Claims

1. Use of a combination therapy for the manufacture of a medicament for treating a cancer expressing CD19 in a subject, wherein the combination therapy comprises:

(i) a T cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) directed against the cancer, wherein the T cell therapy is to be administered on Day 1 of the combination therapy; and

(ii) a compound that is (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione or a pharmaceutically acceptable salt thereof.

2. Use of a combination therapy for the manufacture of a medicament for treating a lymphoma in a subject, wherein the combination therapy comprises:

(i) a T cell therapy comprising a dose of engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) that binds cluster of differentiation 19 (CD19), wherein the T cell therapy is to be administered on Day 1 of the combination therapy; and

(ii) a compound that is (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione or a pharmaceutically acceptable salt thereof.

3. The use of claim 1 or claim 2, wherein:

(i) the administration of the compound is to be initiated subsequently to the administration of the T cell therapy;

(ii) the administration of the compound is to be initiated between Day 1 and Day 29, inclusive, of the combination therapy;

(iii) the compound is to be administered as a plurality of doses, wherein each dose is between at or about 0.1 mg and at or about 0.6 mg, inclusive; and/or

(iv) the compound is to be administered as a plurality of intermittent doses administered no more than once weekly.

4. The use of any one of claims 1-3, wherein:

(i) the administration of the compound is to be initiated between Day 1 and Day 22, inclusive;

(ii) the administration of the compound is to be initiated between Day 1 and Day 15, inclusive;

(iii) the administration of the compound is to be initiated between Day 8 and Day 15, inclusive;

(iv) the administration of the compound is to be initiated at or about Day 1;

(v) the administration of the compound is to be initiated at or about Day 8; or

(vi) the administration of the compound is to be initiated at or about Day 15.

5. The use of claim 3 or 4, wherein each dose of the plurality of intermittent doses is the same.

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

(i) the compound is to be administered (a) once weekly and/or (b) once every 7 days (Q7D); or

(ii) the compound is to be administered (a) once every two weeks and/or (b) once every 14 days (Q14D).

7. The use of any one of claims 1-6, wherein:

(i) the compound is to be administered for at least 12 weeks after the administration of the T cell therapy; or

(ii) the compound is to be administered for up to 12 weeks after the administration of the T cell therapy.

8. The use of any one of claims 1-7, wherein:

(i) the compound is to be administered on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85;

(ii) the compound is to be administered on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85;

(iii) the compound is to be administered on Days 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85; or

(iv) the compound is to be administered on Days 8, 22, 36, 50, 64, and 78.

9. The use of any one of claims 1-8, wherein:

(i) the dose of the compound is between at or about 0.3 mg and at or about 0.6 mg, inclusive;

(ii) the dose of the compound is at or about 0.6 mg;

(iii) the dose of the compound is between at or about 0.2 mg and at or about 0.4 mg, inclusive;

(iv) the dose of the compound is at or about 0.4 mg;

(v) the dose of the compound is less than 0.4 mg;

(vi) the dose of the compound is at or about 0.3 mg; or

(vii) the dose of the compound is at or about 0.2 mg.

10. The use of any one of claims 1-9, wherein:

(i) the compound is a pharmaceutically acceptable salt of (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione; or

(ii) the compound is (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione.

11. The use of any one of claims 1-10, wherein:

(i) at the time of the initiation of the administration of the compound, the subject does not exhibit a severe toxicity following the administration of the T cell therapy, wherein:

(a) the severe toxicity is severe cytokine release syndrome (CRS), optionally grade 3 or higher CRS, prolonged grade 3 or higher CRS, grade 4 CRS, or grade 5 CRS; and/or

(b) the severe toxicity is severe neurotoxicity, optionally grade 3 or higher neurotoxicity, prolonged grade 3 or higher neurotoxicity, grade 4 neurotoxicity, or grade 5 neurotoxicity; and/or

(ii) the administration of the compound is to be suspended and/or the dose of the compound is modified, optionally lowered, if the subject exhibits a toxicity following the administration of the compound, optionally a hematologic toxicity, wherein:

(a) the toxicity is severe thrombocytopenia, optionally grade 4 thrombocytopenia or prolonged grade 4 thrombocytopenia; or

(b) the toxicity is severe neutropenia, optionally grade 4 neutropenia, prolonged grade 4 neutropenia, or febrile neutropenia, optionally grade 3 or higher febrile neutropenia or prolonged grade 3 or higher febrile neutropenia.

