[0007] Provided herein are methods of treatment that involve administering a T cell therapy to a subject having a disease or condition, wherein, at the time of initiation of the administration of the T cell therapy, the subject has been administered, and/or is undergoing treatment with, an immunomodulatory compound and/or a blood or biopsy sample of the subject contains detectable levels of T cells of an engineered T cell therapy.

[0008] Provided herein are methods of treatment that involve administering an immunomodulatory compound to a subject having a disease or condition, wherein, at the time of initiation of administration of the immunomodulatory compound, the subject has been previously administered a T cell therapy for treatment of the disease or condition and/or a blood or biopsy sample of the subject contains detectable levels of T cells of an engineered T cell therapy. In some examples, the method thereby prevents, reduces or ameliorates one or more symptoms or outcomes of the disease or condition.

[0008a] In one aspect, the present disclosure refers to use of an immunomodulatory compound in the manufacture of a medicament for the treatment of a cancer in a subject, wherein: at the time of initiation of administration of the immunomodulatory compound, the subject has been previously administered a T cell therapy for treatment of the cancer, the T cell therapy comprising genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen associated with the cancer; and said immunomodulatory compound is thalidomide (2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione) or an analog or derivative of thalidomide that (i) binds to cereblon (CRBN) and/or to the CRBN E3 ubiquitin-ligase complex, and (ii) promotes degradation of Ikaros (IKZF1) and/or Aiolos (IKZF2), wherein the immunomodulatory compound is to be administered 7 to 21 days after initiation of administration of the T cell therapy and is to be administered daily for up to 21 consecutive days in a cycle.

[0008b] In another aspect, the present disclosure refers to use of a combination comprising a T cell therapy and an immunomodulatory compound in the manufacture of a medicament for the treatment of a cancer, wherein:

(a) the T cell therapy comprises genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen associated with the cancer and is to be administered to a subject having the cancer; and

(b) a therapeutically effective amount of the immunomodulatory compound is to be administered to the subject 7 to 21 days after administration of the T cell therapy and is to be administered daily for up to 21 consecutive days in a cycle, wherein said immunomodulatory compound is thalidomide (2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione) or an analog or derivative of thalidomide that (i) binds to cereblon (CRBN) and/or to the CRBN E3 ubiquitin-ligase complex, and (ii) promotes degradation of Ikaros (IKZF1) and/or Aiolos (IKZF2).

WHAT IS CLAIMED:

1. Use of an immunomodulatory compound in the manufacture of a medicament for the treatment of a cancer in a subject, wherein:
at the time of initiation of administration of the immunomodulatory compound, the subject has been previously administered a T cell therapy for treatment of the cancer, the T cell therapy comprising genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen associated with the cancer; and said immunomodulatory compound is thalidomide (2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione) or an analog or derivative of thalidomide that (i) binds to cereblon (CRBN) and/or to the CRBN E3 ubiquitin-ligase complex, and (ii) promotes degradation of Ikaros (IKZF1) and/or Aiolos (IKZF2), wherein the immunomodulatory compound is to be administered 7 to 21 days after initiation of administration of the T cell therapy and is to be administered daily for up to 21 consecutive days in a cycle.

2. Use of a combination comprising a T cell therapy and an immunomodulatory compound in the manufacture of a medicament for the treatment of a cancer, wherein:

(a) the T cell therapy comprises genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to an antigen associated with the cancer and is to be administered to a subject having the cancer; and

(b) a therapeutically effective amount of the immunomodulatory compound is to be administered to the subject 7 to 21 days after administration of the T cell therapy and is to be administered daily for up to 21 consecutive days in a cycle, wherein said immunomodulatory compound is thalidomide (2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione) or an analog or derivative of thalidomide that (i) binds to cereblon (CRBN) and/or to the CRBN E3 ubiquitin-ligase complex, and (ii) promotes degradation of Ikaros (IKZF1) and/or Aiolos (IKZF2).

