unsuitable because the possibly increased off-target activation induced by the bivalent C-terminal CD3 binding moiety.

[10] Based on the above, there is a need in the art for improved ABPs targeting FLT3 that address at least one of the problems outlined above.

SUMMARY

[10a] In one aspect, the present disclosure provides an antibody, or antigen binding fragment thereof, ~~Antigen Binding Protein (ABP)~~ capable of binding to human fms related tyrosine kinase 3 (FLT3), comprising:

(i) one, preferably two, heavy chain variable domain(s) comprising the CDRH1 region set forth in SEQ ID NO: 01 (SYWMH), the CDRH2 region set forth in SEQ ID NO: 02 (EIDPSDSYKDYNQKFKD), and the CDRH3 region set forth in SEQ ID NO: 03 (AITTTPFDF), or wherein in each case independently the CDRH1, CDRH2 and/or CDRH3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 01, SEQ ID NO: 02, or SEQ ID NO: 03, respectively; ~~and~~

(ii) one, preferably two, light chain variable domain(s) comprising the CDRL1 region set forth in SEQ ID NO: 05 (RASQSISNNLH), the CDRL2 region set forth in SEQ ID NO: 06 (YASQSIS), and the CDRL3 region set forth in SEQ ID NO: 07 (QQSNTWPYT) or wherein in each case independently CDRL1, CDRL2 and/or CDRL3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 05, SEQ ID NO: 06, or SEQ ID NO: 07, respectively; and

(iii) an additional antigen binding domain that binds to human CD3;

characterized in that, said one, preferably two, heavy chain variable domain(s) and said one, preferably two, light chain variable domain(s), each comprise an antibody framework region having at least 95% amino acid sequence identity to ~~a portion of~~ a human antibody consensus framework sequence.

~~**[10b]** In another aspect, the present disclosure provides an antigen binding protein (ABP) or an antigen binding fragment thereof, capable of binding to human FLT3 and that is able to compete with the binding of an ABP as described herein to FLT3.~~

~~**[10c]** In yet another aspect, the present disclosure provides a bispecific antigen binding protein (ABP) which comprises a first antigen binding domain capable of binding to the human fms like tyrosine kinase 3 (FLT3) antigen, and a second antigen binding domain capable of binding to the human cluster of differentiation 3 (CD3) antigen, wherein the bispecific ABP:~~

~~a. binds to FLT3 with an EC_{50} of lower than 10 nM as determined by analyzing the binding of the bispecific ABP to FLT3 positive cells by flow cytometry using a fluorescent activated cell sorting (FACS) device; and~~

~~b. binds to CD3 with an EC_{50} of lower than 200 nM as determined by analyzing the binding of the bispecific ABP to CD3 positive cells by flow cytometry using a fluorescent activated cell sorting (FACS) device.~~

[~~10d~~10b] In yet another aspect, the present disclosure provides an isolated nucleic acid comprising a sequence encoding for an antibody, or antigen binding fragment thereof~~ABP~~, or for an antigen binding fragment or a monomer, such as a heavy or light chain, of an antibody, or antigen binding fragment thereof~~ABP~~, as described herein~~, or encoding for a bispecific ABP as described herein~~.

[~~10e~~10b]In yet another aspect, the present disclosure provides a nucleic acid construct (NAC) comprising a nucleic acid as described herein and one or more additional sequence features permitting the expression of the encoded antibody, or antigen binding fragment thereof~~ABP or bispecific ABP~~, or a component of antibody, or antigen binding fragment thereof ~~said ABP or bispecific ABP~~ (such as an antibody heavy chain or light chain) in a cell.

[~~10f~~10d] In yet another aspect, the present disclosure provides a recombinant host cell comprising a nucleic acid as described herein or a NAC as described herein.

[~~10g~~10e]In yet another aspect, the present disclosure provides a pharmaceutical composition comprising: (i) an antibody, or antigen binding fragment thereof~~ABP or bispecific ABP~~ as described herein, or (ii) a nucleic acid as described herein or a NAC as described herein, or (iii) a recombinant host cell as described herein, and a pharmaceutically acceptable carrier, stabiliser and/or excipient.

[~~10h~~10f] In yet another aspect, the present disclosure provides a component for use in medicine, wherein the component is selected from the list consisting of: an antibody, or antigen binding fragment thereof~~ABP or bispecific ABP~~ as described herein, an isolated nucleic acid as described herein or a NAC as described herein, a recombinant host cell as described herein and a pharmaceutical composition as described herein.

[~~10i~~10g] In yet another aspect, the present disclosure provides an *in vitro* method of enhancing a cell-mediated immune response to a human cell that expresses human FLT3, comprising contacting said cell with an antibody, or antigen binding fragment thereof ~~ABP~~ as described herein, ~~or a bispecific ABP as described herein,~~ or a nucleic acid encoding said antibody, or antigen binding fragment thereof~~ABP or bispecific ABP~~ as described herein, in the presence of an immune cell, such as a T-cell or natural killer (NK) cell, thereby enhancing a cell-mediated immune response against said human cell.**[10j]** In yet another aspect, the present disclosure provides use of a component recited herein in the manufacture of a medicament for preventing and/or treating a proliferative disorder in a subject, wherein the proliferative disorder is characterized by an expression of FLT3 in cells associated with the proliferative disorder.

BRIEF DESCRIPTION OF THE INVENTION

[11] Generally, and by way of brief description, the main aspects of the present invention can be described as follows:

[12] In **a first aspect**, the invention pertains to an An Antigen Binding Protein (ABP) capable of binding to human fms related tyrosine kinase 3 (FLT3), comprising:

(i) one, preferably two, heavy chain variable domain(s) comprising the CDRH1 region set forth in SEQ ID NO: 01 (SYWMH), the CDRH2 region set forth in SEQ ID NO: 02 (EIDPSDSYKDYNQKFKD), and the CDRH3 region set forth in SEQ ID NO: 03 (AITTTPFDF), or wherein in each case independently the CDRH1, CDRH2 and/or CDRH3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 01, SEQ ID NO: 02, or SEQ ID NO: 03, respectively; and

(ii) one, preferably two, light chain variable domain(s) comprising the CDRL1 region set forth in SEQ ID NO: 05 (RASQSISNNLH), the CDRL2 region set forth in SEQ ID NO: 06 (YASQSIS), and the CDRL3 region set forth in SEQ ID NO: 07 (QQSNTWPYT) or wherein in each case independently CDRL1, CDRL2 and/or CDRL3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 05, SEQ ID NO: 06, or SEQ ID NO: 07, respectively;

characterized in that, said one, preferably two, heavy chain variable domain(s) and said one, preferably two, light chain variable domain(s), each comprise an antibody framework region having at least a portion of a human antibody consensus framework sequence.

[13] In **a second aspect**, the invention pertains to an antigen binding protein (ABP) or an antigen-binding fragment thereof, capable of binding to fms related tyrosine kinase 3 (FLT3) and that is able to compete with the binding of an ABP of the first aspect to FLT3.

[14] In **a third aspect**, the invention pertains to a bispecific antigen binding protein (ABP) which comprises a first antigen binding domain capable of binding to the human fms like

CLAIMS

1. **An ~~Antigen Binding Protein (ABP)~~antibody, or antigen binding fragment thereof, capable of binding to human fms related tyrosine kinase 3 (FLT3)**, comprising:

(i) one, preferably two, heavy chain variable domain(s) comprising the CDRH1 region set forth in SEQ ID NO: 01 (SYWMH), the CDRH2 region set forth in SEQ ID NO: 02 (EIDPSDSYKDYNQKFKD), and the CDRH3 region set forth in SEQ ID NO: 03 (AITTTPFDF), or wherein in each case independently the CDRH1, CDRH2 and/or CDRH3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 01, SEQ ID NO: 02, or SEQ ID NO: 03, respectively; ~~and~~

(ii) one, preferably two, light chain variable domain(s) comprising the CDRL1 region set forth in SEQ ID NO: 05 (RASQSISNNLH), the CDRL2 region set forth in SEQ ID NO: 06 (YASQSIS), and the CDRL3 region set forth in SEQ ID NO: 07 (QQSNTWPYT) or wherein in each case independently CDRL1, CDRL2 and/or CDRL3 comprise a sequence having no more than three or two, preferably no more than one amino acid substitution(s), deletion(s) or insertion(s) compared to SEQ ID NO: 05, SEQ ID NO: 06, or SEQ ID NO: 07, respectively; and

(iii) an additional antigen binding domain that binds to human CD3;

characterized in that, said one, preferably two, heavy chain variable domain(s) and said one, preferably two, light chain variable domain(s), each comprise an antibody framework region having at least 95% amino acid sequence identity to ~~a portion of~~ a human antibody consensus framework sequence.

2. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 1, wherein the heavy chain variable domain human antibody consensus framework sequences are derived from IGHV1-46, preferably IGHV1-46*3, and/or wherein the heavy chain variable domain human antibody consensus framework sequences are derived from IGKV3D-15.

3. The ~~ABP~~ antibody, or antigen binding fragment thereof according to claim 1 or 2, wherein the heavy chain variable region comprises the amino acid sequence having a sequence identity of at least 95% to an amino acid sequence selected from SEQ ID

Nos: 15, 17, 19, 21, 23 or 76, or, in each case independently, optionally with no more than ~~ten, nine, eight, seven, six,~~ five, four, preferably no more than three, two or one, amino acid substitution(s), insertion(s) or deletion(s) compared to these sequences; and/or wherein the light chain variable region comprises the amino acid sequence having a sequence identity of at least 95 % to the amino acid sequence selected from SEQ ID Nos: 16, 18, 20, 22, 24 or 77, or, in each case independently, optionally with no more than ~~ten, nine, eight, seven, six,~~ five, four, preferably no more than three, two or one, amino acid substitution(s), insertion(s) or deletion(s) compared to these sequences.

4. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 3, wherein in the heavy chain variable region the amino acid positions 16, 18, 19, 20, 22, 48, 57, 60, 69, 70, 75, 76, 78, 80, 81, 87, and 108 are as in any one of SEQ ID Nos: 15, 17, 19, 21 or 23; and/or wherein in the light chain variable region the amino acid positions 49, 55, and 87 are as in any one of SEQ ID Nos: 16, 18, 20, 22 or 24; wherein the numbering is according to the Kabat system.

5. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 4, wherein the heavy chain variable region comprises an amino acid sequence having a sequence identity of at least 85%, at least 90%, or at least 95% to the amino acid sequence set forth in SEQ ID NO: 21, and the light chain variable region comprises an amino acid sequence having a sequence identity of at least 95 % to the amino acid sequence set forth in SEQ ID NO: 22.

6. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 4, wherein the heavy chain variable region comprises an amino acid sequence having a sequence identity of at least 85%, at least 90%, or at least 95% to the amino acid sequence set forth in SEQ ID NO: 76, and the light chain variable region comprises an amino acid sequence having a sequence identity of at least 95 % to the amino acid sequence set forth in SEQ ID NO: 77.

7. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 6, wherein the heavy chain variable region comprises 48I, and wherein the light chain variable region comprises 87F, wherein the numbering is according to the Kabat system.

8. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 7, wherein the light chain variable region further comprises 49K, wherein the numbering is according to the Kabat system.

9. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 8, wherein the antibody, or antigen binding fragment thereof ~~ABP~~ is an antibody, or an antigen binding fragment thereof, composed of at least one, preferably two, antibody heavy chain sequence(s), and at least one, preferably two, antibody light chain sequence(s), wherein said antibody heavy chain sequence(s) and the antibody light chain sequence(s) comprise(s) each a variable region sequences in one of the following combinations V0 to V5:

	Heavy Chain Variable Region (SEQ ID NO)	**Light Chain Variable Region (SEQ ID NO)**
V0	76	77
V1	15	16
V2	17	18
V3	19	20
V4	21	22
V5	23	24

10. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 9 which binds to said FLT3 with a k_D that is less than 50 µM and more than 50 nM; preferably which binds to said FLT3 with a k_D that is less than 1 µM and more than 300 nM.

11. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 10 which binds to a human cell expressing FLT3 with an EC_{50} that is lower than 10 nM and that is higher than 0.5 nM.

12. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 11 which binds to a human cell expressing FLT3 with an EC_{50} that is lower than 5.5 nM and that is higher than 4.5 nM.

13. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 12, which comprises an effector group and/or which is labelled.

14. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 13, which is isolated and/or substantially pure.

15. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 14 which is an antibody, such as a monoclonal antibody; or which is a fragment of an antibody, such as a fragment of a monoclonal antibody.

16. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 15, wherein said antibody is a chimeric antibody, such as a human-chimeric antibody.

17. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 15 or 16, wherein said antibody is an IgG, IgE, IgD, IgA, or IgM immunoglobulin; preferably an IgG immunoglobulin.

18. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 15 to 17, which is an antibody fragment selected from the list consisting of: Fab, Fab'-SH, Fv, scFv and F(ab')2.

19. The antibody, or antigen binding fragment thereof ~~ABP~~ according to any one of claims 1 to 18, wherein said antibody, or antigen binding fragment thereof ~~ABP~~ is modified or engineered to increase antibody-dependent cellular cytotoxicity (ADCC), preferably wherein said antibody, or antigen binding fragment thereof ~~ABP~~ is afucosylated.

~~**20.** The ABP according to any one of claims 1 to 19, which comprises one or more additional antigen binding domain(s) that bind(s) to antigen(s) other than said FLT3; such as antigen(s) present on a mammalian T-cell, and most preferably human CD3.~~

~~**21.**~~**20.** The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim ~~20~~1, which is a bispecific antibody, or antigen binding fragment thereof, and preferably which comprises two binding sites binding to FLT3 and two binding sites binding to ~~an antigen other than said FLT3, such as antigen(s) present on a mammalian T-cell, and most preferably to~~ human CD3.

~~**22.**~~**21.** The antibody, or antigen binding fragment thereof, ~~ABP~~ according to claim 21, wherein the two binding sites binding to ~~an antigen other than said FLT3 bind to~~ human CD3~~, and preferably~~ comprise an UCHT1 anti-CD3 scFv construct~~, such as the scFv shown in SEQ ID NO: 14~~.

22. The antibody, or antigen binding fragment thereof, according to claim 22, wherein the scFv construct comprises the amino acid sequence of SEQ ID NO: 14.

23. The antibody, or antigen binding fragment thereof ~~ABP~~ according to claim 22, comprising two antibody heavy chain sequences and two antibody light chain sequences, wherein said antibody heavy chain sequences and the antibody light chain sequences each comprise amino acid sequences in any one of the following combinations V0 to V5:

	Heavy Chain Full length Sequence (SEQ ID NO)	Light Chain Full length Sequence (SEQ ID NO)
V0	78	79
V1	28	29
V2	30	31
V3	32	33
V4	34	35
V5	36	37

24.An antigen binding protein (ABP) or an antigen-binding fragment thereof, capable of binding to human FLT3 and that is able to compete with the binding of an ABP according to any one of claims 1 to 23 to FLT3.

25.A bispecific antigen binding protein (ABP) which comprises a first antigen binding domain capable of binding to the human fms like tyrosine kinase 3 (FLT3) antigen, and a second antigen binding domain capable of binding to the human cluster of differentiation 3 (CD3) antigen, wherein the bispecific ABP:

a. binds to FLT3 with an EC_{50} of lower than 10 nM as determined by analyzing the binding of the bispecific ABP to FLT3 positive cells by flow cytometry using a fluorescent activated cell sorting (FACS) device; and

b. binds to CD3 with an EC_{50} of lower than 200 nM as determined by analyzing the binding of the bispecific ABP to CD3 positive cells by flow cytometry using a fluorescent activated cell sorting (FACS) device.

26. The bispecific ABP according to claim 25, wherein the bispecific ABP binds to FLT3 with an EC_{50} of higher than 0.5 nM.

27. The bispecific ABP according to claim 25 or 26, wherein the bispecific ABP binds FLT3 with an k_D of less than 50 µM as measured by surface plasmon resonance.

28. The bispecific ABP according to any one of claims 25 to 27, wherein the bispecific ABP binds to CD3 with an EC_{50} of higher than 1 nM.

29. The bispecific ABP according to any one of claims 25 to 28, which inhibits proliferation and/or viability of leukemic blood mononuclear cells of a patient suffering from acute leukemia in an *in vitro* assay compared to an unrelated control to equal or less than 50%.

