inventors for the first time report on the powerful induction of a GvL effect in the absence of GvHD induced by the CD19xCD3 bispecific single chain antibody engaging donor-derived T-cells in two pediatric patients with chemorefractory relapse of CD19+ALL after allogeneic HSCT.

In summary, treatment with CD19xCD3 bispecific single chain antibody provides for a novel and improved therapy for pediatric ALL, particularly for refractory and/or relapsed pediatric ALL.

In a preferred embodiment of the pharmaceutical methods and means of the invention, the pediatric or childhood acute lymphoblastic leukemia (ALL) is pediatric B-lineage ALL, preferably pediatric B-precursor acute lymphoblastic leukemia ALL, more preferably pediatric pro-B ALL, pre-B ALL, or common ALL (cALL). Even more preferred the pediatric B-precursor ALL is common ALL (cALL).

The vast majority of pediatric or childhood ALL cases (>85%) are of the B precursor cell phenotype (Schultz et al., Blood 109 (2007): 926-935). Since the CD19xCD3 bispecific single chain antibody described herein is directed against the B cell-associated marker CD19, said antibody is particularly suitable as a therapeutic agent for pediatric B-lineage acute lymphoblastic leukemia, more preferably for pediatric B-precursor ALL. Pediatric B-precursor ALL can be further subdivided into pediatric pro-B ALL, pre-B ALL and common ALL (cALL) (see e.g. Behm F.G., Immunophenotyping. In: Childhood Leukemias, C-H Pui ed. Cambridge: Cambridge University Press; 2006, p. 150-209). Pediatric acute lymphoblastic leukemia (ALL), including pediatric B-precursor acute lymphoblastic leukemia and other types of pediatric B (cell) lineage ALL, and treatments thereof are reviewed e.g. in Pui CH, Clin Adv Hematol Oncol. 4 (2006): 884-6; Pui CH, Evans WE, N Engl J Med 354 (2006): 166-178; Pui CH et al., Lancet 371 (2008): 1030-1043; Pui CH, Jeha S, Nat Rev Drug Discov 6 (2007): 149-165). Further information with respect to pediatric ALL can also be found e.g. under http://www.cancer.gov or http://www.leukemia-lymphoma.org.

The results may be briefly summarized as follows:

- Two pediatric patients have been treated on a compassionate use basis.
- Ongoing MRD negativity in said patients.
- No major adverse events (AEs) observed.
- All AEs transient, no treatment interruption necessary.

CLAIMS

1. A method for the treatment, amelioration or elimination of pediatric acute lymphoblastic leukemia (ALL), the method comprising the administration of a pharmaceutical composition comprising a CD19xCD3 bispecific single chain antibody construct to a pediatric ALL patient in the need thereof.

2. The method of claim 1, wherein said pediatric acute lymphoblastic leukemia (ALL) is pediatric B-lineage acute lymphoblastic leukemia (ALL), preferably pediatric B-precursor acute lymphoblastic leukemia ALL, more preferably pediatric pro-B ALL, pre-B ALL or common ALL (cALL).

3. The method of claim 1 or 2, wherein said acute lymphoblastic leukemia (ALL) is refractory and/or relapsed ALL.

4. The method of claim 3, wherein said acute lymphoblastic leukemia (ALL) is relapsed ALL, preferably ALL relapsed within three years of diagnosis.

5. The method of any of claims 1 to 4, wherein the method is for the treatment, amelioration or elimination of minimal residual disease (MRD) in a pediatric ALL patient.

6. The method of claim 5, wherein said pediatric ALL patient is MRD-positive in complete hematological remission.

7. The method of claim 5 or 6, wherein said method converts MRD positive ALL into an MRD negative status.

8. The method of any of claims 5 to 7, wherein MRD is measured with quantitative detection of at least one of the cytogenetic abnormalities or rearrangements selected from the group consisting of:

t(12;21)[TEL-AML1];

t(1;19;)[E2A-PBX];

t(4;11)[AF4-MLL];

t(9;22)[BCR-ABL];

hyperdiploidy or trisomies of chromosomes 4, 10, and 17;

hypodiploidy;

rearrangements of immunoglobulin genes; and

T-cell receptor (TCR) rearrangements.

9. The method of claim 8, wherein said pediatric ALL patient shows a signal for the cytogenetic abnormalities above detection limit and/or at least one marker by rearrangement with a sensitivity of $\geq 10^{-4}$.

10. The method of any of claims 1 to 9, wherein the corresponding variable heavy chain regions (VH) and the corresponding variable light chain regions (VL) regions in said CD19xCD3 bispecific single chain antibody construct are arranged, from N-terminus to C-terminus, in the order, VL(CD19)-VH(CD19)-VH(CD3)-VL(CD3).