12. The use of claim 11, wherein the administration of the compound is to be restarted after the subject no longer exhibits the toxicity.

13. The use of any one of claims 1-12, wherein:

(i) the cancer is a B-cell malignancy; and/or

(ii) the cancer is a non-Hodgkin lymphoma (NHL), optionally wherein the NHL comprises aggressive NHL; diffuse large B cell lymphoma (DLBCL); DLBCL-NOS, optionally transformed indolent; EBV-positive DLBCL-NOS; T cell/histiocyte-rich large B-cell lymphoma; primary mediastinal large B cell lymphoma (PMBCL); follicular lymphoma (FL), optionally follicular lymphoma Grade 3B (FL3B); and/or high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit).

14. The use of any one of claims 1-13, wherein:

(i) the CD19 is a human CD19; and/or

(ii) the chimeric antigen receptor (CAR) comprises an extracellular antigen-recognition domain that specifically binds to the CD19 and an intracellular signaling domain comprising an ITAM.

15. The use of claim 14, wherein:

(i) the intracellular signaling domain comprises a signaling domain of a CD3-zeta (CD3ζ) chain, optionally a human CD3-zeta chain; and/or

(ii) the chimeric antigen receptor (CAR) further comprises a costimulatory signaling region, optionally wherein the costimulatory signaling region comprises a signaling domain of CD28 or 4-1BB, optionally human CD28 or human 4-1BB.

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

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

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

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

17. The use of claim 16, wherein:

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

(ii) the spacer comprises or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4 hinge, or a modified version thereof and/or comprises about 15 amino acids or less;

(iii) the spacer is at or about 12 amino acids in length and/or comprises or consists of all or a portion of an immunoglobulin hinge, optionally an IgG4, or a modified version thereof;

(iv) the spacer has or consists of the sequence of SEQ ID NO: 1; a sequence encoded by SEQ ID NO: 2, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34; or a variant of any of the foregoing having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto;

(v) the cytoplasmic signaling domain derived from a costimulatory molecule comprises the sequence set forth in 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;

(vi) the cytoplasmic signaling domain derived from a primary signaling ITAM-containing molecule comprises the sequence of any of SEQ ID NO: 13-15 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;

(vii) a CDRL1 sequence of RASQDISKYLN (SEQ ID NO: 35), a CDRL2 sequence of SRLHSGV (SEQ ID NO: 36), and/or a CDRL3 sequence of GNTLPYTFG (SEQ ID NO: 37); and/or

(viii) a CDRH1 sequence of DYGVS (SEQ ID NO: 38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO: 39), and/or a CDRH3 sequence of YAMDYWG (SEQ ID NO: 40).

18. The use of claim 16 or 17, wherein the scFv comprises:

a variable heavy chain region of FMC63 and a variable light chain region of FMC63; and/or

a CDRL1 sequence of FMC63, a CDRL2 sequence of FMC63, a CDRL3 sequence of FMC63, a CDRH1 sequence of FMC63, a CDRH2 sequence of FMC63, and a CDRH3 sequence of FMC63; and

optionally wherein the scFv comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 41, and a VL comprising the amino acid sequence set forth in SEQ ID NO: 42.

19. The use of any one of claims 16-18, wherein the scFv has the sequence of amino acids set forth in SEQ ID NO: 43.

20. The use of any one of claims 1-19, wherein:

(i) the dose of engineered cells comprises from or from about 1×10^5 to 5×10^8 total CAR-expressing T cells, 1×10^6 to 2.5×10^8 total CAR-expressing T cells, 5×10^6 to 1×10^8 total CAR-expressing T cells, 1×10^7 to 2.5×10^8 total CAR-expressing T cells, or 5×10^7 to 1×10^8 total CAR-expressing T cells, each inclusive;

(ii) the dose of engineered cells comprises at least or at least about 1×10^5 CAR-expressing cells, at least or at least about 2.5×10^5 CAR-expressing cells, at least or at least about 5×10^5 CAR-expressing cells, at least or at least about 1×10^6 CAR-expressing cells, at least or at least about 2.5×10^6 CAR-expressing cells, at least or at least about 5×10^6 CAR-expressing cells, at least or at least about 1×10^7 CAR-expressing cells, at least or at least about 2.5×10^7 CAR-expressing cells, at least or at least about 5×10^7 CAR-expressing cells, at least or at least about 1×10^8 CAR-expressing cells, at least or at least about 2.5×10^8 CAR-expressing cells, or at least or at least about 5×10^8 CAR-expressing cells;

(iii) the dose of engineered cells comprises at or about 1 x 10^8 CAR-expressing T cells; and/or

(iv) the dose of engineered cells is to be administered parenterally, optionally intravenously.

