

or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 or 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

the subscript p is an integer from 1 to 4.

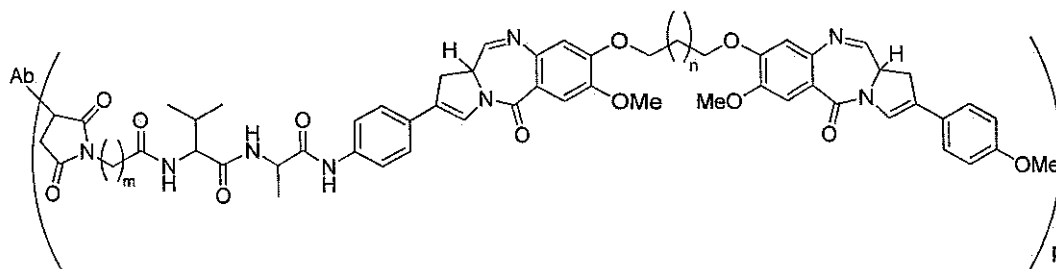
[0003] Antibodies for use in the present disclosure can be intact antibodies or antigen binding fragments thereof. The humanized 7G3 antibody can have a mature heavy chain variable region that is fused to a heavy chain constant region and a mature light chain variable region that is fused to a light chain constant region. The heavy chain constant region can be a naturally occurring or mutant form of a human constant region (e.g., SEQ ID NO:5, a heavy chain IgG1 constant region with cysteine substituting for serine at

position 239, (S239C) or SEQ ID NO:6) . The heavy chain constant region can be of IgG1 isotype. An exemplary light chain constant region amino acid sequence is set forth in SEQ ID NO:7

[0004] The chimeric or humanized 7G3 antibodies described herein are conjugated to drug-linkers, including PBD drug-linkers to provide CD123 antibody-drug conjugates. Attachment can be via conventional or site specific conjugation methods. An exemplary attachment is via an engineered cysteine at position 239 of the heavy chain constant region, according to the EU index as set forth in Kabat. The CD123 directed antibody-drug conjugates are used to treat CD123 expressing disease, including CD123 expressing cancers, such as AML.

[0004a] In another aspect, there is provided use of a pharmaceutical composition described herein for the manufacture of a medicament for treating a cancer that expresses CD123.

[0004b] In another aspect, there is provided use of a pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 to 3;

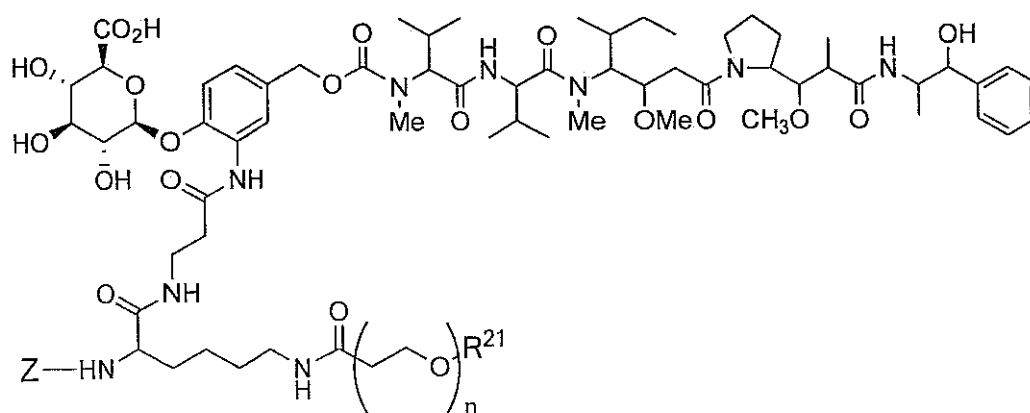
the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2, for the manufacture of a medicament for treating a cancer that expresses CD123.

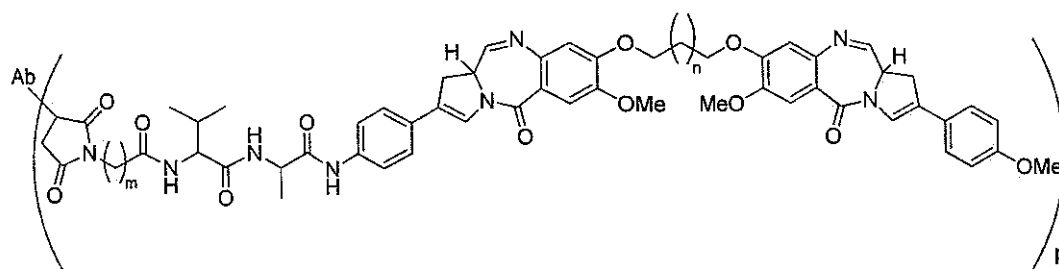
[0005] In other embodiments, the chimeric or humanized 7G3 antibodies described herein are conjugated to drug-linkers, including glucuronide-pegylated MMAE drug-linkers to provide CD123 antibody-drug conjugates.