11. The method of claim 10, wherein said CD19xCD3 bispecific single chain antibody construct comprises an amino acid sequence as set forth in SEQ ID NO. 1, or an amino acid sequence at least 90%, preferably 95% identical to SEQ ID NO. 1.

12. The method of any of claims 1 to 11, wherein the pharmaceutical composition comprising a CD19xCD3 bispecific single chain antibody construct is to be administered by continuous infusion for at least four weeks followed by a 2-week treatment-free interval.

13. The method of claim 12, wherein said administration is to be repeated at least two, three, four, five, six, seven, eight, nine of ten times, after determination of a MRD negative status.

14. The method of claim 12 or 13, wherein the method is prior to allogeneic stem cell transplantation (HSCT) to convert the MRD positive ALL into an MRD negative status.

15. The method of claim 12 or 13, wherein the method is after allogeneic hematopoietic stem cell transplantation (HSCT).

16. The method of claim 15, wherein a CD19xCD3 bispecific single chain antibody construct induces a graft-versus-leukemia (GvL) effect.

17. The method of any of claims 1 to 16, wherein the CD19xCD3 bispecific single chain antibody construct is to be administered in a daily dose of 10µg to 100µg per square meter patient body surface area.

18. The method of claim 17, wherein the CD19xCD3 bispecific single chain antibody construct is to be administered in a daily dose of 15µg to 30µg per square meter patient body surface area.

19. The method of any of claims 1 to 18, wherein said method is for a pediatric ALL patient with high risk of relapse according to the COGAALL03B1 classification of acute lymphoblastic leukemia.

20. The method of claim 1 or 2, wherein said patient is non-eligible for allogeneic stem cell transplantation.

21. A CD19xCD3 bispecific single chain antibody construct for the treatment, ~~amelioration or elimination of pediatric acute lymphoblastic leukemia (ALL).~~

inventors for the first time report on the powerful induction of a GvL effect in the absence of GvHD induced by the CD19xCD3 bispecific single chain antibody engaging donor-derived T-cells in two pediatric patients with chemorefractory relapse of CD19+ALL after allogeneic HSCT.

In summary, treatment with CD19xCD3 bispecific single chain antibody provides for a novel and improved therapy for pediatric ALL, particularly for refractory and/or relapsed pediatric ALL. At least, the present invention provides the public with a useful alternative to known compositions and methods.

In a preferred embodiment of the pharmaceutical methods and means of the invention, the pediatric or childhood acute lymphoblastic leukemia (ALL) is pediatric B-lineage ALL, preferably pediatric B-precursor acute lymphoblastic leukemia ALL, more preferably pediatric pro-B ALL, pre-B ALL, or common ALL (cALL). Even more preferred the pediatric B-precursor ALL is common ALL (cALL).

The vast majority of pediatric or childhood ALL cases (>85%) are of the B precursor cell phenotype (Schultz et al., Blood 109 (2007): 926-935). Since the CD19xCD3 bispecific single chain antibody described herein is directed against the B cell-associated marker CD19, said antibody is particularly suitable as a therapeutic agent for pediatric B-lineage acute lymphoblastic leukemia, more preferably for pediatric B-precursor ALL. Pediatric B-precursor ALL can be further subdivided into pediatric pro-B ALL, pre-B ALL and common ALL (cALL) (see e.g. Behm F.G., Immunophenotyping. In: Childhood Leukemias, C-H Pui ed. Cambridge: Cambridge University Press; 2006, p. 150-209). Pediatric acute lymphoblastic leukemia (ALL), including pediatric B-precursor acute lymphoblastic leukemia and other types of pediatric B (cell) lineage ALL, and treatments thereof are reviewed e.g. in Pui CH, Clin Adv Hematol Oncol. 4 (2006): 884-6; Pui CH, Evans WE, N Engl J Med 354 (2006): 166-178; Pui CH et al., Lancet 371 (2008): 1030-1043; Pui CH, Jeha S, Nat Rev Drug Discov 6 (2007): 149-165). Further information with respect to pediatric ALL can also be found e.g. under http://www.cancer.gov or http://www.leukemia-lymphoma.org.

The results may be briefly summarized as follows:

- Two paediatric patients have been treated on a compassionate use basis.
- Ongoing MRD negativity in said patients.
- No Major adverse events (AEs) observed.
- All AEs transient, not treatment interruption necessary.

The invention is defined in the independent claim. Some optional features of the invention are defined in the dependent claims.

