

methods of treatment that involves administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, the subject having been previously administered a T cell therapy. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered within or within about 1 hour, 2 hours, 6 hours, 12 hours, 24 hours or 48 hours subsequent to initiation of the T cell therapy.

[0009a] In one example, the present disclosure refers to use of a T cell therapy and a tryptophan metabolism and/or kynurenine pathway inhibitor in the manufacture of a medicament for the treatment of a cancer, wherein: (a) the T cell therapy is to be administered to a subject having the cancer; and (b) the tryptophan metabolism and/or kynurenine pathway inhibitor is to be administered to the subject within 14 days subsequent to initiation of administration of the T cell therapy.

[0009b] In another aspect, the present disclosure refers to use of an IDO1 inhibitor in the manufacture of a medicament for the treatment of a cancer, wherein the IDO1 inhibitor is to be administered to a subject having the cancer, the subject is one that has been previously administered a T cell therapy within 14 days prior to the administration of the IDO1 inhibitor.

[0009c] In another aspect, the present disclosure refers to use of a T cell therapy in the manufacture of a medicament for the treatment of a cancer in combination with an IDO1 inhibitor, wherein: (a) the T cell therapy is to be administered to a subject having the cancer; and (b) the IDO1 inhibitor is to be administered to the subject within 14 days subsequent to initiation of administration of the T cell therapy.

[0009d] In another example, the present disclosure refers to use of a tryptophan metabolism and/or kynurenine pathway inhibitor in the manufacture of a medicament for the treatment of a cancer in combination with the T cell therapy, wherein: (a) the T cell therapy is to be administered to a subject having the cancer; and (b) the tryptophan metabolism and/or kynurenine pathway inhibitor is to be administered to the subject within 14 days subsequent to initiation of administration of the T cell therapy.

[0010] In some examples, prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior

CLAIMS

WHAT IS CLAIMED:

1. Use of an IDO1 inhibitor in the manufacture of a medicament for the treatment of a cancer, wherein the IDO1 inhibitor is to be administered to a subject having the cancer, the subject is one that has been previously administered a T cell therapy within 14 days prior to the administration of the IDO1 inhibitor.
2. Use of a T cell therapy in the manufacture of a medicament for the treatment of a cancer in combination with an IDO1 inhibitor, wherein:
 - (a) the T cell therapy is to be administered to a subject having the cancer; and
 - (b) the IDO1 inhibitor is to be administered to the subject within 14 days subsequent to initiation of administration of the T cell therapy.
3. The use of claim 1 or claim 2, wherein the IDO1 inhibitor prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway; and/or the IDO1 inhibitor prevents or reduces catabolism of tryptophan, prevents or reduces synthesis or accumulation of a tryptophan metabolite or decreases the kynurenine to tryptophan ratio.
4. The use of any of claims 1-3, wherein the IDO1 inhibitor is a small molecule, a peptide, a protein, an antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.
5. The use of any one of claims 1-4, wherein the IDO1 inhibitor is selected from 1-methyl-D-tryptophan (1-MT) (indoximod), 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat), 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-chloro-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N'-hydroxy-N-[3-(trifluoromethyl)phenyl]-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-cyano-4-

fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-bromo-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-chloro-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 1-cyclohexyl-2-(5H-imidazo[5,1-a]isoindol-5-yl)ethanol (NLG919), GDC-0919, F001287, PF-06840003 or pharmaceutically acceptable salt or prodrug thereof or a combination thereof.

6. The use of any one of claims 1-5, wherein the IDO1 inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

7. The use of any of claims 1-6, wherein:
the cancer comprises a tumor negative for IDO1 prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor prior to initiation of administration of the T cell therapy; and/or
the cancer comprises a tumor negative for TDO prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of a TDO positive tumor prior to initiation of administration of the T cell therapy.

8. The use of any of claims 1-7, wherein upon administration to the subject the T cell therapy causes an increase or elevation of the level of interferon-gamma (IFN γ) in the subject in the local environment of a tumor or in a serum or plasma sample of the subject compared to the level of IFN γ in the subject prior to initiation of the T cell therapy.

9. The use of claim 8, wherein the increase or elevation of the level of IFN γ in the subject results in an increase or elevation of expression of IDO1 in cells present in the local environment of a tumor.