[0006] In a further embodiment, the drug-linker attached to the humanized 7G3 antibody has the formula:



[0008] In another embodiment, any of the disclosed pegylated-MMAE antibody-drug conjugates has a p value of 8. In another embodiment, the drug-linker is attached to the antibody via the cysteine residues of the interchain disulfide bonds of the antibody.

[0008a] In another aspect, there is provided an antibody-drug conjugate composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

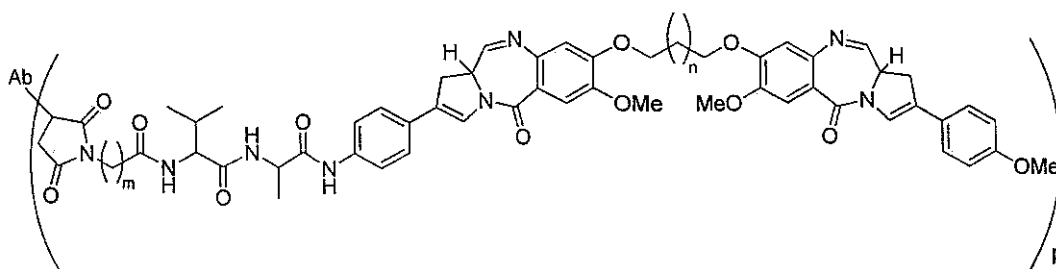
the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

[0008b] In another aspect, there is provided a pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

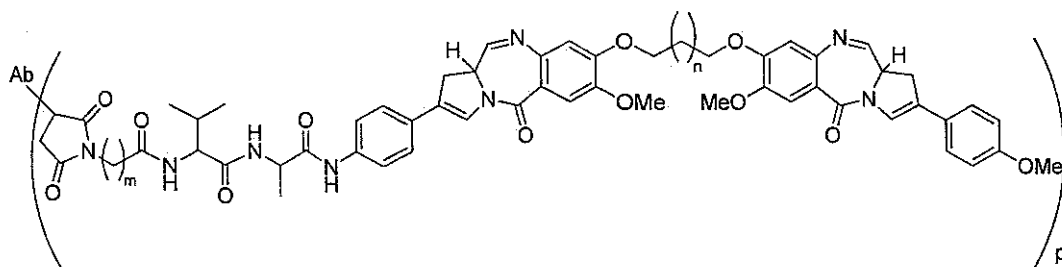
the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

[0008c] In another aspect, there is provided a pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

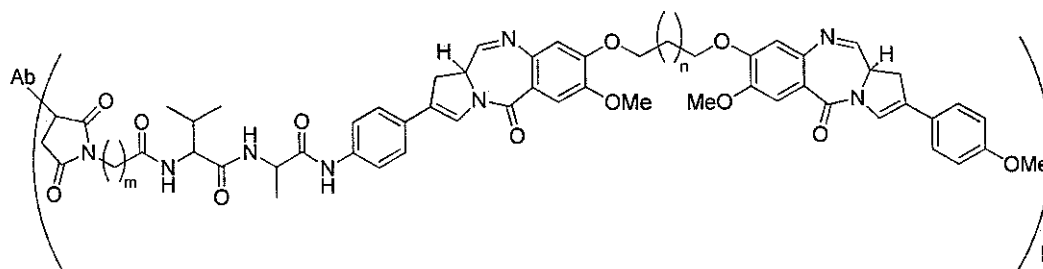
the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:3; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:4 and attachment to Ab is via a sulfur atom or an engineered cysteine residue at

WHAT IS CLAIMED IS:

