

agents, such as engineered cells, that are or have been treated, altered or engineered with or to include one or more such modulators. Also among engineered cells are cells in which the expression, activity, or function of a molecule such as a protein involved in immunosuppressive activity of the cells in response to tryptophan metabolism, such as tryptophan catabolism, is modified, altered, disrupted or affected. Also provided are methods of manufacturing engineered cells, cells, compositions, methods of administration to subjects, nucleic acids, articles of manufacture and kits for use in the methods. In some embodiments, combinations are provided including the immunotherapeutic agent, such as engineered cells, and kynurenine and/or tryptophan modulator and instructions for the administration thereof. In some aspects, features of the methods and cells provide for increased or improved activity, function, persistence, expansion and/or proliferation of cells for adoptive cell therapy or endogenous immune cells recruited by immunotherapeutic agents.

### Background

**[0004]** Various strategies are available for immunotherapy, for example administering engineered T cells for adoptive therapy. For example, strategies are available for engineering T cells expressing genetically engineered antigen receptors, such as CARs, and administering compositions containing such cells to subjects. Improved strategies for cell therapy are needed. For example, in some contexts, strategies are desired with improvements in one or more aspects of cells or outcomes following administration, for example, improving the persistence, activity and/or proliferation of the cells upon administration to subjects. Provided in some embodiments are methods, cells, compositions, kits, and systems that meet such needs.

### Summary

**[0005]** Provided herein are methods of enhancing or modulating proliferation and/or activity of immune cell activity in an immunotherapy, such as a T cell therapy (*e.g.* CAR-expressing T cells) or a T cell-engaging therapy. In some examples, the methods generally involve administering a combination therapy of an immunotherapy, such as a T cell therapy (*e.g.* CAR-expressing T cells) or a T cell-engaging therapy, and a tryptophan metabolism and/or kynurenine pathway modulator.

**[0006]** Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point greater than 1 day prior to initiation of administration of the T cell therapy.

**[0006a]** In one example, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point greater than 1 day prior to initiation of administration of the T cell therapy.

**[0007]** Provided herein are methods of treatment that involve administering a T cell therapy to a subject having a disease or condition, the subject having been previously administered a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator starting at a time point greater than 1 day prior to initiation of the T cell therapy.

**[0008]** In some examples of any of the methods provided herein, the administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point that is within or within about 2 days, 3 days, 6 days, 12 days, 15 days, 30 days, 60 days or 90 days or more prior to initiation of the administration of the T cell therapy. In some examples, the method further includes continuing administration of the tryptophan metabolism and/or kynurenine pathway modulator with or subsequent to initiation of administration of the T cell therapy. In some examples, the method further includes administering the tryptophan metabolism and/or kynurenine pathway modulator subsequent to administering the therapy cell therapy.

**[0009]** Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator subsequent to initiation of administration of the T cell therapy. Also provided are

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 aspect, 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 a tryptophan metabolism and/or kynurenine pathway inhibitor in the manufacture of a medicament for the treatment of a cancer, wherein the tryptophan metabolism and/or kynurenine pathway 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 tryptophan metabolism and/or kynurenine pathway 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 a tryptophan metabolism and/or kynurenine pathway inhibitor, 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.

**[0009d]** In another aspect, 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

administration of a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0011]** Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, 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 a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0011a]** In another example, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, 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 a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0012]** Provided herein are methods of treatment that involve: administering to a subject having a disease or condition a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator to a subject having been administered a T cell therapy, 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 a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0013]** In some examples, the disease or condition is cancer.

**[0014]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is administered prior to, simultaneously with and/or subsequent to initiation of administration of the T cell therapy. In some examples, administration of the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is started at a time point that is within or within about 2 days, 3 days, 6 days, 12 days, 15 days, 30 days, 60 days or 90 days or more prior to initiation of the administration of the T cell therapy.

**[0015]** In some examples, the methods also involve administering the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) subsequent to initiation of administration of the T cell therapy.

**[0016]** In some examples, tryptophan metabolism and/or kynurenine pathway modulator is 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 $\gamma$ ) 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. In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

**[0017]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is administered within or within about 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days subsequent to initiation of the T cell therapy.

**[0018]** In some examples of any of the methods provided herein, the tryptophan metabolism and/or kynurenine pathway modulator is 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; 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; the number of cells of the T cell therapy detectable in the blood is decreased by more than or more than about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 50-fold or 100-fold or more, compared to 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; and/or at a time after a peak or maximum level of the cells of the T cell therapy are detectable in the blood of the subject, the number of cells of the T cell therapy detectable in the blood from the subject is less than 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; the level of IFN-gamma 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. In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more. In some examples, the biological sample is a serum or plasma or tumor sample or is a tumor.

**[0019]** In some examples of any of the methods provided herein, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some examples, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

**[0020]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

**[0021]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of tryptophan 2,3-dioxygenase (TDO). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1).

**[0022]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of IDO1 and the tryptophan metabolism

and/or kynurenine pathway modulator of IDO1 is administered at a time in which there is an increase in the expression or activity of IDO1 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.

**[0023]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0024]** In some examples of any of the methods provided herein, the cancer contains a tumor negative for IDO1 and/or the subject is not selected for expression of an IDO1 positive tumor; and/or the cancer contains a tumor negative for TDO and/or the subject is not selected for expression of a TDO positive tumor. In some examples, the cancer contains a tumor negative for IDO1 and/or the subject is not selected for expression of an IDO1 positive tumor.

**[0025]** In some examples of any of the methods provided herein, 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. In some examples, 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.

**[0026]** Provided herein are methods of treatment that involve (a) administering a T cell therapy to a subject having a disease or condition, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy; and; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator that is an inhibitor of IDO1.

**[0026a]** In another example, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition that is cancer, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject that is an inhibitor of IDO1.

**[0027]** Also provided herein are methods of treatment that involve administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator that is an inhibitor of IDO1, the subject having been administered a T cell

therapy, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy.

**[0028]** Also provided herein are methods of treatment that involve administering to a subject having cancer a T cell therapy, the subject having been administered a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator that is an inhibitor of IDO1, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy.

**[0029]** In some examples, the disease or condition is cancer.

**[0030]** In some examples of any of the methods provided herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered prior to, simultaneously with and/or subsequent to initiation of administration of the T cell therapy.

