

comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0006] Also provided herein is use of a dose of CD4⁺ and CD8⁺ T cells to treat a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: T cells of the dose include a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein at least one of the at least one prior line of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells contains between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells has a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions includes a first composition containing the CD8⁺ CAR-expressing T cells and a second composition containing the CD4⁺ CAR-expressing T cells.

[0006a] In one aspect, the present disclosure refers to use of a dose of CD4⁺ and CD8⁺ T cells, wherein T cells of the dose comprise a chimeric antigen receptor (CAR) that specifically binds to CD19, for the manufacture of a medicament for treatment of indolent follicular lymphoma (FL) Grade 1, 2 or 3A, in a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein at least one of the at least one prior lines of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; a plurality of separate compositions is to be administered, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0006b] In one aspect, the present disclosure refers to a dose of CD4⁺ and CD8⁺ T cells, wherein T cells of the dose comprise a chimeric antigen receptor (CAR) that specifically binds to CD19, for use in the treatment of indolent follicular lymphoma (FL) Grade 1, 2 or 3A in a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein at least one of the at least one prior lines of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; a plurality of separate compositions is to be administered, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0007] Also provided herein is use of a dose of CD4⁺ and CD8⁺ T cells in the manufacture of a medicament for the treatment of a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: T cells of the dose include a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein at least one of the at least one prior line of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells contains between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells has a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions includes a first composition containing the CD8⁺ CAR-expressing T cells and a second composition containing the CD4⁺ CAR-expressing T cells.

[0007a] In one aspect, the present disclosure refers to a dose of CD4⁺ and CD8⁺ T cells for use in treating a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: T cells of the dose comprise a chimeric antigen receptor

(CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein the at least one of the at least one prior line of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0007b] In one aspect, the present disclosure refers to use of a dose of CD4⁺ and CD8⁺ T cells in the manufacture of a medicament for the treatment of a subject having or suspected of having a disease that is relapsed/refractory (r/r) follicular lymphoma (FL) Grade 1, 2 or 3A, wherein: T cells of the dose comprise a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least one prior line of therapy for treating FL Grade 1, 2 or 3A, wherein at least one of the at least one prior line of therapy includes treatment with an anti-CD20 antibody and an alkylating agent; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration as a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0008] In some examples, the at least one prior line of therapy is one prior line of therapy.

[0009] In some of any of the provided examples, the subject had progression of the disease within 24 months of diagnosis after completing the one prior line of therapy (POD24). In some of any of the provided examples, the subject had progression of the disease within 24 months of initiation of the one prior line of therapy after completing the one prior line of therapy (POD24). In some of any of the provided examples, the subject had progression of the disease within 24 months of diagnosis after completing a chemoimmunotherapeutic combination therapy for treating the disease (POD24). In some of any of the provided examples, the subject had progression of the disease within 24 months of initiation of treatment after completing a chemoimmunotherapeutic combination therapy for treating the disease (POD24). In some of any such examples, the chemoimmunotherapeutic combination therapy includes rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP). In some of any of the provided examples, the subject had progression of the disease within 24 months of diagnosis after completing treatment with R-CHOP (POD24). In some of any of the provided examples, the subject had progression of the disease within 24 months of initiation of treatment with R-CHOP (POD24).

[0010] In some of any such examples, the chemoimmunotherapeutic combination therapy includes an anti-CD20 monoclonal antibody and an alkylating agent. In some of any of the provided examples, the subject had progression of the disease within 24 months of diagnosis after completing treatment with an anti-CD20 antibody and an alkylating agent (POD24). In some of any of the provided examples, the subject had progression of the disease within 24 months of initiation of treatment with an anti-CD20 antibody and an alkylating agent (POD24).

[0011] In some examples, the subject has relapsed or is refractory to treatment after one prior line of therapy for treating FL Grade 1, 2 or 3A, and had progression of the disease within 24 months of initiation of the one prior line of therapy that is an anti-CD20 antibody and an alkylating agent (POD24). In some examples, the subject has relapsed or is refractory to treatment after one prior line of therapy for treating FL Grade 1, 2 or 3A, and had progression of the disease within 24 months of diagnosis after completing the one prior line of therapy that includes an anti-CD20 antibody and an alkylating agent (POD24).

