SUMMARY OF THE INVENTION

[0012] The present invention addresses this need and thus provides as a solution to the technical problem embodiments pertaining to means and methods for use in the treatment of tumorous mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient in that a composition comprising a CD19xCD3 bispecific antibody is applied. An example of a CD19xCD3 bispecific (single chain) antibody is Blinatumomab (MT103).

[0013] Blinatumomab is a lymphoma-directed, recombinant bispecific single-chain CD19xCD3 antibody that binds to CD19 on the surface of almost all B cells and B tumor cells and concomitantly can engage a T cell, thereby triggering the T-cell to kill the target B cell or B tumor cell. It is thus a so-called BiTE® (**Bi**specific **T**-cell **E**ngager) antibody. Blinatumomab consists of four immunoglobulin variable domains assembled into a single polypeptide chain. Two of the variable domains form the binding site for CD19, a cell surface antigen expressed on most B cells and B tumor cells. The other two variable domains form the binding site for CD3 epsilon of the CD3 complex on T cells. Blinatumomab is designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells, and is presently in clinical trials.

[0014] Though WO 2007/068354 mentions that a CD19xCD3 bispecific antibody could be used amongst different B-cell non-Hodgkin lymphomas, for the treatment of DLBCL, this document does not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect which directly and unambiguously underlays the claimed therapeutic application of a CD19xCD3 bispecific antibody.

This is even more true when switching to the difficult to-treat and aggressive DLBCL.

[0015] However, to their surprise, the present inventors have found that a CD19xCD3 bispecific antibody is beneficial in the treatment of tumorous mass of lymphoreticular tissue (also referred to herein as lymph node tissue) and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient. Indeed, in clinical trials it was observed that a CD19xCD3 bispecific antibody led to outstanding results in the treatment of patients suffering from DLBCL in that in some patients a tremendous debulking of tumorous mass was observed, already after only a few weeks administration. Of note, the patients treated with a CD19xCD3 bispecific antibody were heavily pre-treated with a combination of various chemotherapeutics, either with the

CLAIMS

1. A composition comprising a CD19xCD3 bispecific antibody for use in a method for the treatment of tumorous mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient.

2. The composition of claim 1, wherein the tumorous mass is characterized by tumours having a size of more than 10 x 10 mm.

3. The composition of claim 1 or 2, wherein the lymph node tissue includes lymph nodes and/or spleen.

4. The composition of claim 1 or 2, wherein the extranodal lymphoma includes central nervous system (CNS), cutaneous tissue, breast, lungs, liver, gastrointestinal tract, genitourinary tract, ocular tissue, bone marrow and/or bones.

5. The composition of any one of the preceding claims, wherein a first dose of the composition is administered for a first period of time and consecutively a second dose of the composition is administered for a second period of time, wherein the second dose exceeds the first dose.

6. The composition of any one of the preceding claims, wherein said first period of time exceeds 3 days.

7. The composition of any one of the preceding claims, wherein said first period of time is between 3 days and 10 days.

8. The composition of any one of the preceding claims, wherein said second period of time exceeds 18 days.

9. The composition of any one of the preceding claims, wherein said second period of time is between 18 days and 81 days, 21 or 49 days being preferred.

10. The composition of any one of the preceding claims, wherein said first period of time is between 3 days and 10 days, and said second period of time is between 18 days and 81 days.

11. The composition of claim 10, wherein said first period of time is 7 days and said second period of time is 21 or 49 days.

12. The composition of any one of the preceding claims, wherein said first dose is between 1 and 15 $\mu g/m^2/d$, 5, 10 or 15 $\mu g/m^2/d$ being preferred.

13. The composition of any one of the preceding claims, wherein said second dose is between 15 and 60 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

14. The composition of claim 5, further comprising administering after a first and second dose for a first and second period of time a third dose of the composition for a third period of time.

15. The composition of claim 14, wherein the third period of time exceeds the first and second period of time, whereby the second dose exceeds said first dose.