**[0031]** 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 administration of a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0032]** In some examples, the method also includes administering the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) subsequent to initiation of administration of the T cell therapy.

**[0033]** In some examples, tryptophan metabolism and/or kynurenine pathway modulator is 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 $\gamma$ ) 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. In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

**[0034]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is administered within or within about 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days subsequent to initiation of the T cell therapy. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) 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.

**[0035]** . In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered from or from about 0 to 96 hours, 0 to 72 hours, 0 to 48 hours, 0 to 24 hours, 0 to 12 hours or 0 to 6 hours or 0 to 2 hours prior to initiation of the T cell therapy; or the tryptophan metabolism and/or kynurenine pathway modulator is administered no more than 96 hours, 72 hours, 48 hours, 24 hours, 12 hours, 6 hours, 2 hours or 1 hour prior to initiation of the T cell therapy.

**[0036]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator 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.

**[0037]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0038]** Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

**[0038a]** In another example, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

**[0039]** Also provided herein are methods of treatment that involve administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat), the subject having been administered a T cell therapy.

**[0040]** Also provided herein are methods of treatment that involve administering to a subject having cancer a T cell therapy, the subject having been administered a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

**[0041]** In some examples, the disease or condition is cancer.

**[0042]** In some examples of any of the examples herein, upon administration to the subject the T cell therapy causes an increase or elevation of the level of IFN-gamma 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-gamma in the subject prior to initiation of the T cell therapy.

**[0043]** In some examples of any of the examples herein, the T cell therapy is or includes tumor infiltrating lymphocytic (TIL) therapy or a T cell therapy that includes genetically engineered cells expressing a recombinant receptor that specifically binds to a ligand. In some examples, the T cell therapy is or includes genetically engineered cells expressing a recombinant receptor that specifically binds to a ligand.

**[0044]** In some examples of any of the examples herein, the genetically engineered cell also includes a modification impacting the expression, presence, or activity of a protein or other factor or molecule associated with one or more activities or outcomes or effects, and/or a nucleic acid encoding such protein or factor. In some examples, the activities, outcomes, or effects may include those associated with, involved in sensing of, or promoted by tryptophan deficiencies or tryptophan starvation. In some examples, the activities, outcomes, or effects may include those associated with, involved in sensing of, or promoted by increased amounts or concentrations of kynurenine or one or more kynurenine pathway metabolites and/or kynurenine mediated immunosuppression, and/or decreased tryptophan/kynurenine ratios in the cell or environment. In some examples, the protein or factor is or includes a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects, such as those that may limit T cell function, e.g., in the tumor environment. Such effects may include inhibition or dampening of T cell activity or function and/or promotion of Treg function, levels, or activity. In some examples, the protein or factor is involved in IDO-induced immunosuppressive effects in the cell and/or neighboring cells.

**[0045]** Provided herein are methods of treatment that involve administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell contains (i) a recombinant receptor that specifically binds to a ligand and (ii) modification of expression of a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects and/or protein associated with IDO-mediated immunosuppressive effects in the cell.

**[0046]** Also provided herein are methods of treatment that involve administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof. In some examples, the methods also include (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator.

**[0046a]** In another example, there is provided use of genetically engineered T cells in the manufacture of a medicament for the treatment of a disease or condition, wherein: genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) 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 immunosuppression in the cell; and/or the genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

**[0047]** Provided herein are methods of treatment that involve: (a) administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell contains (i) a recombinant receptor that specifically binds to a ligand and (ii) a modification of expression of a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects and/or a protein associated with IDO-mediated immunosuppressive effects in the cell; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator.

**[0047a]** In another example, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition, wherein the genetically engineered T

cell comprises (i) a recombinant receptor that specifically binds to a ligand and (ii) 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; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject.

**[0048]** In some examples, the disease or condition is cancer.

**[0049]** In some examples, the subject is selected for having a tumor positive for expression of L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), CD98 heavy chain (4F2hc; CD98hc; SLC3A2) and/or proton-assisted amino-acid transporter 4 (PAT4; SLC36A4), or for having cells in the tumor microenvironment that are positive for expression of LAT1, LAT2, CD98hc and/or PAT4.

**[0050]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some examples, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

**[0051]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

**[0052]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

**[0053]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of tryptophan 2,3-dioxygenase (TDO). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor.

**[0054]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1). In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator 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.

**[0055]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0056]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered subsequent to initiation of administration of the T cell therapy.

**[0057]** In some examples of any of the examples herein, the molecule, protein or factor 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 mTOR or protein kinase C theta (PKC- $\Theta$ ).

**[0058]** 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 administration of a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0059]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered prior to, simultaneously with and/or subsequent to initiation of administration of the T cell therapy. In some examples, comprising administering the tryptophan metabolism and/or kynurenine pathway modulator subsequent to initiation of administration of the T cell therapy.

**[0060]** In some examples, tryptophan metabolism and/or kynurenine pathway modulator is 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 $\gamma$ ) 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. In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

**[0061]** 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, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days subsequent to initiation of the 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.

**[0062]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered from or from about 0 to 96 hours, 0 to 72 hours, 0 to 48 hours, 0 to 24 hours, 0 to 12 hours or 0 to 6 hours or 0 to 2 hours prior to initiation of the T cell therapy; or the tryptophan metabolism and/or kynurenine pathway modulator is administered no more than 96 hours, 72 hours, 48 hours, 24 hours, 12 hours, 6 hours, 2 hours or 1 hour prior to initiation of the T cell therapy.

**[0063]** In some examples, the modification comprises recombinant, engineered and/or ectopic expression of the molecule or a functional and/or catalytically active chain, portion or variant thereof. In some examples, the molecule is mTOR or protein kinase C theta (PKC- $\theta$ ).

**[0064]** In some examples, the molecule is an amino acid transporter or a chain thereof or a functional and/or catalytically active portion or variant thereof. In some examples, the amino acid transporter is a tryptophan transporter. In some examples, the amino acid transporter or a chain thereof is selected from among one or more of 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), and proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof. In some examples, the amino acid transporter or a chain

thereof comprises CD98 heavy chain (4F2hc; SLC3A2) and L-type Amino Acid Transporter 1 (LAT1; SLC7A5) or a portion thereof.