This description may contain subject matter that falls outside the scope of the claims.

This subject matter is included to aid understanding of the invention.

CLAIMS

1. Use of a CD19xCD3 bispecific single chain antibody construct for the manufacture of a medicament for the treatment, amelioration or elimination of pediatric acute lymphoblastic leukemia (ALL) in a patient.

2. The use of claim 1, wherein said pediatric acute lymphoblastic leukemia (ALL) is pediatric B-lineage acute lymphoblastic leukemia (ALL).

3. The use of claim 2, wherein said pediatric B-lineage acute lymphoblastic leukemia (ALL) is pediatric B-precursor acute lymphoblastic leukemia ALL.

4. The use of claim 3, wherein said pediatric B-precursor acute lymphoblastic leukemia (ALL) is pediatric pro-B ALL, pre-B ALL or common ALL (cALL).

5. The use of any one of claims 1 to 4, wherein said acute lymphoblastic leukemia (ALL) is refractory and/or relapsed ALL.

6. The use of claim 5, wherein said acute lymphoblastic leukemia (ALL) is relapsed ALL, and relapsed within three years of diagnosis.

7. The use of any one of claims 1 to 6, wherein the medicament is for the treatment, amelioration or elimination of minimal residual disease (MRD) in a pediatric ALL patient.

8. The use of claim 7, wherein said pediatric ALL patient is MRD-positive in complete hematological remission.

9. The use of claim 7 or 8, wherein said use converts MRD positive ALL into an MRD negative status.

10. The use of any one of claims 7 to 9, wherein MRD is measured with quantitative detection of at least one of the cytogenetic abnormalities or rearrangements selected from the group consisting of:

t(12;21)[TEL-AML1];

t(1;19;)[E2A-PBX];

t(4;11)[AF4-MLL];

t(9;22)[BCR-ABL];

hyperdiploidy or trisomies of chromosomes 4, 10, and 17;

hypodiploidy;

rearrangements of immunoglobulin genes; and

T-cell receptor (TCR) rearrangements.

11. The use of claim 10, wherein said pediatric ALL patient shows a signal for the cytogenetic abnormalities above detection limit and/or at least one marker by rearrangement with a sensitivity of $\geq 10^{-4}$.

12. The use of any one of claims 1 to 11, wherein the corresponding variable heavy chain regions (VH) and the corresponding variable light chain regions (VL) regions in said CD19xCD3 bispecific single chain antibody construct are arranged, from N-terminus to C-terminus, in the order, VL(CD19)-VH(CD19)-VH(CD3)-VL(CD3).

13. The use of claim 12, wherein said CD19xCD3 bispecific single chain antibody construct comprises an amino acid sequence as set forth in SEQ ID NO. 1.

14. The use of claim 13, wherein said CD19xCD3 bispecific single chain antibody construct comprises an amino acid sequence at least 90% identical to SEQ ID NO. 1.

15. The use of claim 13, wherein said CD19xCD3 bispecific single chain antibody construct comprises an amino acid sequence at least 95% identical to SEQ ID NO. 1.

16. The use of any one of claims 1 to 15, wherein the medicament comprising the CD19xCD3 bispecific single chain antibody construct is formulated for administration by continuous infusion for at least four weeks.

17. The use of claim 16, wherein the at least four weeks of continuous infusion is followed by at least a 2-week treatment-free interval.

18. The use of claim 16, wherein said administration is to be repeated at least two, three, four, five, six, seven, eight, nine or ten times, after determination of a MRD negative status.

19. The use of any one of claims 16 to 18, wherein the administration is prior to allogeneic stem cell transplantation (HSCT) to convert the MRD positive ALL into an MRD negative status.

20. The use of any one of claims 16 to 18, wherein the administration is after allogeneic hematopoietic stem cell transplantation (HSCT).

21. The use of claim 20, wherein a CD19xCD3 bispecific single chain antibody construct induces a graft-versus-leukemia (GvL) effect.

22. The use of any one of claims 1 to 21, wherein the medicament is formulated for administration of the CD19xCD3 bispecific single chain antibody construct in a daily dose of 5 µg to 100 µg per square meter patient body surface area.

23. The use of claim 22, wherein the medicament is formulated for administration of the CD19xCD3 bispecific single chain antibody construct in a daily dose of 15 µg to 30 µg per square meter patient body surface area.

24. The use of any one of claims 1 to 23, wherein said patient is a pediatric ALL patient with high risk of relapse according to the COGAALL03B1 classification of acute lymphoblastic leukemia.

25. The use of any one of claims 1 to 24, wherein said patient is non-eligible for allogeneic stem cell transplantation.