

of manufacture that meet such needs.

Summary

[0005] Provided herein are methods of determining the risk of developing a toxicity and methods of determining the likelihood of response after administration of a cell therapy. In some of any [embodimentexamples](#), the methods involve comparing the value of a parameter or the level, concentration or amount of the biomarker or analyte, to a threshold value for that particular parameter, biomarker or analyte. In some of any [embodimentexamples](#), the comparison can be used to determine the risk of toxicity and/or the likelihood of response to a cell therapy. In some of any [embodimentexamples](#), the comparison can be used to determine the risk of toxicity. In some of any [embodimentexamples](#), the comparison can be used to determine the likelihood of response to a cell therapy. In some of any [embodimentexamples](#), the cell therapy includes a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19). In some of any [embodimentexamples](#), the parameter, biomarker or analyte is assessed from a subject or in a sample obtained from a subject, that has a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL). In some [embodimentexamples](#), the subject has a chronic lymphoblastic leukemia (CLL). In some [embodimentexamples](#), the subject has a small lymphocytic lymphoma (SLL). In some of any [embodimentexamples](#), the subject is a candidate for treatment with a cell therapy, and/or has received treatment with a cell therapy. In some of any [embodimentexamples](#), the subject is a candidate for treatment with a cell therapy. In some [embodimentexamples](#), the subject has received treatment with a cell therapy. In some of any [embodimentexamples](#), the provided methods can be used to identify or select subjects with a risk of developing a toxicity and/or that are likely to respond to a cell therapy; and/or select subjects for a particular treatment, such as with additional therapeutic agents. In some of any [embodimentexamples](#), the provided methods can be used to identify or select subjects with a risk of developing a toxicity. In some of any [embodimentexamples](#), the provided methods can be used to identify or select subjects that are likely to respond to a cell therapy. In some of any [embodimentexamples](#), the provided methods can be used to select subjects for a particular treatment, such as with additional therapeutic agents.

[0006] Provided herein are methods of determining the risk of developing a toxicity after administration of a cell therapy, where the methods involve: assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T

cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to administering the cell therapy; and comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy if: the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; the blood tumor burden is below the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio; or identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy if: the lymph node tumor burden is below the threshold level for tumor burden; the blood tumor burden is at or above the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio.

[0006a] In one aspect, the present disclosure refers to a method of determining the risk of developing a toxicity after administration of a cell therapy, the method comprising: assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to administration of the cell therapy; and comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein: (1) identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy if: (a) the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; (b) the blood tumor burden is below the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio; or (2) identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy if: (a) the lymph node tumor burden is below the threshold level for tumor burden; (b) the blood tumor burden is at or above the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio.

[0007] In some of any **embodimentexamples**, if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy, optionally at a reduced dose, optionally wherein the method further includes 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 the administering 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 a hospital for one or more days; or administering to the subject an alternative treatment other than the cell therapy for treating the CLL or SLL. In some of any **embodimentexamples**, if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy at a reduced dose. In some **embodimentexamples**, if the subject is identified as at risk for developing a neurotoxicity, the method further includes 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. In some **embodimentexamples**, if the subject is identified as at risk for developing a neurotoxicity, the administering 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 a hospital for one or more days. In some **embodimentexamples**, if the subject is identified as at risk for developing a neurotoxicity, the method includes administering to the subject an alternative treatment other than the cell therapy for treating the CLL or SLL.

[0008] In some of any **embodimentexamples**, if the subject is identified as not at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy,

optionally wherein 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 1°C after treatment with an antipyretic; and/or the administering 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 1°C after treatment with an antipyretic. In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy. In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, 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. In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, 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 a sustained fever or a fever that is or has not been reduced or not reduced by more than 1°C after treatment with an antipyretic. In some [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the administering 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. In some [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the administering 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, 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 1°C after treatment with an antipyretic.

[0009] Provided herein are methods of selecting a subject for treatment with a cell therapy, wherein the methods involve: assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a

small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to administering the cell therapy; and comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein if the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; the blood tumor burden is below the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio, selecting the subject for administration of the cell therapy at a reduced dose; administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; administration of the cell therapy that is carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; and/or administration of an alternative treatment other than the cell therapy for treating the CLL or SLL; or if the lymph node tumor burden is below the threshold level for tumor burden; the blood tumor burden is at or above the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio, selecting the subject for administration of the cell therapy, optionally wherein 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 1°C after treatment with an antipyretic; and/or 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 1°C after treatment with an antipyretic.

[0009a] In one aspect, the present disclosure refers to a method of selecting a subject for treatment with a cell therapy, wherein the method comprises: assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising

T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to administration of the cell therapy; and comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein: (1) if (a) the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; (b) the blood tumor burden is below the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio, selecting the subject for: (i) administration of the cell therapy at a reduced dose; (ii) administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; (iii) administration of the cell therapy that is carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; and/or (iv) administration of an alternative treatment other than the cell therapy for treating the CLL or SLL; or (2) if (a) the lymph node tumor burden is below the threshold level for tumor burden; (b) the blood tumor burden is at or above the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio, selecting the subject for: (i) administration of the cell therapy, optionally wherein: (a) 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 1°C after treatment with an antipyretic; and/or (b) 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 1°C after treatment with an antipyretic.

[0010] Also provided herein are methods of selecting a subject for treatment with a cell therapy, wherein the methods involve: assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a

chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to administering the cell therapy; and comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein if the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; the blood tumor burden is below the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio, selecting the subject for administration of the cell therapy at a reduced dose; administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; administration of the cell therapy that is carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; and/or administration of an alternative treatment other than the cell therapy for treating the CLL or SLL; or if the lymph node tumor burden is below the threshold level for tumor burden; the blood tumor burden is at or above the threshold level for blood tumor burden; and/or the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio, selecting the subject for administration of the cell therapy. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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, such as 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 1°C after treatment with an antipyretic. In some [embodimentexamples](#), the administration of the cell therapy and any follow-up is carried out on an outpatient basis. In some [embodimentexamples](#), the administration of the cell therapy and any follow-up is carried out without admitting the subject to a hospital. In some [embodimentexamples](#), the administration of the cell therapy and any follow-up is carried out without an overnight stay at a hospital. In some [embodimentexamples](#), the administration of the cell therapy and any follow-up is carried out without requiring admission to or an overnight stay at a hospital. In some [embodimentexample](#), 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 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

1°C after treatment with an antipyretic.

[0011] In some of any [embodimentexamples](#), the method further includes administering 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 and/or the alternative treatment to the subject. In some of any [embodimentexamples](#), the method further includes administering the cell therapy to the subject. In some of any [embodimentexamples](#), the method further includes administering the agent to the subject. In some of any [embodimentexamples](#), the method further includes administering the other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity to the subject. In some of any [embodimentexamples](#), the method further includes administering the alternative treatment to the subject.

[0012] In some of any [embodimentexamples](#), assessing the blood tumor burden includes determining the lymphocyte concentration in the blood of the subject. In some of any [embodimentexamples](#), the concentration is the lymphocyte count per microliter (μL) of blood. In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value between at or about 800 lymphocytes/ μL and at or about 3000 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 800 lymphocytes/ μL , 900 lymphocytes/ μL , 1000 lymphocytes/ μL , 1250 lymphocytes/ μL , 1500 lymphocytes/ μL , 1750 lymphocytes/ μL , 2000 lymphocytes/ μL , 2250 lymphocytes/ μL , 2500 lymphocytes/ μL , 2750 lymphocytes/ μL or 3000 lymphocytes/ μL , or a value between any of the foregoing. In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 800 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 900 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 1000 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 1250 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 1500 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 1750 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 2000 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 2250 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 2500 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a value of at or about 2750 lymphocytes/ μL . In some of any [embodimentexamples](#), the threshold level for blood tumor burden is a

value of at or about 3000 lymphocytes/ μ L.

[0013] In some of any [embodimentexamples](#), assessing the lymph node burden includes determining the largest lymph node diameter. In some of any [embodimentexamples](#), the largest lymph node diameter is measured in centimeters (cm). In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value between at or about 4 cm and at or about 7 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 4 cm, 4.25 cm, 4.5 cm, 4.75 cm, 5 cm, 5.25 cm, 5.5 cm, 5.75 cm, 6 cm, 6.25 cm, 6.5 cm, 6.75 cm or 7 cm, or a value between any of the foregoing. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 4 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 4.25 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 4.5 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 4.75 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 5 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 5.25 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 5.5 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 5.75 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 6.0 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 6.25 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 6.5 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 6.75 cm. In some of any [embodimentexamples](#), the threshold level for the largest lymph node diameter as the lymph node burden is a value of at or about 7.0 cm.

[0014] In some of any [embodimentexamples](#), assessing the ratio of blood tumor burden to lymph node tumor burden includes determining the ratio of the lymphocyte count per microliter (μ L) of blood to the largest lymph node diameter in centimeters (cm). In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μ L) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node

tumor burden is a value between at or about 300 and at or about 1000. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000, or a value between any of the foregoing. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 300. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 350. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 400. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 450. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 500. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 550. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 600. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 650. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 700. In some of any embodimentexamples, the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 750. In some of any embodimentexamples, the threshold level for

ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 800. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 850. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 900. In some of any [embodimentexample](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 950. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 1000.

[0015] In some of any [embodimentexamples](#), assessing the lymph node burden includes determining the sum of the products of diameters (SPD). In some of any [embodimentexamples](#), the SPD is measured in centimeters squared (cm^2). In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value between at or about 10 cm^2 and at or about 40 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 10 cm^2 , 12.5 cm^2 , 15 cm^2 , 17.5 cm^2 , 20 cm^2 , 22.5 cm^2 , 25 cm^2 , 27.5 cm^2 , 30 cm^2 , 32.5 cm^2 , 35 cm^2 , 37.5 cm^2 or 40 cm^2 , or a value between any of the foregoing. In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 10 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 12.5 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 15 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 17.5 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 20 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 22.5 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 25 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 27.5 cm^2 . In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 30 cm^2 . In some of any [embodimentexamples](#), the threshold level for the

SPD as the lymph node burden is a value of at or about 32.5 cm². In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 35 cm². In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 37.5 cm². In some of any [embodimentexamples](#), the threshold level for the SPD as the lymph node burden is a value of at or about 40 cm².

[0016] In some of any [embodimentexamples](#), assessing the ratio of blood tumor burden to lymph node tumor burden includes determining the ratio of the lymphocyte count per microliter (μL) of blood to the sum of the products of diameters (SPD) in centimeters squared (cm²). In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value between at or about 25 and at or about 500. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450 or 500, or a value between any of the foregoing. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 25. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 50. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 75. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 100. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 150. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 200. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 250. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 300. In some of any [embodimentexamples](#), the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio

of blood tumor burden to lymph node tumor burden is a value of at or about 350. In some of any embodiment examples, the threshold level for ratio of the lymphocyte count per microliter (μ L) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 400. In some of any embodiment examples, the threshold level for ratio of the lymphocyte count per microliter (μ L) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 450. In some of any embodiment examples, the threshold level for ratio of the lymphocyte count per microliter (μ L) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 500.

[0017] Provided herein are methods of determining the risk of developing a toxicity after administration of a cell therapy, where the methods involve: assaying a biological sample for the level, amount or concentration of tumor necrosis factor (TNF) and/or interleukin-16 (IL-16), wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering the cell therapy or prior to peak CAR+ T cell expansion and/or within at or about 11 days after the initiation of administration of the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL; and if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy; or if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy.

[0017a] In one aspect, the present disclosure refers to a method of determining the risk of developing a toxicity after administration of a cell therapy, the method comprising: assaying a biological sample for the level, amount or concentration of tumor necrosis factor (TNF) and/or interleukin-16 (IL-16), wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administration of the cell therapy or prior to peak CAR+ T cell expansion and/or within at or about 11 days after the initiation of administration of the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein: the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 1000 pg/mL; and (1) if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy; or (2) if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy.

[0018] Provided herein are methods of determining the risk of developing a toxicity after administration of a cell therapy, where the methods involve: assaying a biological sample for the level, amount or concentration of tumor necrosis factor (TNF) and/or interleukin-16 (IL-16), wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological

sample is obtained from the subject prior to administering the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL; and if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy; or if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy.

[0019] In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy, optionally at a reduced dose, optionally wherein the method further includes 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 the administering 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 a hospital for one or more days; or administering to the subject an alternative treatment other than the cell therapy for treating the CLL or SLL. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy at a reduced dose. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the method further includes 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. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the administering 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 a hospital for one or more days. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the method further includes administering to the subject an alternative treatment other than the cell therapy for treating the CLL or SLL.

[0020] In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy, optionally wherein 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 1°C after treatment with an antipyretic; and/or the administering 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 1°C after treatment with an antipyretic. In some embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, the method further includes administering to the subject the cell therapy. In some embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, 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. In some embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, 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 sustained fever or a fever that is or has not been reduced or not reduced by more than 1°C after treatment with an antipyretic. In some embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, the administering 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. In some embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, the administering 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, 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 1°C after treatment with an antipyretic.

[0021] Provided herein are methods of selecting a subject for treatment with a cell therapy, where the methods involve: assaying a biological sample for the level, amount or concentration of tumor necrosis factor (TNF) and/or interleukin-16 (IL-16), wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including

a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL; and if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, selecting the subject for administration of the cell therapy at a reduced dose; administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity; administration of the cell therapy that is carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; and/or administration of an alternative treatment other than the cell therapy for treating the CLL or SLL; or if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, selecting the subject for administration of the cell therapy, optionally wherein 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 1°C after treatment with an antipyretic; and/or 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 1°C after treatment with an antipyretic.

[0022] In some of any [embodimentexamples](#), the method further includes administering 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 and/or the alternative treatment to the subject. In some of any [embodimentexamples](#), the method further includes administering the cell therapy to the subject. In some of any [embodimentexamples](#), the method further includes administering the agent to the subject. In some of any [embodimentexamples](#), the method further includes administering the other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity. In some of any [embodimentexamples](#), the method further includes administering the alternative treatment to the subject.

[0023] Provided herein are methods of determining the risk of developing a toxicity after administration of a cell therapy, where the methods involve: assaying a biological sample from a subject for the level, amount or concentration of TNF and/or IL-16, said subject having received administration of a cell therapy including a dose of engineered cells including T cells expressing a CAR for treating a CLL or SLL, wherein the biological sample is obtained from the subject prior to peak CAR+ T cell expansion and/or within at or about 11 days after the initiation of administration of the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL; and if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, identifying the subject as at risk for developing a neurotoxicity; or if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, identifying the subject as not at risk for developing a neurotoxicity.

[0024] In some of any embodimentexamples, if the subject is identified as at risk for developing a neurotoxicity, the method further includes 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, optionally prior to peak CAR+ T cell expansion and/or within at or about 11 days of administering the cell therapy to the subject; and/or the follow-up is carried out in an in-patient setting and/or with admission to a hospital for one or more days. In some of any embodimentexamples, if the subject is identified as not at risk for developing a neurotoxicity, the 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 1°C after treatment with an antipyretic. In some of any embodimentexamples, if the subject is identified as at risk for developing a neurotoxicity, the method further includes 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. In some of any embodimentexamples, if the subject is identified as at risk for developing a neurotoxicity, the method further includes 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 prior to peak CAR+ T cell expansion. In some of any embodimentexamples, if the subject is identified as at risk

for developing a neurotoxicity, the method further includes 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 within at or about 11 days of administering the cell therapy to the subject. In some of any [embodimentexamples](#), if the subject is identified as at risk for developing a neurotoxicity, the follow-up is carried out in an in-patient setting and/or with admission to a hospital for one or more days. In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the 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. In some of any [embodimentexamples](#), if the subject is identified as not at risk for developing a neurotoxicity, the 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, 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 1°C after treatment with an antipyretic.