3. The use of claim 1 or claim 2, wherein the immunomodulatory compound is to be administered at 7 days or at 14 days after initiation of administration of the T cell therapy.

4. The use of any of claims 1-3, wherein initiation of administration of the immunomodulatory compound is to be at a time at which, immediately after, or within 1 to 3 days after:

(i) peak or maximum level of the cells of the T cell therapy are detectable in the blood of the subject;

(ii) the number of cells of the T cell therapy detectable in the blood, after having been detectable in the blood, is not detectable or is reduced compared to a preceding time point after administration of the T cell therapy;

(iii) the number of cells of the T cell therapy detectable in the blood is decreased by or more than 1.5-fold, 2.0-fold, 3.0-fold, 4.0-fold, 5.0-fold, 10-fold or more the peak or maximum number cells of the T cell therapy detectable in the blood of the subject after initiation of administration of the T cell therapy;

(iv) at a time after a peak or maximum level of the cells of the T cell therapy is detectable in the blood of the subject, the number of cells of or derived from the T cells detectable in the blood from the subject is less than 10%, less than 5%, less than 1% or less than 0.1% of total peripheral blood mononuclear cells (PBMCs) in the blood of the subject;

(v) the subject exhibits disease progression and/or has relapsed following remission after treatment with the T cell therapy; and/or

(vi) the subject exhibits increased tumor burden as compared to tumor burden at a time prior to or after administration of the T cells and prior to initiation of administration of the immunomodulatory compound.

5. The use of any of claims 1-4, wherein the subject is

a subject in which at or about at day 12 to 15 after initiation of administration of the T cell therapy for treating the cancer:

(i) the number of cells of the T cell therapy in the subject is less than 75% of the average number of cells of the T cell therapy at the same time in a plurality of subjects administered the same or similar dose of the T cell therapy; and/or

(ii) the number of CD3+ or CD8+ cells of the T cell therapy in the blood is less than 10 cells per μL, less than 5 cells per μL or less than per 1 cells per μL.

6. The use of any of claims 1-5, wherein the immunomodulatory compound is to be administered in a cycle comprising an administration period in which the immunomodulatory compound is administered followed by a rest period during which the immunomodulatory compound is not administered.

7. The use of claim 6, wherein the total number of days in the cycle is greater than, greater than about, or is about 21 days, 28 days, 30 days, 40 days, 50 days, 60 days or more.

8. The use of claim 6 or claim 7, wherein the total number of days in the cycle is about 28 days.

9. The use of any of claims 6-8, wherein the immunomodulatory compound is to be administered for at least 2 cycles.

10. The use of any of claims 1-9, wherein the immunomodulatory compound is administered for no more than about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 consecutive days.

11. The use of any of claims 1-10, wherein the immunomodulatory compound is to be administered in a cycle comprising:

(i) administration for up to 21 consecutive days, wherein the cycle comprises greater than 30 days beginning upon initiation of the administration of the immunomodulatory compound; and/or

(ii) administration for a plurality of consecutive days followed by a rest period during which the immunomodulatory compound is not administered, wherein the rest period is greater than 14 consecutive days; and/or

(iii) administration for no more than 14 consecutive days.

12. The use of any of claims 1-11, wherein the administration of the immunomodulatory compound is to be continued until:

the number of cells of or derived from the administered T cell therapy detectable in the blood from the subject is increased compared to in the subject at a preceding time point just prior to administration of the immunomodulatory compound or compared to a preceding time point after administration of the T-cell therapy;

the number of cells of or derived from the T cell therapy detectable in the blood is within 2.0-fold (greater or less) the peak or maximum number observed in the blood of the subject after initiation of administration of the T cells; and/or

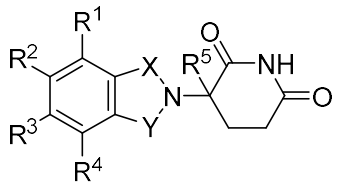
the number of cells of the T cell therapy detectable in the blood from the subject is greater than or greater than about 10%, 15%, 20%, 30%, 40%, 50%, or 60% total peripheral blood mononuclear cells (PBMCs) in the blood of the subject.

