8+ primary human T cells.

[0015] In some examples, the dose of cells enriched in CD4+ and CD8+ engineered T cells comprises greater than or greater than about 70%, greater than or greater than about 75%, greater than or

greater than about 80%, greater than or greater than about 85%, greater than or greater than about 90%, greater than or greater than about 95% or greater than or greater than about 98% CD4+ and CD8+ primary human T cells.

[0016] In some examples, the dose of $CD4^+$ and $CD8^+$ engineered T cells comprises a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR that is or is approximately 1:1. In some examples, the dose of engineered T cells comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.0×10^8 total CAR-expressing cells. In some examples, the dose of engineered T cells comprises or about 2.5×10^7 total CAR-expressing cells. In some examples, the dose of engineered T cells comprises at or about 5×10^7 total cells or total CAR-expressing cells. In some examples, the engineered T cells comprises at or about 1×10^8 total cells or total CAR-expressing cells.

[0017] In some examples, the CAR comprised by the $CD4^+$ T cells and/or the CAR comprised by the $CD8^+$ T cells comprises a CAR that is the same and/or wherein the $CD4^+$ T cells and/or the $CD8^+$ T cells are genetically engineered to express a CAR that is the same.

[0018] In particular examples, the first composition comprises the $CD8^+$ T cells and the second composition comprises the CD4+ T cells. In some examples, the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition.

[0019] In some examples, the administration of the first composition and the administration of the second composition are carried out on the same day, 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, or no more than 1 hour apart or no more than 30 minutes apart. In some 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.

[0020] In some 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 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.

[0021] In some 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.

[0022] In some examples of any of the provided methods, the subject has CLL or is suspected of having CLL; or the subject is identified or selected as having CLL. In some examples, the CLL is relapsed or refractory CLL.

[0023] In some examples, the subject has SLL or is suspected of having SLL; or the subject is identified or selected as having SLL. In some examples, the SLL is a relapsed or refractory SLL.

[0024] In some examples, prior to the administration of the dose of engineered T cells, the subject has been treated with one or more prior therapies for the CLL or SLL, other than another dose of cells expressing CAR or a lymphodepleting therapy. In some examples, the one or more prior therapy comprises at least two prior therapies, optionally three, four, five, six, seven, eight, nine or more.

[0025] In some 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, failed and/or was intolerant to treatment with the one or more prior therapies for the CLL or SLL. In some examples, the subject has relapsed following remission after treatment with, or become refractory to, failed and/or was intolerant to treatment with two or more prior therapies. In some 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, failed and/or was intolerant to treatment with

three or more prior therapies. In some examples, the prior therapies are selected from a kinase inhibitor, optionally an inhibitor of Bruton's tyrosine kinase (BTK), optionally ibrutinib; venetoclax; a combination therapy comprising fludarabine and rituximab; radiation therapy; and hematopoietic stem cell transplantation (HSCT). In some examples, the prior therapies comprise ibrutinib and/or venetoclax. In some examples, the prior therapies comprise ibrutinib and venetoclax.

[0026] In some examples, the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to ibrutinib and/or venetoclax. In some examples, the subject has relapsed following remission after treatment with, become refractory to, failed treatment with and/or is intolerant to ibrutinib and venetoclax.

[0027] In some examples, at or prior to the administration of the dose of cells: the subject is or has been identified as having one or more cytogenetic abnormalities, optionally associated with high-risk CLL, optionally selected from among: complex karyotype or cytogenetic abnormalities, del 17p, unmutated IGVH gene, and TP53 mutation; the subject is or has been identified as having high-risk CLL.

[0028] In some examples, the subject is or has been identified as having an ECOG status of 0 or 1; and/or the subject does not have an ECOG status of >1. In some examples, at or immediately prior to the administration of the dose of engineered cells or the lymphodepleting therapy the subject does not have a Richter's transformation of the CLL or SLL.

[0029] In some examples, the subject is an adult and/or is over at or about 50, 60, or 70 years of age.

[0030] In some examples, the T cells are primary T cells obtained from a subject. In some examples, the T cells are autologous to the subject. In some examples, the dose of engineered cells are viable cells.

[0031] In some examples, prior to the administration of the dose of engineered cells, lymphodepleting therapy is administered to the subject. In some examples, the subject has been preconditioned with a lymphodepleting therapy. In some example, the lymphodepleting therapy comprises the administration of fludarabine and/or cyclophosphamide. In some examples, the lymphodepleting therapy comprises administration of cyclophosphamide at about 200-400 mg/m^2, optionally at or about 300 mg/m^2, inclusive, and/or fludarabine at about 20-40 mg/m^2, optionally 30 mg/m^2, daily for 2-4 days, optionally for 3 days. In some examples, the lymphodepleting therapy comprises administration of cyclophosphamide at or about 300 mg/m^2 and fludarabine at about 30 mg/m^{2}daily for 3 days, optionally wherein the dose of cells is administered at least at or about 2-7 days after the lymphodepleting therapy or at least at or about 2-7 days after the initiation of the lymphodepleting therapy.