[0025] Provided herein are methods of treatment, wherein the methods involve: administering to a subject identified as at risk of developing a 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 CLL or SLL, wherein, at or immediately prior to administering the agent, the subject is selected or identified as being at risk of developing a neurotoxicity if the level or amount or concentration of TNF and/or IL-16 in a biological sample, obtained from the subject prior to peak CAR⁺ T cell expansion and/or within at or about 11 days of the initiation of administration of the cell therapy, is above a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL. In some [embodimentexamples](#), the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL. In some [embodimentexample](#)s, the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL.

[0026] Provided herein are methods of selecting a subject for treatment with an agent, where the methods involve: assaying a biological sample from a subject for the level, amount or concentration of TNF and/or IL-16, said subject having received administration of a cell therapy including a dose of engineered cells including T cells expressing a CAR that binds CD19 for

treating a CLL or SLL, wherein the biological sample is obtained from the subject prior to peak CAR+ T cell expansion and/or within at or about 11 days after the initiation of administration of the cell therapy; and comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 900 pg/mL; and if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, selecting the subject for administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity.

[0027] In some of any [embodimentexamples](#), the method further includes 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. In some of any [embodimentexamples](#), administering the agent or other treatment 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 1°C after treatment with an antipyretic. In some of any [embodimentexamples](#), administering to the subject the cell therapy is carried out on an outpatient basis and, if the level, amount or concentration of TNF and/or IL-16 is above a threshold level the methods involve: admitting the patient to a hospital for one or more days.

[0028] In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 7 pg/mL, 8 pg/mL, 9 pg/mL, 10 pg/mL, 15 pg/mL, 20 pg/mL, or 25 pg/mL, or a value between any of the foregoing. In some of any [embodimentexamples](#), the threshold level for TNF is a value between at or about 8 pg/mL and at or about 10 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 7 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 8 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 9 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 10 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 15 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 20 pg/mL. In some of any [embodimentexamples](#), the threshold level for TNF is a value of at or about 25 pg/mL.

[0029] In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 400 pg/mL, 500 pg/mL, 600 pg/mL, 700 pg/mL, 800 pg/mL, 900 pg/mL or 1000 pg/mL, or a value between any of the foregoing. In some of any [embodimentexamples](#), threshold level for IL-16 is a value between at or about 500 pg/mL and at or about 700 pg/mL. In some of any [embodimentexamples](#),

the threshold level for IL-16 is a value of at or about 400 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 500 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 600 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 700 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 800 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 900 pg/mL. In some of any [embodimentexamples](#), the threshold level for IL-16 is a value of at or about 1000 pg/mL.

[0030] In some of any [embodimentexamples](#), the level, amount or concentration of both TNF and IL-16 are assessed; and the threshold level for TNF is a value of at or about 7 pg/mL, 8 pg/mL, 9 pg/mL, 10 pg/mL, 15 pg/mL, 20 pg/mL, or 25 pg/mL, or a value between any of the foregoing the threshold level for IL-16 is a value of at or about 400 pg/mL, 500 pg/mL, 600 pg/mL, 700 pg/mL, 800 pg/mL, 900 pg/mL or 1000 pg/mL, or a value between any of the foregoing.

[0031] In some of any [embodimentexamples](#), the level, amount or concentration of both TNF and IL-16 are assessed; and the threshold level for TNF is a value between at or about 8 pg/mL and at or about 10 pg/mL; and the threshold level for IL-16 is a value between at or about 500 pg/mL and at or about 700 pg/mL.

[0032] In some of any [embodimentexamples](#), the biological sample is or is obtained from a blood, plasma or serum sample. In some of any [embodimentexamples](#), assessing includes contacting a biological sample with one or more reagent capable of detecting or that is specific for TNF and/or IL-16, optionally wherein the one or more reagent includes an antibody that specifically recognizes TNF and/or IL-16; and detecting the presence or absence of a complex including the one or more reagent and TNF and/or IL-16. In some of any [embodimentexamples](#), assessing includes contacting a biological sample with one or more reagent capable of detecting or that is specific for TNF and detecting the presence or absence of a complex including the one or more reagent and TNF. In some [embodimentexamples](#), the one or more reagent includes an antibody that specifically recognizes TNF. In some of any [embodimentexamples](#), assessing includes contacting a biological sample with one or more reagent capable of detecting or that is specific for IL-16 and detecting the presence or absence of a complex including the one or more reagent and IL-16. In some [embodimentexamples](#), the one or more reagent includes an antibody that specifically recognizes IL16. In some of any [embodimentexamples](#), assessing includes an immunoassay. In some [embodimentexamples](#), the assessing comprises enzyme-linked immunosorbent assay (ELISA), immunoblotting, immunoprecipitation, radioimmunoassay (RIA), immunostaining, a flow cytometry assay, surface plasmon resonance (SPR), a chemiluminescence assay, a lateral flow immunoassay, an

inhibition assay or an avidity assay. In some embodimentexamples, the assessing comprises an enzyme-linked immunosorbent assay (ELISA). In some embodimentexamples, the assessing comprises a sandwich enzyme-linked immunosorbent assay (ELISA). In some embodimentexamples, the ELISA is a bead-based ELISA.

[0033] In some of any embodimentexamples, the agent or other treatment is or includes an anti-IL-6 antibody, anti-IL-6R antibody or a steroid. In some of any embodimentexamples, the agent or other treatment is or includes an anti-IL-6 antibody. In some of any embodimentexamples, the agent or other treatment is or includes an anti-IL-6R antibody. In some of any embodimentexamples, the agent or other treatment is or includes a steroid. In some of any embodimentexamples, the agent is or includes tocilizumab, siltuximab or dexamethasone. In some of any embodimentexamples, the agent is or includes tocilizumab. In some of any embodimentexamples, the agent is or includes siltuximab. In some of any embodimentexamples, the agent is or includes dexamethasone. In some of any embodimentexamples, the neurotoxicity is severe neurotoxicity. In some of any embodimentexamples, the neurotoxicity is grade 3 or higher neurotoxicity. In some of any embodimentexamples, the neurotoxicity is grade 3 neurotoxicity. In some of any embodimentexamples, the neurotoxicity is grade 4 neurotoxicity. In some of any embodimentexamples, the neurotoxicity is grade 5 neurotoxicity.

[0034] Provided herein are methods of assessing likelihood of a response to a cell therapy, where the methods involve: assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering the cell therapy; and comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level; wherein if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy.

[0034a] In one aspect, the present disclosure refers to a method of assessing likelihood of a response to a cell therapy, the method comprising: assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administration of the cell therapy; and comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level; wherein: (1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or (2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy.

[0035] Provided herein are methods of selecting a subject for treatment with a cell therapy, where the methods involve: assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a

biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy including a dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering the cell therapy; and selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level for each; wherein if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy. In some of any embodiment examples, the method further includes administering the cell therapy to the subject selected for treatment.

[0035a] In one aspect, the present disclosure refers to a method of selecting a subject for treatment with a cell therapy, wherein the method comprises: assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administration of the cell therapy; and selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level for each; wherein: (1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or (2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy.

[0036] Provided herein are methods for treatment, where the methods involve: selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, to a threshold level for each, wherein if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy; wherein the biological sample is from a subject having a CLL or a SLL that is a candidate for treatment with a cell therapy, said cell therapy including a

dose of engineered cells including T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering the cell therapy and/or the subject does not include the T cells expressing the CAR; and administering the cell therapy to a subject selected for treatment.

[0036a] In one aspect, the present disclosure refers to use of a cell therapy in the manufacture of a medicament for the treatment of a cancer wherein the cell therapy is to be administered to a subject selected for treatment by a method comprising: (a) selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, to a threshold level for each, wherein: (1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or (2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy; wherein the biological sample is from a subject having a CLL or a SLL that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is to be obtained from the subject prior to administration of the cell therapy and/or the subject does not comprise the T cells expressing the CAR.

[0036b] In one aspect, the present disclosure refers to a pharmaceutical composition for use in the treatment of a cancer comprising a cell therapy, wherein the cell therapy is to be administered to a subject selected for treatment by a method comprising: (a) selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, to a threshold level for each, wherein: (1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or (2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy; wherein the biological sample is from a subject having a CLL or a SLL that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is to be obtained from the subject prior to administration of the cell therapy and/or the subject does not comprise the T cells expressing the CAR.

