

Claims

1. Use of a chimeric antigen receptor (CAR)-T cell therapy and a mitigating therapeutic in the manufacture of a medicament for reducing neurotoxicity associated with said CAR-T cell therapy,

wherein said CAR-T cell therapy is to be administered to a subject;

wherein the mitigating therapeutic is to be administered to said subject based on one or more of (i) the subject's tumor burden prior to the time said CAR-T cell therapy is to be administered, (ii) the subject's IL-6 levels at the time said CAR-T cell therapy is to be administered, (iii) CAR-T cell expansion in said subject after the time said CAR-T cell therapy is to be administered, (iv) CAR-T cell persistence in peripheral blood of said subject after the time said CAR-T cell therapy is to be administered, (v) development of grade ≥ 2 cytokine release syndrome (CRS) in said subject after the time said CAR-T cell therapy is to be administered, (vi) development of immune effector cell associated neurotoxicity syndrome (ICANS) in said subject after the time said CAR-T cell therapy is to be administered, (vii) peak peripheral blood levels of IL-6 in said subject following the time said CAR-T cell therapy is to be administered, (viii) peak peripheral blood levels of INF- γ in said subject after the time said CAR-T cell therapy is to be administered; and (iv) lymphocyte counts in said subject after the time said CAR-T cell therapy is to be administered.

2. The use of claim 1, wherein the subject has multiple myeloma.

3. The use of claim 1 or claim 2, wherein the CAR-T cell therapy is a B-cell maturation agent (BCMA) CAR-T cell therapy.

4. The use of claim 3, wherein the BCMA CAR-T cell therapy is ciltacabtagene autoleucel (cilta-cel).

5. The use of any one of claims 1–4, wherein the neurotoxicity associated with the CAR-T cell therapy comprises one or more movement and motor dysfunction

adverse events, cognitive impairment adverse events, personality change adverse events, or any combination thereof.

6. The use of any one of claims 1–5, wherein the neurotoxicity associated with the CAR-T cell therapy is not ICANS.

7. The use of claim 1, wherein when said subject has a tumor burden characterized by bone marrow plasmacytosis of $\geq 80\%$, serum M protein levels of ≥ 5 g/dL, or serum free light chain levels of ≥ 5000 mg/L, said mitigating therapeutic comprises a bridging therapy, wherein the bridging therapy is to be administered prior to the time the CAR-T cell therapy is to be administered.

8. The use of claim 7, wherein said bridging therapy comprises a chemotherapeutic, an immunomodulatory agent, a proteasome inhibitor, or any combination thereof.

9. The use of claim 8, wherein the chemotherapeutic is an alkylating agent or a topoisomerase inhibitor.

10. The use of claim 8, wherein the immunomodulatory agent comprises a CD38 inhibitor.

11. The use of claim 10, wherein the CD38 inhibitor is daratumumab or isatuximab.

12. The use of claim 8, wherein the immunomodulatory agent is selected from lenalidomide, pomalidomide, thalidomide, and combinations thereof.

13. The use of claim 8, wherein the proteasome inhibitor is selected from bortezomib, carfilzomib, ixazomib, and combinations thereof.

14. The use of any one of claims 1–6, wherein if the subject's IL-6 blood levels at the time said CAR-T cell therapy is to be administered are above the upper limit of normal, said mitigating therapeutic comprises an IL-6 inhibitor, wherein the IL-6 inhibitor is to be administered prior to the time the CAR-T cell therapy is to be administered.

15. The use of any one of claims 1–6, wherein if the subject's peak peripheral blood IL-6 levels after the time said CAR-T cell therapy is to be administered are above the upper limit of normal, said mitigating therapeutic comprises an IL-6 inhibitor.

16. The use of claim 14 or claim 15 wherein the IL-6 inhibitor is tocilizumab.

17. The use of any one of claims 1–6, wherein if the subject's CAR-T cell expansion is >1000 cells/ μ L after the time said CAR-T cell therapy is to be administered, the mitigating therapeutic comprises a chemotherapeutic agent suitable for reducing the number of CAR-T cells in said subject.

18. The use of any one of claims 1–6, wherein if the subject's persisting CAR-T cell concentration in peripheral blood is >300 cells/ μ L after the time said CAR-T cell therapy is to be administered, the mitigating therapeutic comprises a chemotherapeutic agent suitable for reducing the number of CAR-T cells in said subject.

19. The use of claim 17 or claim 18, wherein the chemotherapeutic agent is an alkylating agent or a topoisomerase inhibitor.

20. The use of any one of claims 1–6, wherein if said subject has grade ≥ 2 CRS or any grade of ICANS, the mitigating therapeutic comprises an anti-inflammatory agent suitable for treating said CRS or ICANS.