[0012] In some examples, the subject has relapsed or is refractory to treatment after one prior line of therapy for treating FL Grade 1, 2 or 3A, and has at least one of the following: symptoms attributable to FL; threatened end-organ function, cytopenia secondary to lymphoma, or bulky disease; splenomegaly; and steady progression of disease over the preceding six months or more. In some examples, the subject has symptoms attributable to FL. In some examples, the subject has threatened end-organ function. In some examples, the subject has symptoms attributable to FL. In some examples, the subject has cytopenia secondary to lymphoma. In some examples, the subject has bulky disease. In some examples, bulky disease is a single mass > 7 cm or 3 or more masses > 3 cm. In some examples, the subject has splenomegaly. In some examples, the subject has steady progression of disease over the preceding six months or more.

[0013] In some examples, the at least one prior line of therapy is two prior lines of therapy. In some examples, the other of the two prior lines of therapy is selected from treatment with rituximab; obinutuzumab; bendamustine plus rituximab (BR); bendamustine plus obinutuzumab (BO); R-CHOP; rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); HSCT (optionally autologous or allogeneic HSCT); lenalidomide in combination with rituximab; or a PI3K inhibitor (PI3Ki). In some examples, the PI3Ki is idelalisib, copanlisib, or duvelisib.

[0014] In some examples, the subject is refractory to treatment or has relapsed within 12 months of completion of a prior line of therapy. In some examples, a prior line of therapy is a combination therapy or a monotherapy comprising a PI3Ki. In some examples, the other of the two prior lines of therapy is hematopoietic stem cell transplant (HSCT), and the subject has relapsed after HSCT.

[0015] In some of any of the provided examples, the subject is refractory to treatment with, or has relapsed during or up to 6 months after completing treatment with, an anti-CD20 therapy (anti-CD20 refractory). In some of any of the provided examples, the subject is refractory to treatment with an anti-CD20 therapy (anti-CD20 refractory). In some of any of the provided examples, the subject has relapsed during or up to 6 months after completing treatment with an anti-CD20 therapy (anti-CD20 refractory). In some of any of the provided examples, the subject

is refractory to treatment with, or has relapsed during or up to 6 months after completing treatment with, an anti-CD20 antibody. In some of any of the provided examples, the subject is refractory to treatment with an anti-CD20 antibody. In some of any of the provided examples, the subject has relapsed during or up to 6 months after completing treatment with an anti-CD20 antibody.

[0016] In some of any of the provided examples, the subject is refractory to treatment with, or has relapsed during or up to 6 months after completing treatment with, an anti-CD20 therapy and an alkylating agent. In some of any of the provided examples, the subject is refractory to a prior line of therapy that includes an anti-CD20 therapy and an alkylating agent. In some of any of the provided examples, the subject has relapsed within six months of completing a prior line of therapy that includes an anti-CD20 therapy and an alkylating agent.

[0017] In some of any of the provided examples, the subject relapsed during an anti-CD20 antibody maintenance following 2 or more lines of therapy or within 6 months after maintenance completion. In some of any of the provided examples, the subject relapsed during an anti-CD20 antibody maintenance therapy following 2 or more lines of therapy. In some of any of the provided examples, the subject relapsed within 6 months after completion of the anti-CD20 antibody maintenance therapy. In some examples, the subject was treated with an anti-CD20 antibody maintenance therapy after the two prior lines of therapy, and the subject relapsed during the anti-CD20 maintenance therapy. In some examples, the subject was treated with an anti-CD20 antibody maintenance therapy, and the subject relapsed within six months of completing the anti-CD20 antibody maintenance therapy.

[0018] In some examples, the anti-CD20 antibody is a monoclonal antibody. In some of any such examples, the anti-CD20 monoclonal antibody is rituximab or obinutuzumab. In some of any such examples, the anti-CD20 monoclonal antibody is rituximab. In some of any such examples, the anti-CD20 antibody is obinutuzumab. In some of any such examples, the alkylating agent is bendamustine or chlorambucil. In some of any such examples, the alkylating agent is bendamustine. In some of any such examples, the alkylating agent is chlorambucil.

[0019] In some of any of the provided examples, the subject relapsed after hematopoietic stem cell transplant, optionally allogeneic or autologous HSCT. In some of any of the provided

examples, the subject relapsed after hematopoietic stem cell transplant (HSCT). In some of any of the provided examples, the hematopoietic stem cell transplant is allogeneic HSCT. In some of any of the provided examples, the hematopoietic stem cell transplant is autologous HSCT.