1. An anti-CD123 antibody-drug conjugate compound having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof;
wherein

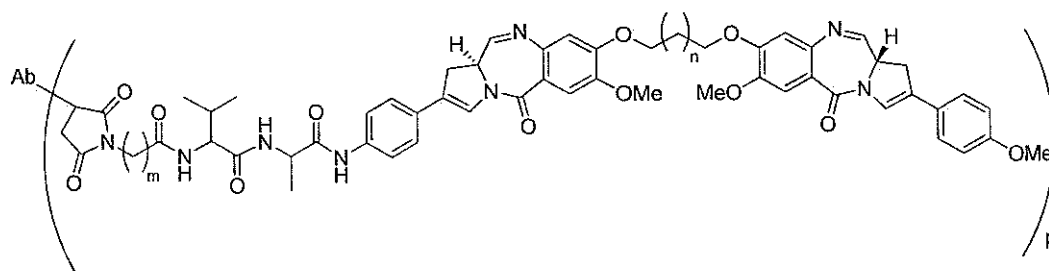
the subscript n is 1 or 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

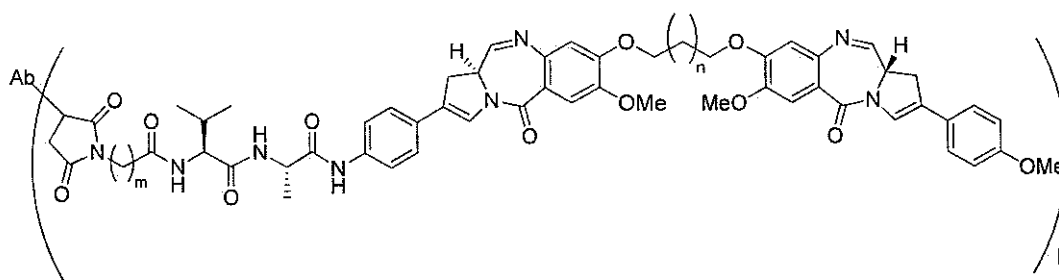
the subscript p is an integer from 1 to 4.

2. The compound of claim 1 having the formula:



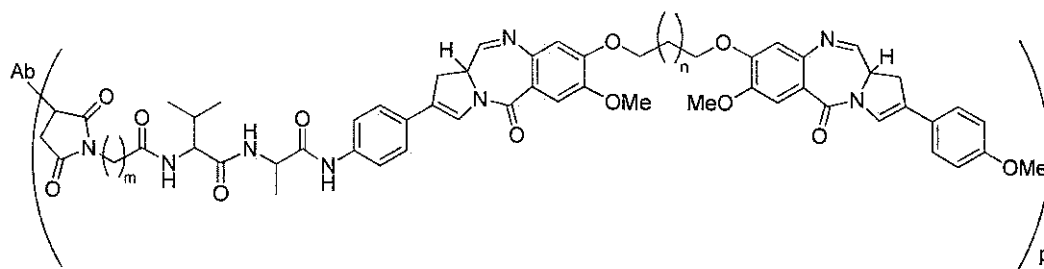
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

3. The compound of claim 1 having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

4. The compound of any one of claims 1 to 3 wherein n is 1.
5. The compound of any one of claims 1 to 3 wherein n is 3.
6. The compound of any one of claims 1 to 5 wherein m is 5.
7. The compound of any one of claims 1 to 6 wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab.
8. The compound of any one of the preceding claims wherein Ab comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1 fused to a human heavy chain constant region; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2 fused to a human light chain constant region.
9. The compound of claim 8 wherein Ab comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO:3 and a light chain having the amino acid sequence set forth in SEQ ID NO:4 and attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering.
10. The compound of any one of the preceding claims wherein p is 2.
11. A pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof;
wherein

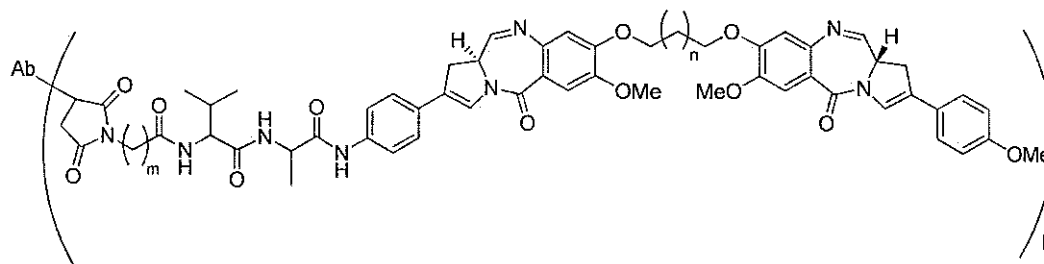
the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