10. The use of claim 9, wherein the local environment of a tumor comprises tumor cells.

11. The use of any of claims 1-10, wherein the IDO1 inhibitor is to be administered at a time in which:

there is a decrease in tryptophan levels, an increase in kynurenine levels and/or an increase in expression or activity of IDO1, IDO2 or TDO in a biological sample from the subject compared to prior to initiation of administration of the T cell therapy or compared to a preceding time point after initiation of administration of the T cell therapy;

at a time before the number of cells of the T cell therapy detectable in the blood from the subject is decreased compared to in the subject at a preceding time point after initiation of administration of the T cell therapy;

at a time before T cells exhibit manifestations of prolonged tryptophan starvation, exhaustion, reduction of effector function, expression of inhibitory receptors and/or loss of proliferative capacity;

at a time before a peak or maximum level of the cells of the T cell therapy are detectable in the blood of the subject; and/or

the level of interferon-gamma (IFN γ) is increased in a biological sample from the subject compared to prior to initiation of administration of the T cell therapy or compared to a preceding time point after initiation of administration of the T cell therapy.

12. The use of claim 11, wherein the increase or decrease is by greater than 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

13. The use of any of claims 1-12, wherein the IDO1 inhibitor is to be administered within 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days subsequent to initiation of the T cell therapy.

14. The use of any of claims 1-13, wherein the T cell therapy is or comprises tumor infiltrating lymphocytic (TIL) therapy or genetically engineered T cells expressing a recombinant receptor that specifically binds to an antigen.

15. The use of claim 14, wherein the genetically engineered T cells further comprise a modification of expression of a molecule associated with IDO-mediated immunosuppressive

signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell.

16. The use of claim 15, wherein the modification comprises recombinant, engineered and/or ectopic expression of the molecule or a functional and/or catalytically active chain, portion or variant thereof.

17. The use of claim 15, wherein:
the modification comprises introducing an inhibitory nucleic acid.

18. The use of claim 17, wherein the inhibitory nucleic acid comprises an RNA interfering agent that reduces expression of the molecule.

19. The use of claim 15, wherein the modification comprises introducing a genetic disruption in the gene encoding the molecule that reduces expression of the molecule.

20. The use of claim 19, wherein the disruption is by introducing an agent into the cell comprising a zinc finger nuclease (ZFN), a TAL-effector nuclease (TALEN), or a CRISPR-Cas9 combination that specifically binds to, recognizes, or hybridizes to the gene encoding the molecule.

21. The use of any of claims 15-20, wherein the molecule is selected from among one or more selected from:

mTOR or protein kinase C theta (PKC- Θ);

rBAT (SLC3A1), CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), Asc-type amino acid transporter 1 (Asc-1; SLC7A10), Sodium- and chloride-dependent neutral and basic amino acid transporter B(0+)(ATB0,+; SLC6A14), Sodium-dependent neutral amino acid transporter B(0)AT1 (B(0)AT1; SLC6A19), Monocarboxylate transporter 10 (TAT1; SLC16A10) or proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof; and

GCN2 kinase, BLIMP-1, aryl hydrocarbon receptor (AHR), AHR nuclear transporter (ARNT), eukaryotic translation initiation factor 2 α (eIF2 α), activating transcription factor 4 (ATF4), CCAAT/enhancer binding protein-homologous protein (CHOP), Gadd45 α , Herp, 4E-BP1, eIF4G, JAK1, NF κ B-2, FK506-BP8 or IFN γ -R2.

22. The use of any of claims 1-21, wherein the T cell therapy comprises genetically engineered T cells comprising a recombinant receptor that specifically binds to an antigen.

23. The use of any of claims 14-22, wherein the recombinant receptor is a chimeric antigen receptor (CAR).

24. The use of claim 23, wherein the recombinant receptor is a CAR and the CAR comprises an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling region comprising an ITAM.

25. The use of claim 24, wherein the intracellular signaling region comprises an intracellular domain of a CD3-zeta (CD3 ζ) chain.

26. The use of any of claims 23-25, wherein the CAR further comprises a costimulatory signaling region.

27. The use of claim 26, wherein the costimulatory signaling region comprises a signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof.