[0020] In some of any of the provided examples, the at least one prior therapy is two prior lines of therapy. In some of any such examples, the other of the two prior lines of therapy is selected from treatment with rituximab; obinutuzumab; bendamustine plus rituximab (BR); bendamustine plus obinutuzumab (BO); R-CHOP; rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); HSCT (optionally autologous or allogeneic HSCT); lenalidomide in combination with rituximab; or a PI3K inhibitor, optionally wherein the PI3K inhibitor is idelalisib, copanlisib, or duvelisib. In some of any such examples, the other of the two prior lines of therapy is selected from treatment with rituximab; obinutuzumab; bendamustine plus rituximab (BR); bendamustine plus obinutuzumab (BO); R-CHOP; rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); HSCT (optionally autologous or allogeneic HSCT); lenalidomide in combination with rituximab; or a PI3K inhibitor. In some examples, the PI3K inhibitor is idelalisib, copanlisib, or duvelisib. In some examples, the PI3K inhibitor is idelalisib. In some examples, the PI3K inhibitor is copanlisib. In some examples, the PI3K inhibitor is duvelisib.

[0021] In some of any of the provided examples, the at least one prior therapy is three prior lines of therapy. In some of any such examples, the other two of the three prior lines of therapy are each independently selected from treatment with rituximab; obinutuzumab; bendamustine plus rituximab (BR); bendamustine plus obinutuzumab (BO); R-CHOP; rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); HSCT (optionally autologous or allogeneic HSCT); lenalidomide in combination with rituximab; or a PI3K inhibitor, optionally wherein the PI3K inhibitor is idelalisib, copanlisib, or duvelisib. In some of any such examples, the other two of the three prior lines of therapy are each independently selected from treatment with rituximab; obinutuzumab; bendamustine plus rituximab (BR); bendamustine plus obinutuzumab (BO); R-CHOP; rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); HSCT (optionally autologous or allogeneic HSCT); lenalidomide in combination with rituximab; or a PI3K inhibitor.

In some examples, the PI3K inhibitor is idelalisib, copanlisib, or duvelisib. In some examples, the PI3K inhibitor is idelalisib. In some examples, the PI3K inhibitor is copanlisib. In some examples, the PI3K inhibitor is duvelisib.

[0022] In some examples, the subject is refractory to treatment with an anti-CD20 antibody. In some examples, the subject is refractory to a prior line of therapy that includes an anti-CD20 antibody and an alkylating agent. In some examples, the subject relapsed within six months of completing treatment with an anti-CD20 antibody. In some examples, the subject relapsed within six months of completing a prior line of therapy that includes an anti-CD20 antibody and an alkylating agent. In some examples, the subject was treated with an anti-CD20 antibody maintenance therapy after the two prior lines of therapy, and the subject relapsed during the anti-CD20 maintenance therapy or within six months of completing the anti-CD20 antibody maintenance therapy.

[0023] In some of any of the provided examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a prior line of therapy, optionally after a treatment with a combination therapy or a monotherapy with a PI3Ki. In some of any of the provided examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a combination therapy. In some of any of the provided examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a monotherapy with a PI3Ki.

[0024] In some of any of the provided examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a prior line of therapy. In some examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a first line of therapy. In some examples, the subject has relapsed or is refractory to treatment within 12 months of completion of a second line of therapy. In some of any of the provided examples, the subject has relapsed within 12 months of completion of a prior line of therapy. In some of any of the provided examples, the subject has relapsed within 12 months of completion of a first line of therapy. In some of any of the provided examples, the subject has relapsed within 12 months of completion of a second line of therapy. In some of any of the provided examples, the subject is refractory to treatment within 12 months of completion of a prior line of therapy. In some of any of

the provided examples, the subject is refractory to treatment within 12 months of completion of a first line of therapy. In some of any of the provided examples, the subject is refractory to treatment within 12 months of completion of a second line of therapy. In some examples, the prior line of therapy is treatment with a combination therapy or a monotherapy with a PI3Ki. In some examples, the prior line of therapy is monotherapy with a PI3Ki. In some examples, the prior line of therapy is treatment with a combination therapy.

[0025] In some examples, the anti-CD20 antibody is a monoclonal antibody. In some of any such examples, the anti-CD20 antibody is rituximab or obinutuzumab. In some of any such examples, the anti-CD20 antibody is rituximab. In some of any such examples, the anti-CD20 antibody is obinutuzumab. In some of any such examples, the alkylating agent is bendamustine or chlorambucil. In some of any such examples, the alkylating agent is bendamustine. In some of any such examples, the alkylating agent is chlorambucil.