**[0065]** In some examples, the amino acid transporter or a chain thereof comprises the amino acid sequence selected from any one of SEQ ID NOs: 36-44 or a portion thereof, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 36-44 or a portion thereof. In some examples, the amino acid transporter or a chain thereof is selected from among one or more of CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), and proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof. In some examples, the amino acid transporter or a chain thereof comprises CD98 heavy chain (4F2hc; SLC3A2) and L-type Amino Acid Transporter 1 (LAT1; SLC7A5) or a portion thereof.

**[0066]** In some examples, the amino acid transporter or a chain thereof comprises the amino acid sequence selected from any one of SEQ ID NOs: 37-39 and 44 or a portion thereof, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 37-39 and 44 or a portion thereof. In some examples, expression of the molecule in the cell is under the control of a conditional promoter or enhancer or transactivator.

**[0067]** In some examples of any of the examples herein, the modification includes recombinant, engineered and/or ectopic expression of the protein or a functional and/or catalytically active portion or variant thereof. In some examples, expression of the protein in the cell is under the control of a conditional promoter or enhancer or transactivator.

**[0068]** In some examples of any of the examples herein, the molecule, protein or factor 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 GCN2 kinase, BLIMP-1, aryl hydrocarbon receptor (AHR) or AHR nuclear transporter (ARNT). In some examples, the molecule is selected from among GCN2 kinase, BLIMP-1, aryl hydrocarbon receptor (AHR), AHR nuclear transporter (ARNT), eukaryotic translation initiation factor 2  $\alpha$  (eIF2 $\alpha$ ), activating transcription factor 4 (ATF4), or CCAAT/enhancer binding protein-homologous protein

(CHOP), Gadd45 $\alpha$ , Herp, 4E-BP1, eIF4G, JAK1, NF $\kappa$ B-2, FK506-BP8 and IFN $\gamma$ -R2. In some examples, the molecule is GCN2 or CHOP.

**[0069]** In some examples of any of the examples herein, the modification includes reduced expression of the molecule. In some examples, the engineered cell includes an inhibitory nucleic acid or a genetic disruption that reduces expression of the molecule. In some examples, expression of the molecule in the cell is reduced by at least 50, 60, 70, 80, 90, or 95 % as compared to the expression in the cell in the absence of the agent or gene disruption.

**[0070]** In some examples of any of the methods provided herein, the method includes introducing the inhibitory nucleic acid into the cell, thereby effecting reduction in expression of the molecule. In some examples, the engineered cell includes an inhibitory nucleic acid and the inhibitory nucleic acid includes an RNA interfering agent. In some examples, the inhibitory nucleic acid is or includes or encodes a small interfering RNA (siRNA), a microRNA-adapted shRNA, a short hairpin RNA (shRNA), a hairpin siRNA, a microRNA (miRNA-precursor) or a microRNA (miRNA). In some examples, the method includes introducing a nucleic acid encoding or producing the inhibitory nucleic acid into the cell, thereby effecting reduction in expression of the molecule.

**[0071]** In some examples of any of the examples herein, expression of the inhibitory nucleic acid is under the control of a conditional promoter or enhancer or transactivator.

**[0072]** In some examples of any of the examples herein, the engineered cell includes a genetic disruption, wherein: the disruption involves disrupting the gene encoding the molecule at the DNA level and/or the disruption is not reversible; and/or the disruption is not transient. In some examples, the disruption involves introducing into the cell a DNA binding protein or DNA-binding nucleic acid that specifically binds to or hybridizes the gene encoding the molecule.

**[0073]** In some examples of any of the examples herein, the disruption involves introducing: (a) a fusion protein that includes a DNA-targeting protein and a nuclease or (b) an RNA-guided nuclease. In some examples, the DNA-targeting protein or RNA-guided nuclease that includes a zinc finger protein (ZFP), a TAL protein, or a clustered regularly interspaced short palindromic nucleic acid (CRISPR) specific for the gene. In some examples, the disruption includes introducing an agent into the cell, including 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. In some examples, the agent is a CRISPR-Cas9 combination and the CRISPR-Cas9 combination that includes a guide RNA (gRNA) containing a guide sequence that is complementary to, and/or capable of hybridizing to, a target sequence in the gene.

**[0074]** In some examples of any of the examples herein, the genetic disruption is inducible.

In some examples, the CRISPR-Cas9 complex is an inducible CRISPR-Cas9 and/or the Cas9 is under the control of a conditional promoter or enhancer or transactivator.

**[0075]** In some examples of any of the examples herein, the disruption contains a deletion of at least a portion of at least one exon of the gene encoding the molecule.

**[0076]** In some examples of any of the examples herein, the disruption contains a deletion, mutation, and/or insertion in the gene resulting in the presence of a premature stop codon in the gene; and/or the disruption contains a deletion, mutation, and/or insertion within a first or second exon of the gene encoding the molecule.

**[0077]** In some examples of any of the examples herein, the conditional promoter or enhancer or transactivator is an inducible promoter, enhancer, or transactivator or a repressible promoter, enhancer, or transactivator. In some examples, the promoter is selected from among an RNA pol I, pol II or pol II promoter. In some examples, the promoter is selected from: a pol III promoter that is a U6 or H1 promoter; or a pol II promoter that is a CMV, SV40 early region or adenovirus major late promoter.

**[0078]** In some examples of any of the examples herein, the promoter is an inducible promoter. In some examples, the promoter contains a Lac operator sequence, a tetracycline operator sequence, a galactose operator sequence or a doxycycline operator sequence, or is an analog thereof.

**[0079]** In some examples of any of the examples herein, the promoter is a repressible promoter. In some examples, the promoter is capable of being bound by a Lac repressor or a tetracycline repressor, or is an analog thereof.

**[0080]** In some examples of any of the examples herein, the genetically engineered receptor that specifically binds to a ligand is a functional non-T cell receptor. In some examples, the genetically engineered receptor that specifically binds to a ligand is a chimeric antigen receptor (CAR). In some examples, the CAR contains an extracellular antigen-

recognition domain that specifically binds to the antigen and an intracellular signaling region that includes an ITAM. In some examples, the intracellular signaling region contains an intracellular domain of a CD3-zeta (CD3 $\zeta$ ) chain.

**[0081]** In some examples of any of the examples herein, the CAR also contains a costimulatory signaling region. In some examples, the costimulatory signaling region contains a signaling domain of CD28 or 4-1BB or an ICOS or a signaling portion thereof. In some examples, the costimulatory signaling region is a signaling domain of a CD28.