[0032] In some examples, at or prior to the administration of the dose of cells: the subject is or has been identified as having one or more cytogenetic abnormalities, optionally associated with high-risk CLL or SLL, optionally selected from among: complex karyotype or cytogenetic abnormalities, del 17p,

unmutated IGVH gene, and TP53 mutation; and/or the subject is or has been identified as having high-risk CLL or SLL.

In some 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, failed and/or was intolerant to treatment with two or more prior therapies. In some examples, at or prior to the administration of the dose of cells, the subject is or has been identified as having a standard-risk CLL or SLL. In some 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, failed and/or was intolerant to treatment with three or more prior therapies. In some examples, at or prior to the administration of the dose of cells, the subject is or has been identified as being intolerant to an inhibitor of Bruton's tyrosine kinase (BTK) and has received an inhibitor of BTK for a duration of less than at or about 6 months, and/or is ineligible for treatment with an inhibitor of BTK.

[0033] In some examples, (i) the subject is or has been identified as having high-risk CLL or SLL, and 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, failed and/or was intolerant to treatment with one or more prior therapies other than the inhibitor of BTK; or (ii) the subject is or has been identified as having a standard-risk CLL or SLL, and 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, failed and/or was intolerant to treatment with two or more prior therapies other than the inhibitor of BTK.

[0034] In some examples, the administration of the cell dose and/or the lymphodepleting therapy is carried out via outpatient delivery. In some examples, the dose of cells is administered parenterally, optionally intravenously.

[0035] In some examples, the response in at least 35%, at least 40 %, at least 50%, at least 60% or at least 70% of subjects treated is complete remission (CR) in the subjects treated according to the method. In some examples, the duration of the response until progression is durable for greater than 3 months or greater than 6 months. In some examples, in the subjects treated according to the method, greater than 50%, greater than 60%, or greater than 70% had undetectable minimal residual disease (MRD) for at least one month, at least two months, at least three months or at least 6 month after administering the dose of cells.

[0036] In some examples, of the subjects treated according to the method, no more than 10% of subjects exhibit a cytokine release syndrome (CRS) higher than grade 2. In some examples, of a plurality of subjects treated according to the method, no more than 10%, no more than 20%, no more than 30% or no more than 40% of the subjects exhibit neurotoxicity higher than grade 2. In some examples, the plurality of subjects treated according to the method comprises a plurality of subjects that have relapsed following remission after treatment with, become refractory to, failed treatment with

and/or is intolerant to ibrutinib and venetoclax.

[0037] In some examples, the method comprises: assaying a biological sample for the level, amount or concentration of TNF-alpha, wherein the biological sample is from a subject that is a candidate for treatment, optionally with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells; and comparing the level, amount or concentration of TNF-alpha to a threshold level, wherein: (1) if the level, amount or concentration of TNF-alpha is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy; and (2) if the level, amount or concentration of TNF-alpha is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy.

[0037a] In one aspect, the present disclosure refers to a method of identifying a subject as at risk for developing a neurotoxicity, comprising: assaying a biological sample for the level, amount or concentration of TNF-alpha, wherein the biological sample is from a subject that is a candidate for treatment, optionally with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells; and comparing the level, amount or concentration of TNF-alpha to a threshold level, wherein: (1) if the level, amount or concentration of TNF-alpha is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy; and (2) if the level, amount or concentration of TNF-alpha is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy.

[0038] In some examples, the subject is identified as at risk for developing a grade 3 or higher neurotoxicity, and the method further comprises: (i) administering to the subject the cell therapy, optionally at a reduced dose, optionally wherein (a) the method further comprises administering to the subject an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; and/or (b) the administering the cell therapy to the subject of the cell therapy is carried out or is specified to be carried out in an in-patient setting and/or with admission to the hospital for one or more days; or (ii) administering to the subject an alternative treatment other than the cell therapy for treating the disease or condition.

[0039] In some examples, the subject is identified as not at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy, : (i) the subject is not administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity unless or until the subjects exhibits a sign or symptom of a toxicity, optionally at or after 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; and/or (ii) the administration and any follow-up is carried out on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until 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.

[0040] In some examples, the assaying comprises: (a) contacting a biological sample with one or more reagent capable of detecting or that is specific for TNF-alpha, optionally wherein the one or more reagent comprises an antibody that specifically recognizes TNF-alpha; and (b) detecting the presence or absence of a complex comprising the one or more reagent and TNF-alpha.

