

[0006] There is an unmet medical need for interventions that can effectively treat MM, including relapsed/refractory MM. Provided herein are methods and compositions that address this need.

SUMMARY

[0007] Chimeric antigen receptors (CARs) that bind to BCMA are provided herein; as well as dosing paradigms for use in the treatment of multiple (MM), including relapsed and/or refractory MM.

[0008] More specifically, in one example provided herein is a method of treating MM in a subject comprising administering to the subject at least one dose of allogeneic chimeric antigen receptor (CAR)-T cells comprising an anti-human BCMA CAR (BCMA CAR-T cells), wherein the at least one dose is about 7×10^6 cells/dose to about 480×10^6 cells/dose.

[0008a] In one aspect, the present disclosure refers to use of at least one dose of allogeneic chimeric antigen receptor (CAR)-T cells comprising an anti-human BCMA CAR (BCMA CAR-T cells) in the manufacture of a medicament for treating multiple myeloma in a subject, wherein the at least one dose is about 7×10^6 cells/dose to about 480×10^6 cells/dose.

[0009] In some examples, the weight of the subject is ≥ 50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20×10^6 cells/dose to about 480×10^6 cells/dose. In some examples, the at least one dose is about 20×10^6 cells/dose, about 40×10^6 cells/dose, about 120×10^6 cells/dose, about 360×10^6 cells/dose, or about 480×10^6 cells/dose. In some examples, the at least one dose is from about 20×10^6 cells/dose to about 40×10^6 cells/dose, from about 40×10^6 cells/dose to about 120×10^6 cells/dose, from about 120×10^6 cells/dose to about 360×10^6 cells/dose, or from about 360×10^6 cells/dose to about 480×10^6 cells/dose.

[0010] In some examples, the weight of the subject is >50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20×10^6 cells/dose to about 480×10^6 cells/dose. In some examples, the at least one dose is about 20×10^6 cells/dose, about 40×10^6 cells/dose, about 160×10^6 cells/dose, about 240×10^6 cells/dose, about 320×10^6 cells/dose, or about 480×10^6 cells/dose. In some examples, the at least one dose is from about 20×10^6 cells/dose to about 40×10^6 cells/dose, from about 40×10^6 cells/dose to about 160×10^6 cells/dose, from about 160×10^6 cells/dose to about 240×10^6 cells/dose, from about 240×10^6 cells/dose to about 320×10^6 cells/dose, from about 160×10^6 cells/dose to about 320×10^6 cells/dose, or from about 320×10^6 cells/dose to about 480×10^6 cells/dose.

[0011] In some examples, the weight of the subject is <50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 7×10^6 cells/dose to about 360×10^6 cells/dose. In some examples, the at least one dose is about 7×10^6 cells/dose, about 14×10^6 cells/dose, about 20×10^6 cells/dose, about
5 80×10^6 cells/dose, about 240×10^6 cells/dose, or about 360×10^6 cells/dose. In some examples, the at least one dose is from about 7×10^6 or 14×10^6 cells/dose to about 20×10^6 cells/dose, from about 20×10^6 cells/dose to about 80×10^6 cells/dose, from about 80×10^6 cells/dose to about 240×10^6 cells/dose, or from about 240×10^6 cells/dose to about 360×10^6 cells/dose.

10 **[0012]** In some examples, the weight of the subject is ≤ 50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 14×10^6 cells/dose to about 320×10^6 cells/dose. In some examples, the at least one dose is about 14×10^6 cells/dose, about 20×10^6 cells/dose, about 80×10^6 cells/dose, about 160×10^6 cells/dose about 200×10^6 cells/dose, or about 320×10^6 cells/dose. In
15 some examples, the at least one dose is about 14×10^6 cells/dose to about 20×10^6 cells/dose, from about 20×10^6 cells/dose to about 80×10^6 cells/dose, from about 80×10^6 cells/dose to about 200×10^6 cells/dose, from about 80×10^6 cells/dose to about 160×10^6 cells/dose, from about 160×10^6 cells/dose to about 200×10^6 cells/dose, or from about 200×10^6 cells/dose to about 320×10^6 cells/dose.

20 **[0013]** In some examples the subject has not received any prior therapy for multiple myeloma. In some examples the subject has received at least one, two, or three prior therapies for multiple myeloma. In some examples, the dosing regimens are a first line therapy. In some examples, the dosing regimens are a second line therapy. In some examples, the dosing regimens are a third line therapy. In some examples, the dosing
25 regimens are a fourth line therapy.

[0014] In some examples the subject has received a prior chemotherapeutic regimen; a prior biologics-based regimen, and/or a prior autologous cell therapy-based regimen (e.g. stem cell therapy).