**[0082]** In some examples of any of the examples herein, the recombinant receptor is a transgenic T cell receptor (TCR). In some examples, the recombinant receptor is a chimeric antigen receptor (CAR).

**[0083]** In some examples of any of the examples herein, the T cell therapy recognizes or targets an antigen associated with the cancer. In some examples, the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer. In some examples, 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 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).

**[0084]** In some examples of any of the examples herein, the cancer includes a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or the subject is not selected for expression of an IDO1 positive tumor. In some examples, the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (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. In some examples, the cancer comprises a tumor positive for expression of L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), CD98 heavy chain (4F2hc; CD98hc; SLC3A2) and/or proton-

assisted amino-acid transporter 4 (PAT4; SLC36A4), or the cancer comprises cells in the tumor microenvironment that are positive for expression of LAT1, LAT2, CD98hc and/or PAT4.

**[0085]** In some examples of any of the examples herein, the cancer is a myeloma, lymphoma, leukemia. In some examples, the cancer is non-Hodgkin lymphoma (NHL), an acute lymphoblastic leukemia (ALL), a chronic lymphocytic leukemia (CLL), diffuse large B-Cell lymphoma (DLBCL), and myeloma. In some examples, the cancer does not express a B cell antigen or is not a B cell malignancy. In some examples, the cancer does not express CD19 and/or the T cell therapy does not include a recombinant receptor that specifically binds CD19 and/or the T cell therapy is a CAR-T cell therapy that does not include an anti-CD19 antigen-binding domain.

**[0086]** In some examples of any of the examples herein, the cancer is a non-hematological cancer or is a solid tumor.

**[0087]** In some examples, the method 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, optionally a serum, plasma or tumor sample, compared to a method involving administration of the T cell therapy but in the absence of the tryptophan metabolism and/or kynurenine pathway modulator or compared to a method in which the cell are administered that 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.

**[0088]** In some examples of any of the examples herein, the T cell therapy exhibits increased or prolonged expansion and/or persistence in the subject as compared to a method in which the T cell therapy is administered to the subject in the absence of the tryptophan metabolism and/or kynurenine pathway modulator.

**[0089]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered orally, subcutaneous or intravenously. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered orally.

**[0090]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered in an amount from or from about 2.5 mg to about 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. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered six times daily, five times daily, four times daily, three times daily, twice daily or once daily. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered at a total daily dosage amount of at least or at least about 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.

**[0091]** In some examples of any of the examples herein, the administration of the tryptophan metabolism and/or kynurenine pathway modulator is continued after initiation of administration of the T cell therapy until: there is 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 tryptophan metabolism and/or kynurenine pathway modulator or compared to just prior to initiation of administration of the T-cell therapy; the number of cells of the 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 tryptophan metabolism and/or kynurenine pathway modulator 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 is within 2.0-fold (greater or less) 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; 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.

**[0092]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered until: the concentration or number of engineered cells in the blood of the subject is (i) at least at or about 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 or at least about  $1 \times 10^5$  engineered cells; or (iv) the blood contains at least 5,000 copies of recombinant receptor-encoding DNA per micrograms DNA; and/or at day 90 following the initiation of the administration in (a), CAR-expressing cells are detectable in the blood or serum of the subject; and/or at day 90 following the initiation of the administration in (a), the blood of the subject contains at least 20 % CAR-expressing cells, at least 10 CAR-expressing cells per microliter or at least  $1 \times 10^4$  CAR-expressing cells.

**[0093]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is administered for a time period up to 2 days, up to 7 days, up to 14 days, up to 21 days, up to one month, up to two months, up to three months, up to 6 months or up to 1 year after initiation of the administration of the T cell therapy.

**[0094]** In some examples of any of the examples herein the T cell therapy includes T cells that are CD4+ or CD8+. In some examples, the T cell therapy includes cells that are autologous to the subject. In some examples, the T cell therapy includes T cells that are allogeneic to the subject.

**[0095]** In some examples of any of the examples herein, T cell therapy is administered in an amount to upregulate IDO1 expression in the tumor microenvironment. In some examples, IDO1 expression is upregulated in or from myeloid cells, stromal cells or tumor cells. In some examples, IDO1 expression is upregulated in or from bone marrow stromal cells.

**[0096]** In some examples of any of the methods provided herein, the cell therapy includes administration of a dose that contains a number of cells between or between about  $0.5 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between or between about  $0.5 \times 10^6$  cells/kg body weight of the subject and  $3 \times 10^6$  cells/kg, between or between about  $0.5 \times 10^6$  cells/kg body weight of the subject and  $2 \times 10^6$  cells/kg, between or between about  $0.5 \times 10^6$  cells/kg body weight of the subject and  $1 \times 10^6$  cell/kg, between or between about  $1.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between or between about  $1.0 \times 10^6$  cells/kg body weight of the subject and  $3 \times 10^6$  cells/kg, between or between about  $1.0 \times 10^6$

cells/kg body weight of the subject and  $2 \times 10^6$  cells/kg, between or between about  $2.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between or between about  $2.0 \times 10^6$  cells/kg body weight of the subject and  $3 \times 10^6$  cells/kg, or between or between about  $3.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, each inclusive.

**[0097]** In some examples of any of the examples herein, the dose of cells administered is less than the dose in a method in which the cell therapy is administered without administering the tryptophan metabolism and/or kynurenine pathway modulator or a method in which the 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 immunosuppression. In some examples, the dose is at least 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold or 10-fold less.

**[0098]** In some examples of any of the methods provided herein, the T cell therapy is administered as a single pharmaceutical composition that contains the cells. In some examples, the T cell therapy includes a dose of cell that is a split dose, wherein the cells of the dose are administered in a plurality of compositions, which collectively contains the cells of the dose, over a period of no more than three days.

**[0099]** In some examples of any of the examples herein, the method further involves administering a lymphodepleting chemotherapy prior to administration of the T cell therapy. In some examples, the method does not include administering fludarabine to the subject. In some examples of any of the examples herein, the provided methods do not involve administering a lymphodepleting chemotherapy to the subject prior to administration of the T cell therapy.

**[0100]** In some examples, the recombinant receptor is engineered by introduction of a first nucleic acid sequence encoding the recombinant receptor into the cell, and one or more second nucleic acid sequence(s) encoding an agent that is capable of or involved in 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 immunosuppression in the cell, into the cell. In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more polynucleotides. In some examples, the first

nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some examples, the first nucleic acid and the second nucleic acid(s) are comprised in one or more vector(s), which optionally are viral vector(s).