~~30. The bispecific ABP according to any one of claims 25 to 29, which comprises not more and not less than two first antigen binding domains and two second antigen binding domains.~~

~~31. The bispecific ABP according to any one of claims 25 to 30, wherein at least one amino acid residue of the CH2 domain that is able to mediate binding to Fc receptors in said antibody is lacking or mutated.~~

~~32. The bispecific ABP according to any one of claims 25 to 31, wherein the first antigen binding domain comprises the ABP, or antigen binding domain thereof, according to any one of claims 1 to 24.~~

~~33. The bispecific ABP of any one of claims 25 to 32, having an activity to bind to a T-cell and to an FLT3 expressing tumor cell, preferably wherein the antibody increases the recruitment of T-cells to a FLT3 expressing tumor cell by binding to FLT3 and CD3.~~

~~34. The bispecific ABP according to any one of claims 25 to 33, wherein the second antigen binding domain comprises the heavy chain variable region and a light chain variable region of UCHT1.~~

~~35.~~24. **An isolated nucleic acid** comprising a sequence encoding for an antibody, or antigen binding fragment thereof~~ABP~~, or for an antigen binding fragment or a monomer, such as a heavy or light chain, of an antibody, or antigen binding fragment thereof~~ABP~~, of any one of claims 1 to 2324, ~~or encoding for a bispecific ABP according to any one of claims 25 to 34~~.

~~36.~~25. **A nucleic acid construct (NAC)** comprising a nucleic acid of claim ~~35~~ 24 and one or more additional sequence features permitting the expression of the encoded antibody, or antigen binding fragment thereof ~~ABP or bispecific ABP~~, or a component of said antibody, or antigen binding fragment thereof, ~~ABP or bispecific ABP~~ (such as an antibody heavy chain or light chain) in a cell.

~~37.~~26. **A recombinant host cell** comprising a nucleic acid of claim ~~35~~ 24 or a NAC according to claim ~~36~~25.

~~38.~~27. **A pharmaceutical composition** comprising: (i) an antibody, or antigen binding fragment thereof ~~ABP or bispecific ABP~~ of any one of claims 1 to ~~34~~23, or (ii) a nucleic acid of claim ~~35~~ 24 or a NAC according to claim ~~36~~25, or (iii) a recombinant host cell according to claim ~~37~~26, and a pharmaceutically acceptable carrier, stabiliser and/or excipient.

~~39.~~28. **A component for use in medicine**, wherein the component is selected from the list consisting of: an antibody, or antigen binding fragment thereof ~~ABP or bispecific ABP~~ of any one of claims 1 to ~~34~~23, an isolated nucleic acid of claim ~~35~~ 24 or a NAC according to claim ~~36~~25, a recombinant host cell according to claim ~~37~~ 26 and a pharmaceutical composition according to claim ~~38~~27.

~~40.~~29. The component for use of claim ~~39~~28, wherein the component is for use in enhancing T cell-mediated killing of and/or inhibiting the proliferation of FLT3 positive tumor cells.

~~41.~~30. The component for use according to claim ~~33 to 34~~28 or 29, wherein the component is for use in the diagnosis, prevention and/or treatment of a proliferative disease, wherein the proliferative disorder is associated with the expression FLt3, and is preferably cancer, such as a cancer selected from leukemia, such as acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), or a solid cancer selected from prostate cancer, colorectal cancer, cancer of the stomach, lung carcinoma, osteosarcoma, mammary cancer, pancreatic cancer, or squamous cell carcinoma; preferably the cancer is leukemia, such as AML or ALL.

~~42.~~31. **An *in vitro* method of enhancing a cell-mediated immune response to a human cell that expresses human FLT3**, comprising contacting said cell with an antibody, or antigen binding fragment thereof ~~ABP~~ of any one of claims 1 to ~~24~~23, ~~or a bispecific ABP according to any one of claims 25 to 34,~~ or a nucleic acid encoding said antibody, or antigen binding fragment thereof ~~ABP or bispecific ABP~~ according to claim ~~35~~24, in the presence of an immune cell, such as a T-cell or natural killer (NK) cell, thereby enhancing a cell-mediated immune response against said human cell.

~~43.~~32. **Use of a component recited in any of claim ~~39~~ 28 to 30 in the manufacture of a medicament for preventing and/or treating a proliferative disorder in a subject,** wherein the proliferative disorder is characterized by an expression of FLT3 in cells associated with the proliferative disorder.