[0026] In some of any of the provided examples, the subject has relapsed to the at least one prior line of therapy, and the relapse is after an initial response of complete response (CR) or partial response (PR) to the prior line of therapy. In some of any of the provided examples, the relapse is after an initial response of complete response (CR) to the prior line of therapy. In some of any of the provided examples, the relapse is after an initial response of partial response (PR) to the prior line of therapy. In some of any of the provided examples, the subject is refractory to treatment with the at least one or more prior therapy, and the refractory treatment is a best response of stable disease (SD) or progressive disease (PD) after the prior line of therapy. In some examples, the refractory treatment is a best response of stable disease (SD) after the prior line of therapy. In some examples, the refractory treatment is a best response of progressive disease (PD) after the prior line of therapy.

[0027] In some examples, the subject has relapsed to one prior line of therapy. In some examples, the subject has relapsed to two prior lines of therapy. In some examples, the subject has relapsed to three prior lines of therapy. In some examples, the subject has relapsed to more than three prior lines of therapy. In some examples, the subject is refractory to one prior line of therapy. In some examples, the subject is refractory to two prior lines of therapy. In

some examples, the subject is refractory to three prior lines of therapy. In some examples, the subject is refractory to more than three prior lines of therapy.

[0028] In some of any of the provided examples, the subject has at least one PET-positive lesion and at least one measurable nodal lesion or extranodal lesion, optionally wherein the a measurable nodal lesion is greater than 1.5 cm in the long axis regardless of the short axis and a measurable extranodal lesion is greater than 1.0 cm in the long and short axis. In some of any of the provided examples, the subject has at least one PET-positive lesion and at least one measurable nodal lesion or extranodal lesion. In some of any of the provided examples, the a measurable nodal lesion is greater than 1.5 cm in the long axis regardless of the short axis and a measurable extranodal lesion is greater than 1.0 cm in the long and short axis.

[0029] Also provided herein is a method of treating marginal zone lymphoma (MZL), the method comprising administering to a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL) a dose of CD4⁺ and CD8⁺ T cells, wherein T cells of the dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein: the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the administration comprises administering a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0030] Also provided hereis is use of a dose of CD4⁺ and CD8⁺ T cells to treat a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL), wherein: T cells of the dose include a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells contains between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells has a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for

administration of a plurality of separate compositions, wherein the plurality of separate compositions includes a first composition containing the CD8⁺ CAR-expressing T cells and a second composition containing the CD4⁺ CAR-expressing T cells.

[0030a] In one aspect, the present disclosure refers to use of a dose of CD4⁺ and CD8⁺ T cells, wherein T cells of the dose comprise a chimeric antigen receptor (CAR) that specifically binds to CD19 for the manufacture of a medicament for treatment of marginal zone lymphoma (MZL) in a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL) wherein: the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; a plurality of separate compositions is to be administered, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0030b] In one aspect, the present disclosure refers to a dose of CD4⁺ and CD8⁺ T cells, wherein T cells of the dose comprise a chimeric antigen receptor (CAR) that specifically binds to CD19 for use in the treatment of marginal zone lymphoma (MZL) in a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL), wherein: the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; a plurality of separate compositions is to be administered, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0031] Also provided herein is use of a dose of CD4⁺ and CD8⁺ T cells in the manufacture of a medicament for treatment of a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL), wherein: T cells of the dose include a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells contains between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells has a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration of a plurality of separate compositions, wherein the plurality of separate compositions includes a first composition containing the CD8⁺ CAR-expressing T cells and a second composition containing the CD4⁺ CAR-expressing T cells.