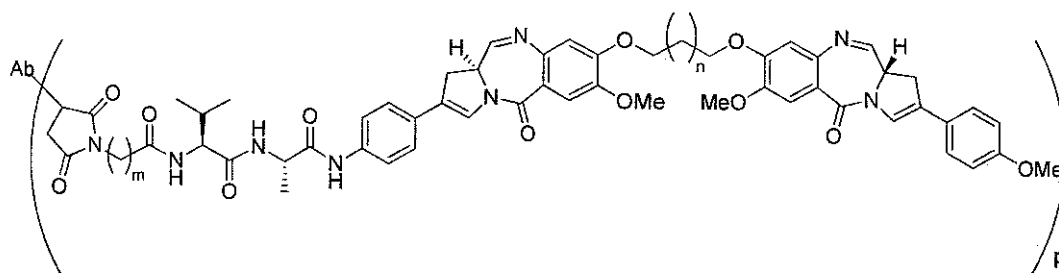
the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

12. The pharmaceutical composition of claim 11 wherein the antibody-drug conjugate molecules have the formula:



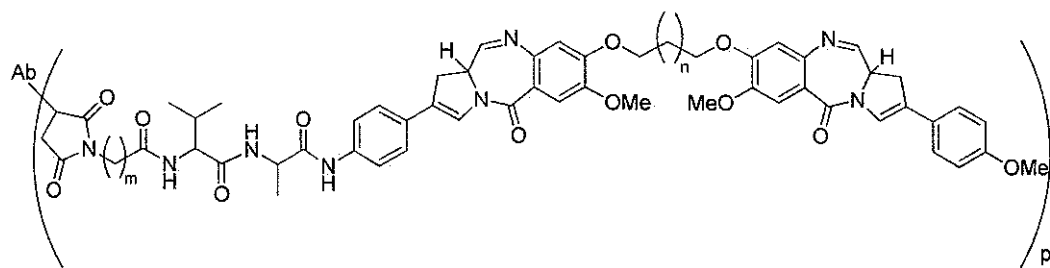
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

13. The pharmaceutical composition of claim 11 wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

14. The pharmaceutical compositions of any one of claims 11 to 13 wherein n is 1.
15. The pharmaceutical compositions of any one of claims 11 to 13 wherein n is 3.
16. The pharmaceutical composition of any one of claims 11 to 15 wherein m is 5.
17. The pharmaceutical composition of any one of claims 11 to 16 wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab.
18. The pharmaceutical composition of any one of the preceding claims wherein Ab comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1 fused to a human heavy chain constant region; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2 fused to a human light chain constant region.
19. The pharmaceutical composition of claim 18 wherein Ab comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO:3 and a light chain having the amino acid sequence set forth in SEQ ID NO:4 and attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering.
20. The pharmaceutical composition of any one of claims 11 to 19 wherein p is 1 or 2.
21. The pharmaceutical composition of any one of claims 11 to 20 in aqueous form.
22. The pharmaceutical composition of any one of claims 11 to 20 in lyophilized form.
23. An antibody-drug conjugate composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof;
wherein

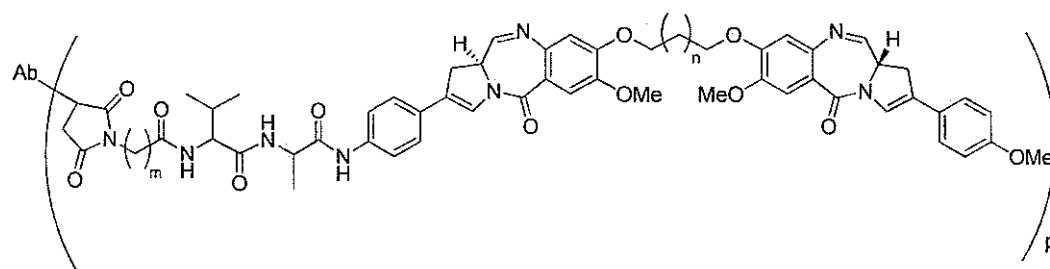
the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2; and

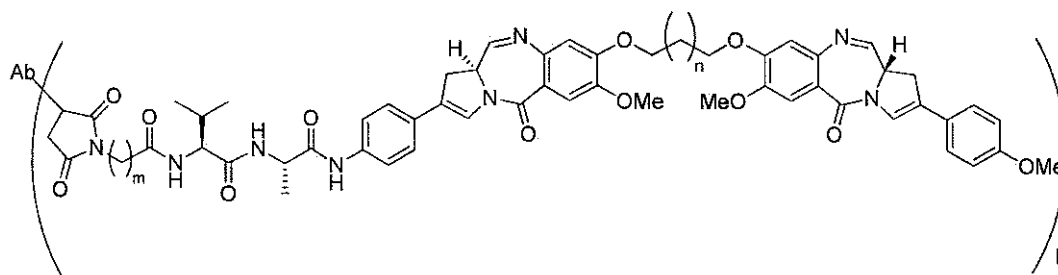
the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