13. The use of any of claims 1-12, wherein the administration of the immunomodulatory compound is to be continued until:

the subject exhibits a reduction in tumor burden as compared to tumor burden at a time immediately prior to the administration of the T cell therapy or at a time immediately prior to the administration of the immunomodulatory compound; and/or

the subject exhibits complete or clinical remission.

14. The use of any of claims 1-13, wherein the immunomodulatory compound is a compound of the following formula:



wherein

one of X and Y is –C(O)- and the other of X and Y is –C(O)- or –CH_2-;

(1) each of R^1, R^2, R^3, and R^4 are independently halo, alkyl of 1 to 4 carbon atoms, or alkoxy or 1 to 4 carbon atoms, or

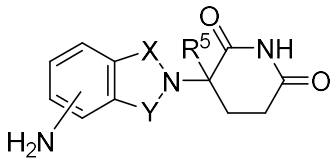
(2) one of R^1, R^3 , R^4 , and R^5 is –NHR^a and the remaining of R^1, R^2, R^3, and R^4 is are hydrogen, wherein R^a is hydrogen or alkyl of 1 to 8 carbon atoms;

R^5 is hydrogen or alkyl of 1 to 8 carbon atoms, benzyl, or halo;

provided that R^5 is other than hydrogen if X and Y are –C(O)- and (i) each of R^1, R^2, R^3, and R^4 is fluoro; or (ii) one of R^1, R^2, R^3, and R^4 is amino;

or a pharmaceutically acceptable salt thereof.

15. The use of any of claims 1-13, wherein the immunomodulatory compound is a compound of the following formula:



wherein one of X and Y is –C(O)- and the other of X and Y is –C(O)- or –CH_2-, and R^5 is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof.

16. The use of any of claims 1-13, wherein the immunomodulatory compound is 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione, pomalidomide, 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione, a stereoisomer of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione, a stereoisomer of pomalidomide, a stereoisomer of 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

17. The use of any of claims 1-13, wherein the immunomodulatory compound is 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione.

18. The use of any of claims 1-13, wherein the immunomodulatory compound is pomalidomide.

19. The use of any of claims 1-13, wherein the immunomodulatory compound is 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione.

20. The use of any of claims 1-13, wherein the immunomodulatory compound is 3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione.

21. The use of any of claims 1-20, wherein the immunomodulatory compound is to be administered orally.

22. The use of any of claims 1-21, wherein the immunomodulatory compound is to be administered in an amount from or from about 0.1 mg to about 100 mg.

23. The use of any of claims 1-22, wherein the immunomodulatory compound is to be administered in an amount from or from about 0.1 mg to about 25 mg.

24. The use of any of claims 1-23, wherein the immunomodulatory compound is to be administered in an amount from or from about 0.1 mg to about 5 mg.

25. The use of any of claims 1-24, wherein the immunomodulatory compound is to be administered in an amount from or from about 0.1 mg to about 1 mg.

26. The use of any of claims 1-25, wherein the administration of the immunomodulatory compound:

stimulates an increased expansion of T cells associated with the T cell therapy compared to the expansion of T cells associated with the T cell therapy following administration of the T cell therapy in absence of the immunomodulatory compound;

stimulates an increase in T cell-mediated cytolytic activity of T cells associated with the T cell therapy compared to the cytolytic activity following the administration of the T cells in absence of the immunomodulatory compound; and/or

stimulates an increase in the cytokine production of T cells associated with the T cell therapy compared to cytokine production following the administration of the T cells in absence of the immunomodulatory compound.