[0015] In some examples, the subject has relapsed MM. In some examples, the subject has
30 refractory MM. In some examples, the subject has refractory and relapsed MM.

[0016] In some examples, the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region comprises a VH complementary determining region 1 (VH CDR1), a VH complementary determining region 2 (VH CDR2), and a VH complementary determining region 3 (VH CDR3) and the VL region comprises a VL complementary determining region 1 (VL CDR1), a VL complementary determining region 2 (VL CDR2), and a VL complementary determining region 3 (VL CDR3), wherein: (a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 153 or 154; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 222; (b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 187 or 188; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 249; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; (c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 165 or 166; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 226; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 227; (d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 159 or 162; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 251; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 253; (e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 190 or 191; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 262; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence

of SEQ ID NO: 263; (f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 154 or 169; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 271; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 272; (g) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 139 or 140; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 134; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 217; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 216; (h) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 158 or 159; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; or (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 132 or 133; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 137; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 377; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 214.

[0017] In some examples, the VH region of the scFv of a BCMA CAR comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region of the scFv comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 222.

[0018] In some examples, the VH region of the scFv of a BCMA CAR comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region of the scFv

comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 225.

[0019] In some examples, the BCMA CAR-T cells comprise a CAR comprising the amino acid sequence shown in SEQ ID NO: 344. In some of these examples, the CAR further comprises a CD20 epitope. In some of these examples, the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

[0020] In some examples, the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0021] In some examples, the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0022] In some examples, the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0023] In some examples, the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0024] In some examples, the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a VH region and a VL region, wherein the combination of VH and VL regions are chosen from the combinations presented in Table 1. In some examples, the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3 ζ signaling domain and/or a 4-1BB signaling domain. In some examples, the VH comprises SEQ ID NO: 33 and the VL comprises SEQ ID NO: 34. In some examples, the VH comprises SEQ ID NO: 112 and the VL comprises SEQ ID NO: 38.

[0025] In some examples, the CAR-T cells are deficient in CD52. In some examples, the CAR-T cells are deficient in TCR α and/or TCR β . In some examples, the CAR-T cells do not express a safety switch. In some examples the genotype of the cells is TCR $\alpha\beta^-$ and CD52 $^{+/-}$.

[0026] In some examples, the subject receives a first lymphodepletion regimen prior to administration of the at least one dose. In some examples, the first lymphodepletion regimen comprises administering fludarabine and cyclophosphamide. In some examples, the first lymphodepletion regimen comprises administering fludarabine,

cyclophosphamide, and an anti-CD52 antibody. In some examples, the first lymphodepletion regimen comprises administering an anti-CD52 antibody. In some examples, the first lymphodepletion regimen comprises administering only an anti-CD52 antibody. In some examples, the fludarabine is administered at a dosage of about 30 mg/m²/day; cyclophosphamide is administered at a dosage of about 300 mg/m²/day; and CD52 antibody is administered at a dosage of about 10 to about 13 mg/day, about 13 to 20 mg/day, about 13 to 30 mg/day, or about 20 to 30 mg/day. In some examples, the first lymphodepletion regimen is initiated between about 1 to 15 days prior to administration of the at least one dose. In some examples, the first lymphodepletion regimen is administered over the course of 1, 2, 3, 4, or 5 days. In some examples, the first lymphodepletion regimen is administered 5 days prior to administration of the at least one dose in the course of 3 days. In some examples, the first lymphodepletion regimen is administered 7 days prior to administration of the at least one dose in the course of 3 days.

[0027] In some examples, the subject receives a subsequent dose of the CAR-T cells.

[0028] In another example provided herein is a formulation comprising BCMA CAR-T cells. In one example the formulation comprises a solution comprising about 5% dimethyl sulfoxide (DMSO) and 14×10^6 cells /mL. In another example the cells are formulated in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, wherein the dosage strength of the formulation is 14×10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_{TCRαβ}-_{CD52}+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

[0028a] In another aspect, the present disclosure refers to a formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a solution comprising about 5% dimethyl sulfoxide, wherein the dosage strength of the formulation is 14×10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_{TCRαβ}-_{CD52}+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

[0028b] In another aspect, the present disclosure refers to a formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, wherein the dosage strength of the formulation is 14×10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_{TCRαβ}-_{CD52}+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

WHAT IS CLAIMED IS:

1. Use of at least one dose of allogeneic chimeric antigen receptor (CAR)-T cells comprising an anti-human BCMA CAR (BCMA CAR-T cells) in the manufacture of a medicament for treating multiple myeloma in a subject, wherein the at least one dose is about
5 7×10^6 cells/dose to about 480×10^6 cells/dose.
2. The use of claim 1, wherein the weight of the subject is ≥ 50 kg, and at least one dose of BCMA CAR-T cells is to be administered, wherein the dose ranges from about 20×10^6 cells/dose to about 480×10^6 cells/dose.
3. The use of claim 2, wherein the at least one dose is about 20×10^6 cells/dose, about
10 40×10^6 cells/dose, about 120×10^6 cells/dose, about 360×10^6 cells/dose, or about 480×10^6 cells/dose.
4. The use of claim 2, wherein the at least one dose is from about 20×10^6 cells/dose to about 40×10^6 cells/dose, from about 40×10^6 cells/dose to about 120×10^6 cells/dose, from about 120×10^6 cells/dose to about 360×10^6 cells/dose, or from about 360×10^6
15 cells/dose to about 480×10^6 cells/dose.
5. The use of claim 1, wherein the weight of the subject is < 50 kg, and at least one dose of BCMA CAR-T cells is to be administered, wherein the dose ranges from about 7×10^6 cells/dose to about 360×10^6 cells/dose.
6. The use of claim 5, where in the at least one dose is about 7×10^6 cells/dose, about
20 14×10^6 cells/dose, about 20×10^6 cells/dose, about 80×10^6 cells/dose, about 240×10^6 cells/dose, or about 360×10^6 cells/dose.
7. The use of claim 5, where in the at least one dose is from about 7×10^6 or 14×10^6 cells/dose to about 20×10^6 cells/dose, from about 20×10^6 cells/dose to about 80×10^6 cells/dose, from about 80×10^6 cells/dose to about 240×10^6 cells/dose, or from about 240
25 $\times 10^6$ cells/dose to about 360×10^6 cells/dose.
8. The use of claim 1, wherein the weight of the subject is > 50 kg, and at least one dose of BCMA CAR-T cells is to be administered, wherein the dose ranges from about 20×10^6 cells/dose to about 480×10^6 cells/dose.
9. The use of claim 8, wherein the at least one dose is about 20×10^6 cells/dose, about
30 40×10^6 cells/dose, about 160×10^6 cells/dose, about 240×10^6 cells/dose, about $320 \times$

10⁶ cells/dose, or about 480 x 10⁶ cells/dose.

10. The use of claim 8, wherein the at least one dose is from about 20 x 10⁶ cells/dose to about 40 x 10⁶ cells/dose, from about 40 x 10⁶ cells/dose to about 160 x 10⁶ cells/dose, from about 160 x 10⁶ cells/dose to about 240 x 10⁶ cells/dose, from about 240 x 10⁶ cells/dose to about 320 x 10⁶ cells/dose, from about 160 x 10⁶ cells/dose to about 320 x 10⁶ cells/dose, or from about 320 x 10⁶ cells/dose to about 480 x 10⁶ cells/dose.

11. The use of claim 1, wherein the weight of the subject is ≤50 kg, and at least one dose of BCMA CAR-T cells is to be administered, wherein the dose ranges from about 14 x 10⁶ cells/dose to about 320 x 10⁶ cells/dose.

12. The use of claim 11, where in the at least one dose is about 14 x 10⁶ cells/dose, about 20 x 10⁶ cells/dose, about 80 x 10⁶ cells/dose, about 160 x 10⁶ cells/dose, about 200 x 10⁶ cells/dose, or about 320 x 10⁶ cells/dose.

13. The use of claim 12, where in the at least one dose is from about 14 x 10⁶ cells/dose to about 20 x 10⁶ cells/dose, from about 20 x 10⁶ cells/dose to about 80 x 10⁶ cells/dose, from about 80 x 10⁶ cells/dose to about 200 x 10⁶ cells/dose, from about 80 x 10⁶ cells/dose to about 160 x 10⁶ cells/dose, from about 160 x 10⁶ cells/dose to about 200 x 10⁶ cells/dose, or from about 200 x 10⁶ cells/dose to about 320 x 10⁶ cells/dose.

14. The use of any one of claims 1 to 13, wherein the multiple myeloma is refractory multiple myeloma.

15. The use of any one of claims 1 to 14, wherein the multiple myeloma is relapsed multiple myeloma.

16. The use of any one of claims 1 to 13, wherein the multiple myeloma is refractory and relapsed multiple myeloma.

17. The use of any one of claims 1 to 13, wherein the subject is one that has not received any prior therapy for multiple myeloma.

18. The use of any one of claims 1 to 13, wherein the subject is one that has received at least one, two, or three prior therapies for multiple myeloma.

19. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a heavy chain variable (VH) region and a light chain

variable (VL) region, wherein the VH region comprises a VH complementary determining region 1 (VH CDR1), a VH complementary determining region 2 (VH CDR2), and a VH complementary determining region 3 (VH CDR3) and the VL region comprises a VL complementary determining region 1 (VL CDR1), a VL complementary determining region 2 (VL CDR2), and a VL complementary determining region 3 (VL CDR3), wherein:

(a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 153 or 154; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 222;

(b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 187 or 188; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 249; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225;

(c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 165 or 166; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 226; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 227;

(d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 159 or 162; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 251; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 253;

(e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 190 or 191; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 262; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 263;

(f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the

VH CDR2 comprises the amino acid sequence of SEQ ID NO: 154 or 169; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 271; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 272;

5 (g) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 139 or 140; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 134; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 217; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 216;

10 (h) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 158 or 159; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; or

15 (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 132 or 133; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 137; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 377; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 214

20 **20.** The use of claim 19, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 222.

21. The use of claim 19, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence

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of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 225.

22. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a VH region and a VL region, wherein the combination
5 of VH and VL regions are chosen from the combinations presented in Table 1.

23. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv
10 comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3 ζ signaling domain and/or a
15 4-1BB signaling domain.

24. The use of claim 23, wherein the VH comprises SEQ ID NO: 33 and the VL comprises SEQ ID NO: 34.

25. The use of claim 23, wherein the VH comprises SEQ ID NO: 112 and the VL comprises SEQ ID NO: 38.

26. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising the amino acid sequence shown in SEQ ID NO: 344.

27. The use of claim 26, wherein the CAR further comprises a CD20 epitope.

28. The use of claim 27, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

29. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ
30 ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO:

323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

30. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

31. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

32. The use of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8 α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8 α hinge having the sequence of SEQ ID NO: 320; a CD8 α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3 ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

33. The use of any one of claims 1 to 32, wherein the CAR-T cells are deficient in CD52.

34. The use of any one of claims 1 to 30, wherein the CAR-T cells are deficient in TCR α and/or TCR β .

35. The use of any one of claims 1 to 34, wherein the genotype of the cells is TCR $\alpha\beta^-$ and CD52 $^{+/-}$.

36. The use of any one of claims 1 to 32, wherein the CAR-T cells do not express a safety switch.

37. The use of any one of claims 1 to 32, wherein the CAR-T cells express a rituximab epitope.

38. The use of any one of claims 1 to 37, wherein a first lymphodepletion regimen is to be administered to the subject prior to administration of the at least one dose.

5 **39.** The use of claim 38, wherein in the first lymphodepletion regimen fludarabine and cyclophosphamide are to be administered.

40. The use of claim 38, wherein in the first lymphodepletion regimen fludarabine, cyclophosphamide, and an anti-CD52 antibody are to be administered.

10 **41.** The use of claim 38, wherein in the first lymphodepletion regimen an anti-CD52 antibody is to be administered.

42. The use of claim 38, wherein in the first lymphodepletion regimen only an anti-CD52 antibody is to be administered.

15 **43.** The use of claim 38, wherein fludarabine is to be administered at a dosage of about 30 mg/m²/day; cyclophosphamide is to be administered at a dosage of about 300 mg/m²/day; and the CD52 antibody is to be administered at a dosage of about 10 to about 13 mg/day.

44. The use of claim 40, wherein fludarabine is to be administered at a dosage of about 30 mg/m²/day; cyclophosphamide is to be administered at a dosage of about 300 mg/m²/day; and the CD52 antibody is to be administered at a dosage of about 13 to about 30 mg/day, about 13 to 20 mg/day, about 13 to 30 mg/day, or about 20 to 30 mg/day.

20 **45.** The use of claim 44, wherein the CD52 antibody is to be administered at a dosage of about 13 mg/day, about 20 mg/day or about 30 mg/day.

46. The use of any one of claims 38 to 45, wherein the first lymphodepletion regimen is to be initiated between about 1 to 15 days prior to administration of the at least one dose.

25 **47.** The use of any one of claims 38 to 46, wherein the first lymphodepletion regimen is to be administered over the course of 1, 2, 3, 4, or 5 days.

48. The use of any one of claims 36-47, wherein the first lymphodepletion regimen is to be administered 5 days prior to administration of the at least one dose in the course of 3 days.

49. The use of any one of claims 1 to 48, wherein a subsequent dose of the CAR-T cells is to be administered to the subject.

50. A formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a solution comprising about 5% dimethyl sulfoxide, wherein the dosage strength of the formulation is 14×10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_TCR $\alpha\beta$ -_CD52+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3 ζ signaling domain and/or a 4-1BB signaling domain.

51. A formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, wherein the dosage strength of the formulation is 14×10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_TCR $\alpha\beta$ -_CD52+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3 ζ signaling domain and/or a 4-1BB signaling domain.