**[0101]** Provided herein are methods of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, that involve: (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 $\gamma$ ) in one or more biological samples from the subject, wherein the biological sample is from a subject that is a candidate for treatment with a T cell therapy; and (b) selecting a subject in which: (i) the level of tryptophan in the sample is below a threshold level; (ii) the level of the tryptophan metabolite is above a threshold level; (iii) the level of expression or activity of IDO1, IDO2 or TDO is above a threshold level; or (iv) the level of the IFN $\gamma$  is above a threshold level.

**[0101a]** In another example, there is provided a method of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, the 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 $\gamma$ ) 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 $\gamma$  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.

**[0102]** In some examples, the one or more biological sample is obtained prior to administration of the T cell therapy.

**[0103]** In some examples, the methods also involve administering the T cell therapy to the subject. In some examples, the methods also involve administering the tryptophan metabolism and/or kynurenine pathway modulator to the selected subject. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered to the selected subject prior to or concurrently with initiation of administration of the T cell therapy. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is administered subsequent to initiation of administration of the T cell therapy.

**[0104]** Provided herein are methods of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, that involve: (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 $\gamma$ ) 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 $\gamma$  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.

**[0105]** In some examples, the one or more biological sample is obtained subsequent to administration of the T cell therapy. In some examples, the methods also involve, prior to the assessing, administering the cell therapy to the subject. In some examples, the methods also involve administering the kynurenine pathway modulator to the subject.

**[0106]** In some examples, tryptophan metabolism and/or kynurenine pathway modulator is 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 $\gamma$ ) 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. In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

**[0107]** 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, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days subsequent to

initiation of the 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.

**[0108]** In some examples, the disease or condition is cancer.

**[0109]** In some examples, the subject is selected if the level of expression or activity of IDO1, IDO2 or TDO is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy. In some examples, the subject is selected if 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.

**[0110]** In some examples, the threshold level is within 25%, within 20%, within 15%, within 10% or within 5% of the average level, concentration or amount, and/or is within a standard deviation of the average level, concentration or amount in a biological sample from among a plurality of control subjects. In some examples, the control subjects are healthy or normal subjects, are subjects who do not have a cancer and/or are subjects prior to receiving administration of the T cell therapy.

**[0111]** In some examples, the increase or decrease is by greater than or greater than about 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

**[0112]** In some examples, wherein prior to the assessing, 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 a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

**[0113]** In some examples, the biological sample is or is obtained from a serum, plasma or tumor sample.

**[0114]** In some examples, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

**[0115]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

**[0116]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

**[0117]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of tryptophan 2,3-dioxygenase (TDO). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor.

**[0118]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1). In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator 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.

**[0119]** In some examples of any of the examples herein, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0120]** In some examples, the T cell comprises a recombinant receptor that specifically binds to a ligand that is a functional non-T cell receptor.

**[0121]** In some examples of any of the examples herein, the genetically engineered receptor that specifically binds to a ligand is a functional non-T cell receptor. In some examples, the genetically engineered receptor that specifically binds to a ligand is a chimeric antigen receptor (CAR). In some examples, the CAR contains an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling region that includes an ITAM. In some examples, the intracellular signaling region contains an intracellular domain of a CD3-zeta (CD3 $\zeta$ ) chain.

**[0122]** In some examples of any of the examples herein, the CAR also contains a costimulatory signaling region. In some examples, the costimulatory signaling region contains a signaling domain of CD28 or 4-1BB or an ICOS or a signaling portion thereof. In some examples, the costimulatory signaling region is a signaling domain of a CD28.

**[0123]** In some examples of any of the examples herein, the recombinant receptor is a transgenic T cell receptor (TCR). In some examples, the recombinant receptor is a chimeric antigen receptor (CAR).

**[0124]** In some examples of any of the examples herein, the T cell therapy recognizes or targets an antigen associated with the cancer. In some examples, the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer. In some examples, 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).

**[0125]** Provided herein are engineered cells that contain (a) a genetically engineered receptor that specifically binds to a ligand; and (b) a modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling in the cell, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression.

**[0125a]** In another example, there is provided an engineered cell, comprising: (a) a recombinant receptor that specifically binds to a ligand; and (b) a modification in 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.

**[0126]** In some examples, the molecule is mTOR or protein kinase C theta (PKC- $\Theta$ ).

**[0127]** Provided are engineered cells that include (a) a recombinant receptor that specifically binds to a ligand; and (b) a modification in 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.

**[0128]** In some examples, the modification comprises recombinant, engineered and/or ectopic expression in the cell of the molecule or a functional and/or catalytically active portion or variant thereof. In some examples, the molecule is mTOR or protein kinase C theta (PKC- $\Theta$ ).

**[0129]** In some examples, the molecule is an amino acid transporter or a chain thereof or a functional and/or catalytically active portion or variant thereof.

**[0130]** Also provided are engineered cells that include (a) a recombinant receptor that specifically binds to a ligand; and (b) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

**[0130a]** In another example, there is provided an engineered cell, comprising: (a) a recombinant receptor that specifically binds to a ligand; and (b) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof, optionally wherein the amino acid transporter is a tryptophan transporter.

**[0131]** In some examples, the amino acid transporter is a tryptophan transporter. In some examples, T (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), and proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof. In some examples, the amino acid transporter or a chain thereof comprises CD98 heavy chain (4F2hc; SLC3A2) and L-type Amino Acid Transporter 1 (LAT1; SLC7A5) or a portion thereof.

**[0132]** In some examples, the amino acid transporter or a chain thereof comprises the amino acid sequence selected from any one of SEQ ID NOs: 36-115, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 36-115. In some examples, the amino acid transporter or a chain thereof is selected from among one or more of CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2

(SLC7A8), and proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof. In some examples, the amino acid transporter or a chain thereof comprises CD98 heavy chain (4F2hc; SLC3A2) and L-type Amino Acid Transporter 1 (LAT1; SLC7A5) or a portion thereof.

**[0133]** In some examples, the amino acid transporter or a chain thereof comprises the amino acid sequence selected from any one of SEQ ID NOs:37-39 and 115, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 37-39 and 115.