16. The composition of claim 14 or 15, wherein the third dose exceeds the first and second dose

17. The composition of any one of claims 14 to 16, wherein said first period of time exceeds 3 days.

18. The composition of any one of claims 14 to 17, wherein said first period of time is between 3 days and 10 days, with 7 days being preferred.

19. The composition of claim 14, wherein said second period of time exceeds 3 days.

20. The composition of any one of claims 14 to 19, wherein said second period of time is between 3 days and 10 days, with 7 days being preferred.

21. The composition of claim 14, wherein said third period of time exceeds 8 days.

22. The composition of any one of claims 14 to 21, wherein said third period of time is between 8 days and 78 days, with 14 or 42 days being preferred

23. The composition of any one of claims 14 to 22, wherein said first period of time is between 3 days and 10 days, and said second period of time is between 3 days and 10 days, and said third period of time is between 8 days and 78 days

24. The composition of claim 23, wherein said first period of time is 7 days, said second period of time is 7 days and said third period of time is 14 or 42 days.

25. The composition of any one of claims 14 to 24, wherein said first dose is between 1 and 15 $\mu g/m^2/d$, 5 $\mu g/m^2/d$ being preferred.

26. The composition of any one of claims 14 to 25, wherein said second dose is between 1 and 15 $\mu g/m^2/d$, 15 $\mu g/m^2/d$ being preferred.

27. The composition of any one of claims 14 to 26, wherein said third dose is between 15 and 60 $\mu g/m^2/d$ or 15 and 90 or 120 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

28. The composition of any one of claims 1 to 4, wherein during treatment the antibody is dosed at a constant dose selected from the group consisting of 5 $\mu g/m^2/d$, 15 $\mu g/m^2/d$ or 60 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

29. The composition of any one of the preceding claims, wherein the method further comprises the administration of at least one chemotherapeutic agent, preferably a glucocorticoid.

30. The composition of claim 29, wherein the glucocorticoid is selected from the group consisting of at least one of cortisone, cortisol, cloprednol, prednisone, prednisolone, methylprednisolone, deflazacort, fluocortolone, triamcinolone, dexamethasone, and betamethasone, flusticasonepropionate, triamcinolonacetonide dexamethasone being preferred.

31. The composition of claim 29 or 30, wherein the glucocorticoid is administered prior to the administration of the CD19xCD3 bispecific antibody.

32. The composition of claim 31, wherein the glucocorticoid is administered between 6 and 48 hours prior to the administration of the CD19xCD3 bispecific antibody, preferably between 6 and 12 hours,

33. The composition of claim 31 or 32, wherein the glucocorticoid is administered at about 1 hour prior to the administration of the CD19xCD3 bispecific antibody.

34. The composition of claim 33, wherein the glucocorticoid is administered after the administration of the CD19xCD3 bispecific antibody.

35. The composition of claim 34, wherein the CD19xCD3 bispecific antibody is administered in three doses, wherein the second dose exceeds the first dose, and the third dose exceeds the second dose, and the glucocorticoid is administered after the administration of each dose of the CD19xCD3 bispecific antibody for at least 2 days.

36. The composition of claim 35, wherein the glucocorticoid is administered at a dose of between 6 to 40 mg prior to and after the administration of the CD19xCD3 bispecific antibody, and the antibody is administered at a first dose of 5 $\mu g/m^2/d$, at a second dose of 15 $\mu g/m^2/d$ and at a third dose of 60 $\mu g/m^2/d$.

37. A composition of any one of the preceding claims for use in a method of treating tumor mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient in need thereof, comprising administering a therapeutically effective amount of the composition to the patient in need thereof.

38. A pharmaceutical kit for treating tumor mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient comprising a composition of any one of the preceding claims and optionally means for instructions (instruction sheet).

39. Use of a composition of any one of the preceding claims for the preparation of a pharmaceutical composition for treating tumor mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL).

40. A pharmaceutical package or kit comprising the first dose and the second dose as defined in any one of the preceding claims.

41. The pharmaceutical package or kit of claim 40, further comprising a third dose as defined in any one of the preceding claims.

