Summary

[0005] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, such as a B-ALL or a B-NHL, including a malignancy thereof that is relapsed and/or refractory, the method comprising administering, to a subject at or younger than 25 years of age, or in some cases younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR). Such methods and uses include therapeutic methods and uses, for example, involving administration of the anti-CD19 CAR-expressing T cell compositions in an effective amount to effect treatment of the disease or disorder. Uses include uses of such anti-CD19 CAR-expressing in such methods and treatments, and in the preparation of a medicament in order to carry out such therapeutic methods. In some examples, the methods thereby treat the disease or condition or disorder in the subject.

[0006] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0006a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein: (i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, the medicament is formulated for administration of from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0006b] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age having or suspected of having a B cell malignancy, wherein: (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration of from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration of from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0007] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0008] In some of any examples, (i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is

between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

[0009] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0010] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0011] In some of any examples, (i) if the subject is less than 100 kilograms (kg) in body weight, the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

[0012] In some of any examples, if the subject is less than 100 kilograms (kg) in body weight the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1 x 10^6 CAR+ T cells/kg body weight of the subject. In some of any examples, if the subject is less than 100 kilograms (kg) in body weight the T cell composition is administered in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1 x 10^6 CAR+ T cells/kg body weight of the subject.

[0013] In some of any examples, if the subject is at or greater than 100 kilograms (kg) in body weight, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells. In some of any examples, if the subject is at or greater than 100 kilograms (kg) in body weight, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 1 x 10^8 CAR+ T cells. In some of any examples, if the subject is at or greater than 100 kilograms (kg) in body weight the T cell composition is administered in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells. In some of any

examples, if the subject is at or greater than 100 kilograms (kg) in body weight the T cell composition is administered in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1 x 10^8 CAR+ T cells.

[0014] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.05 x 10^8 CAR+ T cells.

[0015] In some of any examples, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; further comprising administering to the subject an additional dose of the T cell composition in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.1 x 10^8 CAR+ T cells.

[0016] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.15 x 10^8 CAR+ T cells.

[0017] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.3 x 10^8 CAR+ T cells.

[0018] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.5 x 10^8 CAR+ T cells.

[0019] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms

(kg) in body weight, at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.75 x 10^8 CAR+ T cells.

[0020] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject that is younger than 18 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 1.0 x 10^8 CAR+ T cells.

[0020a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age having or suspected of having a B cell malignancy, wherein the T cell composition is to be administered in an amount selected from: (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration of at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject; and (ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration of at or about 1.0 x 10^8 CAR+ T cells.

[0021] Provided herein are methods of treating a subjecting having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells; or (ii) if the subject is between 18 and 25 years of age, inclusive, from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0021a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein the composition is to be administered in an amount selected from: (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0022] Provided herein are methods of treating a subjecting having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells; or (ii) if the subject is between 18 and 25 years of age, inclusive, from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

[0023] In some of any examples,: (i) if the subject is younger than 18 years of age, the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

[0024] Provided herein are methods of treating a subjecting having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

[0024a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein the medicament is formulated for administration in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

[0025] In some of any examples, the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells.

[0026] In some of any examples, the T cell composition is administered in an amount that is at least at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.05 x 10^8 total CAR+ T cells. In some of any examples, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; further comprising administering to the subject an additional dose of the T cell composition wherein, the additional dose of the T cell composition is administered in an amount that is at least at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.1 x 10^8 total CAR+ T cells. In some of any examples, the T cell composition is administered in an amount that is at least at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.15 x 10^8 total CAR+ T cells. In some of any examples, the T cell composition is administered in an amount that is at least at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.3 x 10^8 total CAR+ T cells. In some of any examples, the T cell composition is administered in an amount that is at least at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.5 x 10^8 total CAR+ T cells. In some of any examples, the T cell composition is administered in an amount that is at least at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells. In some of any examples, the T cell composition is administered in an amount that is at least at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0027] In some of any examples, if the subject is younger than 18 years of age the T cell composition is administered in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0028] In some of any examples, if the subject is younger than 18 years of age the T cell composition is administered in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0029] In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.05 x 10^8 total CAR+ T cells. In some of any examples, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; further comprising administering to the subject an additional dose of the T cell composition wherein, if the subject is younger than 18 years of age, the additional dose of the T cell composition is administered in

an amount that is at least at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.1 x 10^8 total CAR+ T cells. In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.15 x 10^8 total CAR+ T cells. In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.3 x 10^8 total CAR+ T cells. In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.5 x 10^8 total CAR+ T cells. In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells. In some of any examples, if the subject is younger than 18 years of age, the T cell composition is administered in an amount that is at least at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0030] In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.0 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.0 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 0.05 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 0.15 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 0.3 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 0.5 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 0.75 x 10^8 CAR+ T cells. In some of any examples, if the subject is between 18 and 25 years of age, inclusive, the T cell composition is administered in an amount that is at or about 1.0 x 10^8 CAR+ T cells.

