Claims

1. A cell composition in combination with an additional therapeutic agent for use in the treatment of cancer using an additional therapeutic treatment,

wherein the cell composition to be administered to the subject comprises γδ T cells expressing at least a chimeric antigen receptor (CAR) directed to a tumor antigen, a receptor for a stress-induced antigen and a survival factor that allows the immune system cell expressing the CAR to survive in a treatment environment resulting from the additional therapeutic treatment, wherein the survival factor is O^6-Methylguanine-DNA methyltransferase (MGMT), multidrug resistance protein 1 (MDR1), 5' nucleotidase II (NT5C2), drug resistant variant of dihydrofolate reductase (L22Y-DHFR), or thymidylate synthase, and wherein the receptor for the stress induced antigen is the NKG2D receptor; and

wherein the additional therapeutic treatment to be administered to the subject is either before administration of the cell composition to the subject, after administration of the cell composition to the subject, concurrently with administration of the cell composition to the subject or any combination of the foregoing, wherein the CAR comprises an endodomain, and wherein the endodomain comprises only one signaling domain.

2. Use of a cell composition in the manufacture of a medicament for the treatment of cancer wherein the medicament is to be used in combination with an additional therapeutic treatment and wherein

the cell composition forming the medicament to be administered to the subject comprises γδ T cells expressing at least a chimeric antigen receptor (CAR) directed to a tumor antigen, a receptor for a stress-induced antigen and a survival factor that allows the immune system cell expressing the CAR to survive in a treatment environment resulting from the additional therapeutic treatment, wherein the survival factor is MGMT, MDR1, NT5C2, L22Y-DHFR, or

thymidylate synthase, wherein the receptor for the stress-induced antigen is a NKG2D receptor; and wherein the CAR comprises an endodomain, and wherein the endodomain comprises only one signaling domain; and

wherein the additional therapeutic treatment to be administered to the subject is either before administration of the medicament to the subject, after administration of the medicament to the subject, concurrently with administration of the medicament to the subject or any combination of the foregoing.

3. The use of claim 2, further comprising at least one additional therapeutic treatment to be administered to the subject.

4. The use of claim 2, wherein the cell composition to be administered to the subject on day X and the additional therapeutic treatment to be administered to the subject is 12 to 72 hours prior to day X, 12 to 72 hours after day X or both 12 to 72 hours prior to and after day X.

5. The use of claim 2, wherein the cell composition to be administered to the subject on day X and the additional therapeutic treatment to be administered to the subject is 12 to 72 hours prior to day X, 12 to 72 hours after day X or both 12 to 72 hours prior to and after day X, followed by an additional administration of the cell composition to the subject on day Y, with administration of the additional therapeutic treatment to the subject 12 to 72 hours prior to day Y, 12 to 72 hours after day Y or both 12 to 72 hours prior to and after day Y.

6. The use of claim 2, wherein the cancer is selected from the group consisting of brain cancer, breast cancer, prostate cancer, lung cancer, colon cancer, epithelial cancer, head and neck cancer, skin cancer, cancers of the genito-urinary tract, ovarian cancer, endometrial cancer,

cervical cancer, kidney cancer, gastric cancer, cancer of the small intestine, liver cancer, pancreatic cancer, gall bladder cancer, cancers of the bile duct, esophageal cancer, cancer of the salivatory glands, thyroid cancer, and hematological malignancies leukemia, lymphoma, multiple myeloma, and myelodysplastic syndromes.

7. The use of claim 2, wherein the cancer is selected from the group consisting of pineal tumors, pituitary tumors, PNET, schwannoma, lymphoma, medulloblastoma, meningioma, metastatic brain cancer, neurofibroma, neuronal & mixed neuronal-glial tumors, oligoastrocytoma, oligodendroglioma, astrocytoma, atypical teratoid rhaboid tumor (ATRT), chondrosarcoma, choroid plexus tumors, craniopharyngioma, ependymoma, germ cell tumor, neuroblastoma, glioblastoma and glioma.

