syndrome in certain patient populations and/or for treating certain diseases or conditions. Among the provided embodiments are methods and uses that address such needs.

5. SUMMARY

In one aspect, the present disclosure refers to a dose of cells expressing a recombinant receptor that binds to an antigen in the manufacture of a medicament for the treatment of a disease or condition;

wherein the medicament is to be administered to a subject having said disease or condition;

wherein said subject is to be further administered with radiation.

wherein initiation of administration of the radiation is no later than about two weeks after administration of the recombinant receptor-expressing cells.

Provided are methods and compositions for treatment of subjects having or suspected of having a disease or condition, such as cancer or other proliferative disorder. In certain examples, the method includes (a) administering to a subject having a disease or condition a dose of cells expressing a recombinant receptor that binds to an antigen; and (b) administering to said subject radiation, wherein initiation of administration of the radiation is no later than about two weeks after administration of the recombinant receptor-expressing cells.

In certain examples, initiation of administration of the radiation is no later than about one week after administration of the recombinant receptor-expressing cells. In certain examples, initiation of administration of the radiation is between about 5 days and about 10 days after administration of the recombinant receptor-expressing cells. In certain examples, the subject has not relapsed at the time of or immediately prior to initiation of administration of the radiation.

In certain examples, the disease or condition is a tumor or a cancer. The disease or condition can be selected from the group consisting of blood cancers, B cell malignancies, colon cancer, lung cancer, liver cancer, breast cancer, prostate cancer, ovarian cancer, skin cancer, melanoma, bone cancer, brain cancer, ovarian cancer, epithelial cancers, renal cell carcinoma, pancreatic adenocarcinoma, cervical carcinoma, colorectal cancer, glioblastoma, neuroblastoma, Ewing sarcoma, medulloblastoma, osteosarcoma, synovial sarcoma, mesothelioma, and combinations thereof. In certain examples, the blood cancer is selected from the group consisting of leukemia, lymphoma, chronic lymphocytic leukemia (CLL), acute-lymphoblastic leukemia (ALL), Hodgkin

Lymphoma, non-Hodgkin's lymphoma, Waldenstrom's Macroglobulinemia, acute myeloid leukemia, multiple myeloma, mantle cell lymphoma,
and indolent B cell lymphoma. In certain examples, the disease or condition is multiple myeloma.

The antigen can be a tumor antigen or a pathogen antigen. In certain examples, the antigen is a tumor antigen. The tumor antigen can be selected from the group consisting of BCMA, GPRC5D, FcRL5, orphan tyrosine kinase receptor ROR1, tEGFR, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, CEA, and hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, EGP-2,

EGP-4, 0EPHa2, Erb-B2, Erb-B3, Erb-B4, FBP, fetal acethycholine 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, ROR1, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, Her2/neu, estrogen receptor, progesterone receptor, ephrinB2, CD123, c-Met, GD-2, and MAGE A3, CE7, Wilms Tumor 1 (WT-1), a cyclin, and biotinylated molecules. In certain examples, the tumor antigen is BCMA.

In certain examples, the recombinant receptor is a T cell receptor (TCR) or a functional non-T cell receptor. In certain examples, the recombinant receptor is a chimeric antigen receptor (CAR).

The CAR can include an extracellular antigen-binding domain that specifically binds to the antigen and an intracellular signaling domain. In certain examples, the intracellular signaling domain comprises an intracellular domain of a CD3-zeta (CD3ζ) chain. The intracellular signaling domain can further include a costimulatory signaling region. The costimulatory signaling region can include a signaling domain of CD28 or a portion thereof, a signaling domain of 4-1BB or a portion thereof, a signaling domain of OX40 or a portion thereof, a signaling domain of ICOS or a portion thereof, a signaling domain of DAP-10 or a portion thereof, or a combination thereof. In certain examples, the costimulatory signaling region comprises a signaling domain of 4-1BB or a portion thereof.

The CAR can further include a transmembrane domain. The transmembrane domain can include a transmembrane domain of CD8 or a portion thereof, or a transmembrane domain of CD28 or a portion thereof. In certain examples, the transmembrane domain comprises a transmembrane domain of a CD8 or a portion thereof.

In certain examples, the extracellular antigen-binding domain comprises a scFv. In certain examples, the extracellular antigen-binding domain comprises: a heavy chain variable region ("V_H") CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1; a V_H CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 2; a V_H CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 3; a light chain variable region ("V_L") CDR1 comprising the amino acid sequence set forth in

SEQ ID NO: 4; a V_L CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 5; and a V_L CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 6.