[0031] In some of any of the provided methods or uses, the subject is at least at or about 6 kg in body weight. In some of any of the provided methods or uses, the subject is at least at or about 12 kg in body weight.

[0032] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric

antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.05 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.05 x 10^8 CAR+ T cells.

[0033] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.15 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.15 x 10^8 CAR+ T cells.

[0034] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.3 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.3 x 10^8 CAR+ T cells.

[0035] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.5 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.5 x 10^8 CAR+ T cells.

[0035a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age and weighing 12 kg or more having or suspected of having a B cell malignancy, wherein : (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.5 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5 x 10^8 CAR+ T cells.

[0036] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.75 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.75 x 10^8 CAR+ T cells.

[0037] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age and weighing 12 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, at or about 1 x 10^6 CAR+ T cells/kg body weight of the

subject, but not exceeding at or about 1 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 1 x 10^8 CAR+ T cells.

[0038] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age and weighing 6 kg or more, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from (i) if the subject is younger than 18 years of age at or about 1 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 1 x 10^8 total CAR+ T cells; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 1.0 x 10^8 CAR+ T cells.

[0038a] In one aspect, the present disclosure refers to the use of a composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age and weighing 6 kg or more having or suspected of having a B cell malignancy, wherein the medicament is formulated for administration in an amount that is at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

[0039] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject younger than 18 years of age and weighing 12 kg or more, a composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount that is at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0040] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject younger than 18 years of age and weighing 12 kg or more, a composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the composition is administered in an amount that is at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0041] In some of any examples, the composition is administered in an amount that is at least at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.05 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount that is at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount that is at least at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.15 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount that is at least at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.3 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an

amount that is at least at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.5 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount that is at least at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells. In some of any examples, the composition is administered in an amount that is at least at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

[0042] In some of any examples, a total volume of at least 0.05 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is administered. In some of any examples, a total volume of at least at or about 0.1 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is administered. In some of any of the provided methods or uses, a total volume of at least at or about 0.5 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is administered.

[0043] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 1.5 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, less than at or about 1.5 x 10^8 CAR+ T cells.

[0044] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.05 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.05 x 10^8 CAR+ T cells.

[0045] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.15 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.15 x 10^8 CAR+ T cells.

[0046] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.3 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.3 x 10^8 CAR+ T cells.

[0047] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.5×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.5×10^8 CAR+ T cells.

[0048] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.75×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.75×10^8 CAR+ T cells.

[0048a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein: (A) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 1.5×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of less than at or about 1.5×10^8 CAR+ T cells; (B)(i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.05×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.05×10^8 CAR+ T cells; (C) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.15×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.15×10^8 CAR+ T cells; (D) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.3×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.3×10^8 CAR+ T cells; (E) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.5×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5×10^8 CAR+ T cells; or (F)(i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.75×10^8 total CAR+ T cells in a volume of at least 0.1 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.75×10^8 CAR+ T cells.

[0049] In some of any examples, the concentration of the T cells is at or greater than 2.5 x 10^6 cells/mL.

[0050] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.05 x 10^8 total CAR+ T cells in a volume of at least 0.05 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.05 x 10^8 CAR+ T cells.

[0051]

[0052] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.15 x 10^8 total CAR+ T cells in a volume of at least 0.15 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.15 x 10^8 CAR+ T cells.

[0053] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.3 x 10^8 total CAR+ T cells in a volume of at least 0.3 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.3 x 10^8 CAR+ T cells.

[0054] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.5 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.5 x 10^8 CAR+ T cells.

[0055] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method involving administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 0.75 x 10^8 total CAR+ T cells in a volume of at least 0.75 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 0.75 x 10^8 CAR+ T cells.