27. The use of any of claims 1-26, wherein the antigen is selected from among ROR1, B cell maturation antigen (BCMA), carbonic anhydrase 9 (CAIX), Her2/neu (receptor tyrosine kinase erbB2), L1-CAM, CD19, CD20, CD22, mesothelin, CEA, and hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, epithelial glycoprotein 2

(EPG-2), epithelial glycoprotein 40 (EPG-40), EPHa2, erb-B2, erb-B3, erb-B4, erbB dimers, EGFR vIII, folate binding protein (FBP), FCRL5, FCRH5, fetal acetylcholine receptor, GD2, GD3, HMW-MAA, IL-22R-alpha, IL-13R-alpha2, kinase insert domain receptor (kdr), kappa light chain, Lewis Y, L1-cell adhesion molecule, (L1-CAM), Melanoma-associated antigen (MAGE)-A1, MAGE-A3, MAGE-A6, Preferentially expressed antigen of melanoma (PRAME), survivin, TAG72, B7-H6, IL-13 receptor alpha 2 (IL-13Ra2), CA9, GD3, HMW-MAA, CD171, G250/CAIX, HLA-AI MAGE Al, HLA-A2 NY-ESO-1, PSCA, folate receptor-a, CD44v6, CD44v7/8, avb6 integrin, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, CD44v6, dual antigen, a cancer-testes antigen, mesothelin, murine CMV, mucin 1 (MUC1), MUC16, PSCA, NKG2D, NY-ESO-1, MART-1, gp100, G Protein Coupled Receptor 5D (GPCR5D), oncofetal antigen, ROR1, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), Her2/neu, estrogen receptor, progesterone receptor, ephrinB2, CD123, c-Met, GD-2, O-acetylated GD2 (OGD2), CE7, Wilms Tumor 1 (WT-1), a cyclin, cyclin A2, CCL-1, CD138, optionally a human antigen of any of the foregoing; a pathogen-specific antigen; and an antigen associated with a universal tag.

28. The use of any of claims 1-27, wherein the antigen is CD19.

29. The use of any of claims 1-27, wherein the antigen is BCMA.

30. The use of any of claims 1-29, wherein the T cell therapy comprises:

T cells selected from the group consisting of central memory T cells, effector memory T cells, naïve T cells, stem central memory T cells, effector T cells and regulatory T cells; and/or

a plurality of cells, the plurality comprising at least 50 % of a population of cells selected from the group consisting of CD4+ T cells, CD8+ T cells, central memory T cells, effector memory T cells, naïve T cells, stem central memory T cells, effector T cells and regulatory T cells.

31. The use of any of claims 1-30, wherein the T cell therapy comprises T cells that are CD4+ or CD8+.

32. The use of any of claims 1-31, wherein the T cell therapy comprises cells that are autologous to the subject.

33. The use of any of claims 1-31, wherein the T cell therapy comprises T cells that are allogeneic to the subject.

34. The use of any of claims 1-33, wherein the T cell therapy is to be administered in an amount of from or from about 1×10^5 to 5×10^8 total recombinant receptor-expressing cells, total T cells, or total peripheral blood mononuclear cells (PBMCs).

35. The use of any of claims 1-34, wherein the subject is to be administered a lymphodepleting chemotherapy prior to administration of the T cell therapy.

36. The use of any of claims 1-35, wherein the cancer is a B cell malignancy and/or a myeloma, lymphoma or leukemia.

37. The use of any of claims 1-36, wherein the cancer is a lymphoma.

38. The use of any of claims 1-37, wherein the cancer is mantle cell lymphoma (MCL), non-Hodgkin lymphoma (NHL), Diffuse Large B-Cell Lymphoma (DLBCL) or follicular lymphoma (FL).

39. The use of any of claims 1-36, wherein the cancer is a myeloma or leukemia.

40. The use of any of claims 1-36 and 39, wherein the cancer is multiple myeloma (MM), acute lymphoblastic leukemia (ALL), adult ALL, or chronic lymphoblastic leukemia (CLL).

41. The use of any of claims 1-36, 39, and 40, wherein the cancer is multiple myeloma (MM).

42. The use of any of claims 1-35, wherein the cancer is a non-hematological cancer or is a solid tumor.