24. The composition of claim 23 wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

25. The composition of claim 23 wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

26. The compositions of any one of claims 23 to 25 wherein n is 1.

27. The compositions of any one of claims 23 to 25 wherein n is 3.

28. The composition of any one of claims 23 to 27 wherein m is 5.

29. The composition of any one of claims 23 to 28 wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab.

30. The composition of any one of claims 23 to 29 wherein Ab comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1 fused to a human heavy chain constant region; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2 fused to a human light chain constant region.

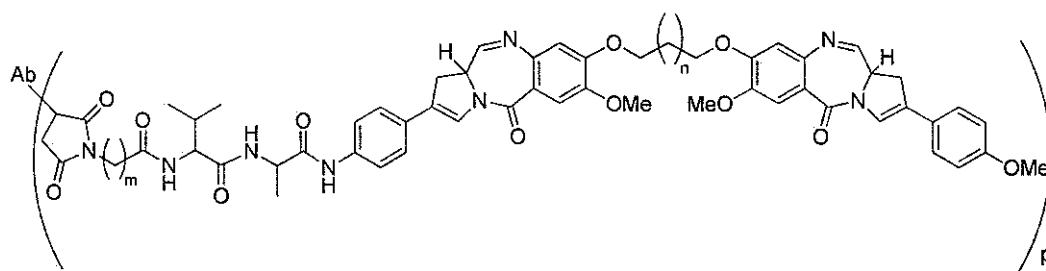
31. The composition of claim 30 wherein Ab comprising a heavy chain having the amino acid sequence set forth in SEQ ID NO:3 and a light chain having the amino acid sequence set forth in SEQ ID NO:4 and attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering.

32. Use of a pharmaceutical composition of any one of claims 11 to 21 for the manufacture of a medicament for treating a cancer that expresses CD123.

33. The use of claim 32 wherein the cancer is acute myeloid leukemia (AML).

34. The use of claim 32 wherein the cancer is myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), hairy cell leukemia, Fanconi anemia, Blastic plasmacytoid dendritic cell neoplasm (BPDCN), Hodgkin's disease, Immature T-cell acute lymphoblastic leukemia (Immature T-ALL), Burkitt's lymphoma, Follicular lymphoma, chronic lymphocytic leukemia (CLL), or mantle cell lymphoma.

35. A pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof;
wherein

the subscript n is 1 to 3;

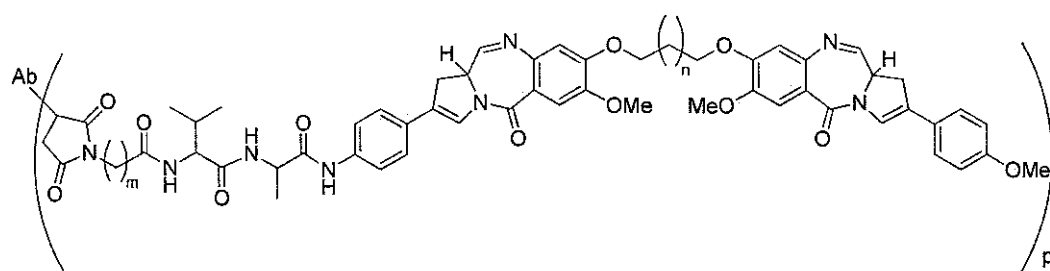
the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:3; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:4 and attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering;

the subscript p is 1 or 2;

and the average drug load of the composition is about 2.

36. Use of a pharmaceutical composition comprising a population of anti-CD123 antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof;
wherein

the subscript n is 1 to 3;

the subscript m is 2 to 5

Ab is an anti-CD123 intact antibody or antigen binding fragment thereof comprising a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:1; and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:2;

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2, for the manufacture of a medicament for treating a cancer that expresses CD123.

37. The use of claim 36 wherein the cancer is acute myeloid leukemia (AML).

38. The use of claim 36 wherein the cancer is myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), hairy cell leukemia, Fanconi anemia, Blastic plasmacytoid dendritic cell neoplasm (BPDCN), Hodgkin's disease, Immature T-cell acute lymphoblastic leukemia (Immature T-ALL), Burkitt's lymphoma, Follicular lymphoma, chronic lymphocytic leukemia (CLL), or mantle cell lymphoma.