21. The use of any one of claims 1-20, wherein:

(i) the T cells are (a) primary T cells obtained from the subject and/or (b) autologous to the subject; or

(ii) the T cells are allogeneic to the subject.

22. The use of any one of claims 1-21, wherein the dose of engineered cells comprises CD4+ T cells expressing the CAR and CD8+ T cells expressing the CAR and the administration of the dose comprises administration of a plurality of separate compositions, said plurality of separate compositions comprising a first composition comprising one of the CD4+ T cells and the CD8+ T cells and a second composition comprising the other of the CD4+ T cells and the CD8+ T cells.

23. The use of claim 22, wherein:

(i) the first composition and second composition are to be 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 to be carried out on the same day, are to be 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;

(ii) the initiation of administration of the first composition and the initiation of administration of the second composition are to be carried out between about 1 minute and about 1 hour apart or between about 5 minutes and about 30 minutes apart; and/or

(iii) the first composition and second composition are to be 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.

24. The use of claim 22 or 23, wherein:

(i) the first composition comprises (a) the CD4+ T cells or (b) the CD8+ T cells; and/or

(ii) the first composition is to be administered prior to the second composition.

25. The use of any one of claims 1-24, wherein, prior to the administration of the T cell therapy, the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

26. The use of any one of claims 1-24, wherein the combination therapy further comprises a lymphodepleting therapy, wherein the lymphodepleting therapy is to be administered immediately prior to the administration of the T cell therapy, and wherein administration of the lymphodepleting therapy to the subject comprises the administration of fludarabine and/or cyclophosphamide.

27. The use of claim 25 or claim 26, wherein the lymphodepleting therapy comprises administration of cyclophosphamide at about 200-400 mg/m^2, inclusive, optionally at or about 300 mg/m^2, and/or fludarabine at about 20-40 mg/m^2, optionally 30 mg/m^2, daily for 2-4 days, optionally for 3 days, or wherein the lymphodepleting therapy comprises administration of cyclophosphamide at about 500 mg/m^2.

28. The use of any one of claims 1-27, wherein the subject is a human.

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

at least 35%, at least 40 % or at least 50% of subjects treated according to the use achieve a complete response (CR) that is durable, or is durable in at least 60, 70, 80, 90, or 95 % of subjects achieving the CR, for at or greater than 6 months or at or greater than 9 months; and/or

at least 60, 70, 80, 90, or 95 % of subjects achieving a CR by six months remain in response, remain in CR, and/or survive or survive without progression, for at or greater than 3 months and/or at or greater than 6 months and/or at or greater than nine months; and/or

at least 50%, at least 60% or at least 70% of the subjects treated according to the use achieve objective response (OR), optionally wherein the OR is durable, or is durable in at least 60, 70, 80, 90, or 95 % of subjects achieving the OR, for at or greater than 6 months or at or greater than 9 months; and/or

at least 60, 70, 80, 90, or 95 % of subjects achieving an OR by six months remain in response or surviving for at or greater than 3 months and/or at or greater than 6 months.

30. The use of any one of claims 1-29, wherein at or immediately prior to the time of the administration of the dose of engineered cells, the subject has relapsed following remission after treatment with, or become refractory to, one or more prior therapies for the lymphoma, optionally one, two, or three prior therapies other than another dose of engineered cells expressing the CAR.

31. The use of any one of claim 1-30, wherein at or prior to the administration of the dose of engineered cells:

the subject is or has been identified as having a double/triple hit lymphoma;

the subject is or has been identified as having a chemorefractory lymphoma, optionally a chemorefractory DLBCL; and/or

the subject has not achieved complete remission (CR) in response to a prior therapy.

32. The use of any one of claims 1-31, wherein the administration of the compound:

reverses an exhaustion phenotype in CAR-expressing T cells in the subject;

prevents, inhibits, or delays the onset of an exhaustion phenotype in CAR-expressing T cells in the subject;

reduces the level or degree of an exhaustion phenotype in CAR-expressing T cells in the subject; or

reduces the percentage or the total number of CAR-expressing T cells in the subject that have an exhaustion phenotype.