[0031a] In one aspect, the present disclosure refers to a dose of CD4⁺ and CD8⁺ T cells for use in treating a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL), wherein: T cells of the dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least two prior lines of

therapy for treating MZL; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration of a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0031b] In one aspect, the present disclosure refers to use of a dose of CD4⁺ and CD8⁺ T cells in the manufacture of a medicament for treatment of a subject having or suspected of having relapsed/refractory (r/r) marginal zone lymphoma (MZL), wherein: T cells of the dose comprises a chimeric antigen receptor (CAR) that specifically binds to CD19; the subject has relapsed or is refractory to treatment after at least two prior lines of therapy for treating MZL; the dose of T cells comprises between at or about 5×10^7 CAR-expressing T cells and at or about 1.5×10^8 CAR-expressing T cells, inclusive; the dose of T cells comprises a ratio of approximately 1:1 CD4⁺ T cells expressing the CAR to CD8⁺ T cells expressing the CAR; and the dose is formulated for administration of a plurality of separate compositions, wherein the plurality of separate compositions comprises a first composition comprising the CD8⁺ CAR-expressing T cells and a second composition comprising the CD4⁺ CAR-expressing T cells.

[0032] In some of any of the provided examples, the MZL is a subtype selected from among extra-nodal MZL (ENMZL, mostly gastric), splenic MZL (SMZL), and nodal MZL (NMZL). In some examples, the MZL is extra-nodal MZL (ENMZL, mostly gastric). In some examples, the MZL is splenic MZL (SMZL). In some examples, the MZL is nodal MZL (NMZL).

[0033] In some of any of the provided examples, at least one of the at least two prior lines of therapy is a combination systemic therapy for treating the MZL or is a hematopoietic stem cell transplant (HSCT). In some of any of the provided examples, at least one of the at least two prior therapies is a combination systemic therapy for treating the MZL. In some of any of the provided examples, at least one of the at least two prior therapies is a hematopoietic stem cell transplant (HSCT).

[0034] In some of any of the provided examples, at least one of the at least two prior lines of therapy is a combination systemic therapy and the combination systemic therapy is selected from rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), or a therapy with an anti-CD20 antibody and an alkylating agent. In some of any of the provided examples,

at least one of the at least two prior lines of therapy is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). In some of any of the provided examples, at least one of the at least two prior lines of therapy is a combination systemic therapy that is an anti-CD20 antibody and an alkylating agent.

[0035] In some examples, the anti-CD20 antibody is a monoclonal antibody. In some of any such examples, the anti-CD20 antibody is rituximab or obinutuzumab. In some of any such examples, the anti-CD20 antibody is rituximab. In some of any such examples, the anti-CD20 antibody is obinutuzumab. In some of any such examples, the alkylating agent is bendamustine or chlorambucil. In some of any such examples, the alkylating agent is bendamustine. In some of any such examples, the alkylating agent is chlorambucil.

[0036] In some of any of the provided examples, at least one of the at least two prior therapies is rituximab and bendamustine or rituximab and chlorambucil. In some of any of the provided examples, at least one of the at least two prior lines of therapy is rituximab and bendamustine. In some of any of the provided examples, at least one of the at least two prior lines of therapy is rituximab and chlorambucil.

[0037] In some of any of the provided examples, the subject has splenic MZL (SMZL) and at least one of the at least two prior lines of therapy is a Splenectomy. In some of any of the provided examples, the subject has extra-nodal MZL (ENMZL) and an antibiotic is not one of the at least two prior lines of therapy.

[0038] In some of any of the provided examples, the subject has PET non-avid disease with at least one measurable nodal lesion greater than 2.0 cm in the long axis or at least one measurable extranodal lesion. In some of any of the provided examples, the subject has PET non-avid disease with at least one measurable nodal lesion greater than 2.0 cm in the long axis. In some of any of the provided examples, the subject has PET non-avid disease with at least one measurable extranodal lesion.

[0039] In some of any of the provided examples, the subject does not have FL grade 3B (FL3B). In some of any of the provided examples, the subject does not have evidence of composite DLBCL and FL, or of transformed FL. In some of any of the provided examples, the

subject does not have evidence of composite DLBCL and FL. In some of any of the provided examples, the subject does not have evidence of transformed FL. In some of any of the provided examples, the subject does not have World Health Organization (WHO) subclassification of duodenal-type FL.

[0040] In some of any of the provided examples, the subject has relapsed to the at least one prior line of therapy, and the relapse is after an initial response of complete response (CR) or partial response (PR) to the prior line of therapy. In some of any of the provided examples, the relapse is after an initial response of complete response (CR) to the prior line of therapy. In some of any of the provided examples, the relapse is after an initial response of partial response (PR) to the prior line of therapy. In some of any of the provided examples, the subject is refractory to treatment with the at least one or more prior therapy, and the refractory treatment is a best response of stable disease (SD) or progressive disease (PD) after the prior line of therapy. In some examples, the refractory treatment is a best response of stable disease (SD) after the prior line of therapy. In some examples, the refractory treatment is a best response of progressive disease (PD) after the prior line of therapy.