[0037] In some of any embodiment examples, the threshold level is within 25%, within 20%, within 15%, within 10% or within 5% and/or is within a standard deviation is at or about or above the median or mean level, amount or concentration of VEGFC and/or VEGFR1 in a biological

sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group achieved a response, after administration of a dose of engineered cells expressing the CAR for treating the CLL or the SLL; 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 VEGFC and/or VEGFR1 in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group achieved a response, after administration of a dose of engineered cells expressing the CAR for treating the CLL or the SLL; 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 VEGFC and/or VEGFR1 in a biological sample obtained from a group of normal or healthy subjects that are not candidates for treatment with the cell therapy. In some of any embodimentexamples, the threshold level for VEGFC is a value between at or about 60 pg/mL and at or about 70 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value between at or about 80 pg/mL and at or about 120 pg/mL. In some of any embodimentexamples, the level, amount or concentration of both VEGFC and VEGFR1 are assessed; and the threshold level for VEGFC is a value between at or about 60 pg/mL and at or about 70 pg/mL; and the threshold level for VEGFR1 is a value between at or about 80 pg/mL and at or about 120 pg/mL. In some of any embodimentexamples, the threshold level for VEGFC is a value at or about 60 pg/mL. In some of any embodimentexamples, the threshold level for VEGFC is a value at or about 65 pg/mL. In some of any embodimentexamples, the threshold level for VEGFC is a value at or about 70 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value at or about 80 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value at or about 90 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value at or about 100 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value at or about 110 pg/mL. In some of any embodimentexamples, the threshold level for VEGFR1 is a value at or about 120 pg/mL.

[0038] In some of any embodimentexamples, the biological sample is or is obtained from a blood, plasma or serum sample. In some of any embodimentexamples, assessing includes contacting a biological sample with one or more reagent capable of detecting or that is specific for VEGFC and/or VEGFR1, optionally wherein the one or more reagent includes an antibody that specifically recognizes VEGFC and/or VEGFR1; and detecting the presence or absence of a complex including the one or more reagent and VEGFC and/or VEGFR1. In some of any embodimentexamples, assessing includes contacting a biological sample with one or more reagent

capable of detecting or that is specific for VEGFC and detecting the presence or absence of a complex including the one or more reagent and VEGFC. In some of any [embodimentexamples](#), the one or more reagent includes an antibody that specifically recognizes VEGFC. In some of any [embodimentexamples](#), assessing includes contacting a biological sample with one or more reagent capable of detecting or that is specific for VEGFR1 and detecting the presence or absence of a complex including the one or more reagent and VEGFR1. In some of any [embodimentexamples](#), the one or more reagent includes an antibody that specifically recognizes VEGFR1. In some of any [embodimentexamples](#), the assessing includes an immunoassay. In some of any [embodimentexamples](#), the response includes objective response. In some of any [embodimentexamples](#), the objective response includes complete response (CR; also known in some cases as complete remission), complete remission with incomplete blood count recovery (CRi), complete remission (CR), CR with incomplete marrow recovery (CRi), nodular partial remission (nPR), partial response (PR). In some of any [embodimentexamples](#), the response is assessed at or about 1, 2, or 3 months or more after the initiation of administration of the cell therapy.

[0039] In some of any [embodimentexamples](#), the response is assessed at or about 1 month after the initiation of administration of the cell therapy. In some of any [embodimentexamples](#), the response is assessed at or about 2 months after the initiation of administration of the cell therapy. In some of any [embodimentexamples](#), the response is response that is assessed at or about 3 months after the initiation of administration of the cell therapy.

[0040] In some of any [embodimentexamples](#), the method further includes, prior to the administration of the cell therapy, administering a lymphodepleting therapy to the subject. In some of any [embodimentexamples](#), the subject has been preconditioned with a lymphodepleting therapy. In some of any [embodimentexamples](#), the lymphodepleting therapy includes the administration of fludarabine and/or cyclophosphamide. In some [embodimentexamples](#), the biological sample is obtained from the subject prior to administration of the lymphodepleting therapy to the subject. In some [embodimentexamples](#), the value of the one or more parameters of disease burden is the value of the one or more parameters of disease burden prior to administration of a lymphodepleting therapy to the subject. In some [embodimentexamples](#), the one or more parameters of disease burden is assessed prior to administration of a lymphodepleting therapy to the subject.

[0041] In some of any [embodimentexamples](#), the lymphodepleting therapy includes the administration of fludarabine. In some of any [embodimentexamples](#), the lymphodepleting therapy includes the administration of cyclophosphamide. In some of any [embodimentexamples](#), the lymphodepleting therapy includes the administration of fludarabine and cyclophosphamide. In

some of any [embodimentexamples](#), the lymphodepleting therapy includes administration of cyclophosphamide at about 200-400 mg/m², optionally at or about 300 mg/m², inclusive, and/or fludarabine at about 20-40 mg/m², optionally 30 mg/m², daily for 2-4 days, optionally for 3 days. In some of any [embodimentexamples](#), the lymphodepleting therapy includes administration of cyclophosphamide at or about 300 mg/m² and fludarabine at about 30 mg/m² 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.

[0042] In some of any [embodimentexamples](#), the method further includes administering a Bruton's Tyrosine Kinase inhibitor (BTKi) to the subject. In some of any [embodimentexamples](#), the BTKi is ibrutinib. In some of any [embodimentexamples](#), the BTKi administration is initiated prior to the initiation of administration of the cell therapy. In some of any [embodimentexamples](#), the BTKi administration is continued until after the initiation of administration of the cell therapy. In some of any [embodimentexamples](#), the BTKi administration is continued for at least at or about 90 days after the initiation of administration of the cell therapy. In some of any [embodimentexamples](#), the ibrutinib is administered at a dose of at or about 140 mg to at or about 840 mg per day. In some of any [embodimentexamples](#), the ibrutinib is administered at a dose of at or about 280 mg to at or about 560 mg per day. In some of any [embodimentexamples](#), the ibrutinib is administered at a dose of at or about 420 mg per day. In some of any [embodimentexamples](#), the disease or condition is a relapsed or refractory (r/r) CLL. In some of any [embodimentexamples](#), the disease or condition is a relapsed or refractory (r/r) SLL.

[0043] In some of any [embodimentexamples](#), the dose of engineered cells includes 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 of any [embodimentexamples](#), the dose of engineered cells includes a defined ratio of CD4⁺ cells expressing the CAR to CD8⁺ cells expressing the CAR. In some [embodimentexamples](#), the ratio is between approximately 1:3 and approximately 3:1. In some of any [embodimentexamples](#), the dose of engineered cells includes a defined ratio of CD4⁺ cells expressing the CAR to CD8⁺ cells expressing the CAR that is or is approximately 1:1. In some of any [embodimentexamples](#), the dose of engineered cells includes at or about 2.5 x 10⁷ total CAR-expressing cells to at or about 1.0 x 10⁸ total CAR-expressing cells. In some of any [embodimentexamples](#), the dose of engineered cells includes at or about 2.5 x 10⁷ total CAR-expressing cells.

[0044] In some of any [embodimentexamples](#), the dose of engineered cells includes at or about 5 x

10⁷ total cells or total CAR-expressing cells. In some of any [embodimentexamples](#), the dose of engineered cells includes at or about 1 x 10⁸ total cells or total CAR-expressing cells. In some of any [embodimentexample](#), administration of the cell therapy includes administering a plurality of separate compositions, wherein the plurality of separate compositions includes a first composition including one of the CD4⁺ T cells and the CD8⁺ T cells and a second composition including the other of the CD4⁺ T cells and the CD8⁺ T cells. In some of any [embodimentexamples](#), the first composition includes the CD8⁺ T cells and the second composition includes the CD4⁺ T cells.