33. The use of any one of claims 1-32, wherein the initiation of the administration of the compound is to be carried out subsequently to the administration of the T cell therapy and, following administration of the compound or initiation thereof, the subject exhibits a restoration or rescue of an antigen- or tumor-specific activity or function of the CAR-expressing T cells in said subject, optionally wherein said restoration, rescue, and/or initiation of administration of said compound is at a point in time after CAR-expressing T cells in the subject or in the blood of the subject have exhibited an exhausted phenotype.

34. The use of any one of claims 1-33, wherein the administration of the compound comprises administration at an amount, frequency and/or duration effective to:

(a) effect an increase in antigen-specific or antigen receptor-driven activity of naïve or non-exhausted T cells in the subject, which optionally comprise T cells expressing said CAR, following exposure of the T cells to CD19 antigen or to an antigen receptor-specific agent, as compared to the absence of said administration of said compound;

(b) prevent, inhibit or delay the onset of an exhaustion phenotype in naïve or non-exhausted T cells in the subject, which optionally comprise T cells expressing said CAR, following exposure of the T cells to CD19 antigen or to an antigen receptor-specific agent, as compared to the absence of said administration of said compound; and/or

(c) reverse an exhaustion phenotype in exhausted T cells, optionally comprising T cells expressing said CAR, in the subject, as compared to the absence of said administration of said compound.

35. The use of claim 34, wherein the T cells in the subject comprise T cells expressing said CAR and/or the exposure is to CD19 antigen.

36. The use of any one of claims 32-35, wherein the exhaustion phenotype, with reference to a T cell or population of T cells, comprises:

an increase in the level or degree of surface expression on the T cell or T cells, or in the percentage of said population of T cells exhibiting surface expression, of one or more exhaustion markers, optionally 2, 3, 4, 5 or 6 exhaustion markers, compared to a reference T cell population under the same conditions, optionally wherein the increase in the level, degree or percentage is by greater than at or about 1.2-fold, at or about 1.5-fold, at or about 2.0-fold, at or about 3-fold, at or about 4-fold, at or about 5-fold, at or about 6-fold, at or about 7-fold, at or about 8-fold, at or about 9-fold, at or about 10-fold or more; or

a decrease in the level or degree of an activity exhibited by said T cells or population of T cells upon exposure to a CD19 antigen or antigen receptor-specific agent, compared to a reference T cell population under the same conditions, optionally wherein the decrease in the level, degree or percentage is by greater than at or about 1.2-fold, at or about 1.5-fold, at or about 2.0-fold, at or about 3-fold, at or about 4-fold, at or about 5-fold, at or about 6-fold, at or about 7-fold, at or about 8-fold, at or about 9-fold, at or about 10-fold or more.

37. The use of claim 36, wherein:

(i) the reference T cell population is a population of T cells known to have a non-exhausted phenotype, is a population of naïve T cells, is a population of central memory T cells, or is a population of stem central memory T cells, optionally from the same subject, or of the same species as the subject, from which the T cell or T cells having the exhaustion phenotype are derived;

(ii) the reference T cell population (a) is a subject-matched population comprising bulk T cells isolated from the blood of the subject from which the T cell or T cells having the exhaustion phenotype is derived, optionally wherein the bulk T cells do not express the CAR and/or (b) is obtained from the subject from which the T cell or T cells having the exhaustion phenotype is derived, prior to receiving administration of a dose of T cells expressing the CAR; and/or

(iii) the reference T cell population is a composition comprising a sample of T cells expressing the CAR, or pharmaceutical composition comprising T cells expressing the CAR, prior to its administration to the subject, optionally wherein the composition is a cryopreserved sample.

38. The use of claim 36 or 37, wherein:

(i) the one or more exhaustion markers is an inhibitory receptor; and/or

(ii) the one or more exhaustion markers is selected from among PD-1, CTLA-4, TIM-3, LAG-3, BTLA, 2B4, CD160, CD39, VISTA, and TIGIT.

39. The use of any one of claims 36-38, wherein the activity is one or more of proliferation, cytotoxicity or production of one or a combination of inflammatory cytokines, optionally wherein the one or a combination of cytokines is selected from the group consisting of IL-2, IFN-gamma and TNF-alpha.

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

(i) the exposure to said CD19 antigen or antigen receptor-specific agent comprises incubation with the CD19 antigen or antigen receptor-specific agent, optionally an agent that binds the antigen-binding domain of the CAR; and/or

(ii) the exposure to the CD19 antigen or antigen receptor-specific agent comprises exposing the T cells to CD19 antigen-expressing target cells, optionally cells of the B cell malignancy.