[0041] In some examples, the subject has relapsed to one prior line of therapy. In some examples, the subject has relapsed to two prior lines of therapy. In some examples, the subject has relapsed to three prior lines of therapy. In some examples, the subject has relapsed to more than three prior lines of therapy. In some examples, the subject is refractory to one prior line of therapy. In some examples, the subject is refractory to two prior lines of therapy. In some examples, the subject is refractory to three prior lines of therapy. In some examples, the subject is refractory to more than three prior lines of therapy.

[0042] In some of any of the provided examples, the subject has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In some of any of the provided examples, the subject has ECOG performance status of 0. In some of any of the provided examples, the subject has ECOG performance status of 1.

[0043] In some of any of the provided examples, prior to the administration of the dose of CD4⁺ and CD8⁺ T cells, the subject has been administered a lymphodepleting therapy. In some of

any provided examples, the lymphodepleting therapy is completed within about 7 days prior to initiation of the administration of the dose of CD4⁺ and CD8⁺ T cells. In some of any provided examples, the lymphodepleting therapy is completed about 2 to 7 days prior to initiation of the administration of the dose of CD4⁺ and CD8⁺ T cells.

[0044] In some of any such examples, the lymphodepleting therapy comprises the administration of fludarabine and/or cyclophosphamide. In some of any such examples, the lymphodepleting therapy comprises the administration of fludarabine. In some of any such examples, the lymphodepleting therapy comprises the administration of cyclophosphamide. In some of any such examples, the lymphodepleting therapy comprises the administration of fludarabine and cyclophosphamide. In some of any such examples, the lymphodepleting therapy comprises administration of cyclophosphamide at or about 200-400 mg/m², optionally at or about 300 mg/m², inclusive, and/or fludarabine at or about 20-40 mg/m², optionally 30 mg/m², daily for 2-4 days, optionally for 3 days. In some of any such examples, the lymphodepleting therapy comprises administration of cyclophosphamide at or about 300 mg/m², inclusive and/or fludarabine at or about 30 mg/m², daily for 3 days. In some of any such examples, the lymphodepleting therapy comprises administration of cyclophosphamide at or about 300 mg/m² and fludarabine at or about 30 mg/m² daily concurrently for 3 days.

[0045] In some of any of the provided examples, the CD19 is human CD19.

[0046] In some of any of the provided examples, the chimeric antigen receptor (CAR) comprises an scFv comprising the variable heavy chain region and the variable light chain region of the antibody FMC63, a spacer that is 15 amino acids or less and contains an immunoglobulin hinge region or a modified version thereof, a transmembrane domain, and an intracellular signaling domain comprising a signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region that is a signaling domain of 4-1BB.

[0047] In some of any such examples, the immunoglobulin hinge region or a modified version thereof comprises the formula X₁PPX₂P, wherein X₁ is glycine, cysteine or arginine and X₂ is cysteine or threonine (SEQ ID NO:58). In some examples, X₁ is glycine. In some examples, X₁ is cysteine. In some examples, X₁ is arginine. In some examples, X₂ is

cysteine. In some examples, X₂ is threonine. In some of any such examples, the immunoglobulin hinge or a modified version thereof is an IgG1 hinge or a modified version thereof. In some of any such examples, the immunoglobulin hinge or a modified version thereof is an IgG1 hinge. In some of any such examples, the immunoglobulin hinge or a modified version thereof is modified version of an IgG1 hinge. In some of any such examples, the immunoglobulin hinge or a modified version thereof is an IgG4 hinge or a modified version thereof. In some of any such examples, the immunoglobulin hinge or a modified version thereof is an IgG4 hinge. In some of any such examples, the immunoglobulin hinge or a modified version thereof is a modified version of an IgG4 hinge.

[0048] In some of any such examples, the spacer comprises or consists of the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto. In some of any such examples, the spacer is at or about 12 amino acids in length. In some of any such examples, the spacer comprises the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, or SEQ ID NO: 34. In some of any such examples, the spacer consists of the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, or SEQ ID NO: 34. In some of any such examples, the spacer comprises the sequence set forth in SEQ ID NO: 1. In some of any such examples, the spacer is at or about 12 amino acids in length. In some of any such examples, the spacer consists of the sequence set forth in SEQ ID NO: 1.