**[0134]** In some examples, expression of the molecule or amino acid transporter in the cell is under the control of a conditional promoter or enhancer or transactivator.

**[0135]** In some examples, the molecule is selected from among GCN2 kinase, BLIMP-1 aryl hydrocarbon receptor (AHR), AHR nuclear transporter (ARNT), eukaryotic translation initiation factor 2  $\alpha$  (eIF2 $\alpha$ ), activating transcription factor 4 (ATF4), or CCAAT/enhancer binding protein-homologous protein (CHOP), Gadd45 $\alpha$ , Herp, 4E-BP1, eIF4G, JAK1, NF $\kappa$ B-2, FK506-BP8 and IFN $\gamma$ -R2. In some examples, the molecule is GCN2 or CHOP.

**[0136]** In some examples, the modification includes recombinant, engineered and/or ectopic expression in the cell of the molecule or a functional and/or catalytically active portion or variant thereof. In some examples, the expression of the molecule in the cell is under the control of a conditional promoter or enhancer or transactivator.

**[0137]** In some examples, wherein the molecule is GCN2 kinase, aryl hydrocarbon receptor (AHR) or AHR nuclear transporter (ARNT).

**[0138]** In some examples, the modification includes reduced expression of the molecule in the cell. In some examples, the engineered cell contains an inhibitory nucleic acid or a genetic disruption that reduces expression of the molecule. In some examples, the expression of the molecule in the cell is reduced by at least 50, 60, 70, 80, 90, or 95 % as compared to the expression in the cell in the absence of the inhibitory nucleic acid or gene disruption.

**[0139]** In some examples, the cell contains an inhibitory nucleic acid, thereby effecting reduction in expression of the molecule. In some examples, the inhibitory nucleic acid includes an RNA interfering agent. In some examples, the inhibitory nucleic acid is or includes or encodes a small interfering RNA (siRNA), a microRNA-adapted shRNA, a short

hairpin RNA (shRNA), a hairpin siRNA, a microRNA (miRNA-precursor) or a microRNA (miRNA). In some examples, expression of the inhibitory nucleic acid is under the control of a conditional promoter or enhancer or transactivator.

**[0140]** In some examples, the engineered cell contains a disrupted gene encoding the molecule, an agent for disruption of a gene encoding the molecule and/or a disruption of a gene encoding the molecule. In some examples, the disruption includes disrupting the gene encoding the molecule at the DNA level and/or the disruption is not reversible; and/or the disruption is not transient.

**[0141]** In some examples, the disruption is mediated by a DNA binding protein or DNA-binding nucleic acid that specifically binds to or hybridizes the gene encoding the molecule. In some examples, the disruption is mediated by (a) a fusion protein including a DNA-targeting protein and a nuclease or (b) an RNA-guided nuclease. In some examples, the disruption is mediated by a gene editing nuclease, a zinc finger nuclease (ZFN), a TAL-effector nuclease (TALEN), or a clustered regularly interspaced short palindromic nucleic acid (CRISPR)/Cas9. In some examples, the disruption is mediated by a CRISPR/Cas9 and the CRISPR/Cas9 includes a guide RNA (gRNA) containing a guide sequence that is complementary to, and/or capable of hybridizing to, a target sequence in the gene.

**[0142]** In some examples, the genetic disruption is conditional or inducible. In some examples, the CRISPR-Cas9 complex is an inducible CRISPR-Cas9 and/or the Cas9 is under the control of a conditional promoter or enhancer or transactivator.

**[0143]** In some examples, the disruption includes a deletion of at least a portion of at least one exon of the gene encoding the molecule. In some examples, the disruption includes a deletion, mutation, and/or insertion in the gene resulting in the presence of a premature stop codon in the gene; and/or the disruption includes a deletion, mutation, and/or insertion within a first or second exon of the gene encoding the molecule.

**[0144]** In some examples, the conditional promoter or enhancer or transactivator is an inducible promoter, enhancer, or transactivator or a repressible promoter, enhancer, or transactivator, such as an RNA pol I, pol II or pol III promoter. In some examples, the promoter is selected from: a pol III promoter that is a U6 or H1 promoter; or a pol II promoter that is a CMV, SV40 early region or adenovirus major late promoter.

**[0145]** In some examples, the promoter is an inducible promoter. In some examples, the promoter includes a binding site for NFκB or NFAT. In some examples, the promoter includes a Lac operator sequence, a tetracycline operator sequence, a galactose operator sequence or a doxycycline operator sequence, or is an analog thereof.

**[0146]** In some examples, the promoter is a repressible promoter. In some examples, the promoter is capable of being bound by a Lac repressor or a tetracycline repressor, or is an analog thereof.

**[0147]** In some examples, the cell is a T cell. In some examples, the T cell is a CD8+ T cell. In some examples, the T cell is a CD4+ T cell. In some examples, the cell is a natural killer (NK) cell. In some examples, the cell is an iPS-derived cell.

**[0148]** In some examples, the genetically engineered receptor that specifically binds to a ligand is a functional non-T cell receptor. In some examples, the genetically engineered receptor that specifically binds to a ligand is a chimeric antigen receptor (CAR).

**[0149]** In some examples, the CAR includes an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling region that includes an ITAM.

**[0150]** In some examples, the intracellular signaling region includes an intracellular domain of a CD3-zeta (CD3ζ) chain.

**[0151]** In some examples, the CAR also includes a costimulatory signaling region. In some examples, the costimulatory signaling region includes a signaling domain of CD28 or 4-1BB or an ICOS or a signaling portion thereof. In some examples, costimulatory signaling region is a signaling domain of a CD28.

**[0152]** In some examples, the genetically engineered receptor that specifically binds to a ligand is a recombinant receptor.

**[0153]** In some examples, the genetically engineered receptor that specifically binds to a ligand is a transgenic T cell receptor (TCR).

**[0154]** In some examples, the cell is engineered by introduction of a first nucleic acid sequence encoding the recombinant receptor into the cell, and one or more second nucleic acid sequence(s) encoding an agent that is capable of or involved in modifying 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, into the cell. In some

examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more polynucleotides. In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more vector(s), which optionally are viral vector(s).

**[0155]** Also provided herein are compositions that include any of the engineered cell described herein. In some examples of the compositions, the cells are CD4+ or CD8+ cells. In some examples, the compositions also include a pharmaceutically acceptable carrier.