28. The use of any of claims 14-27, wherein the recombinant receptor is a transgenic T cell receptor (TCR).

29. The use of any of claims 14-28, wherein the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer.

30. The use of claim 29, wherein the antigen is selected from ROR1, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, CEA, hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, EGP-2, EGP-4, EPHA2, ErbB2, ErbB3, ErbB4, FBP, fetal acetylcholine e receptor, GD2, GD3, HMW-MAA, IL-22R-alpha, IL-13R-alpha2, kdr, kappa light chain, Lewis Y, L1-cell adhesion molecule, MAGE-A1, mesothelin, MUC1, MUC16, PSCA, NKG2D Ligands, NY-ESO-1, MART-1, gp100, oncofetal antigen, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, estrogen receptor, progesterone receptor, ephrinB2, CD123, CS-1, c-Met, GD-2, MAGE A3, CE7, Wilms Tumor 1 (WT-1), and cyclin A1 (CCNA1).

31. The use of any of claims 1-30, wherein the cancer is a myeloma, lymphoma, leukemia.

32. The use of any of claims 1-31, wherein the cancer is non-Hodgkin lymphoma (NHL), an acute lymphoblastic leukemia (ALL), a chronic lymphocytic leukemia (CLL), diffuse large B-Cell lymphoma (DLBCL), or myeloma.

33. The use of any of claims 1-30, wherein the cancer is a non-hematological cancer or is a solid tumor.

34. The use of any of claims 1-30, wherein the cancer does not express a B cell antigen or is not a B cell malignancy.

35. The use of claim 34, wherein the cancer does not express CD19 and/or the T cell therapy does not comprise genetically engineered T cells expressing a recombinant receptor that specifically binds CD19 and/or the T cell therapy comprises genetically engineered T cells expressing a CAR that does not comprise an anti-CD19 antigen-binding domain.

36. The use of any of claims 1-35, wherein the T cell therapy results in an increase in tryptophan levels and/or a decrease in kynurenine levels in the tumor or in a biological sample

from the subject, compared to a use of the T cell therapy but in the absence of the IDO1 inhibitor.

37. The use of claim 36, wherein the biological sample is or comprises a serum, plasma or tumor sample.

38. The use of any of claims 1-37, wherein the use results in:
increased or prolonged expansion and/or persistence of T cells of the T cell therapy in the subject as compared to a use in which the T cell therapy is to be administered to the subject in the absence of the IDO1 inhibitor or a use in which a T cell therapy comprising the same T cells except in which the T cells do not comprise modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression is to be administered; and/or

reduced expression or level of CD25 on the surface of the T cells of the T cell therapy following said administration to the subject as compared to the expression or level in a use in which the T cell therapy is to be administered to the subject in the absence of the IDO1 inhibitor or a use in which a T cell therapy comprising the same T cells except in which the T cells do not comprise modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression is to be administered.

39. The use of any of claims 1-38, wherein the IDO1 inhibitor is to be administered orally, subcutaneously or intravenously.

40. The use of any of claims 1-39, wherein the IDO1 inhibitor is to be administered orally.

41. The use of any of claims 1-40, wherein the IDO1 inhibitor is formulated for administration in an amount from 2.5 mg to 5000 mg, 2.5 mg to 2000 mg, 2.5 mg to 1000 mg,

2.5 mg to 500 mg, 2.5 mg to 200 mg, 2.5 mg to 100 mg, 2.5 mg to 50 mg, 2.5 mg to 25 mg, 2.5 mg to 10 mg, 25 mg to 5000 mg, 25 mg to 2000 mg, 25 mg to 1000 mg, 25 mg to 500 mg, 25 mg to 200 mg, 25 mg to 100 mg, 25 mg to 50 mg, 50 mg to 5000 mg, 50 mg to 2000 mg, 50 mg to 1000 mg, 50 mg to 500 mg, 50 mg to 200 mg, 50 mg to 100 mg, 100 mg to 5000 mg, 100 mg to 2000 mg, 100 mg to 1000 mg, 100 mg to 500 mg, 100 mg to 200 mg, 200 mg to 5000 mg, 200 mg to 2000 mg, 200 mg to 1000 mg, 200 mg to 500 mg, 500 mg to 5000 mg, 500 mg to 2000 mg, 500 mg to 1000 mg or 1000 mg to 2000 mg, each inclusive.

42. The use of any of claims 1-41, wherein the IDO1 inhibitor is formulated for administration at a total daily dosage amount of at least 5 mg/day, 10 mg/day, 25 mg/day, 50 mg/day, 100 mg/day, 200 mg/day, 400 mg/day, 500 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day, 1200 mg/day, 1600 mg/day, 2000 mg/day, 5000 mg/day or 10000 mg/day.