[0041] In some examples, the method comprises administering to a subject a cell therapy for treating a disease or condition, said cell therapy comprising a dose of engineered cells comprising T cells

expressing a CAR, wherein: (1) if the subject has a level, amount or concentration of TNF-alpha in a biological sample from the subject that is at or above a threshold level, the subject is identified as at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy, and the method comprises: (i) administering to the subject the cell therapy at a reduced dose, (ii) further administering to the subject an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity; and/or (iii) the administering the cell therapy to the subject is carried out or is specified to be carried out in an in-patient setting and/or with admission to the hospital for one or more days; or (2) if the subject is selected or identified as having a level, amount or concentration of TNF-alpha in a biological sample from the subject that is below a threshold level, the subject is identified as not at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy, (i) not administering to the subject an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity unless or until the subjects exhibits a sign or symptom of a toxicity, optionally at or after 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; and/or (ii) the administering and any follow-up is carried out on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until 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, wherein the subject is a candidate for treatment with the cell therapy, said biological sample obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells.

[0041a] In one aspect, the present disclosure refers to the use of a cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR in the manufacture of a medicament for treatment of a disease or condition, wherein: (1) if the subject has a level, amount or concentration of TNF-alpha in a biological sample from the subject that is at or above a threshold level, the subject is identified as at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy: (i) the cell therapy is formulated for administration to the subject at a reduced dose, (ii) the subject is further administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity; and/or (iii) the administration of the cell therapy to the subject is carried out or is specified to be carried out in an in-patient setting and/or with admission to the hospital for one or more days; or (2) if the subject is selected or identified as having a level, amount or concentration of TNF-alpha in a biological sample from the subject that is below a threshold level, the subject is identified as not at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy: (i) the subject is not administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity unless or until the subjects exhibits a sign or symptom of a toxicity, optionally at or after 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; and/or (ii) the administration of the cell therapy and any follow-up is carried out on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until 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, wherein the subject is a candidate for treatment with the cell therapy, said biological sample obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells.

[0042] In some examples, the subject is identified as at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy and the method comprises administering the agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity, wherein the agent is administered to the subject concurrently with the cell therapy or within three days of administering the cell therapy to the subject.

[0043] 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, or is or is about the median or mean level, amount or concentration, of the TNF-alpha 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 exhibit any grade of neurotoxicity, after administration of a dose of engineered cells expressing the CAR for treating the same disease or condition; the threshold level is at or greater than 1.25-fold higher, at or greater than 1.3-fold higher, at or greater than 1.4-fold higher or at or greater than 1.5-fold higher than the median or mean level, amount or concentration, of the TNF-alpha 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 exhibit any grade of neurotoxicity, after administration of a dose of engineered cells expressing the CAR for treating the same disease or condition; the threshold level is at or greater than 1.25-fold higher, at or greater than 1.3-fold higher, at or greater than 1.4-fold higher or at or greater than 1.5-fold higher than the level, amount or concentration, of the TNF-alpha in a biological sample obtained from a group of normal or healthy subjects that are not candidates for treatment with the cell therapy.

[0044] In some examples, the threshold level is at or greater than 1000 pg/mL of the biological sample, at or greater than 1100 pg/mL of the biological sample, at or greater than 1200 pg/mL of the biological sample, at or greater than 1300 pg/mL of the biological sample, at or greater than 1400 pg/mL of the biological sample, or at or greater than 1500 pg/mL of the biological sample.

[0045] In some examples, the method comprises: (a) assaying a biological sample from a subject for the level, amount or concentration of IL-16, said subject having received administration of a cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject within one, two, or three days after the initiation of administration of the cell therapy; and (b) comparing the level, amount or concentration of IL-16 to a threshold level, wherein: (1) if the level, amount or concentration of IL-16 is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity; and (2) if the level, amount or concentration of IL-16 is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity.

[0045a] In one aspect, the present disclosure refers to a method of identifying a subject as at risk for developing a neurotoxicity, wherein the method comprises: (a) assaying a biological sample from a subject for the level, amount or concentration of IL-16, said subject having received administration of a cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject within one, two, or three days after the initiation of administration of the cell therapy; and (b) comparing the level, amount or concentration of IL-16 to a threshold level, wherein: (1) if the level, amount or concentration of IL-16 is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity; and (2) if the level, amount or concentration of IL-16 is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity.

[0046] In some examples, if the subject is identified at risk of developing a grade 3 or higher neurotoxicity, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity is administered.

[0047] In some examples, the assaying comprises: (a) contacting a biological sample with one or more reagent capable of detecting or that is specific for IL-16, optionally wherein the one or more reagent comprises an antibody that specifically recognizes IL16; (b) detecting the presence or absence of a complex comprising the reagent and IL-16. In some examples, the method further comprises prior to the assaying, administering to the subject the cell therapy.

[0048] In some examples, the method comprises administering to a subject, identified as at risk of developing a grade 3 or higher neurotoxicity, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity, said subject having previously received administration of a cell therapy for treating a disease or condition, wherein, at or immediately prior to administering the agent, the subject is selected or identified as being at risk of developing a grade 3 or higher neurotoxicity if the level or amount or concentration of IL-16 in a biological sample, obtained from the subject within one, two, or three days of the initiation of administration of the cell therapy, is above a threshold level.

[0048a] In one aspect, the present disclosure refers to the use of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity in the manufacture of a medicament for treatment of a subject, identified as at risk of developing a grade 3 or higher neurotoxicity, said subject having previously received administration of a cell therapy for treating a disease or condition, wherein, at or immediately prior to administration of the medicament, the subject is selected or identified as being at risk of developing a grade 3 or higher neurotoxicity if the level or amount or concentration of IL-16 in a biological sample, obtained from the subject within one, two, or three days of the initiation of administration of the cell therapy, is above a threshold level.

[0049] In some examples, administering the agent is carried out at a time when 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. In some examples, the administering to the subject the cell therapy was carried out on an outpatient basis and, if the level, amount or concentration of IL-16 is above a threshold level the method comprises admitting the patient to the hospital for one or more days.

[0050] 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, or is or is about the median or mean level, amount or concentration, of the IL-16 in a biological sample obtained, from a group of subjects, within one, two or three days after receiving a cell therapy comprising administration of a dose of engineered cells expressing the CAR for treating the same disease or condition, wherein each of the subjects of the group did not exhibit any grade of neurotoxicity, after administration of the cell therapy.

[0051] In some examples, the threshold level is at or greater than 1.3-fold higher, at or greater than 1.4-fold higher, at or greater than 1.5-fold higher, at or greater than 1.6-fold higher, at or greater than 1.7-fold higher, at or greater than 1.8-fold higher, at or greater than 1.9-fold higher or at or greater than 2.0-fold higher than the median or mean level, amount or concentration, of the IL-16 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 exhibit any grade of neurotoxicity, after administration of a dose of engineered cells expressing the CAR for treating the same disease or condition.

[0052] In some examples, the threshold level is at or greater than 1.3-fold higher, at or greater than 1.4-fold higher, at or greater than 1.5-fold higher, at or greater than 1.6-fold higher, at or greater than 1.7-fold higher, at or greater than 1.8-fold higher, at or greater than 1.9-fold higher or at or greater than 2.0-fold higher than the level, amount or concentration, of the IL-16 in a biological sample obtained from a group of normal or healthy subjects that are not candidates for treatment with the cell therapy.

[0053] In some examples, the threshold level is at or greater than 1000 pg/mL of the biological sample, at or greater than 1500 pg/mL of the biological sample, at or greater than 2000 pg/mL of the biological sample, at or greater than 2500 pg/mL of the biological sample, or at or greater than 3000 pg/mL of the biological sample.

[0054] In some examples, the biological sample is or is obtained from a blood, plasma or serum sample. In some examples, the biological sample is a serum sample. In some examples, assaying or assessing cells the analyte comprises an immunoassay. In some examples, the disease or condition is a cancer. In some examples, the disease or condition is a myeloma, leukemia or lymphoma.

[0055] In some examples, the antigen is ROR1, B cell maturation antigen (BCMA), carbonic anhydrase 9 (CAIX), tEGFR, Her2/neu (receptor tyrosine kinase erbB2), L1-CAM, CD19, CD20, CD22, mesothelin, CEA, and hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, epithelial glycoprotein 2 (EPG-2), epithelial glycoprotein 40 (EPG-40), EPHa2,

erb-B2, erb-B3, erb-B4, erbB dimers, EGFR vIII, folate binding protein (FBP), FCRL5, FCRH5, fetal acetylcholine receptor, GD2, GD3, HMW-MAA, IL-22R-alpha, IL-13R-alpha2, kinase insert domain receptor (kdr), kappa light chain, Lewis Y, L1-cell adhesion molecule, (L1-CAM), Melanoma-associated antigen (MAGE)-A1, MAGE-A3, MAGE-A6, Preferentially expressed antigen of melanoma (PRAME), survivin, TAG72, B7-H6, IL-13 receptor alpha 2 (IL-13Ra2), CA9, GD3, HMW-MAA, CD171, G250/CAIX, HLA-AI MAGE Al, HLA-A2 NY-ESO-1, PSCA, folate receptor-a, CD44v6, CD44v7/8, avb6 integrin, 8H9, NCAM, VEGF receptors, 5T4, Foetal AchR, NKG2D ligands, CD44v6, dual antigen, a cancer-testes antigen, mesothelin, murine CMV, mucin 1 (MUC1), MUC16, PSCA, NKG2D, NY-ESO-1, MART-1, gp100, oncofetal antigen, ROR1, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), Her2/neu, estrogen receptor, progesterone receptor, ephrinB2, CD123, c-Met, GD-2, O-acetylated GD2 (OGD2), CE7, Wilms Tumor 1 (WT-1), a cyclin, cyclin A2, CCL-1, CD138, G Protein Coupled Receptor 5D (GPCR5D), or a pathogen-specific antigen.

[0056] In some examples, the antigen is CD19.

[0057] In some examples, the disease or condition is a B cell malignancy and/or is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphoblastic leukemia (CLL), small lymphocytic lymphoma (SLL), non-Hodgkin lymphoma (NHL), and Diffuse Large B-Cell Lymphoma (DLBCL). In some examples, the disease or condition is CLL or SLL.

[0058] In some examples, the agent is or comprises tocilizumab, siltuximab or dexamethasone.

[0059] In some examples, the CAR comprises an extracellular antigen-binding domain specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is a 4-1 BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is a CD3zeta; the CAR comprises, in order, an extracellular antigen-binding domain specific for CD19, 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.

[0060] In some examples, the antigen-binding domain is an scFv.

[0061] In some examples, the scFv comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and/or a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37) and/or a CDRH1 sequence of DYGVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and/or a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40); 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; the scFv comprises a VH set forth in SEQ ID NO:41 and a VL set forth in SEQ ID NO: 42, optionally wherein the VH and VL are separated by a flexible linker, optionally wherein the flexible linker is or

comprises the sequence set forth in SEQ ID NO:24; and/or the scFv is or comprises the sequence set forth in SEQ ID NO:43.

[0062] In some examples, the costimulatory signaling region is a signaling domain of CD28 or 4-1BB. In some examples, the costimulatory signaling region is a signaling domain of 4-1BB.

[0063] In some 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. In some examples, the primary signaling domain is a CD3zeta signaling domain. In some examples, the primary signaling domain comprises SEQ ID NO: 13 or 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.

[0064] In some examples, the CAR further comprises a spacer between the transmembrane domain and the scFv. In some 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, optionally an IgG4 hinge, or a modified version thereof. In some 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 examples, the spacer is at or about 12 amino acids in length.

[0065] In some 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 comprises or consists of the formula X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

[0066] In some of any of the examples, the subject is a human subject.

[0067] In some of any of the provided articles of manufacture, the article of manufacture comprises a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to any of the provided methods.

[0067a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the use, method, or dose disclosed herein.

Brief Description of the Drawings

[0068] **FIG. 1** shows a box plot of the frequency of CAR T cells in whole blood as measured by flow cytometry. The boxes extend from the 1st to the 3rd quartile, with the median shown as a horizontal line. The whiskers extend to 1.5 times the inter-quartile range, with measurements outside this range plotted as individual points.

[0069] **FIG. 2** shows a graph of the median cells/μl over time by dose level. Patients, N = 16; samples, n. Upper error bar represents the third quartile; lower error bar represents the first quartile. The dose was given on day 1.

Claims

1. Use of a dose of engineered T cells comprising $CD4^+$ and $CD8^+$ T cells, the $CD4^+$ and the $CD8^+$ T cells comprising a chimeric antigen receptor (CAR) that specifically binds to CD19, for the manufacture of a medicament for treatment of a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), wherein:

(a) the dose of engineered T cells (i) is enriched for CD4+ and CD8+ primary human T cells; (ii) comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR; and (iii) comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells;

(b) the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to a Bruton's Tyrosine Kinase inhibitor (BTKi) and venetoclax; or

(c) the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising one of the CD4+ T cells and the CD8+ T cells and a second composition comprising the other of the CD4+ T cells and the CD8+ T cells.

2. A dose of engineered T cells comprising $CD4^+$ and $CD8^+$ T cells, the $CD4^+$ and the $CD8^+$ T cells comprising a chimeric antigen receptor (CAR) that specifically binds to CD19 for use in the treatment of a subject having chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), wherein:

(a) the dose of engineered T cells: (i) is enriched for CD4+ and CD8+ primary human T cells; (ii) comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR, and (iii) comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells;

(b) the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to a Bruton's Tyrosine Kinase inhibitor (BTKi) and venetoclax; or

(c) the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising one of the $CD4^+$ T cells and the $CD8^+$ T cells and a second composition comprising the other of the CD4+ T cells and the $CD8^+$ T cells.

3. The use of claim 1 or the dose of claim 2, wherein the BTKi is ibrutinib.

4. The use of claim 1 or claim 3 or the dose or claim 2 or claim 3, wherein a plurality of separate compositions are administered to the subject, wherein the plurality of separate compositions comprises a first composition comprising one of the $CD4^+$ T cells and the $CD8^+$ T cells and a second composition comprising the other of the $CD4^+$ T cells and the $CD8^+$ T cells.

5. The use of any of claims 1, 3, and 4 or the dose of any of claims 2-4, wherein the dose of engineered T cells comprises a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR is between approximately 1:3 and approximately 3:1, optionally wherein the dose of engineered T cells comprises a defined ratio of CD4+ cells expressing the CAR to CD8+ cells expressing the CAR that is or is approximately 1:1.

6. The use of any of claims 1 and 3-5 or the dose of any of claims 2-5, wherein the dose of engineered T cells comprises at or about 2.5×10^7 total CAR-expressing cells to at or about 1.5×10^8 total CAR-expressing cells.

7. The use of any of claims 1 and 3-6 or the dose of any of claims 2-6, wherein the dose of engineered T cells is enriched for CD4+ and CD8+ primary human T cells.

8. The use of any of claims 1 and 3-7 or the dose of any of claims 2-7, wherein the dose of engineered T cells comprises:

(a) at or about 2.5×10^7 total CAR-expressing cells to at or about 1.0×10^8 total CAR-expressing cells; and/or

(b) at or about 2.5×10^7 total CAR-expressing cells;

at or about 5×10^7 total cells or total CAR-expressing cell; or

at or about 1×10^8 total cells or total CAR-expressing cells.

9. The use of any of claim 1 and 3-8 or the dose of any of claims 2-8, wherein the CAR comprised by the $CD4^+$ T cells and/or the CAR comprised by the $CD8^+$ T cells comprises a CAR that is the same and/or wherein the $CD4^+$ T cells and/or the $CD8^+$ T cells are genetically engineered to express a CAR that is the same.

10. The use of any of claims 1 and 3-9 or the dose of any of claims 2-9, wherein the first composition comprises the $CD8^+$ T cells and the second composition comprises the CD4+ T cells.

11. The use or dose of claim 10, 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 the administration of the first composition and the administration of the second composition are carried out no more than 48 hours apart, further optionally

wherein 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.

12. The use of any of claims 1 and 3-11 or the dose of any of claims 2-11, wherein:

(a) the subject has CLL or is suspected of having CLL; or

the subject is identified or selected as having CLL,

optionally wherein the CLL is a relapsed or refractory CLL; or

(b) the subject has SLL or is suspected of having SLL; or

the subject is identified or selected as having SLL,

optionally wherein the SLL is a relapsed or refractory SLL.

13. The use of claims 1 and 3-12 or the dose of any of claims 2-12, wherein, prior to the administration of the dose of engineered T cells, the subject has been treated with one or more prior therapies for the CLL or SLL, other than another dose of cells expressing CAR or a lymphodepleting therapy, optionally

wherein the one or more prior therapy comprises at least two prior therapies, optionally 3, 4, 5, 6, 7, 8, 9 or more prior therapies.

14. The use of any of claims 1 and 3-13 or the dose of any of claims 2-13, wherein, at or immediately prior to the time of the administration of the dose of engineered T cells, the subject has relapsed following remission after treatment with, or become refractory to, failed and/or was intolerant to treatment with the one or more prior therapies, two or more prior therapies, or three or more prior therapies, for the CLL or SLL.

15. The use of any of claims 1 and 3-14 or the dose of any of claims 2-14, wherein the one or more prior therapies are selected from a kinase inhibitor, optionally an inhibitor of Bruton's tyrosine kinase (BTK), optionally ibrutinib; venetoclax; a combination therapy comprising fludarabine and

rituximab; radiation therapy; and hematopoietic stem cell transplantation (HSCT), further optionally wherein the one or more prior therapies comprise ibrutinib and venetoclax.

16. The use of any of claims 1 and 3-15 or the dose of any of claims 2-15, wherein at or prior to the administration of the dose of cells:

(a) the subject is or has been identified as having one or more cytogenetic abnormalities, optionally associated with high-risk CLL or SLL, optionally selected from among: complex karyotype or cytogenetic abnormalities, del 17p, unmutated IGVH gene, and TP53 mutation; and/or

the subject is or has been identified as having high-risk CLL or SLL; or

(b) the subject is or has been identified as having a standard-risk CLL or SLL.

17. The use of any of claims 1 and 3-16 or the dose of any of claims 2-16, wherein at or prior to the administration of the dose of cells, the subject is or has been identified (1) as being intolerant to an inhibitor of Bruton's tyrosine kinase (BTK), and has received an inhibitor of BTK for a duration of less than at or about 6 months, or (2) is ineligible for treatment with an inhibitor of BTK, optionally wherein:

(i) the subject is or has been identified as having high-risk CLL or SLL, and 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, failed and/or was intolerant to treatment with one or more prior therapies other than the inhibitor of BTK; or

(ii) the subject is or has been identified as having a standard-risk CLL or SLL, and 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, failed and/or was intolerant to treatment with two or more prior therapies other than the inhibitor of BTK.