[0045] In some of any [embodimentexamples](#), the initiation of the administration of the first composition is carried out prior to the initiation of the administration of the second composition, optionally carried out no more than 48 hours apart. In some of any [embodimentexamples](#), the initiation of the administration of the first composition is carried out no more than 48 hours prior to the initiation of the administration of the second composition. In some of any [embodimentexamples](#), the CAR included by the CD4⁺ T cells and/or the CAR included by the CD8⁺ T cells includes 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. In some of any [embodimentexamples](#), the CAR expressed by the CD4⁺ T cells and the CAR expressed by the CD8⁺ T cells is the same. In some [embodimentexamples](#), the CD4⁺ T cells and the CD8⁺ T cells are genetically engineered to express a CAR that is the same. In some of any [embodimentexamples](#), prior to the administration of the cell therapy, 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 at least two prior therapies. In some of any [embodimentexamples](#), prior to the administration of the cell therapy, 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 of any [embodimentexamples](#), prior to the administration of the cell therapy, the subject has been treated with at least two prior therapies for the CLL or SLL, other than another dose of cells expressing CAR or a lymphodepleting therapy. In some of any [embodimentexample](#), prior to the administration of the cell therapy, 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.

[0046] In some of any [embodimentexamples](#), 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 including fludarabine and rituximab; radiation therapy; and hematopoietic stem cell transplantation (HSCT). In some of any [embodimentexamples](#), the one or more

prior therapies includes ibrutinib. In some of any [embodimentexamples](#), the one or more prior therapies includes venetoclax. In some of any [embodimentexamples](#), the one or more prior therapies include an inhibitor of Bruton's tyrosine kinase (BTK) and/or venetoclax. In some of any [embodimentexamples](#), the one or more prior therapies include ibrutinib and venetoclax.

[0047] In some of any [embodimentexamples](#), the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to an inhibitor of Bruton's tyrosine kinase (BTK) and/or venetoclax. In some of any [embodimentexamples](#), the subject has relapsed following remission after treatment with, become refractory to, failed treatment with and/or is intolerant to ibrutinib. In some of any [embodimentexamples](#), the subject has relapsed following remission after treatment with, become refractory to, failed treatment with and/or is intolerant to venetoclax. In some of any [embodimentexamples](#), the subject has relapsed following remission after treatment with, become refractory to, failed treatment with and/or is intolerant to ibrutinib and venetoclax. In some of any [embodimentexamples](#), the engineered cells are primary T cells obtained from a subject. In some of any [embodimentexamples](#), the engineered cells are autologous to the subject.

[0048] In some of any [embodimentexamples](#), the CAR includes an extracellular antigen-binding domain specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is a 4-1BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is a CD3zeta and the CAR includes, 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. In some of any [embodimentexamples](#), the antigen-binding domain is an scFv.

[0049] In some of any [embodimentexamples](#), the scFv includes 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 VIWGSETTYNSALKS (SEQ ID NO: 39), and/or a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40); the scFv includes 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 includes a V_H set forth in SEQ ID NO: 41 and a V_L set forth in SEQ ID NO: 42, optionally wherein the V_H and V_L are separated by a flexible linker, optionally wherein the flexible linker

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

[0050] In some of any [embodimentexamples](#), the costimulatory signaling region is a signaling domain of CD28 or 4-1BB. In some of any [embodimentexamples](#), the costimulatory signaling region is a signaling domain of 4-1BB. In some of any [embodimentexamples](#), the costimulatory domain includes 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 of any [embodimentexamples](#), the primary signaling domain is a CD3zeta signaling domain. In some of any [embodimentexamples](#), the primary signaling domain includes 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.

[0051] In some of any [embodimentexamples](#), the CAR further includes a spacer between the transmembrane domain and the scFv. In some of any [embodimentexamples](#), the spacer is a polypeptide spacer that includes 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 of any [embodimentexamples](#), the spacer is about 15 amino acids or less, and does not include a CD28 extracellular region or a CD8 extracellular region. In some of any [embodimentexamples](#), the spacer is at or about 12 amino acids in length. In some of any [embodimentexamples](#), 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 includes or consists of the formula X_1PPX_2P , where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

[0052] In some of any [embodimentexamples](#), the scFv includes an amino acid sequence of RASQDISKYLN (SEQ ID NO: 35), an amino acid sequence of SRLHSGV (SEQ ID NO: 36), and/or an amino acid sequence of GNTLPYTFG (SEQ ID NO: 37) and/or an amino acid sequence of DYGVN (SEQ ID NO: 38), an amino acid sequence of VIWGSETTYNSALKS (SEQ ID NO: 39), and/or an amino acid sequence of YAMDYWG (SEQ ID NO: 40) or wherein the scFv includes a variable heavy chain region of FMC63 and a variable light chain region of FMC63 and/or a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63 or binds to the same epitope as or competes for binding with any of the foregoing, and optionally wherein the scFv includes, in order, a V_H , a linker, optionally

including SEQ ID NO: 24, and a V_L, and/or the scFv includes a flexible linker and/or includes the amino acid sequence set forth as SEQ ID NO: 43; and/or the spacer is a polypeptide spacer that (a) includes or consists of all or a portion of an immunoglobulin hinge or a modified version thereof or includes about 15 amino acids or less, and does not include a CD28 extracellular region or a CD8 extracellular region, (b) includes or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4 hinge, or a modified version thereof and/or includes about 15 amino acids or less, and does not include a CD28 extracellular region or a CD8 extracellular region, or (c) is at or about 12 amino acids in length and/or includes or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4, or a modified version thereof; or (d) has or consists of the sequence of SEQ ID NO: 1, a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto, or (e) includes or consists of the formula X₁PPX₂P, where X₁ is glycine, cysteine or arginine and X₂ is cysteine or threonine; and/or the costimulatory domain includes SEQ ID NO: 12 or a variant thereof having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto; and/or the primary signaling domain includes SEQ ID NO: 13, 14 or 15 having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto.

[0053] In some of any [embodiment examples](#), the antigen binding domain includes an scFv that includes a variable heavy chain region of FMC63 and a variable light chain region of FMC63; the spacer is a polypeptide spacer that includes the sequence of SEQ ID NO: 1; the costimulatory domain includes SEQ ID NO: 12; and the primary signaling domain includes SEQ ID NO: 13, 14 or 15. In some of any [embodiment examples](#), the subject is a human subject.

[0054] Provided herein is an article of manufacture including a composition for a cell therapy, or one of a plurality of compositions for a cell therapy, including T cells expressing a CAR that binds CD19, and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to any of the provided methods.

[0054a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition for a cell therapy, or one of a plurality of compositions for a cell therapy, comprising T cells expressing a CAR that binds CD19, and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the methods or the use or the pharmaceutical composition for use disclosed herein.

[0054b] In one aspect, the present disclosure refers to a cell therapy comprising T cells expressing a CAR that binds CD19 for use in treating a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL), according to the methods or the use or the pharmaceutical composition for use disclosed herein.

Brief Description of the Drawings

[0055] **FIG. 1A** show results of the best overall response in subjects with R/R CLL (N=22) administered anti-CD19 CAR+ T cells at DL1 (5 x 10⁷ CAR-expressing T cells) or DL2 (1 x 10⁸ CAR-expressing T cells). PD, progressive disease; SD, stable disease; PR, partial response;

Claims

1. A method of determining the risk of developing a toxicity after administration of a cell therapy, the method comprising:

assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to ~~administering administration of~~ the cell therapy; and

comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein:

(1) identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy if: (a) the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; (b) the blood tumor burden is below the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio; or

(2) identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy if: (a) the lymph node tumor burden is below the threshold level for tumor burden; (b) the blood tumor burden is at or above the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio.

2. The method of claim 1, wherein if the subject is identified as at risk for developing a neurotoxicity, ~~the method further comprises:~~

(i) ~~administering to~~ the subject is to be administered the cell therapy, optionally at a reduced dose, optionally wherein:

(a) ~~the method further comprises administering to~~ the subject is to be 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 ~~administering-administration~~ of the cell therapy to the subject is to be carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; or

(ii) ~~administering to~~ the subject is to be administered an alternative treatment other than the cell therapy for treating the CLL or SLL.

3. The method of claim 1, wherein if the subject is identified as not at risk for developing a neurotoxicity, ~~the method further comprises:~~

(i) ~~administering to~~ the subject is to be administered the cell therapy, optionally wherein:

(a) 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 1°C after treatment with an antipyretic; and/or

(b) the ~~administering-administration~~ of the cell therapy and any follow-up is to be 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 1°C after treatment with an antipyretic.

4. A method of selecting a subject for treatment with a cell therapy, wherein the method comprises:

assessing one or more parameters of disease burden selected from among lymph node tumor burden, blood tumor burden and the ratio of blood tumor burden to lymph node tumor burden, in a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the parameter is assessed from the subject prior to ~~administering-administration of~~ the cell therapy; and

comparing, individually, the value of the one or more parameters to a threshold level for the respective parameter, wherein:

(1) if (a) the lymph node tumor burden is at or above the threshold level for lymph node tumor burden; (b) the blood tumor burden is below the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is below the threshold level for the ratio, selecting the subject for:

(i) administration of the cell therapy at a reduced dose;

(ii) administration of an agent or other treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of the neurotoxicity;

(iii) administration of the cell therapy that is carried out or is specified to be carried out in an in-patient setting and/or with admission to a hospital for one or more days; and/or

(iv) administration of an alternative treatment other than the cell therapy for treating the CLL or SLL; or

(2) if (a) the lymph node tumor burden is below the threshold level for tumor burden; (b) the blood tumor burden is at or above the threshold level for blood tumor burden; and/or (c) the ratio of blood tumor burden to lymph node tumor burden is above the threshold level for the ratio, selecting the subject for:

(i) administration of the cell therapy, optionally wherein:

(a) 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 1°C after treatment with an antipyretic; and/or

(b) 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 1°C after treatment with an antipyretic.

5. The method of claim 4, ~~further comprising administering wherein~~ 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 and/or the alternative treatment is to be administered to the subject.

6. The method of any of claims 1-5, wherein the assessing the blood tumor burden comprises determining the lymphocyte concentration in the blood of the subject, optionally wherein the concentration is the lymphocyte count per microliter (μL) of blood.

~~7. The method of claim 6 wherein the concentration is the lymphocyte count per microliter (μL) of blood.~~

~~7~~8. The method of any of claims 1-~~6~~7, wherein the threshold level for blood tumor burden is a value between at or about 800 lymphocytes/ μL and at or about 3000 lymphocytes/ μL , optionally wherein the threshold level for blood tumor burden is a value of at or about 800 lymphocytes/ μL , 900 lymphocytes/ μL , 1000 lymphocytes/ μL , 1250 lymphocytes/ μL , 1500 lymphocytes/ μL , 1750 lymphocytes/ μL , 2000 lymphocytes/ μL , 2250 lymphocytes/ μL , 2500 lymphocytes/ μL , 2750 lymphocytes/ μL or 3000 lymphocytes/ μL , or a value between any of the foregoing.

~~9. The method of claim 8, wherein the threshold level for blood tumor burden is a value of at or about 800 lymphocytes/ μL , 900 lymphocytes/ μL , 1000 lymphocytes/ μL , 1250 lymphocytes/ μL , 1500 lymphocytes/ μL , 1750 lymphocytes/ μL , 2000 lymphocytes/ μL , 2250 lymphocytes/ μL , 2500 lymphocytes/ μL , 2750 lymphocytes/ μL or 3000 lymphocytes/ μL , or a value between any of the foregoing.~~

~~8~~10. The method of any of claims 1-~~7~~9, wherein the assessing the lymph node tumor burden comprises determining the largest lymph node diameter, optionally wherein the largest lymph node diameter is measured in centimeters (cm).

~~11. The method of claim 10, wherein the largest lymph node diameter is measured in centimeters (cm).~~

912. The method of claim ~~810 or claim 11~~, wherein the threshold level for the largest lymph node diameter as the lymph node tumor burden is a value between at or about 4 cm and at or about 7 cm.

~~13.—The method of any of claims 10-12, wherein the threshold level for the largest lymph node diameter as the lymph node tumor burden is a value of at or about 4 cm, 4.25 cm, 4.5 cm, 4.75 cm, 5 cm, 5.25 cm, 5.5 cm, 5.75 cm, 6 cm, 6.25 cm, 6.5 cm, 6.75 cm or 7 cm, or a value between any of the foregoing.~~

104. The method of any of claims 1-~~79~~, wherein the assessing the ratio of blood tumor burden to lymph node tumor burden comprises determining the ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm), optionally wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value between at or about 300 and at or about 1000.

~~15.—The method of claim 14, wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value between at or about 300 and at or about 1000.~~

~~16.—The method of claim 14 or claim 15, wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to the largest lymph node diameter in centimeters (cm) as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000, or a value between any of the foregoing.~~

117. The method of any of claims 1-~~79~~, wherein the assessing the lymph node tumor burden comprises determining the sum of the products of diameters (SPD).

~~18.—The method of claim 17, wherein the SPD is measured in centimeters squared (cm^2).~~

129. The method of claim 1~~17~~ or claim 18, wherein the threshold level for the SPD as the lymph node tumor burden is a value between at or about 10 cm² and at or about 40 cm².

~~20.—The method of any of claims 17-19, wherein the threshold level for the SPD as the lymph node tumor burden is a value of at or about 10 cm², 12.5 cm², 15 cm², 17.5 cm², 20 cm², 22.5 cm², 25 cm², 27.5 cm², 30 cm², 32.5 cm², 35 cm², 37.5 cm² or 40 cm², or a value between any of the foregoing.~~

1321. The method of any of claims 1-79 and 1~~17-1220~~, wherein the assessing the ratio of blood tumor burden to lymph node tumor burden comprises determining the ratio of the lymphocyte count per microliter (μL) of blood to the sum of the products of diameters (SPD) in centimeters squared (cm²), optionally wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value between at or about 25 and at or about 500.

~~22.—The method of claim 21, wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value between at or about 25 and at or about 500.~~

~~23.—The method of claim 21 or claim 22, wherein the threshold level for ratio of the lymphocyte count per microliter (μL) of blood to SPD as the ratio of blood tumor burden to lymph node tumor burden is a value of at or about 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450 or 500, or a value between any of the foregoing.~~

214. The method of any of claims 1-213, wherein the value of the one or more parameters of disease burden is the value of the one or more parameters of disease burden prior to administration of a lymphodepleting therapy to the subject.

215. A method of determining the risk of developing a toxicity after administration of a cell therapy, the method comprising:

assaying a biological sample for the level, amount or concentration of tumor necrosis factor (TNF) and/or interleukin-16 (IL-16), wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is

a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to administering administration of the cell therapy or prior to peak CAR+ T cell expansion and/or within at or about 11 days after the initiation of administration of the cell therapy; and

comparing, individually, the level, amount or concentration of TNF and/or IL-16 to a threshold level for each, wherein:

the threshold level for TNF is a value between at or about 7 pg/mL and at or about 25 pg/mL; and/or

the threshold level for IL-16 is a value between at or about 400 pg/mL and at or about 1000 pg/mL; and

(1) if the level, amount or concentration of TNF and/or IL-16 is at or above the respective threshold level, identifying the subject as at risk for developing a neurotoxicity following administration of the cell therapy; or

(2) if the level, amount or concentration of TNF and/or IL-16 is below the respective threshold level, identifying the subject as not at risk for developing a neurotoxicity following administration of the cell therapy.

216. The method of any of claims 2-~~21~~4, wherein the agent or other treatment is or comprises an anti-IL-6 antibody, anti-IL-6R antibody or a steroid or the agent is or comprises tocilizumab, siltuximab or dexamethasone.

~~27. The method of any of claims 2-24, wherein the agent is or comprises tocilizumab, siltuximab or dexamethasone.~~

1728. The method of any of claims 1-~~162~~7, wherein the neurotoxicity is severe neurotoxicity and/or the neurotoxicity is grade 3 or higher neurotoxicity.