8. The use of claim 2, wherein the cancer is sensitive to the additional therapeutic treatment.

9. The use of claim 2, wherein the cancer is resistant to the additional therapeutic treatment.

10. The use of claim 2, wherein the tumor antigen is selected from the group consisting of EphA2, B cell maturation antigen (BCMA), B7-H3, B7-H6, CAIX, CA9, CD22, CD19, CD20, ROR1, kappa or light chain, carcinoembryonic antigen, alpha-fetoprotein, CA-125, Glypican-3, epithelial tumor antigen, melanoma-associated antigen, EGP2, EGP40, EPCAM, ERBB3, ERBB4, ErbB3/4, PAP, FAR, FBP, fetal AchR, Folate Receptor α, mutated p53, mutated ras, HER2, ERBB2, HER3, folate binding protein, HIV-1 envelope glycoprotein gp120, HIV-1 envelope glycoprotein gp41, 5T4, 8H9, GD2, CD123, CD23, CD33, CD30, CD38, CD56, c-Met, fap, mesothelin, GD3, HERV-K, IL-11Rα, IL-13Rα, CSPG4, Lewis-Y, MCSP, Mucl, Muc16, NCAM, NKG2D ligands, NY-ES0-1, PRAME, PSCA, PSCl, PSMA, EGFR, Sp17, SURVIVIN, TAG72, TEMl, TEM8, EGFRvIII and VEGFR2.

11. The use of claim 2, wherein the cancer is glioblastoma and the tumor antigen is selected from the group consisting of NKG2D ligands, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A, MIC-B, EGFRvIII and IL13Rα.

12. The use of claim 2, wherein the cancer is glioblastoma and the tumor antigen is EGFRvIII or IL13Rα.

13. The use of claim 2, wherein the cancer is neuroblastoma and the tumor antigen is selected from the group consisting of NKG2D ligands, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A, MIC-B and GD2.

14. The use of claim 2, wherein the cancer is neuroblastoma and the tumor antigen is GD2.

15. The use of claim 2, wherein the cell composition comprises γδ T cells and at least one of αβ T cells and NK cells.

16. The use of claim 2, wherein the cell composition comprises γδ T cells and αβ T cells and NK cells.

17. The use of claim 2, wherein the cell composition comprises greater than or equal to 60% γδ T cells and less than or equal to 5% αβ T cells and less than or equal to 25% NK cells.

18. The use of claim 2, wherein the additional therapeutic treatment is treatment with a nucleoside-analog, alkylating agent, antimetabolite, antibiotic, topoisomerase inhibitor, mitotic

inhibitor, differentiating agent, or hormone therapy agent and the survival factor provides resistance to the additional therapeutic treatment.

19. The use of claim 2, wherein the survival factor is MGMT, MDR1, or NT5C2.

20. The use of claim 2, wherein the additional therapeutic treatment is treatment with an alkylating agent and the survival factor is MGMT.

21. The use of claim 2, wherein the additional therapeutic treatment is treatment with temozolomide and the survival factor is MGMT.

22. The use of claim 2, wherein the γδ T cells are engineered to express the CAR directed to a tumor antigen and the survival factor and the receptor for the stress-induced antigen occurs naturally on the immune system cell.

23. The use of claim 2, wherein the γδ T cells are engineered to express the CAR directed to a tumor antigen, the survival factor and the receptor for the stress-induced antigen.

24. The use of claim 2, wherein the γδ T cells further express a suicide gene.

25. The use of claim 2, wherein the additional therapeutic treatment provides at least one of the
following benefits:

a. increased effectiveness of the cell composition through induction of stress-induced antigens;
b. increased homeostatic reconstitution of the cell composition;

c. increased *in vivo* proliferation of the cell composition; and

d. increased persistence of the cell composition.

26. The use of claim 2, wherein the additional therapeutic treatment increases the expression of a stress-induced antigen selected from the group consisting of ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A and MIC-B.