[0056] Provided herein are methods of treating a subject having or suspected of having a B cell malignancy, the method comprising administering, to a subject at or younger than 25 years of age, a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein the T cell composition is administered in an amount selected from: (i) if the subject is younger than 18 years of age, an amount not exceeding at or about 1 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, at or about 1.0 x 10^8 CAR+ T cells. In some of any examples, a total volume of at least at or about 0.05 mL of the T cell composition is administered. In some of any examples, a total volume of at least at or about 0.1 mL of the T cell composition is administered. In some of any examples, a total volume of at least at or about 0.5 mL of the T cell composition is administered. In some of any examples, a total volume of at least at or about 1.0 mL of the T cell composition is administered.

[0056a] In one aspect, the present disclosure refers to the use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein: (A) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.5 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5 x 10^8 CAR+ T cells; or (B) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 1 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and (ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 1.0 x 10^8 CAR+ T cells.

[0057] In some of any examples, the total volume of the T cell composition administered is at least 0.05 mL. In some of any examples, the total volume of the T cell composition administered is at least 0.1 mL. In some of any of the provided examples, the total volume of the T cell composition administered is at least 1.0 mL. In some of any of the provided examples, the concentration of the T cell composition is greater than at or about 5 x 10^6 cells/mL or is or is about 5 x 10^6 cells/mL In some of any of the provided examples, the concentration of the T cell composition is greater than at or about 10 x 10^6 cells/mL or is or is about 10 x 10^6 cells/mL. In some of any of the provided examples, the concentration of the T cell composition is greater than or greater than about 15 x 10^6 cells/mL or is or is about 15 x 10^6 cells/mL.

[0058] In some of any of the provided examples, the T cell composition comprises $CD4^+$ and $CD8^+$ CAR+ T cells. In some of any examples, the composition 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. In some of any examples, the first composition and the second composition are administered separately. In some of any examples, the first composition and the second composition are administered simultaneously. In some of any examples, the first composition and the second composition are administered sequentially, in either order. In some examples, the first composition comprises $CD4^+$ CAR+ T cells and the second composition comprises CD8+ T cells. In other examples, the first composition comprises $CD8^+$ CAR+ T cells and the second composition comprises CD4+ CAR+ T cell.

[0059] In some of any of the provided examples, the amount of the T cell composition administered comprises a defined ratio of $CD4^+$ CAR+ T cells to $CD8^+$ CAR+ T cells and/or of $CD4^+$ T cells to $CD8^+$ T cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any examples, such as involving administration of a first and second composition, the $CD4^+$ CAR+ T cells in the one of the first and second compositions and the $CD8^+$ CAR+ T cells in the other of the first and second compositions are present at a defined ratio that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any examples, such as involving administration of a first and second composition, the $CD4^+$ CAR+ T cells and the $CD8^+$ CAR+ T cells administered in the first and second compositions are present at a defined ratio, which ratio is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1. In some of any of the provided examples, the defined ratio is or is approximately 1:1.

[0060] In some of any of the provided methods or uses, the B cell malignancy is a lymphoma or a leukemia. In some of any examples, the B cell malignancy is relapsed and/or refractory.

[0061] In some of any of the provided methods or uses, the B cell malignancy is a B-cell acute lymphoblastic leukemia (B-ALL). In some of any examples, the B cell malignancy is a B-cell acute lymphoblastic leukemia (B-ALL), optionally CD19+ B-ALL. In some of any examples, the B cell malignancy is relapsed or refractory (r/r) B-cell Acute Lymphoblastic Leukemia (B-ALL). In some of any examples, subject with r/r B-ALL has morphological evidence of disease in bone marrow, optionally wherein the subject has 5% or greater lymphoblast by morphology. In some of any of the examples, the subject has a B-ALL that is any of the following: first or greater marrow relapse, any marrow relapse after allogeneic hematopoietic stem cell transplantation (HSCT); primary refractory, optionally following 2 or more separate induction regimens; chemo-refractory, optionally after 1 cycle of chemotherapy for relapsed leukemia; or is ineligible for allogeneic HSCT. In some of any of the examples, the B-ALL is relapsed and/or refractory. In some of any examples, the subject has a B-ALL comprising any of the following: first or greater marrow relapse, any marrow relapse after allogeneic hematopoietic stem cell transplantation (HSCT); primary refractory, optionally not achieving a complete response (CR) or complete response with incomplete blood count recovery (CRi), optionally following 2 or more separate induction regimens; chemo-refractory, optionally not achieving CR/Cri, optionally after 1 cycle of chemotherapy for relapsed leukemia; or is ineligible for allogeneic HSCT.