In certain examples, the cell is a T cell. The T cell can be selected from the group consisting of a cytotoxic T lymphocyte (CTL), a regulatory T cell, a tumor-infiltrating lymphocyte (TIL), and a Natural Killer T (NKT) cell. The cell can be autologous or allogenic to the subject.

In certain examples, the dose of cells comprises cells in an amount sufficient for reduction in burden of a disease or condition in the subject. In certain examples, the method includes administering to the subject a consecutive dose of the recombinant receptor-expressing cells after administration of a first dose of the recombinant receptor-expressing cells.

The radiation can be selected from the group consisting of external beam radiation, a radiopharmaceutical agent, and a combination thereof. In certain examples, the radiation is external beam radiation. In certain examples, a total of at least about 10 Gy of radiation is administered to a lesion site of the subject. In certain examples, a total of between about 10 Gy and about 30 Gy of radiation is administered to a lesion site of the subject. In certain examples, a total of about 20 Gy of radiation is administered to a lesion site of the subject.

In certain examples, administration of the radiation and administration of the recombinant receptor-expressing cells provide a synergistic abscopal effect. In certain examples, administration of the radiation and administration of the recombinant receptor-expressing cells provide delayed or reduced CRS-like response. In certain examples, administration of the radiation and administration of the recombinant receptor-expressing cells provide systemic expansion of new T-cell receptor (TCR) clone.

The present discourse also provides radiation and cells expressing a recombinant receptor that binds to an antigen are for use in a therapy, wherein initiation of administration of the radiation is no later than about two weeks after administration of the recombinant receptor-expressing cells. .

6. BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A-1F depict BCMA-targeted CAR T-cell therapy followed by radiation therapy (XRT) led to clinical response, expansion of TCR clonality, and CRS-like findings after XRT. The subject received conditioning therapy with cyclophosphamide and fludarabine followed by CAR T cells on day 0. Radiation therapy (XRT) took place

WHAT IS CLAIMED IS:

1. Use of a dose of cells expressing a recombinant receptor that binds to an antigen in the manufacture of a medicament for the treatment of a disease or condition;

wherein the medicament is to be administered to a subject having said disease or condition;

wherein said subject is to be further administered with radiation,

wherein initiation of administration of the radiation is no later than about two weeks after administration of the recombinant receptor-expressing cells.

2. The use of claim 1, wherein initiation of administration of the radiation is no later than about one week after administration of the recombinant receptor-expressing cells.

3. The use of claim 1, wherein initiation of administration of the radiation is between about 5 days and about 10 days after administration of the recombinant receptor-expressing cells.

4. The use of any one of claims 1-3, wherein the subject has not relapsed at the time of or immediately prior to initiation of administration of the radiation.

5. The use of any one of claims 1-4, wherein the disease or condition is a tumor or a cancer.

6. The use of any one of claims 1-5, wherein the disease or condition is selected from the group consisting of blood cancers, B cell malignancies, colon cancer, lung cancer, liver cancer, breast cancer, prostate cancer, ovarian cancer, skin cancer, melanoma, bone cancer, brain cancer, ovarian cancer, epithelial cancers, renal cell carcinoma, pancreatic adenocarcinoma, cervical carcinoma, colorectal cancer, glioblastoma, neuroblastoma, Ewing sarcoma, medulloblastoma, osteosarcoma, synovial sarcoma, mesothelioma, and combinations thereof.

7. The use of claim 6, wherein the blood cancer is selected from the group consisting of leukemia, lymphoma, chronic lymphocytic leukemia (CLL), acute-lymphoblastic leukemia (ALL), Hodgkin Lymphoma, non-Hodgkin’s lymphoma, Waldenstrom’s Macroglobulinemia, acute myeloid leukemia, multiple myeloma, mantle cell lymphoma, and indolent B cell lymphoma.

8. The use of any one of claims 1-7, wherein the disease or condition is multiple myeloma.

9. The use of any one of claims 1-8, wherein the antigen is a tumor antigen.

10. The use of claim 9, wherein the tumor antigen is selected from the group consisting of BCMA, GPRC5D, FcRL5, orphan tyrosine kinase receptor ROR1, tEGFR, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, CEA, and hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, EGP-2, EGP-4, 0EPHa2, Erb-B2, Erb-B3, Erb-B4, FBP, fetal acethycholine 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, ROR1, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, Her2/neu, estrogen receptor, progesterone receptor, ephrinB2, CD123, c-Met, GD-2, and MAGE A3, CE7, Wilms Tumor 1 (WT-1), a cyclin, and biotinylated molecules.

11. The use of any one of claims 1-10, wherein the tumor antigen is BCMA.

12. The use of any one of claims 1-11, wherein the recombinant receptor is a T cell receptor (TCR) or a functional non-T cell receptor.

13. The use of any one of claims 1-11, wherein the recombinant receptor is a chimeric antigen receptor (CAR).

14. The use of claim 13, wherein the CAR comprises an extracellular antigen-binding domain that specifically binds to the antigen and an intracellular signaling domain.

15. The use of claim 14, wherein the intracellular signaling domain comprises an intracellular domain of a CD3-zeta (CD3ζ) chain.

16. The use of claim 14 or 15, wherein the intracellular signaling domain further comprises a costimulatory signaling region.

17. The use of claim 16, wherein the costimulatory signaling region comprises a signaling domain of CD28 or a portion thereof, a signaling domain of 4-1BB or a portion thereof, a signaling domain of OX40 or a portion thereof, a signaling domain of ICOS or a portion thereof, a signaling domain of DAP-10 or a portion thereof, or a combination thereof

18. The use of claim 17, wherein the costimulatory signaling region comprises a signaling domain of 4-1BB or a portion thereof.

19. The use of any one of claims 10-18, wherein the CAR further comprises a transmembrane domain.

20. The use of claim 19, wherein the transmembrane domain comprises a transmembrane domain of CD8 or a portion thereof, or a transmembrane domain of CD28 or a portion thereof.

21. The use of claim 19 or 20, wherein the transmembrane domain comprises a transmembrane domain of CD8 or a portion thereof.

22. The use of any one of claims 14-21, wherein the extracellular antigen-binding domain comprises a scFv.

23. The use of any one of claims 14-22, wherein the extracellular antigen-binding domain comprises: a heavy chain variable region ("V_H") CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1; a V_H CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 2; a V_H CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 3; a light chain variable region ("V_L") CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 4; a V_L CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 5; and a V_L CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 6.

24. The use of claim of any one of claims 1-23, wherein the cell is a T cell.

25. The use of claim 24, wherein the T cell is selected from the group consisting of a cytotoxic T lymphocyte (CTL), a regulatory T cell, a tumor-infiltrating lymphocyte (TIL), and a Natural Killer T (NKT) cell.

26. The use of any one of claims 1-25, wherein the cell is autologous or allogenic to the subject.

27. The use of any one of claims 1-26, wherein the dose of cells comprises cells in an amount sufficient for reduction in burden of a disease or condition in the subject.

28. The use of any one of claims 1-27, wherein a consecutive dose of the recombinant receptor-expressing cells is to be administered to the subject after administration of a first dose of the recombinant receptor-expressing cells.

29. The use of any one of claims 1-28, wherein the radiation is selected from the group consisting of external beam radiation, a radiopharmaceutical agent, and a combination thereof.

30. The use of any one of claims 1-29, wherein the radiation is external beam radiation.

31. The use of any one of claims 1-30, wherein a total of at least about 10 Gy of radiation is to be administered to a lesion site of the subject.

32. The use of any one of claims 1-31, wherein a total of between about 10 Gy and about 30 Gy of radiation is to be administered to a lesion site of the subject.

33. The use of any one of claims 1-32, wherein a total of about 20 Gy of radiation is to be administered to a lesion site of the subject.

34. The use of any one of claims 1-33, wherein administration of the radiation and administration of the recombinant receptor-expressing cells provide a synergistic abscopal effect.

35. The use of any one of claims 1-34, wherein administration of the radiation and administration of the recombinant receptor-expressing cells provide delayed or reduced CRS-like response.

36. The use of any one of claims 1-34, wherein administration of the radiation and administration of the recombinant receptor-expressing cells provide systemic expansion of new T-cell receptor (TCR) clone.

37. Radiation and cells expressing a recombinant receptor that binds to an antigen for use in a therapy, wherein initiation of administration of the radiation is no later than about two weeks after administration of the recombinant receptor-expressing cells.