27. The use of claim 2, wherein the γδ T cells are obtained from the subject and expanded ex vivo.

28. A cell composition comprising γδ T cells expressing at least a chimeric antigen receptor (CAR) directed to a tumor antigen, and a survival factor that allows the immune system cell to survive in a treatment environment created by an additional therapeutic treatment and further expressing a receptor for a stress-induced antigen, wherein the survival factor is MGMT, MDR1, NT5C2, L22Y-DHFR, or thymidylate synthase, wherein the receptor for a stress-induced antigen is a NKG2D receptor, and wherein the CAR comprises an endodomain comprising only one signaling domain.

29. The cell composition of claim 28, wherein the tumor antigen is glioma-specific or neuroblastoma specific.

30. The cell composition of claim 28, wherein the tumor antigen is selected from the group consisting of EphA2, B cell maturation antigen (BCMA), B7-H3, B7-H6, CAIX, CA9, CD22, CD19, CD20, ROR1, kappa or light chain, carcinoembryonic antigen, alpha-fetoprotein, CA-125, Glypican-3, epithelial tumor antigen, melanoma-associated antigen, EGP2, EGP40, EPCAM, ERBB3, ERBB4, ErbB3/4, PAP, FAR, FBP, fetal AchR, Folate Receptor α, mutated

p53, mutated ras, HER2, ERBB2, HER3, folate binding protein, HIV-1 envelope glycoprotein gp120, HIV-1 envelope glycoprotein gp41, 5T4, 8H9, GD2, CD123, CD23, CD33, CD30, CD38, CD56, c-Met, fap, mesothelin, GD3, HERV-K, IL-11Rα, IL-13Rα, CSPG4, Lewis-Y, MCSP, Mucl, Muc16, NCAM, NKG2D ligands, NY-ES0-1, PRAME, PSCA, PSCl, PSMA, EGFR, Sp17, SURVIVIN, TAG72, TEMl, TEM8, EGFRvIII and VEGFR2.

31. The cell composition of claim 29, wherein the tumor antigen is selected from the group consisting of NKG2D ligands, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A, MIC-B, EGFRvIII and IL13Rα.

32. The cell composition of claim 29, wherein the tumor antigen is EGFRvIII or IL13Rα.

33. The cell composition of claim 29, wherein the tumor antigen is selected from the group consisting of NKG2D ligands, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A, MIC-B and GD2.

34. The cell composition of claim 29, wherein the tumor antigen is GD2.

35. The cell composition of claim 28, wherein the cell composition comprises γδ T cells and at least one of αβ T cells and NK cells.

36. The cell composition of claim 28, wherein the cell composition comprises γδ T cells and αβ T cells and NK cells.

37. The cell composition of claim 28, wherein the cell composition comprises greater than or equal to 60% γδ T cells and less than or equal to 5% αβ T cells and less than or equal to 25% NK cells.

38. The cell composition of claim 28, wherein the γδ T cells are engineered to express the CAR and the survival factor and are engineered to further express the receptor for the stress-induced antigen.

39. The cell composition of claim 28, wherein the γδ T cells naturally express the receptor for a stress-induced antigen.

40. The cell composition of claim 28, wherein the additional therapeutic treatment is treatment with a nucleoside-analog, alkylating agent, antimetabolite, antibiotic, topoisomerase inhibitor, mitotic inhibitor, differentiating agent, or hormone therapy agent and the survival factor provides resistance to the additional therapeutic treatment.

41. The cell composition of claim 28, wherein the survival factor is MGMT, MDR1, or NT5C2.

42. The cell composition of claim 28, wherein the additional therapeutic treatment is treatment with an alkylating agent and the survival factor is MGMT.

43. The cell composition of claim 28, wherein the additional therapeutic treatment is treatment with temozolomide and the survival factor is MGMT.

44. The cell composition of claim 28, wherein the γδ T cells are engineered to further express a suicide gene.

45. The cell composition of claim 28, wherein the additional therapeutic treatment increases the expression of a stress-induced antigen.

46. The cell composition of claim 28, wherein the additional therapeutic treatment increases the expression of a stress-induced antigen selected from the group consisting of ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6, MIC-A and MIC-B.

47. The cell composition of claim 1 or claim 28, or the use of claim 2, wherein the only one signaling domain is CD3-zeta.