21. The use of claim 20, wherein said anti-inflammatory agent is an IL-6 inhibitor.

22. The use of claim 21, wherein the IL-6 inhibitor is tocilizumab.
23. The use of claim 20, wherein said anti-inflammatory agent is a steroid.
24. The use of claim 23, wherein the steroid is selected from dexamethasone, prednisone, methylprednisolone, and combinations thereof.
25. Use of a chimeric antigen receptor (CAR)-T cell therapy in the manufacture of a medicament for the treatment of multiple myeloma while reducing neurotoxicity associated with said CAR-T cell therapy, wherein said CAR-T cell therapy is to be administered to a subject having multiple myeloma, wherein said subject has a tumor burden characterized by bone marrow plasmacytosis of <80%, serum M Protein levels of < 5g/dL, and serum free light chain levels of < 5000mg/L.
26. The use of claim 25, wherein said subject has a tumor burden characterized by bone marrow plasmacytosis of < 50%, serum M Protein levels of < 3g/dL, and serum free light chain levels of < 3000mg/L.
27. Use of a chimeric antigen receptor (CAR)-T cell therapy and a bridging therapy in the manufacture of a medicament the treatment of multiple myeloma while reducing neurotoxicity associated with said CAR-T cell therapy,
wherein said CAR-T cell therapy is to be administered to a subject having multiple myeloma, wherein said subject has a tumor burden characterized by bone marrow plasmacytosis of <80%, serum M Protein levels of < 5g/dL, and serum free light chain levels of < 5000mg/L;
wherein the bridging therapy is to be administered to the subject to achieve a tumor burden characterized by bone marrow plasmacytosis of <80%, serum M Protein levels of < 5g/dL, and serum free light chain levels of < 5000mg/L; and

wherein the bridging therapy is to be administered prior to the time said CAR-T cell therapy is to be administered.

28. The use of claim 27, wherein said bridging therapy comprises a chemotherapeutic, an immunomodulatory agent, a proteasome inhibitor or a combination thereof.

29. The use of claim 28, wherein the chemotherapeutic is an alkylating agent or a topoisomerase inhibitor.

30. The use of claim 28, wherein the immunomodulatory agent comprises a CD38 inhibitor.

31. The use of claim 30, wherein the CD38 inhibitor is daratumamab.

32. The use of claim 28, wherein the immunomodulatory agent is selected from lenalidomide, pomalidomide, thalidomide, and combinations thereof.

33. The use of claim 28, wherein the proteasome inhibitor is selected from bortezomib, carfilzomib, ixazomib, and combinations thereof.

34. Use of a chimeric antigen receptor (CAR)-T cell therapy in the manufacture of a medicament for the treatment of multiple myeloma while reducing neurotoxicity associated with said CAR-T cell therapy, wherein the CAR-T cell therapy is to be administered to a subject having multiple myeloma and an IL-6 serum level that is within normal reference range of 0-2 pg/mL.

35. Use of a chimeric antigen receptor (CAR)-T cell therapy and an IL-6 inhibitor in the manufacture of a medicament for the treatment of multiple myeloma while reducing neurotoxicity associated with said CAR-T cell therapy,

wherein said CAR-T cell therapy is to be administered to a subject having multiple myeloma and an IL-6 serum level that is within normal reference range of 0-2 pg/mL; and

wherein the IL-6 inhibitor is to be administered to achieve the normal reference range of IL-6 in the subject prior to the CAR-T cell therapy.

36. Use of a chimeric antigen receptor (CAR)-T cell therapy and an anti-inflammatory agent in the manufacture of a medicament for reducing neurotoxicity in a subject receiving said CAR-T cell therapy for the treatment of multiple myeloma, wherein the anti-inflammatory agent is to be administered to a subject having received CAR-T cell therapy and having symptoms of CAR-T cell therapy associated cytokine release syndrome (CRS) or immune effector cell associated neurotoxicity syndrome (ICANS), in an amount effective to reduce neurotoxicity in said subject.

37. The use of claim 36, wherein said anti-inflammatory is an IL-6 inhibitor.

38. The use of claim 37, wherein the IL-6 inhibitor is tocilizumab.

39. The use of claim 37, wherein said anti-inflammatory is a steroid.

40. The use of claim 39, wherein the steroid is selected from dexamethasone and methylprednisolone.

41. The use of claim 36, wherein the CRS is grade ≥ 2 .

42. The use of claim 36, wherein the ICANS is grade ≥ 1 .

43. Use of a chimeric antigen receptor (CAR)-T cell therapy and a chemotherapeutic in the manufacture of a medicament for reducing neurotoxicity in a subject receiving said CAR-T cell therapy for the treatment of multiple myeloma, wherein the chemotherapeutic is to be administered to the subject having received CAR-

T cell therapy and having a CAR-T cell maximum plasma concentration (C_{max}) of >1,000 cells/μL and/or a persisting CAR-T cell concentration in peripheral blood of >300 cells/μL after the time said CAR-T cell is to be administered, to reduce CAR-T cell therapy associated neurotoxicity.

44. Use of a chimeric antigen receptor (CAR)-T cell therapy and an IL-6 inhibitor in the manufacture of a medicament for reducing neurotoxicity in a subject receiving said CAR-T cell therapy for the treatment of multiple myeloma, wherein the IL-6 inhibitor is to be administered to the subject having received CAR-T cell therapy and having a peak peripheral blood IL-6 level that is above the upper limit of normal after the time said CAR-T cell therapy is to be administered, to reduce CAR-T cell therapy associated neurotoxicity.

45. The use of any one of claims 25–44, wherein the CAR-T cell therapy is a B-cell maturation agent (BCMA) CAR-T cell therapy.

46. The use of claim 45, wherein the BCMA CAR-T cell therapy is ciltacabtagene autoleucel (cilta-cel).

47. The use of any one of claims 25–44, wherein the neurotoxicity associated with the CAR-T cell therapy comprises movement adverse events, neurocognitive adverse events, personality change adverse events, or any combination thereof.

48. The use of any one of claims 25–44, wherein the neurotoxicity associated with the CAR-T cell therapy is not ICANS.