[0049] In some of any such examples, the transmembrane domain is a transmembrane domain of CD28. In some of any such examples, the transmembrane domain comprises the sequence of amino acids set forth in SEQ ID NO: 8 or a sequence of amino acids that exhibits at least or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:8. In some of any such examples, the transmembrane domain comprises the sequence of amino acids set forth in SEQ ID NO: 8. In some of any such examples, the transmembrane domain consists of the sequence of amino acids set forth in SEQ ID NO: 8.

[0050] In some of any such examples, the costimulatory domain comprises the sequence set forth in SEQ ID NO: 12 or is 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 to the sequence set forth in SEQ ID NO:12. In some of any such examples, the costimulatory domain comprises the sequence set forth in SEQ ID NO: 12. In some of any such examples, the costimulatory domain consists of the sequence set forth in SEQ ID NO: 12. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain comprises the sequence set forth in SEQ ID NO: 13, 14, or 15, or is 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 to the sequence set forth in SEQ ID NO:13, 14 or 15. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain comprises the sequence set forth in SEQ ID NO: 13. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain comprises the sequence set forth in SEQ ID NO: 14. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain comprises the sequence set forth in SEQ ID NO: 15. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain consists of the sequence set forth in SEQ ID NO: 13. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain consists of the sequence set forth in SEQ ID NO: 14. In some of any such examples, the signaling domain of a CD3-zeta (CD3 ζ) chain consists of the sequence set forth in SEQ ID NO: 15.

[0051] In some of any such examples, the scFv comprises a CDRL1 sequence of SEQ ID NO: 35, a CDRL2 sequence of SEQ ID NO: 55, and/or a CDRL3 sequence of SEQ ID NO: 56 and

a CDRH1 sequence of SEQ ID NO: 38, a CDRH2 sequence of SEQ ID NO: 39, and/or a CDRH3 sequence of SEQ ID NO: 54. In some of any such examples, the scFv comprises a CDRL1 sequence of SEQ ID NO: 35, a CDRL2 sequence of SEQ ID NO: 55, and a CDRL3 sequence of SEQ ID NO: 56 and a CDRH1 sequence of SEQ ID NO: 38, a CDRH2 sequence of SEQ ID NO: 39, and a CDRH3 sequence of SEQ ID NO: 54. In some of any such examples, the scFv comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and/or a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37) and a CDRH1 sequence of DYGVVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYNSALKS (SEQ ID NO: 39), and/or a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40). In some of any such examples, the scFv comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and/ a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37) and a CDRH1 sequence of DYGVVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYNSALKS (SEQ ID NO: 39), and a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40). In some of any such examples, the scFv comprises, in order, a V_H, comprising the sequence set forth in SEQ ID NO: 41, and a V_L comprising the sequence set forth in SEQ ID NO: 42. In some of any such examples, the scFv comprises the sequence set forth in SEQ ID NO: 43. In some examples, the scFv comprises, in order from N-terminus to C-terminus, a V_L comprising the sequence set forth in SEQ ID NO: 42, and a V_H, comprising the sequence set forth in SEQ ID NO: 41.

[0052] In some of any of the provided examples, the CAR contains in order from N-terminus to C-terminus: an extracellular antigen-binding domain that is the scFv set forth in SEQ ID NO: 43, the spacer set forth in SEQ ID NO: 1, the transmembrane domain set forth in SEQ ID NO: 8, the 4-1BB costimulatory signaling domain set forth in SEQ ID NO: 12, and the signaling domain of a CD3-zeta (CD3ζ) chain set forth in SEQ ID NO: 13.

[0053] In some examples, the dose of CD4⁺ and CD8⁺ T cells is between about 5 x 10⁷ CAR⁺ T cells and about 1.1 x 10⁸ CAR⁺ T cells, inclusive of each. In some of any of the provided examples, the dose of CD4⁺ and CD8⁺ T cells is 5 x 10⁷ CAR⁺ T cells. In some of any of the provided examples, the dose of CD4⁺ and CD8⁺ T cells is 6 x 10⁷ CAR⁺ T cells. In some of

any of the provided examples, the dose of CD4+ and CD8+ T cells is 7×10^7 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 8×10^7 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 9×10^7 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1×10^8 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1.1×10^8 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1.2×10^8 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1.3×10^8 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1.4×10^8 CAR+ T cells. In some of any of the provided examples, the dose of CD4+ and CD8+ T cells is 1.5×10^8 CAR+ T cells.

[0054] In some of any of the provided examples, the first composition and second composition are administered 0 to 12 hours apart, 0 to 6 hours apart or 0 to 2 hours apart or wherein the administration of the first composition and the administration of the second composition are carried out on the same day, are carried out between about 0 and about 12 hours apart, between about 0 and about 6 hours apart or between about 0 and 2 hours apart; and/or the initiation of administration of the first composition and the initiation of administration of the second composition are carried out between about 1 minute and about 1 hour apart or between about 5 minutes and about 30 minutes apart. In some of any of the provided examples, the first composition and second composition are administered 0 to 12 hours apart. In some of any of the provided examples, the first composition and second composition are administered 0 to 6 hours apart. In some of any of the provided examples, the first composition and second composition are administered 0 to 2 hours apart. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out on the same day. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out between about 0 and about 12 hours apart. In some of any of the provided examples, the administration of the first composition and the administration of the second composition are carried out between about 0 and about 6 hours apart. In some of any of the provided examples, the administration of the first

composition and the administration of the second composition are carried out between about 0 and 2 hours apart. In some examples, the initiation of administration of the first composition and the initiation of administration of the second composition are carried out between about 1 minute and about 1 hour apart. In some examples, the initiation of administration of the first composition and the initiation of administration of the second composition are carried out between about 5 minutes and about 30 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 2 hours, no more than 1 hour, no more than 30 minutes, no more than 15 minutes, no more than 10 minutes or no more than 5 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 2 hours apart. In some of any of the provided examples, the first composition and second composition are administered less than 2 hours apart. In some of any of the provided examples, the first composition and second composition are administered no more than 1 hour apart. In some of any of the provided examples, the first composition and second composition are administered no more than 30 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 15 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 10 minutes apart. In some of any of the provided examples, the first composition and second composition are administered no more than 5 minutes apart. In some of any of the provided examples, the first composition is administered prior to the second composition. In some examples, the first composition comprises the CD8⁺ CAR-expressing T cells and the second composition comprises the CD4⁺ T CAR-expressing cells.

[0055] In some of any of the provided examples, the dose of CD4⁺ T cells and CD8⁺ T cells is administered intravenously. In some of any of the provided examples, the T cells are primary T cells obtained from the sample from the subject. In some of any of the provided examples, the T cells are autologous to the subject. In some examples, the sample from which the cells are derived or isolated is a blood or a blood-derived sample. In some examples, the sample from which the cells are derived or isolated is or is derived from an apheresis or

leukapheresis product. In some examples, the sample is obtained from the subject prior to administration of a lymphodepleting therapy to the subject. In some examples, a leukapheresis sample is obtained from a subject approximately four or five weeks prior to administration of the dose of CD4⁺ T cells and CD8⁺ T cells to the subject. In some of any such examples, the subject is human.

[0056] In some of any of the provided examples, the complete response rate (CRR) among a plurality of subjects treated according to the method is greater than at or about 50%, greater than at or about 60%, greater than at or about 70%, or greater than at or about 80%. In some of any of the provided examples, the complete response rate (CRR) among a plurality of subjects treated according to the method is greater than at or about 50%. In some of any of the provided examples, the complete response rate (CRR) among a plurality of subjects treated according to the method is greater than at or about 60%. In some of any of the provided examples, the complete response rate (CRR) among a plurality of subjects treated according to the method is greater than at or about 70%. In some of any of the provided examples, the complete response rate (CRR) among a plurality of subjects treated according to the method is greater than at or about 80%. In some of any such examples, CRR is the percentage of subjects with a best overall response (BOR) up to 24 months of complete response (CR).

[0057] In some of any of the provided examples, the subject has FL Grade 1, 2 or 3A and CRR is assessed by PET-CT. In some of any of the provided examples, the subject has FL Grade 1 and CRR is assessed by PET-CT. In some of any of the provided examples, the subject has FL Grade 2 and CRR is assessed by PET-CT. In some of any of the provided examples, the subject has FL Grade 3A and CRR is assessed by PET-CT. In some of any of the provided examples, the subject has MZL and CRR is assessed by CT. In some of any of the provided examples, the subject has MZL and CRR is assessed by MRI. In some of any of the provided examples, the subject has MZL and CRR is assessed by CT and MRI scans.

Brief Description of the Drawings