

CLAIMS

1. Use of a composition comprising cells expressing a chimeric antigen receptor (CAR) for manufacture of a medicament for treatment of a disease or condition in a subject previously treated with a first dose of CAR-expressing cells, wherein:

the composition is for use 14 to 28 days after the previous treatment; and/or

the composition is formulated for administration of a consecutive dose in an amount sufficient for reduction in burden of a disease or condition in the subject having been previously treated with the first dose of CAR-expressing cells.

2. The use of claim 1, wherein the first dose of CAR-expressing cells in the previous treatment reduced tumor burden in the subject prior to use of the consecutive dose and/or the subject does not exhibit morphologic disease prior to use of the consecutive dose and/or the subject does not exhibit greater than 5% blast cells in the bone marrow prior to use of the consecutive dose.

3. Use of cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for use in a method for treating a disease or condition, said method comprising:

(a) administering to a subject having the disease or condition a first dose of cells expressing the CAR, said first dose comprising no more than about 1×10^6 of the cells per kilogram body weight of the subject, no more than about 1×10^8 of the cells, and/or no more than about 1×10^8 of the cells/m² of the subject; and

(b) administering to the subject a consecutive dose of cells expressing a CAR at a time point that is at least or more than about 14 days after and less than about 28 days after initiation of said administration in (a).

4. The use of any of claims 1-3, wherein the composition comprising cells of the consecutive dose is formulated for administration in an amount that (i) does not induce severe CRS in the subject or does not induce CRS in the subject; (ii) does not induce grade 3 or higher neurotoxicity in the subject; (iii) based on clinical data, does not induce severe CRS in a majority of subjects so-treated; and/or (iv) based on clinical data, does not induce grade 3 or higher neurotoxicity in a majority of subjects so-treated.

5. The use of any of claims 1-4, wherein the composition comprising cells of the consecutive dose is formulated for administration of about the same number of CAR-expressing cells as the number of CAR-expressing cells in the first dose or an increased number of CAR-expressing cells as compared to the first dose.

6. The use of claim 5, wherein the increased number is at least 2-fold, 5-fold, or 10-fold greater than the number in the first dose.

7. The use of any of claims 1-6, wherein the composition is for use in a subject in which:

- (i) the serum level in the subject of a factor indicative of cytokine release syndrome (CRS) is less than about 10 times, less than about 25 times, and/or less than about 50 times that in the subject immediately prior to administration of the first dose of CAR-expressing cells;
- (ii) the subject does not exhibit grade 3 or higher neurotoxicity;
- (iii) a CRS-related outcome or symptom of neurotoxicity in the subject following said administration of said first dose of CAR-expressing cells has reached a peak level and begun to decline following administration of the first dose of CAR-expressing cells, and/or
- (iv) the subject does not exhibit a detectable humoral or cell-mediated immune response against the CAR expressed by the cells of said first dose of cells.

8. The use of any of claims 1-7, wherein the consecutive dose is formulated for administration of a number of cells that is:

between about 2×10^6 cells per kilogram (cells/kg) body weight and about 6×10^6 cells/kg, between about 2.5×10^6 cells/kg and about 5.0×10^6 cells/kg, or between about 3.0×10^6 cells/kg and about 4.0×10^6 cells/kg, each inclusive;

between about 1.5×10^8 cells and 4.5×10^8 cells, between about 1.5×10^8 cells and 3.5×10^8 cells or between about 2×10^8 cells and 3×10^8 cells, each inclusive; or

between about 1.5×10^8 cells/m² and 4.5×10^8 cells/m², between about 1.5×10^8 cells/m² and 3.5×10^8 cells/m² or between about 2×10^8 cells/m² and 3×10^8 cells/m², each inclusive.

9. The use of any of claims 1-8, wherein: the composition comprising the first and/or consecutive dose is formulated for administration in one or more unit dose, each unit dose

comprising about between 5×10^7 of the cells and about 5×10^8 cells, about between 5×10^7 of the cells and about 2.5×10^8 cells or about between 2.5×10^8 cells and 4×10^8 cells; or

the composition comprising cells of the first and/or consecutive dose is formulated in a unit dose comprising no more than about 5×10^7 cell, no more than about 1×10^8 cells, no more than about 2×10^8 of the cells, no more than about 2.5×10^8 of the cells, no more than about 3.0×10^8 of the cells or no more than about 4×10^8 of the cells.

10. The use of any of claims 1-9, wherein the composition comprising the first and/or consecutive dose of cells is formulated for administration of a single unit dose.

11. The use of any of claims 1-9, wherein the composition comprising the first and/or consecutive dose of cells is formulated for administration of two or more unit doses.