42. The pharmaceutical package or kit of claim 40 or 41, further comprising means to administer the first and/or the second and/or third dose to a patient.

[0011a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

SUMMARY OF THE INVENTION

[0011b] According to one aspect, the present invention provides use of a CD19xCD3 bispecific antibody for the preparation of a pharmaceutical composition for the treatment of tumorous mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient, wherein said pharmaceutical composition is to be administered in combination with at least one glucocorticoid.

[0011c] Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

[0012] The present invention addresses this need and thus provides as a solution to the technical problem embodiments pertaining to means and methods for use in the treatment of tumorous mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient in that a composition comprising a CD19xCD3 bispecific antibody is applied. An example of a CD19xCD3 bispecific (single chain) antibody is Blinatumomab (MT103).

[0013] Blinatumomab is a lymphoma-directed, recombinant bispecific single-chain CD19xCD3 antibody that binds to CD19 on the surface of almost all B cells and B tumor cells and concomitantly can engage a T cell, thereby triggering the T-cell to kill the target B cell or B tumor cell. It is thus a so-called BiTE® (**Bi**specific **T**-cell **E**ngager) antibody. Blinatumomab consists of four immunoglobulin variable domains assembled into a single polypeptide chain. Two of the variable domains form the binding site for CD19, a cell surface antigen expressed on most B cells and B tumor cells. The other two variable domains form the binding site for CD3 epsilon of the CD3 complex on T cells. Blinatumomab is designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells, and is presently in clinical trials.

[0014] Though WO 2007/068354 mentions that a CD19xCD3 bispecific antibody could be used amongst different B-cell non-Hodgkin lymphomas, for the treatment of DLBCL, this document does not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect which directly and unambiguously underlays the claimed therapeutic application of a CD19xCD3 bispecific

antibody. This is even more true when switching to the difficult to-treat and aggressive DLBCL.

[0015] However, to their surprise, the present inventors have found that a CD19xCD3 bispecific antibody is beneficial in the treatment of tumorous mass of lymphoreticular tissue (also referred to herein as lymph node tissue) and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient. Indeed, in clinical trials it was observed that a CD19xCD3 bispecific antibody led to outstanding results in the treatment of patients suffering from DLBCL in that in some patients a tremendous debulking of tumorous mass was observed, already after only a few weeks administration. Of note, the patients treated with a CD19xCD3 bispecific antibody were heavily pre-treated with a combination of various chemotherapeutics, either with the

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of a CD19xCD3 bispecific antibody for the preparation of a pharmaceutical composition for the treatment of tumorous mass of lymph node tissue and/or extranodal lymphoma caused by diffuse large B cell lymphoma (DLBCL) in a patient, wherein said pharmaceutical composition is to be administered in combination with at least one glucocorticoid.

2. The use of claim 1, wherein the tumorous mass is characterized by tumours having a size of more than 10 x 10 mm.

3. The use of claim 1 or claim 2, wherein the lymph node tissue includes lymph nodes and/or spleen.

4. The use of claim 1 or claim 2, wherein the extranodal lymphoma includes central nervous system (CNS), cutaneous tissue, breast, lungs, liver, gastrointestinal tract, genitourinary tract, ocular tissue, bone marrow and/or bones.

5. The use of any one of the preceding claims, wherein a first dose of the composition is to be administered for a first period of time and consecutively a second dose of the composition is to be administered for a second period of time, wherein the second dose exceeds the first dose.

6. The use of claim 5, wherein said first period of time exceeds 3 days.

7. The use of claim 5 or claim 6, wherein said first period of time is between 3 days and 10 days.

8. The use of any one of claims 5 to 7, wherein said second period of time exceeds 18 days.

9. The use of any one of claims 5 to 8, wherein said second period of time is between 18 days and 81 days, 21 or 49 days being preferred.

10. The use of any one of claims 5 to 9, wherein said first period of time is between 3 days and 10 days, and said second period of time is between 18 days and 81 days.