~~29. The method of any of claims 1-28, wherein the neurotoxicity is grade 3 or higher neurotoxicity.~~

1830. A method of assessing likelihood of a response to a cell therapy, the method comprising:

assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to ~~administering~~ administration ~~of~~ the cell therapy; and

comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level; wherein:

(1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or

(2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy.

1931. A method of selecting a subject for treatment with a cell therapy, wherein the method comprises:

assessing the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, wherein the biological sample is from a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL) that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is obtained from the subject prior to ~~administering~~ administration ~~of~~ the cell therapy; and

selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of the VEGFC and/or VEGFR1 in the sample to a threshold level for each; wherein:

(1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or

(2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy.

~~32. The method of claim 30 or claim 31, further comprising administering the cell therapy to the subject selected for treatment.~~

2033. Use of a cell therapy in the manufacture of a medicament for the treatment of a cancer wherein the cell therapy is to be administered to a subject selected for treatment by a method comprising~~A method for treatment, wherein the method comprises:~~

(a) selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, to a threshold level for each, wherein:

(1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or

(2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy;

wherein the biological sample is from a subject having a CLL or a SLL that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is to be obtained from the subject prior to ~~administering administration of~~ the cell therapy and/or the subject does not comprise the T cells expressing the CAR;~~and~~

~~(b) administering the cell therapy to a subject selected for treatment.~~

21. A pharmaceutical composition for use in the treatment of a cancer comprising a cell therapy, wherein the cell therapy is to be administered to a subject selected for treatment by a method comprising:

(a) selecting a subject who is likely to respond to treatment based on the results of determining a likelihood that a subject will achieve a response to the cell therapy by comparing, individually, the level, amount or concentration of vascular endothelial growth factor C (VEGFC) and/or vascular endothelial growth factor receptor 1 (VEGFR1) in a biological sample, to a threshold level for each, wherein:

(1) if the level, amount or concentration of VEGFC and/or VEGFR1 is below the respective threshold level, identifying the subject as having a high likelihood of achieving a response to the cell therapy; or

(2) if the level, amount or concentration of VEGFC and/or VEGFR1 is at or above the respective threshold level, identifying the subject as having a low likelihood of achieving a response to the cell therapy;

wherein the biological sample is from a subject having a CLL or a SLL that is a candidate for treatment with a cell therapy, said cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the biological sample is to be obtained from the subject prior to administration of the cell therapy and/or the subject does not comprise the T cells expressing the CAR.

2234. The method of or the use of or the pharmaceutical composition for use of any of claims 1830-2133, wherein:

the threshold level is within 25%, within 20%, within 15%, within 10% or within 5% and/or is within a standard deviation is at or about or above the median or mean level, amount or concentration of VEGFC and/or VEGFR1 in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects of the group achieved a response, after administration of a dose of engineered cells expressing the CAR for treating the CLL or the SLL;

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 VEGFC and/or VEGFR1 in a biological sample obtained from a group of subjects prior to receiving a cell therapy, wherein each of the subjects

of the group achieved a response, after administration of a dose of engineered cells expressing the CAR for treating the CLL or the SLL;

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 VEGFC and/or VEGFR1 in a biological sample obtained from a group of normal or healthy subjects that are not candidates for treatment with the cell therapy.

2335. The method of or the use of or the pharmaceutical composition for use of any of claims 1830-2234, the threshold level for VEGFC is a value between at or about 60 pg/mL and at or about 70 pg/mL, and/or the threshold level for VEGFR1 is a value between at or about 80 pg/mL and at or about 120 pg/mL.

~~36.—The method of any of claims 30-35, the threshold level for VEGFR1 is a value between at or about 80 pg/mL and at or about 120 pg/mL.~~

~~37.—The method of any of claims 30-36, wherein:
the level, amount or concentration of both VEGFC and VEGFR1 are assessed;
the threshold level for VEGFC is a value between at or about 60 pg/mL and at or about 70 pg/mL; and
the threshold level for VEGFR1 is a value between at or about 80 pg/mL and at or about 120 pg/mL.~~

2438. The method of or the use of or the pharmaceutical composition for use of any of claims 1830-2337, wherein the biological sample is or is obtained from a blood sample, a plasma sample, or a serum sample.

~~39.—The method of any of claims 30-38, wherein the assessing comprises:
(a) contacting a biological sample with one or more reagents capable of detecting, or that is specific for, VEGFC and/or VEGFR1, optionally wherein the one or more reagents comprise an antibody that specifically recognizes VEGFC and/or VEGFR1; and
(b) detecting the presence or absence of a complex comprising the one or more reagents and VEGFC and/or VEGFR1.~~

40. — ~~The method of any of claims 30-39, wherein the assessing comprises an immunoassay.~~

41. — ~~The method of any of claims 30-40, wherein the assessing comprises an enzyme-linked immunosorbent assay (ELISA), immunoblotting, immunoprecipitation, radioimmunoassay (RIA), immunostaining, a flow cytometry assay, surface plasmon resonance (SPR), a chemiluminescence assay, a lateral flow immunoassay, an inhibition assay or an avidity assay.~~

42. — ~~The method of any of claims 30-41, wherein the assessing comprises an enzyme-linked immunosorbent assay (ELISA), optionally a bead-based ELISA.~~

2543. The method of or the use of or the pharmaceutical composition for use of any of claims 1830-2442, wherein the response comprises objective response, optionally wherein the objective response comprises complete response (CR; also known in some cases as complete remission), complete remission with incomplete blood count recovery (CRi), complete remission (CR), CR with incomplete marrow recovery (CRi), nodular partial remission (nPR), partial response (PR); and/or

the response is response that is assessed at or about 1, 2, or 3 months or more after the initiation of administration of the cell therapy; and/or the response is response that is assessed at or about 3 months after the initiation of administration of the cell therapy.

44. — ~~The method of claim 43, wherein the objective response comprises complete response (CR; also known in some cases as complete remission), complete remission with incomplete blood count recovery (CRi), complete remission (CR), CR with incomplete marrow recovery (CRi), nodular partial remission (nPR), partial response (PR).~~

45. — ~~The method of any of claims 30-44, wherein the response is response that is assessed at or about 1, 2, or 3 months or more after the initiation of administration of the cell therapy.~~

46. — ~~The method of any of claims 30-45, wherein the response is response that is assessed at or about 3 months after the initiation of administration of the cell therapy.~~

2647. The method of or the use of or the pharmaceutical composition for use of any of claims 1-2546, ~~further comprising wherein~~, prior to the administration of the cell therapy, ~~administering~~ a lymphodepleting therapy is to be administered to the subject.

~~48.—The method of any of claims 1-47, wherein the subject has been preconditioned with a lymphodepleting therapy.~~

~~49.—The method of claim 48, wherein the biological sample is obtained from the subject prior to administration of the lymphodepleting therapy to the subject.~~

~~50.—The method of claim 48, wherein the one or more parameters of disease burden is assessed prior to administration of the lymphodepleting therapy to the subject.~~

~~51.—The method of any of claims 47-50, wherein the lymphodepleting therapy comprises the administration of fludarabine and/or cyclophosphamide.~~

~~52.—The method of any of claims 47-51, wherein the lymphodepleting therapy comprises administration of cyclophosphamide at about 200-400 mg/m², optionally at or about 300 mg/m², inclusive, and/or fludarabine at about 20-40 mg/m², optionally 30 mg/m², daily for 2-4 days, optionally for 3 days.~~

~~53.—The method of any of claims 47-52, wherein the lymphodepleting therapy comprises administration of cyclophosphamide at or about 300 mg/m² and fludarabine at about 30 mg/m² 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.~~

2754. The method of or the use of or the pharmaceutical composition for use of any of claims 1-2653, ~~further comprising administering wherein~~ a Bruton's Tyrosine Kinase inhibitor (BTKi) is to be administered to the subject, optionally wherein the BTKi is ibrutinib.

~~55.—The method of claim 54, wherein the BTKi is ibrutinib.~~

~~2856.~~ The method of or the use of or the pharmaceutical composition for use of claim ~~2754 or claim 55~~, wherein the BTKi administration is initiated prior to the initiation of administration of the cell therapy.