12. The use of any of claims 1-11, wherein the disease or condition is a tumor or a cancer.

13. The use of claim 12, wherein the tumor or cancer is leukemia or lymphoma.

14. The use of any of claims 1-13, wherein the composition comprising the consecutive dose of cells is formulated for administration of an increased number of CAR-expressing cells as compared to the first dose or previous dose.

15. The use of claim 14, wherein the composition is for use in treating acute lymphoblastic leukemia.

16. The use of any of claims 1-15, wherein the composition comprising the consecutive dose of cells is formulated for administration of less than or about the same number of CAR-expressing cells as the number of CAR-expressing cells in the first dose.

17. The use of any of claims 1-13 and claim 16, wherein the composition is for use in treating non-Hodgkin lymphoma (NHL).

18. The use of any of claims 1-17, wherein the antigen bound by the CAR expressed by the cells in the first dose and the antigen bound by the CAR expressed by the cells in the

consecutive dose is the same antigen and/or the CAR expressed by the cells in the first dose and the CAR expressed by the cells in the consecutive dose contain the same antigen-binding domain.

19. The use of any of claims 1-18, wherein the CAR expressed by the cells in the consecutive dose contains at least one immunoreactive epitope present in the CAR expressed by the cells in the first dose.

20. The use of any of claims 1-19, wherein the CAR expressed by the cells in the consecutive dose is identical to the CAR expressed by the cells in the first dose or is substantially identical to the CAR expressed by the cells in the first dose.

21. The use of any of claims 1-20, wherein the CAR expressed by the cells in the consecutive dose specifically binds to an antigen expressed by a cell or tissue of the disease or condition or associated with the disease or condition.

22. The use of any of claims 1-21, wherein the subject has been previously treated with a chemotherapeutic agent prior to administration of the first dose and/or prior to the administration of the consecutive dose.

23. The use of claim 22, wherein the chemotherapeutic agent comprises conditioning chemotherapy, which reduces burden of the disease or condition in the subject.

24. The use of claim 22 or claim 23, wherein the chemotherapeutic agent comprises an agent selected from the group consisting of cyclophosphamide and fludarabine.

25. The use of any of claims 22-25, wherein the chemotherapeutic agent comprises a combination of cyclophosphamide and fludarabine.

26. The use of any of claims 1-25, wherein the cells are or comprise T cells.

27. The use of claim 26, wherein the T cells are CD4+ and/or CD8+ T cells

28. The use of any of claims 1-27, wherein the cells of the first and/or second dose are autologous to the subject to whom they are to be administered.

29. An article of manufacture, comprising:

a plurality of sealable containers, each individually comprising a unit dose of cells expressing a chimeric antigen receptor (CAR) for administration to a subject, said unit dose comprising about 1×10^8 of the cells, no more than about 1×10^8 of the cells, about 5×10^7 of the cells, no more than about 5×10^7 of the cells, about 1×10^6 cells per kg of the subject, or no more than about 1×10^6 of the cells per kg of the subject;

packaging material; and

a label or package insert comprising instructions for administering a plurality of said unit doses to the subject by carrying out a first administration and a consecutive administration, said first administration comprising delivering one of said unit doses to the subject and said consecutive administration comprising administering one or a plurality of said unit doses to the subject.

30. The article of manufacture of claim 29, wherein the instructions specify that said consecutive administration is to be carried out at a time between about 14 or 15 and 27 days, optionally at about day 17 or about day 21, following said first administration.

31. The article of manufacture of claim 29 or claim 30, wherein the instructions specify that said consecutive administration is to be carried out at a time after which it has been determined that a serum level of a factor indicative of cytokine-release syndrome (CRS) in the subject is less than about 10 times, less than about 25 times, and/or less than about 50 times the serum level of said indicator in the subject immediately prior to said first administration.

32. The article of manufacture of any of claims 29-31, wherein the instructions specify that said consecutive administration is to be carried out at a time after which it has been determined that an indicator of CRS has peaked and is declining, and/or that the subject does not exhibit a detectable adaptive host immune response specific for the CAR expressed by the cells of said first dose.

33. The article of manufacture of any of claims 29-32, wherein the cells have been derived from and/or are autologous to the subject.

34. The article of manufacture of any of claims 29-33, wherein said label and/or said packaging material further comprises an identifier specific to the subject, indicating that the cells were derived from the subject and/or to be administered to the subject specifically.

35. The article of manufacture of any of claims 29-34, wherein the containers are or comprise flexible cell infusion bags.

36. The article of manufacture of any of claims 29-35, wherein the cells are T cells.

37. The article of manufacture of claim 36, wherein the T cells are CD4+ and/or CD8+ T cells.