11. The use of claim 10, wherein said first period of time is 7 days and said second period of time is 21 or 49 days.

12. The use of any one of claims 5 to 11, wherein said first dose is between 1 and 15 $\mu g/m^2/d$, 5, 10 or 15 $\mu g/m^2/d$ being preferred.

13. The use of any one of claims 5 to 12, wherein said second dose is between 15 and 60 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

14. The use of claim 5, wherein, after a first and second dose for a first and second period of time, a third dose of the pharmaceutical composition is to be administered for a third period of time.

15. The use of claim 14, wherein the third period of time exceeds the first and second period of time, whereby the second dose exceeds said first dose.

16. The use of claim 14 or claim 15, wherein the third dose exceeds the first and second dose.

17. The use of any one of claims 14 to 16, wherein said first period of time exceeds 3 days.

18. The use of any one of claims 14 to 17, wherein said first period of time is between 3 days and 10 days, with 7 days being preferred.

19. The use of claim 14, wherein said second period of time exceeds 3 days.

20. The use of any one of claims 14 to 19, wherein said second period of time is between 3 days and 10 days, with 7 days being preferred.

21. The use of claim 14, wherein said third period of time exceeds 8 days.

22. The use of any one of claims 14 to 21, wherein said third period of time is between 8 days and 78 days, with 14 or 42 days being preferred.

23. The use of any one of claims 14 to 22, wherein said first period of time is between 3 days and 10 days, and said second period of time is between 3 days and 10 days, and said third period of time is between 8 days and 78 days.

24. The use of claim 23, wherein said first period of time is 7 days, said second period of time is 7 days and said third period of time is 14 or 42 days.

25. The use of any one of claims 14 to 24, wherein said first dose is between 1 and 15 $\mu g/m^2/d$, 5 $\mu g/m^2/d$ being preferred.

26. The use of any one of claims 14 to 25, wherein said second dose is between 1 and 15 $\mu g/m^2/d$, 15 $\mu g/m^2/d$ being preferred.

27. The use of any one of claims 14 to 26, wherein said third dose is between 15 and 60 $\mu g/m^2/d$ or 15 and 90 or 120 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

28. The use of any one of claims 1 to 4, wherein during treatment the antibody is dosed at a constant dose selected from the group consisting of 5 $\mu g/m^2/d$, 15 $\mu g/m^2/d$ or 60 $\mu g/m^2/d$, 60 $\mu g/m^2/d$ being preferred.

29. The use of any one of claims 1 to 28, wherein the glucocorticoid is selected from the group consisting of at least one of cortisone, cortisol, cloprednol, prednisone, prednisolone, methylprednisolone, deflazacort, fluocortolone, triamcinolone, dexamethasone, and betamethasone, flusticasonepropionate, triamcinolonacetonide dexamethasone being preferred.

30. The use of claim 29, wherein the glucocorticoid is to be administered prior to or during the administration of the CD19xCD3 bispecific antibody.

31. The use of claim 30, wherein the glucocorticoid is to be administered between 6 and 48 hours prior to the administration of the CD19xCD3 bispecific antibody, preferably between 6 and 12 hours.

32. The use of claim 30 or claim 31, wherein the glucocorticoid is to be administered at about 1 hour prior to the administration of the CD19xCD3 bispecific antibody.

33. The use of claim 32, wherein the glucocorticoid is to be administered after the administration of the CD19xCD3 bispecific antibody.

34. The use of claim 33, wherein the CD19xCD3 bispecific antibody is to be administered in three doses, wherein the second dose exceeds the first dose, and the third dose exceeds the second dose, and the glucocorticoid is administered after the administration of each dose of the CD19xCD3 bispecific antibody for at least 2 days.

35. The use of claim 34, wherein the glucocorticoid is to be administered at a dose of between 6 to 40 mg prior to and after the administration of the CD19xCD3 bispecific antibody, and the antibody is administered at a first dose of 5 $\mu g/m^2/d$, at a second dose of 15 $\mu g/m^2/d$ and at a third dose of 60 $\mu g/m^2/d$.