~~57.—The method of claim 56, wherein the BTKi administration is continued until after the initiation of administration of the cell therapy.~~

~~58.—The method of claim 56 or claim 57, wherein the BTKi administration is continued for at least about or about 90 days after the initiation of administration of the cell therapy.~~

~~529.~~ The method of or the use of or the pharmaceutical composition for use of claim ~~27~~any of claims 55-58, wherein:

the ibrutinib is to be administered at a dose of at or about 140 mg to at or about 840 mg per day;

the ibrutinib is to be administered at a dose of at or about 280 mg to at or about 560 mg per day;

the ibrutinib is to be administered at a dose of at or about 420 mg per day.

~~60.—The method of any of claims 55-59, wherein the ibrutinib is administered at a dose of at or about 280 mg to at or about 560 mg per day.~~

~~61.—The method of any of claims 55-60, wherein the ibrutinib is administered at a dose of at or about 420 mg per day.~~

~~3062.~~ The method of or the use of or the pharmaceutical composition for use of any of claims 1-~~2961~~, wherein the disease or condition is a relapsed or refractory (r/r) CLL; and/or wherein the disease or condition is a relapsed or refractory (r/r) SLL.

~~63.—The method of any of claims 1-62, wherein the disease or condition is a relapsed or refractory (r/r) SLL.~~

3164. The method of or the use of or the pharmaceutical composition for use of any of claims 1-3063, wherein the dose of engineered 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.

~~65.—The method of any of claim 1-64, wherein the dose of engineered cells comprises a defined ratio of CD4⁺ cells expressing the CAR to CD8⁺ cells expressing the CAR that is or is approximately 1:1.~~

3266. The method of any of claims 1-3165, wherein the dose of engineered 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.

~~67.—The method of any of claims 1-66, wherein the dose of engineered cells comprises at or about 2.5×10^7 total CAR-expressing cells.~~

~~68.—The method of any of claims 1-66, wherein the dose of engineered cells comprises at or about 5×10^7 total cells or total CAR-expressing cells.~~

~~69.—The method of any of claims 1-66, wherein the dose of engineered cells comprises at or about 1×10^8 total cells or total CAR-expressing cells.~~

~~70.—The method of any of claims 1-69, wherein administration of the cell therapy comprises administering 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.~~

~~71.—The method of any of claims 1-70, wherein the first composition comprises the CD8⁺ T cells and the second composition comprises the CD4⁺ T cells.~~

~~72.—The method of claim 71, 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 initiation of the administration of the first composition and the initiation of the administration of the second composition are carried out no more than 48 hours apart.~~

~~73.—The method of any of claim 64-72, 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.~~

3374. The method of or the use of or the pharmaceutical composition for use of any of claims 1-~~3273~~, wherein, prior to the administration of the cell therapy;

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 at least two prior therapies and/or

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.

~~75.—The method of any of claims 1-74, wherein, prior to the administration of the cell therapy, 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.~~

3476. The method of or the use of or the pharmaceutical composition for use of claim ~~3374 or claim 75~~, 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).

~~77.—The method of any of claims 74-76, wherein the one or more prior therapies comprise an inhibitor of Bruton's tyrosine kinase (BTK) and/or venetoclax.~~

~~78.—The method of any of claims 74-77, wherein the one or more prior therapies comprise ibrutinib and venetoclax.~~

~~79. The method of any of claims 74-77, wherein the subject has relapsed following remission after treatment with, become refractory to failed treatment with and/or is intolerant to an inhibitor of Bruton's tyrosine kinase (BTK) and/or venetoclax.~~

3580. The method of or the use of or the pharmaceutical composition for use of any of claims ~~74-79~~33 or claim 34, wherein the subject has relapsed following remission after treatment with, become refractory to, failed treatment with and/or is intolerant to ibrutinib and venetoclax.

3681. The method of or the use of or the pharmaceutical composition for use of any of claims 1-~~3580~~, wherein the engineered cells are primary T cells obtained from a subject.

3782. The method of or the use of or the pharmaceutical composition for use of any of claims 1-~~3681~~, wherein the engineered cells are autologous to the subject.

3883. The method of or the use of or the pharmaceutical composition for use of any of claims 1-~~3782~~, 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 4-1BB, 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.

~~84. The method of claim 83, wherein the antigen-binding domain is an scFv.~~

~~85. The method of claim 84, wherein:~~

~~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 DYGVVS (SEQ ID NO: 38), a CDRH2 sequence of~~

VIWGSETTYYN SALKS (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 V_H set forth in SEQ ID NO: 41 and a V_L set forth in SEQ ID NO: 42, optionally wherein the V_H and V_L 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.

86. — The method of any of claims 83–85, wherein the costimulatory signaling region is a signaling domain of CD28 or 4-1BB.

87. — The method of any of claims 83–86, wherein the costimulatory signaling region is a signaling domain of 4-1BB.

88. — The method of any of claims 83–87, wherein 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.

89. — The method of any of claims 83–88, wherein the primary signaling domain is a CD3zeta signaling domain.

90. — The method of any of claims 83–89, wherein the primary signaling domain comprises SEQ ID NO: 13, 14, or 15 having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto.

91. — The method of any of claims 83–90, wherein the CAR further comprises a spacer between the transmembrane domain and the antigen-binding domain.

92. ~~The method of claim 91, 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.~~

93. ~~The method of claim 91 or claim 92, wherein the spacer is about 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region.~~

94. ~~The method of any of claims 91-93, wherein the spacer is at or about 12 amino acids in length.~~

95. ~~The method of any of claims 91-94, wherein:~~

~~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.~~

96. ~~The method of any of claims 83-95, wherein:~~

~~the scFv comprises an amino acid sequence of RASQDISKYLN (SEQ ID NO: 35), an amino acid sequence of SRLHSGV (SEQ ID NO: 36), and/or an amino acid sequence of GNTLPYTTFG (SEQ ID NO: 37) and/or an amino acid sequence of DYGVVS (SEQ ID NO: 38); an amino acid sequence of VIWGSETTYNSALKS (SEQ ID NO: 39), and/or an amino acid sequence of YAMDYWG (SEQ ID NO: 40) or wherein the scFv comprises a variable heavy chain region of FMC63 and a variable light chain region of FMC63 and/or a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63 or binds to the same epitope as or competes for binding with any of the foregoing, and optionally wherein the scFv comprises, in order, a V_H , a linker, optionally comprising SEQ ID NO: 24, and a V_L , and/or the scFv comprises a flexible linker and/or comprises the amino acid sequence set forth as SEQ ID NO: 43;~~

~~the spacer is a polypeptide spacer that (a) comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof or comprises about 15 amino acids or less,~~

~~and does not comprise a CD28 extracellular region or a CD8 extracellular region, (b) comprises or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4 hinge, or a modified version thereof and/or comprises about 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region, or (c) is at or about 12 amino acids in length and/or comprises or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4, or a modified version thereof; or (d) has or consists of the sequence of SEQ ID NO: 1, a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto, or (e) comprises or consists of the formula X_1PPX_2P , where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine;~~

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

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

~~97. The method of any of claims 83-96, wherein:~~

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

~~the CAR further comprises a spacer that is a polypeptide spacer comprising the sequence of SEQ ID NO: 1;~~

~~the costimulatory domain comprises SEQ ID NO: 12; and~~

~~the primary signaling domain comprises SEQ ID NO: 13, 14 or 15.~~

~~98. The method of any of claims 1-97, wherein the subject is a human subject.~~

3999. An article of manufacture comprising a composition for a cell therapy, or one of a plurality of compositions for a cell therapy, comprising T cells expressing a CAR that binds CD19, and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the methods of or the use of or the pharmaceutical composition for use of any of claims 1-3898.

1040. A cell therapy comprising T cells expressing a CAR that binds CD19 for use in a ~~method of~~ treating a subject having a chronic lymphoblastic leukemia (CLL) or a small lymphocytic lymphoma (SLL), according to the methods of or the use of or the pharmaceutical composition for use of any of claims 1-3898.