**[0155a]** In another example, there is provided a composition comprising the engineered cell as described herein.

**[0156]** Also provided herein are combinations that include genetically engineered cells expressing a recombinant receptor that binds to a ligand, wherein the recombinant receptor optionally is a T cell receptor (TCR) or a chimeric antigen receptor (CAR); and a tryptophan metabolism and/or kynurenine pathway modulator.

**[0156a]** In another example, there is provided a combination, comprising: genetically engineered cells expressing a recombinant receptor that binds to a ligand, wherein the recombinant receptor optionally is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR); and a tryptophan metabolism and/or kynurenine pathway modulator.

**[0157]** Also provided herein are combinations that include any of the engineered cells described herein or any of the compositions described herein, and a tryptophan metabolism and/or kynurenine pathway modulator.

**[0157a]** In another example, there is provided a combination, comprising: the engineered cells as described herein or the composition as described herein; and a tryptophan metabolism and/or kynurenine pathway modulator.

**[0158]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway, and/or reduces the kynurenine/tryptophan ratio.

**[0159]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some examples, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

**[0160]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

**[0161]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

**[0162]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of

tryptophan 2,3-dioxygenase (TDO). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1).

**[0163]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator 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.

**[0164]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0165]** In some examples, the combination provided herein is packaged as an article of manufacture such as a kit. In some examples, article and/or kit further comprises instructions or literature providing for the administration of the engineered cells and/or tryptophan metabolism and/or kynurenine pathway modulator.

**[0166]** Also provided are methods of engineering immune cells expressing a recombinant receptor, that includes contacting a population of cells comprising immune cells with a tryptophan metabolism and/or kynurenine pathway modulator; and introducing a nucleic acid encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed.

**[0166a]** In another example, there is provided a method of engineering immune cells expressing a recombinant receptor, comprising: contacting a population of cells comprising immune cells with a tryptophan metabolism and/or kynurenine pathway modulator; and introducing a nucleic acid encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed.

**[0167]** In some examples, the recombinant receptor binds to a ligand, optionally an antigen. In some examples, the recombinant receptor is a T cell receptor (TCR) or a chimeric antigen receptor (CAR). In some examples, the population of cells is or comprises peripheral blood mononuclear cells. In some examples, the population of cells is or comprises T cells. In some examples, the T cells are CD4+ and/or CD8+. In some examples, the population of cells are isolated from a subject, optionally a human subject.

**[0168]** In some examples, the contacting occurs prior to and/or during the introducing.

**[0169]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some examples, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

**[0170]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

**[0171]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

**[0172]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of tryptophan 2,3-dioxygenase (TDO). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor. In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1).

**[0173]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator 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.

**[0174]** In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some examples, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

**[0175]** Also provided are methods of engineering immune cells expressing a recombinant receptor, that includes introducing a first nucleic acid sequence encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed; and introducing one or more second nucleic acid sequence(s) encoding an agent capable of or involved in 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 immunosuppression in the cell into the population of cells under conditions such that the agent is expressed.

**[0176]** Also provided are methods of engineering immune cells expressing a recombinant receptor, that includes introducing a first nucleic acid sequence encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed; and introducing one or more second nucleic acid sequence(s) encoding a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

**[0176a]** In another example, there is provided a method of engineering immune cells expressing a recombinant receptor, wherein the method is selected from: (A) a method comprising: (i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and (ii) introducing one or more second nucleic acid sequence(s) encoding an agent capable of or involved in 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 into the population of cells under conditions such that the agent is expressed; and/or (B) a method comprising: (i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and (ii) introducing one or more second nucleic acid sequence(s) encoding a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

**[0177]** In some examples, the modification comprises recombinant, engineered and/or ectopic expression of the molecule or a functional and/or catalytically active chain, portion or variant thereof. In some examples, the modification comprises reduced expression of the molecule. In some examples, the method comprises an inhibitory nucleic acid or a genetic disruption that reduces expression of the molecule.

**[0178]** In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more polynucleotides. In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some examples, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more vector(s), which optionally are viral vector(s).

**[0179]** In some examples, the combination provided herein is packaged as a kit. In some examples, the kit also includes instructions for administration of the engineered cells and tryptophan metabolism and/or kynurenine pathway modulator. In some examples, provided are articles of manufacture and/or kits, such as those comprising the tryptophan metabolism and/or kynurenine pathway modulator, e.g., in a therapeutically effective dose. In some examples, the articles of manufacture further comprise instructions and/or literature specifying administration of the modulator(s) to a subject having received or that is intended to receive the therapy such as the cell therapy such as an engineered T cell therapy. In some examples, the instructions or literature further specify the administration to the subject with a disease or condition, where the disease or condition or associated cells or tissues are or have been confirmed to express IDO—optionally following administration of the therapy—and/or one or more amino acid transporters such as LAT-1. In some examples, the instructions or literature do not indicate the expression of IDO and/or do not indicate expression of a transporter or other marker, as a prerequisite for administration of the cell therapy.

## CLAIMS

### WHAT IS CLAIMED:

1. 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.
2. Use of a tryptophan metabolism and/or kynurenine pathway inhibitor in the manufacture of a medicament for the treatment of a cancer, wherein the tryptophan metabolism and/or kynurenine pathway 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 tryptophan metabolism and/or kynurenine pathway inhibitor.
3. Use of a T cell therapy in the manufacture of a medicament for the treatment of a cancer in combination with a tryptophan metabolism and/or kynurenine pathway inhibitor, 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.
4. 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.

5. The use of any of claims 1-4, wherein the tryptophan metabolism and/or kynurenine pathway 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 tryptophan metabolism and/or kynurenine pathway inhibitor prevents or reduces catabolism of tryptophan, prevents or reduces synthesis or accumulation of a tryptophan metabolite or decreases the kynurenine to tryptophan ratio.

6. The use of any of claims 1-5, wherein the tryptophan metabolism and/or kynurenine pathway 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.

7. The use of any of claims 1-6, wherein the tryptophan metabolism and/or kynurenine pathway inhibitor is selected from among: an antagonist of the enzyme kynureninase; an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO); tryptophan; an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or a dual-acting IDO/TDO inhibitor.

8. The use of any of claims 1-7, wherein the tryptophan metabolism and/or kynurenine pathway inhibitor is an IDO1 inhibitor.