18. The use of any of claims 1 and 3-17 or the dose of any of claims 2-17, wherein:

(a) the subject is or has been identified as having an ECOG status of 0 or 1; and/or

the subject does not have an ECOG status of >1;

(b) at or immediately prior to the administration of the dose of engineered cells or the lymphodepleting therapy the subject does not have a Richter's transformation of the CLL or SLL; and/or

(c) the subject is an adult and/or is over at or about 50, 60, or 70 years of age.

19. The use of any of claims 1 and 3-18 or the dose of any of claims 2-18, wherein the engineered T cells are autologous to the subject.

20. The use of any of claims 1 and 3-19 or the dose of any of claims 2-19, wherein, prior to the administration of the dose of engineered T cells, the subject is administered a lymphodepleting therapy, optionally: wherein the lymphodepleting therapy comprises:
(a) administration of fludarabine and/or cyclophosphamide;

(b) the administration of cyclophosphamide at about 200-400 mg/m^2, optionally at or about 300 mg/m^2, inclusive, and/or fludarabine at about 20-40 mg/m^2, optionally 30 mg/m^2, daily for 2-4 days, optionally for 3 days; and/or
(c) administration of cyclophosphamide at or about 300 mg/m^2 and fludarabine at about 30 mg/m^2daily for 3 days, optionally wherein the dose of cells is administered at least at or about 2-7 days after the lymphodepleting therapy or at least at or about 2-7 days after the initiation of the lymphodepleting therapy.

21. The use of any of claims 1 and 3-20 or the dose of any of claims 2-20, wherein the administration of the dose of engineered T cells and/or the lymphodepleting therapy is carried out via outpatient delivery.

22. The use of any of claims 1 and 3-21 or the dose of any of claims 2-21, wherein, of a plurality of subjects treated:
(a) the response in at least 50%, at least 60%, at least 70%, at least 80%, at least 90% of the subjects treated is an objective response rate; and/or
(b) the response in at least 35%, at least 40 %, at least 50%, at least 60% or at least 70% of subjects treated is complete remission (CR), optionally
wherein the duration of the response until progression is durable for greater than 3 months or greater than 6 months; and/or
(c) greater than 50%, greater than 60%, or greater than 70% had undetectable minimal residual disease (MRD) for at least one month, at least two months, at least three months or at least 6 months after administering the dose of engineered T cells.

23. The use of any of claims 1 and 3-22 or the dose of any of claims 2-22, wherein, of a plurality of subjects treated:
(a) no more than 10% of subjects exhibit a cytokine release syndrome (CRS) higher than grade 2; and/or
(b) no more than 10%, no more than 20%, no more than 30% or no more than 40% of the subjects exhibit neurotoxicity higher than grade 2.

24. A method of identifying a subject as at risk for developing a neurotoxicity, comprising:

assaying a biological sample for the level, amount or concentration of TNF-alpha, wherein the biological sample is from a subject that is a candidate for treatment, optionally with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject prior to administering the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells; and

comparing the level, amount or concentration of TNF-alpha to a threshold level, wherein: (1) if the level, amount or concentration of TNF-alpha is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy; and (2) if the level, amount or concentration of TNF-alpha is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy.

25. The method of claim 24, wherein:

(1) if the subject is identified as at risk for developing a grade 3 or higher neurotoxicity:

(i) the subject is administered the cell therapy, optionally at a reduced dose, optionally wherein (a) the subject is further administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; and/or (b) the administration of the cell therapy to the subject is carried out or is specified to be carried out in an in-patient setting and/or with admission to the hospital for one or more days; or

(ii) the subject is administered an alternative treatment other than the cell therapy for treating the disease or condition; or

(2) the subject is identified as not at risk for developing a grade 3 or higher neurotoxicity following administration of the cell therapy:

(i) the subject is not administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity unless or until the subjects exhibits a sign or symptom of a toxicity, optionally at or after 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; and/or

(ii) the administration and any follow-up is carried out on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until 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.

26. Use of a cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR in the manufacture of a medicament for treatment of a disease or condition, wherein:

(1) if the subject has a level, amount or concentration of TNF-alpha in a biological sample from the subject that is at or above a threshold level, the subject is identified as at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy: (i) the cell therapy is formulated for administration to the subject at a reduced dose, (ii) the subject is further administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity; and/or (iii) the administration of the cell therapy to the subject is carried out or is specified to be carried out in an in-patient setting and/or with admission to the hospital for one or more days; or

(2) if the subject is selected or identified as having a level, amount or concentration of TNF-alpha in a biological sample from the subject that is below a threshold level, the subject is identified as not at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy: (i) the subject is not administered an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity unless or until the subjects exhibits a sign or symptom of a toxicity, optionally at or after 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; and/or (ii) the administration of the cell therapy and any follow-up is carried out on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until 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,

wherein the subject is a candidate for treatment with the cell therapy, said biological sample obtained from the subject prior to administration of the cell therapy and/or said biological sample does not comprise the CAR and/or said engineered cells.