[0062] In some of any examples, the B-ALL is minimum residual disease positive (MRD+). . In some of any examples, subjects with B-ALL has less than 5% lymphoblast by morphology and/or minimum residual disease positive (MRD+) disease as detected by a validated assay at a frequency of 1 $x10^{-4}$ or greater in bone marrow cells after two lines of therapy.

[0063] In some of any examples, the subject has Philadelphia chromosome positive ALL and is intolerant to or have failed one or more lines of tyrosine-kinase inhibitor (TKI) therapy, or TKI therapy is contraindicated.

[0064] In some of any of the provided methods or uses, the B cell malignancy is a B-cell non-Hodgkin lymphoma (B-NHL). In some of any examples, the B cell malignancy is a B-cell non-Hodgkin lymphoma (B-NHL), optionally CD19+ B-NHL. In some of any examples, the B cell malignancy is relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL).

[0065] In some of any examples, the B-NHL is diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), or Burkitt's lymphoma. In some of any of the examples, the subject has a B-NHL in which there is measurable disease after 1 or more lines of chemotherapy, has failed HSCT, or is ineligible for HSCT. In some of any of the examples, the B-NHL is relapsed and/or refractory.

[0066] In some of any of the provided methods or uses, prior to the administration, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide. In some of any of the provided methods or uses, the method further comprises, immediately prior to the administration, administering a lymphodepleting therapy to the subject comprising the administration of fludarabine and/or cyclophosphamide. In some of any examples, the lymphodepleting therapy comprises administration of cyclophosphamide at about 200-400 mg/m^2, optionally at or about 300 mg/m^2, inclusive, and/or fludarabine at about 20-40 mg/m^2, optionally 30 mg/m^2, daily for 2-4 days, optionally for 3 days. In some of any examples, the lymphodepleting therapy comprises administration of cyclophosphamide at about 300 mg/m^2 daily for 3 days and fludarabine at about 30 mg/m^2 daily for 3 days. In some of any examples, the cyclophosphamide and fludarabine are administered concurrently. In some of any examples, the cyclophosphamide and fludarabine are administered intravenously. In some of any examples, the lymphodepleting therapy is administered 2-7 days prior to the administration of the T cell composition.

[0067] In any of the provided methods or uses, the subject is a human.

[0068] In any of the provided methods or uses, the CAR comprises an scFv specific for human 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 examples, the CAR comprises, in order, an scFv specific for human 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 such examples, the cytoplasmic domain derived from a costimulatory molecule is or comprises a

human 4-1BB. In some of any such examples, the cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule is or comprises a human CD3zeta signaling domain. In some of any such examples, the CAR optionally further comprises a spacer between the transmembrane domain and the scFv.

[0069] In any of the provided examples, the CAR comprises, in order, an scFv specific for human CD19, a spacer, 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 such examples, the cytoplasmic domain derived from a costimulatory molecule is or comprises a human 4-1BB. In some of any such examples, the cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule is or comprises a human CD3zeta signaling domain.

[0070] In some of any of the provided examples, the spacer is a polypeptide spacer that comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof, optionally an IgG4 hinge, or a modified version thereof. In some of any of the provided examples, the spacer is about 15 amino acids or less, and does not comprise a CD28 extracellular region or a CD8 extracellular region. In some of any of the provided examples, the spacer is at or about 12 amino acids in length. In some of any of the provided examples, the spacer has or consists of the sequence of SEQ ID NO: 1, a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID O:N 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. In some of any of the provided examples, the spacer comprises or consists of the formula X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

[0071] In some of any of the provided examples, the cytoplasmic signaling domain derived from a costimulatory molecule, i.e., 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.

[0072] In some of any of the provided examples, the cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, i.e., 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.

[0073] In some of any of the provided examples, the scFv comprises a variable light (V_L) chain comprising a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37), and a variable heavy (V_H) chain comprising a CDRH1 sequence of DYGVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40). In some of any of the provided examples, the scFv comprises a V_L comprising a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, and a VH

comprising a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63. In some of any of the provided examples, the scFv comprises a V_H set forth in SEQ ID NO:41 and a V_L set forth in SEQ ID NO: 42. In some of any of the provided examples, the V_H and V_L are separated by a flexible linker. In some of any of the provided examples, the flexible linker is or comprises the sequence set forth in SEQ ID NO:24. In some of any of the provided examples, the scFv is or comprises the sequence set forth in SEQ ID NO:43.

[0074] In some of any of the provided examples, the T cells are primary T cells obtained from a subject. In some of any of the provided examples, the T cells are autologous to the subject.

[0075] In some of any of the provided examples, prior to administering the composition, the subject is or has been identified as having cells expressing CD19. In some of any of the provided examples, the expression of CD19 is detected by flow cytometry in the peripheral blood or bone marrow, and/or by immunohistochemistry of a bone marrow biopsy. In some of any examples, the expression of CD19 is detected by flow cytometry, optionally in the peripheral blood or bone marrow, and/or by immunohistochemistry, optionally of a bone marrow biopsy.

[0076] In some of any examples, the subject has not received prior cell therapy that comprises administration of a T cell composition comprising T cells expressing a CAR. In some of any examples, the subject has received a prior cell therapy that comprises administration of a T cell composition comprising T cells expressing a CAR. In some of any examples, the subject has received a prior therapy targeting CD19, optionally wherein the subject is or has been identified as having cells expressing CD19 or having a CD19-positive disease after completion of the prior therapy targeting CD19.

[0077] In some of any examples, at least at or about 35%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7, CD27, CD45RA and/or CD28.In some of any examples, at least at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7. In some of any examples, at least at or about 35%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% o or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7 and CD45RA.

[0078] In some of any examples, at least at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CD27. In some of any examples, at least at or about 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% o or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CD27 and CD28. In some of any

examples, at least at or about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are negative for active Caspase 3.

[0079] Also provided herein is an article of manufacture comprising a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to any of the provided methods.

[0079a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the use disclosed herein.

Detailed Description

[0080] Among the provided embodiments are methods and uses, such as therapeutic methods or uses, that involve administration of engineered cells (e.g., T cells) and/or compositions thereof, for the treatment of subjects having a disease or condition, which generally is or includes a B cell malignancy or a hematological malignancy. In some embodiments, the B cell malignancy is a B-cell acute lymphoblastic leukemia (B-ALL) or a B-cell non-Hodgkin lymphoma (B-NHL). In some embodiments, the engineered cells express a recombinant receptor, such as a chimeric antigen receptor (CAR), that can target, bind and/or recognize an antigen that is associated with the B cell malignancy. In some aspects, the subjects include subjects who are at or younger than 25 years of age, such as pediatric subjects or young adult subjects. In some aspects, the methods involve determining the amount, number or dose of engineered cells for administration for treatment in a particular group of subjects, such as subjects who are at or younger than 25 years of age, such as pediatric subjects or young adult subjects. In some embodiments, the subjects are pediatric subjects. In some embodiments, the subjects are young adults. Also provided are compositions for use in cell therapy, for example, in accordance with the methods and uses described herein. Also provided are articles of manufacture and kits, e.g., for use in the methods or uses provided herein. In some embodiments, the articles of manufacture and kits optionally contain instructions for using, according to the methods or uses provided herein.

[0081] Adoptive cell therapies (including those involving the administration of cells expressing chimeric receptors such as chimeric antigen receptors (CARs) and/or other recombinant antigen receptors, specific for a disease or disorder of interest, as well as other adoptive immune cell and adoptive T cell therapies) can be effective in the treatment of hematological malignancies or B cell malignancies, and other diseases and disorders, such as other cancers. In certain contexts, available approaches to adoptive cell therapy may not always be entirely satisfactory. In some contexts, optimal response to therapy can depend on the ability of the administered cells to recognize and bind to a target, *e.g.*, target antigen, to traffic, localize to and successfully enter appropriate sites within the subject, tumors, and environments thereof, to become activated, expand, to exert various effector functions, including cytotoxic killing and secretion of various factors such as cytokines, to persist, including long-term, to differentiate, transition or engage in reprogramming into certain phenotypic states, to provide effective and robust recall responses following clearance and re-exposure to target ligand or antigen, and

Claims

WHAT IS CLAIMED:

1. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, the medicament is formulated for administration of from at or about 0.05×10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5×10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of from at or about 0.05×10^8 CAR+ T cells to at or about 1.5×10^8 CAR+ T cells.

2. The use of claim 1, wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, the medicament is formulated for administration in an amount from at or about 0.5×10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5×10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, the medicament is formulated for administration in an amount from at or about 0.5×10^8 CAR+ T cells to at or about 1.5×10^8 CAR+ T cells; or wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight and is younger than 18 years of age, the medicament is formulated for administration in an amount from at or about 0.05×10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75×10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight or is between 18 and 25 years of age, inclusive, the medicament is formulated for administration in an amount from at or about 0.05×10^8 CAR+ T cells to at or about 0.75×10^8 CAR+ T cells.

3. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age having or suspected of having a B cell malignancy, wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration of from at or about 0.05×10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5×10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration of from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

4. The use of claim 4, wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

5. The use of any of claims 1-4, wherein:

(i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

6. The use of claim 3, wherein:

(A) (i) if the subject is less than 100 kilograms (kg) in body weight, at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, at or about 0.05 x 10^8 CAR+ T cells; optionally wherein, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; the subject is to be administered an additional dose of the T cell composition in an amount selected from:

(a) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject; and

(b) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.1 x 10^8 CAR+ T cells;

(B) (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.15 x 10^8 CAR+ T cells;

(C) (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.3 x 10^8 CAR+ T cells;

(D) (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.5 x 10^8 CAR+ T cells;

(E) (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 0.75 x 10^8 CAR+ T cells.; or

(F) (i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration at or about 1.0 x 10^8 CAR+ T cells.

7. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age having or suspected of having a B cell malignancy, wherein the T cell composition is to be administered in an amount selected from:

(i) if the subject is less than 100 kilograms (kg) in body weight, the medicament is formulated for administration of at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject; and

(ii) if the subject is at or greater than 100 kilograms (kg) in body weight, the medicament is formulated for administration of at or about 1.0 x 10^8 CAR+ T cells.

8. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein the composition is to be administered in an amount selected from:

(i) if the subject is younger than 18 years of age, the medicament is formulated for administration of from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of from at or about 0.05 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells.

9. The use of claim 8, wherein:

(i) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount from at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration in an amount from at or about 0.5 x 10^8 CAR+ T cells to at or about 1.5 x 10^8 CAR+ T cells; or, wherein

(i) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

10. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein the medicament is formulated for administration in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

11. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age and weighing 12 kg or more having or suspected of having a B cell malignancy, wherein :

(i) if the subject is younger than 18 years of age, the medicament is formulated for administration of at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject, but not exceeding at or about 0.5 x 10^8 total CAR+ T cells; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5 x 10^8 CAR+ T cells.

12. The use of any of claims 2, 8, 9, or 11, wherein if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration in an amount from at or about 0.05 x 10^8 CAR+ T cells to at or about 0.75 x 10^8 CAR+ T cells.

13. Use of a composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 18 years of age and weighing 6 kg or more having or suspected of having a B cell malignancy, wherein the medicament is formulated for administration in an amount that is at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

14. The use of any of claims 1-13, wherein if the subject is younger than 18 years of age the medicament is formulated for administration in an amount from at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells.

15. The use of any of claims 1-14, wherein:

(a) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.05 x 10^8 total CAR+ T cells, optionally

wherein, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; and if the subject is younger than 18 years of age, an additional dose of the medicament is formulated for administration in an amount that is at least at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.1 x 10^8 total CAR+ T cells;

(b) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.15 x 10^8 total CAR+ T cells;

(c) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.3 x 10^8 total CAR+ T cells;

(d) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.5 x 10^8 total CAR+ T cells;

(e) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells;

(f) if the subject is younger than 18 years of age, the medicament is formulated for administration in an amount that is at least at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells; or

(g) the medicament is formulated for administration in an amount that is at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 1.5 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 1.5 x 10^8 total CAR+ T cells.

16. The use of any of claims 1-14, wherein the medicament is formulated for administration in an amount that is at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject to at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject, but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells.

17. The use of any of claims 1-14 and 16, wherein:

(a) the medicament is formulated for administration in an amount that is at least at or about 0.05 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.05 x 10^8 total CAR+ T cells, optionally

wherein, if the subject exhibits no response and does not develop a toxicity at or about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 days after administration of the T cell composition; an additional dose of the medicament is formulated for administration in an amount that is at least at or about 0.1 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.1 x 10^8 total CAR+ T cells;

(b) the medicament is formulated for administration in an amount that is at least at or about 0.15 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.15 x 10^8 total CAR+ T cells;

(c) the medicament is formulated for administration in an amount that is at least at or about 0.3 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.3 x 10^8 total CAR+ T cells;

(d) the medicament is formulated for administration in an amount that is at least at or about 0.5 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.5 x 10^8 total CAR+ T cells;

(e) the medicament is formulated for administration in an amount that is at least at or about 0.75 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 0.75 x 10^8 total CAR+ T cells; or

(f) the medicament is formulated for administration in an amount that is at least at or about 1.0 x 10^6 CAR+ T cells/kg body weight of the subject but that does not exceed at or about 1.0 x 10^8 total CAR+ T cells.

18. The use of any of claims 1-17, wherein the subject is at least at or about 6 kg in body weight.

19. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, wherein:

(A) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 1.5 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of less than at or about 1.5 x 10^8 CAR+ T cells;

(B) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.05 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.05 x 10^8 CAR+ T cells;

(C) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.15 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.15 x 10^8 CAR+ T cells;

(D) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.3 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.3 x 10^8 CAR+ T cells;

(E) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.5 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5 x 10^8 CAR+ T cells; or

(F) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.75 x 10^8 total CAR+ T cells in a volume of at least 0.1 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.75 x 10^8 CAR+ T cells.

20. Use of a T cell composition comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR) for the manufacture of a medicament for treatment of a subject at or younger than 25 years of age having or suspected of having a B cell malignancy, at a concentration of at or greater than 2.5 x 10^6 cells/mL, wherein:

(A) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 0.5 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 0.5 x 10^8 CAR+ T cells; or

(B) (i) if the subject is younger than 18 years of age, the medicament is formulated for administration of an amount not exceeding at or about 1 x 10^8 total CAR+ T cells in a volume of at least 0.5 mL; and

(ii) if the subject is between 18 and 25 years of age, inclusive, the medicament is formulated for administration of at or about 1.0 x 10^8 CAR+ T cells.

21. The use of any of claims 1-20, wherein a total volume of at least at or about 0.05 mL, at least at or about 0.1 mL, at least at or about 0.5 mL, or at least or about 1 mL of the T cell composition is to be administered.

22. The use of any of claims 1-21, wherein the concentration of the T cells is at or greater than 2.5 x 10^6 cells/mL.

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

(a) a total volume of at least at or about 0.1 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is to be administered;

(b) a total volume of at least at or about 0.5 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is to be administered; or

(c) a total volume of at least at or about 1 mL at a concentration of at or greater than 2.5 x 10^6 cells/mL of the T cell composition is to be administered.

24. The use of any of claims 1-23, wherein the T cell composition comprises $CD4^+$ and $CD8^+$ CAR^+ T cells.

25. The use of claim 24, wherein the composition 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, optionally

wherein the first composition and the second composition are to be administered separately, further optionally wherein (i) the first composition and the second composition are to be administered simultaneously or (ii) the first composition and the second composition are to be administered sequentially in either order.

26. The use of claim 24, wherein the first composition comprises $CD4^+$ CAR^+ T cells and the second composition comprises $CD8^+$ CAR^+ T cells; or wherein the first composition comprises CD8+ CAR+ T cells and the second composition comprises CD4+ CAR+ T cell.

27. The use of claim 25 or claim 26, wherein the amount of the T cell composition administered comprises a defined ratio of $CD4^+$ CAR^+ T cells to $CD8^+$ CAR^+ T cells and/or of $CD4^+$ T cells to $CD8^+$ T cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1, optionally wherein the defined ratio is or is approximately 1:1.

28. The use of any of claims 1-27, wherein:

(a) the B cell malignancy is a lymphoma or a leukemia;

(b) the B cell malignancy is relapsed and/or refractory;

(c) the B cell malignancy is a B-cell acute lymphoblastic leukemia (B-ALL), optionally CD19+ B-ALL; and/or

(d) the B cell malignancy is relapsed or refractory (r/r) B-cell Acute Lymphoblastic Leukemia (B-ALL), optionally

wherein the subject with r/r B-ALL has morphological evidence of disease in bone marrow, further optionally wherein the subject has 5% or greater lymphoblast by morphology.

29. The use of claim 28, wherein:

(a) the subject has a B-ALL comprising any of the following: first or greater marrow relapse, any marrow relapse after allogeneic hematopoietic stem cell transplantation (HSCT); primary refractory, optionally not achieving a complete response (CR) or complete response with incomplete blood count recovery (CRi), optionally following 2 or more separate induction regimens; chemo-refractory, optionally not achieving CR/Cri, optionally after 1 cycle of chemotherapy for relapsed leukemia; or is ineligible for allogeneic HSCT;

(b) the B-ALL is minimum residual disease positive (MRD^+); and/or

(c) subjects with B-ALL have less than 5% lymphoblast by morphology and/or minimum residual disease positive (MRD+) disease as detected by a validated assay at a frequency of 1×10^{-4} or greater in bone marrow cells after two lines of therapy.

30. The use of any of claims 1-29, wherein the subject has Philadelphia chromosome positive ALL and is intolerant to or have failed one or more lines of tyrosine-kinase inhibitor (TKI) therapy, or TKI therapy is contraindicated.

31. The use of any of claims 1-28, wherein the B cell malignancy is a B-cell non-Hodgkin lymphoma (B-NHL), optionally CD19+ B-NHL, optionally wherein:

(a) the B cell malignancy is relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL);

(b) the subject has a B-NHL in which there is measurable disease after 1 or more lines of chemotherapy, has failed HSCT, or is ineligible for HSCT; and/or

(c) the B-NHL is diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), or Burkitt's lymphoma (BL).

32. The use of any of claims 1-31, wherein the subject has not received prior cell therapy that comprises administration of a T cell composition comprising T cells expressing a CAR; or

the subject has received a prior cell therapy that comprises administration of a T cell composition comprising T cells expressing a CAR.

33. The use of any of claims 1-32, wherein the subject has received a prior therapy targeting CD19, optionally wherein the subject is or has been identified as having cells expressing CD19 or having a CD19-positive disease after completion of the prior therapy targeting CD19.

34. The use of any of claims 1-33, wherein, prior to the administration of the medicament, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

35. The use of claim 34, wherein:

(a) the lymphodepleting therapy comprises administration of cyclophosphamide at about 200-400 mg/m^2, optionally at or about 300 mg/m^2, inclusive, and/or fludarabine at about 20-40 mg/m^2, optionally 30 mg/m^2, daily for 2-4 days, optionally for 3 days;

(b) the lymphodepleting therapy comprises administration of cyclophosphamide at about 300 mg/m^2 daily for 3 days and fludarabine at about 30 mg/m^2 daily for 3 days;

(c) the cyclophosphamide and fludarabine are to be administered concurrently; and/or

(d) the lymphodepleting therapy is to be administered 2-7 days prior to the administration of the T cell composition.

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

(a) the CAR comprises an scFv specific for a human CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is or comprises a human 4-1BB, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is or comprises a human CD3zeta signaling domain, and wherein the CAR optionally further comprises a spacer between the transmembrane domain and the scFv; and/or

(b) the CAR comprises, in order, an scFv specific for a human CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, which optionally is or comprises a human 4-1BB signaling domain, and a cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule, which optionally is or comprises a human CD3zeta signaling domain.

37. The use of claim 36, wherein (a) the spacer is a polypeptide spacer that comprises or consists of all or a portion of an immunoglobulin hinge or a modified version thereof, optionally an IgG4 hinge, or a modified version thereof;

(b) the spacer is about 15 amino acids or less, optionally at or about 12 amino acids in length; and/or

(c) the spacer comprises 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 O:N 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto; and/or

the spacer comprises the formula X_1PPX_2P, where X_1 is glycine, cysteine or arginine and X_2 is cysteine or threonine.

38. The use of claim 36 or claim 37, wherein (a) the cytoplasmic signaling domain derived from a costimulatory molecule comprises SEQ ID NO: 12 or a variant thereof having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto; and/or

(b) the cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule 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.

39. The use of any of claims 36-38, wherein:

(a) the scFv comprises a variable light (V_L) chain comprising a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37), and a variable heavy (V_H) chain comprising a CDRH1 sequence of DYGVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40); or

the scFv comprises a V_L comprising a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, and a V_H comprising a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63; or

(b) 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 (c) wherein the scFv is or comprises the sequence set forth in SEQ ID NO:43.

40. The use of any of claims 1-39, wherein:

(a) at least at or about 35%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7, CD27, CD45RA and/or CD28; and/or

(b) at least at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7; and/or

(c) at least at or about 35%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CCR7 and CD45RA; and/or

(d) at least at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CD27; and/or

(e) at least at or about 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are surface positive for CD27 and CD28; and/or

(f) at least at or about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of the CAR-expressing T cells, CAR-expressing CD4+ T cells or CAR-expressing CD8+ T cells in the composition, are negative for active Caspase.

41. The use of any of claims 1-40, wherein the T cells are primary T cells obtained from a subject; optionally wherein the T cells are autologous to the subject.

42. An article of manufacture comprising a composition of a cell therapy, or one of a plurality of compositions of a cell therapy, comprising T cells expressing an anti-CD19 chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify administering the T cell composition according to the use of any of claims 1-41.