9. The use of claim 8, 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.

10. The use of claim 8 or 9, 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).

11. The use of any of claims 1-10, 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.

12. The use of any of claims 1-11, wherein upon administration to the subject the T cell therapy causes an increase or elevation of the level of interferon-gamma (IFN $\gamma$ ) 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 $\gamma$  in the subject prior to initiation of the T cell therapy.

13. The use of claim 12, wherein the increase or elevation of the level of IFN $\gamma$  in the subject results in an increase or elevation of expression of IDO1 in cells present in the local environment of a tumor.

14. The use of claim 13, wherein the local environment of a tumor comprises tumor cells.

15. The use of any of claims 1-14, wherein tryptophan metabolism and/or kynurenine pathway 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 $\gamma$ ) 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.

16. The use of claim 15, 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.

17. The use of any of claims 1-16, wherein the tryptophan metabolism and/or kynurenine pathway 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.

18. The use of any of claims 1-17, 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.

19. The use of claim 18, 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.

20. The use of claim 19, 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.

21. The use of claim 19, wherein:  
the modification comprises introducing an inhibitory nucleic acid.

22. The use of claim 21, wherein the inhibitory nucleic acid comprises an RNA interfering agent that reduces expression of the molecule.

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

24. The use of claim 23, 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.

25. The use of any of claims 19-24, wherein the molecule is selected from among one or more selected from:

mTOR or protein kinase C theta (PKC- $\Theta$ );

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  $\alpha$  (eIF2 $\alpha$ ), activating transcription factor 4 (ATF4), CCAAT/enhancer binding protein-homologous protein (CHOP), Gadd45 $\alpha$ , Herp, 4E-BP1, eIF4G, JAK1, NF $\kappa$ B-2, FK506-BP8 or IFN $\gamma$ -R2.

26. The use of any of claims 1-25, wherein the T cell therapy comprises genetically engineered T cells comprising a recombinant receptor that specifically binds to an antigen.

27. The use of any of claims 18-26, wherein the recombinant receptor is a chimeric antigen receptor (CAR).

28. The use of claim 27, 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.

29. The use of claim 28, wherein the intracellular signaling region comprises an intracellular domain of a CD3-zeta (CD3 $\zeta$ ) chain.

30. The use of any of claims 27-29, wherein the CAR further comprises a costimulatory signaling region.

31. The use of claim 30, wherein the costimulatory signaling region comprises a signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof.

32. The use of any of claims 18-31, wherein the recombinant receptor is a transgenic T cell receptor (TCR).

33. The use of any of claims 18-32, wherein the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer.

34. The use of claim 33, 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).

35. The use of any of claims 1-34, wherein the cancer is a myeloma, lymphoma, leukemia.

36. The use of any of claims 1-35, 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.

37. The use of any of claims 1-34, wherein the cancer is a non-hematological cancer or is a solid tumor.

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

39. The use of claim 38, 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.

40. The use of any of claims 1-39, wherein the T cell therapy or genetically engineered T cells 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 tryptophan metabolism and/or kynurenine pathway inhibitor.

41. The use of claim 40, wherein the biological sample is or comprises a serum, plasma or tumor sample.

42. The use of any of claims 1-41, 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 tryptophan metabolism and/or kynurenine pathway 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 tryptophan metabolism and/or kynurenine pathway 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.

43. The use of any of claims 1-42, wherein the tryptophan metabolism and/or kynurenine pathway inhibitor is to be administered orally, subcutaneously or intravenously.

44. The use of any of claims 1-43, wherein the tryptophan metabolism and/or kynurenine pathway inhibitor is to be administered orally.

45. The use of any of claims 1-44, wherein the tryptophan metabolism and/or kynurenine pathway 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.

46. The use of any of claims 1-45, wherein the tryptophan metabolism and/or kynurenine pathway 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.

47. The use of any of claims 1-46, wherein the tryptophan metabolism and/or kynurenine pathway inhibitor is to be administered six times daily, five times daily, four times daily, three times daily, twice daily or once daily.

48. The use of any of claims 1-47, 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 tryptophan metabolism and/or kynurenine pathway 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 tryptophan metabolism and/or kynurenine pathway 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  $1 \times 10^5$  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  $1 \times 10^4$  CAR-expressing cells.

49. The use of any of claims 1-48, wherein the T cell therapy comprises CD4+ T cells and/or CD8+ T cells.

50. The use of any of claims 1-49, wherein the T cell therapy comprises cells that are autologous to the subject or comprises cells that are allogeneic to the subject.

51. The use of any of claims 1-50, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising between  $1 \times 10^6$  and  $3 \times 10^8$ ,  $1 \times 10^7$  and  $2 \times 10^8$  total recombinant receptor-expressing cells.

52. The use of any of claims 1-51, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising  $1 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$  or  $1.5 \times 10^8$  total recombinant receptor-expressing cells, or the range between any two of the foregoing values.

53. The use of any of claims 1-50, wherein the T cell therapy is formulated for administration of a dose of recombinant receptor-expressing cells comprising a number of cells between  $0.5 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between  $0.5 \times 10^6$  cells/kg and  $3 \times 10^6$  cells/kg, between  $0.5 \times 10^6$  cells/kg and  $2 \times 10^6$  cells/kg, between  $0.5 \times 10^6$  cells/kg and  $1 \times 10^6$  cell/kg, between  $1.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between  $1.0 \times 10^6$  cells/kg and  $3 \times 10^6$  cells/kg, between  $1.0 \times 10^6$  cells/kg and  $2 \times 10^6$  cells/kg, between  $2.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, between  $2.0 \times 10^6$  cells/kg and  $3 \times 10^6$  cells/kg, or between  $3.0 \times 10^6$  cells/kg body weight of the subject and  $5 \times 10^6$  cells/kg, each inclusive.

54. The use of any of claims 1-53, wherein a lymphodepleting chemotherapy is to be further administered prior to administration of the T cell therapy.

55. The use of any of claims 1-54, 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 a tryptophan metabolism and/or kynurenine pathway inhibitor.

56. The use of claim 55, wherein the prior administration was carried out in combination with an immunomodulatory agent.

57. The use of claim 56, wherein the immunomodulatory agent is a checkpoint inhibitor.

58. The use of any of claims 1-57, wherein, prior to administration of the tryptophan metabolism and/or kynurenine pathway 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 ( $\text{IFN}\gamma$ ) 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 $\gamma$  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.