27. The method of claim 25 or the use of claim 26, wherein if the subject is identified as at risk of developing grade 3 or higher neurotoxicity following administration of the cell therapy, the agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity is administered to the subject, wherein the agent is administered to the subject concurrently with the cell therapy or within three days of administering the cell therapy to the subject.

28. A method of identifying a subject as at risk for developing a neurotoxicity, wherein the method comprises:

(a) assaying a biological sample from a subject for the level, amount or concentration of IL-16, said subject having received administration of a cell therapy comprising a dose of engineered cells comprising T cells expressing a CAR for treating a disease or condition, wherein the biological sample is obtained from the subject within one, two, or three days after the initiation of administration of the cell therapy; and

(b) comparing the level, amount or concentration of IL-16 to a threshold level, wherein: (1) if the level, amount or concentration of IL-16 is at or above a threshold level, identifying the subject as at risk for developing a grade 3 or higher neurotoxicity; and (2) if the level, amount or concentration of IL-16 is below the threshold level, identifying the subject as not at risk for developing a grade 3 or higher neurotoxicity.

29. The method of claim 28, wherein if the subject is identified at risk of developing a grade 3 or higher neurotoxicity, an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity is administered to the subject.

30. Use of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity in the manufacture of a medicament for treatment of a subject, identified as at risk of developing a grade 3 or higher neurotoxicity, said subject having previously received administration of a cell therapy for treating a disease or condition, wherein, at or immediately prior to administration of the medicament, the subject is selected or identified as being at risk of developing a grade 3 or higher neurotoxicity if the level or amount or concentration of IL-16 in a biological sample, obtained from the subject within one, two, or three days of the initiation of administration of the cell therapy, is above a threshold level.

31. The method of claim 29 or the use of claim 30, wherein:

(a) the administration of the agent is carried out at a time when 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; and/or

(b) the administration of the cell therapy was carried out on an outpatient basis and, if the level, amount or concentration of IL-16 is above a threshold level, the patient is admitted to the hospital for one or more days.

32. The method of any of claims 24-25, 27-29, and 31 or the use of any of claims 26, 27, and 30-31, wherein the biological sample is or is obtained from a blood sample, a plasma sample, or a serum sample.

33. The method of any of claims 24-25, 27-29, and 31-32 or the use of any of claims 26, 27, and 30-32, wherein the disease or condition is a cancer, optionally wherein the disease or condition is a myeloma, leukemia or lymphoma.

34. The method of any of claims 24-25, 27-29, and 31-33 or the use of any of claims 26, 27, and 30-33, wherein the disease or condition is a B cell malignancy and/or is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphoblastic leukemia (CLL), small lymphocytic lymphoma (SLL), non-Hodgkin lymphoma (NHL), and Diffuse Large B-Cell Lymphoma (DLBCL), optionally

wherein the disease or condition is CLL or SLL.

35. The method of any of claims 25, 27, 29, and 31-34 or the use of any of claims 26-27 and 30-34, wherein the agent or other treatment is or comprises an anti-IL-6 antibody, and anti-IL-6R antibody or a steroid; and/or

wherein the agent is or comprises tocilizumab, siltuximab or dexamethasone.

36. The use, method, or dose of any of claims 1-35, wherein:

the CAR comprises an extracellular antigen-binding domain specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is a 4-1 BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is a CD3zeta; and/or

the CAR comprises, in order, an extracellular antigen-binding domain specific for CD19, 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, optionally wherein the antigen-binding domain is an scFv, further optionally wherein:

the scFv comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37) and 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);

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;

the scFv comprises a VH set forth in SEQ ID NO:41 and a VL set forth in SEQ ID NO: 42, optionally wherein the VH and VL are separated by a flexible linker, optionally wherein the flexible linker is or comprises the sequence set forth in SEQ ID NO:24; and/or

the scFv is or comprises the sequence set forth in SEQ ID NO:43.

37. The use, method, or dose of claim 36, wherein:

(a) the costimulatory signaling region is a signaling domain of CD28 or 4-1BB, optionally wherein:

(i) the costimulatory signaling region is a signaling domain of 4-1BB; and/or

(ii) 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; and/or

(b) the primary signaling domain is a CD3zeta signaling domain, optionally

wherein the primary signaling domain comprises SEQ ID NO: 13 or 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.

38. The use, method, or dose of claim 36 or claim 37, wherein the CAR further comprises a spacer between the transmembrane domain and the scFv.

39. The use, method, or dose of claim 38, wherein 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, further optionally wherein the spacer is at or about 12 amino acids in length and comprises or consists of the formula X1PPX2P, where X1 is glycine, cysteine or arginine and X2 is cysteine or threonine.

40. An article of manufacture comprising a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the use, method, or dose of any of claims 1-39.