43. The use of any of claims 1-42, wherein the IDO1 inhibitor is to be administered six times daily, five times daily, four times daily, three times daily, twice daily or once daily.

44. The use of any of claims 1-43, wherein the use results in:
an increase in tryptophan levels, a decrease in kynurenine levels and/or an decrease in expression or activity of IDO1, IDO2 or TDO in a biological sample from the subject compared to just prior to administration of the IDO1 inhibitor or compared to just prior to initiation of administration of the T-cell therapy;

an increase in the number of cells of the T cell therapy detectable in the blood from the subject compared to in the subject at a preceding time point just prior to administration of the IDO1 inhibitor or compared to a preceding time point after administration of the T-cell therapy;

the number of cells of the T cell therapy detectable in the blood being within 2.0-fold (greater or less) of the peak or maximum number of the cells of the T cell therapy detectable in the blood of the subject after initiation of administration of the T cell therapy;

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

the concentration or number of engineered cells in the blood of the subject being (i) at least 10 engineered cells per microliter, (ii) at least 20%, 30%, 40% or 50 % of the total number of peripheral blood mononuclear cells (PBMCs), (iii) at least 1×10^5 engineered cells; or (iv) the blood of the subject contains at least 5,000 copies of recombinant receptor-encoding DNA per micrograms DNA;

at day 90 following the initiation of the T cells, CAR-expressing cells are detectable in the blood or serum of the subject; and/or

at day 90 following the initiation of the T cells, the blood of the subject contains at least 20 % CAR-expressing cells, at least 10 CAR-expressing cells per microliter or at least 1×10^4 CAR-expressing cells.

45. The use of any of claims 1-44, wherein the T cell therapy comprises CD4⁺ T cells and/or CD8⁺ T cells.

46. The use of any of claims 1-45, wherein the T cell therapy comprises cells that are autologous to the subject or comprises cells that are allogeneic to the subject.

47. The use of any of claims 1-46, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising between 1×10^6 and 3×10^8 , 1×10^7 and 2×10^8 total recombinant receptor-expressing cells.

48. The use of any of claims 1-47, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising 1×10^7 , 5×10^7 , 1×10^8 or 1.5×10^8 total recombinant receptor-expressing cells, or the range between any two of the foregoing values.

49. The use of any of claims 1-46, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising a number of cells between 0.5×10^6 cells/kg body weight of the subject and 5×10^6 cells/kg, between 0.5×10^6 cells/kg and 3×10^6 cells/kg, between 0.5×10^6 cells/kg and 2×10^6 cells/kg, between 0.5×10^6 cells/kg and 1×10^6 cell/kg, between 1.0×10^6 cells/kg body weight of the subject and 5×10^6

cells/kg, between 1.0×10^6 cells/kg and 3×10^6 cells/kg, between 1.0×10^6 cells/kg and 2×10^6 cells/kg, between 2.0×10^6 cells/kg body weight of the subject and 5×10^6 cells/kg, between 2.0×10^6 cells/kg and 3×10^6 cells/kg, or between 3.0×10^6 cells/kg body weight of the subject and 5×10^6 cells/kg, each inclusive.

50. The use of any of claims 1-49, wherein a lymphodepleting chemotherapy is to be further administered prior to administration of the T cell therapy.

51. The use of any of claims 1-50, wherein prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior administration of an IDO1 inhibitor.

52. The use of claim 51, wherein the prior administration was carried out in combination with an immunomodulatory agent.

53. The use of claim 52, wherein the immunomodulatory agent is a checkpoint inhibitor.

54. The use of any of claims 1-53, wherein, prior to administration of the IDO1 inhibitor, the subject to be administered is selected according to a method comprising:

(a) assessing the level of tryptophan or a tryptophan metabolite, the level of expression or activity of IDO1, IDO2 or TDO, or the level of interferon-gamma (IFN γ) in one or more biological samples from the subject, wherein the biological sample is obtained from a subject having been administered a T cell therapy; and

(b) selecting a subject in which:

(i) the level of tryptophan in the sample is below a threshold level or is decreased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy;

(ii) the level of the tryptophan metabolite is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy;

(iii) the level of expression or activity of IDO1, IDO2 or TDO is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; or

(iv) the level of the IFN γ is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy.