

CLAIMS

What is claimed is:

1. An isolated anti-CD117 antibody, or antigen-binding fragment thereof, comprising

(i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 148, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 150; or

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 144.

2. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody, or antigen-binding fragment thereof, binds CD117 with a K_D of about 100 nM or less, about 90 nM or less, about 80 nM or less, about 70 nM or less, about 60 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 8 nM or less, about 6 nM or less, about 4 nM or less, about 2 nM or less, or about 1 nM or less as determined by a Bio-Layer Interferometry (BLI) assay.

3. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody, or antigen-binding fragment thereof, is human.

4. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody is an intact antibody.

5. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody is an IgG.

6. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 5, wherein the IgG is an IgG1 or an IgG4.
7. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody, or antigen-binding fragment thereof, is a monoclonal antibody.
8. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, comprising a heavy chain constant region having an amino acid sequence as set forth in SEQ ID NO: 169 and/or a light chain constant region comprising an amino acid sequence as set forth in SEQ ID NO: 183.
9. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, comprising an Fc region comprising at least one amino acid substitution selected from the group consisting of D265C, H435A, L234A, and L235A (numbering according to the EU index).
10. The anti-CD117 antibody, or antigen-binding fragment thereof, of claim 1, comprising an Fc region, wherein the Fc region comprises amino acid substitutions D265C, L234A, and L235A (numbering according to the EU index).
11. An intact anti-CD117 human antibody comprising a light chain comprising an amino acid sequence as set forth in SEQ ID NO: 184, and a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, and SEQ ID NO: 178.
12. An intact anti-CD117 human antibody comprising a light chain comprising an amino acid sequence as set forth in SEQ ID NO: 185, and a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, and SEQ ID NO: 182.
13. A pharmaceutical composition comprising the antibody, or antigen-binding fragment thereof, of claim 1, and a pharmaceutically acceptable carrier.

14. An antibody drug conjugate comprising an anti-CD117 antibody conjugated to a cytotoxin via a linker, wherein the antibody comprises the antibody, or antigen-binding fragment thereof, of claim 1, wherein the cytotoxin is selected from the group consisting of an amatoxin, a pseudomonas exotoxin A, deBouganin, a diphtheria toxin, saporin, a maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, and an indolinobenzodiazepine dimer.

15. The antibody drug conjugate of claim 14, wherein the amatoxin is selected from the group consisting of α -amanitin, β -amanitin, γ -amanitin, ϵ -amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.

16. An antibody drug conjugate (ADC) comprising an isolated anti-CD117 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker, wherein the antibody, or antigen-binding fragment thereof, comprises

(i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 148, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 150; or

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 144.

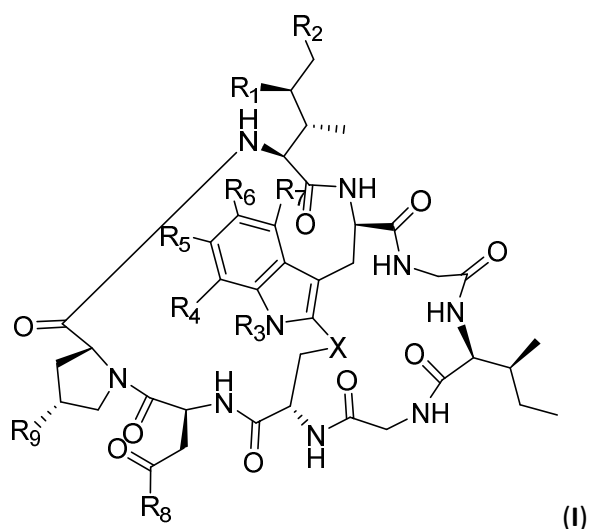
17. The ADC of claim 16, wherein the cytotoxin is selected from the group consisting of an amatoxin, an auristatin, a maytansine, a maytansinoid, a pyrrolobenzodiazepine, and a pyrrolobenzodiazepine dimer.

18. An antibody drug conjugate (ADC) represented by the formula Ab-Z-L-Am, wherein Ab is an antibody, or antigen-binding fragment thereof, that binds CD117, L is a linker, Z is a chemical moiety, and Am is an amatoxin, wherein the antibody, or antigen-binding fragment thereof, comprises

(i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 148, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 150; or

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 144.

19. The ADC of claim 18, wherein the Am-L-Z is represented by formula (I)



wherein R1 is H, OH, OR_A, or OR_C;

R₂ is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R₃ is H, R_C, or R_D;

R₄, R₅, R₆, and R₇ are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R₈ is OH, NH₂, OR_C, OR_D, NHR_C, or NR_CR_D;

R₉ is H, OH, OR_C, or OR_D;

X is —S—, —S(O)—, or —SO₂—;

R_C is -L-Z;

R_D is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

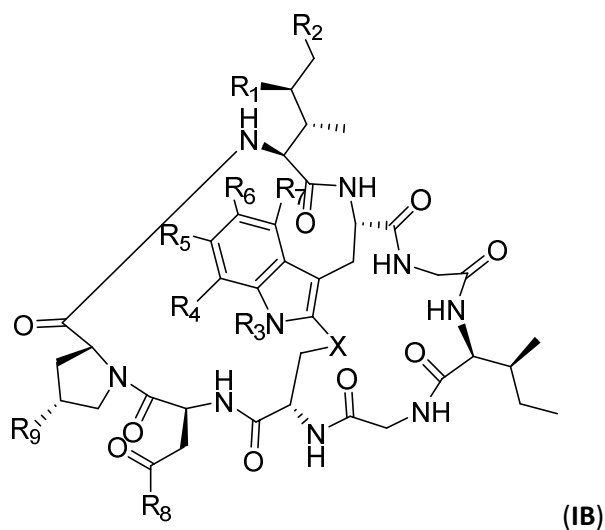
L is optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted C₂-C₆ alkynylene, optionally substituted C₂-C₆ heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally

substituted heteroarylene, a dipeptide, —(C=O)—, a peptide, or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

20. The ADC of claim 18, wherein Am-L-Z is represented by formula (IB)



wherein R_1 is H, OH, OR_A , or OR_C ;

R_2 is H, OH, OR_B , or OR_C ;

R_A and R_B , when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R_3 is H, R_C , or R_D ;

R_4 , R_5 , R_6 , and R_7 are each independently H, OH, OR_C , OR_D , R_C , or R_D ;

R_8 is OH, NH_2 , OR_C , OR_D , NHR_C , or $NR_C R_D$;

R_9 is H, OH, OR_C , or OR_D ;

X is $-S-$, $-S(O)-$, or $-SO_2-$;

R_C is -L-Z;

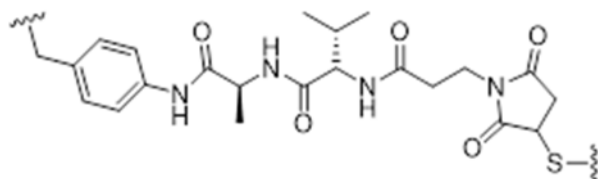
R_D is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_2 - C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted C₂-C₆ alkynylene, optionally substituted C₂-C₆ heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, —(C=O)—, a peptide, or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody, or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

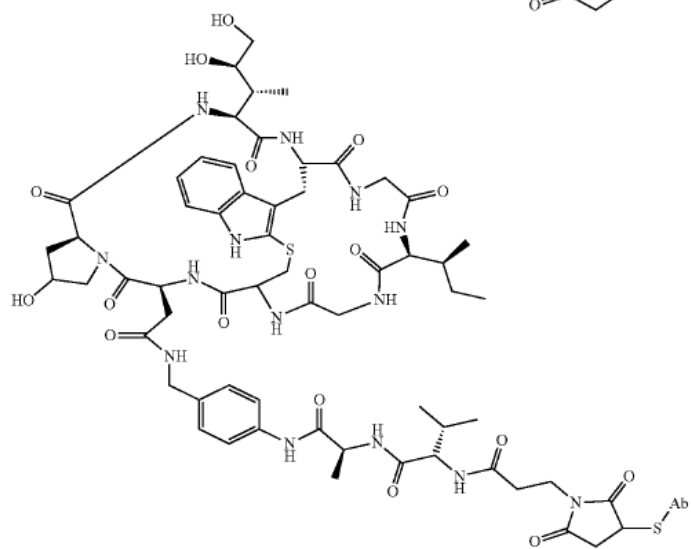
21. The ADC of claim 20, wherein L-Z is



22. The ADC of claim 18, wherein the antibody, or antigen-binding fragment thereof, is conjugated to the amatoxin by way of a cysteine residue in an Fc domain of the antibody, or antigen-binding fragment thereof.

23. The ADC of claim 22, wherein the cysteine residue is introduced by way of a mutation in the Fc domain of the antibody, or antigen-binding fragment thereof.

24. An antibody drug conjugate (ADC) represented by any one of the following:



wherein Ab is an anti-CD117 antibody or antigen-binding fragment thereof comprising

(i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and comprising a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 148, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 150; or

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 144.

25. The ADC of claim 16, wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain constant region having an amino acid sequence as set forth in SEQ ID NO: 169 and/or a light chain constant region comprising an amino acid sequence as set forth in SEQ ID NO: 183.

26. The ADC of claim 16, wherein the antibody, or antigen-binding fragment thereof, comprises an Fc region comprising at least one amino acid substitution selected from the group consisting of D265C, H435A, L234A, and L235A (numbering according to the EU index).

27. The ADC of claim 16, wherein the antibody, or antigen-binding fragment thereof, comprises an Fc region, wherein the Fc region comprises D265C, L234A, and L235A (numbering according to the EU index).

28. The ADC of claim 16, wherein the antibody is an intact antibody and comprises

a light chain comprising an amino acid sequence as set forth in SEQ ID NO: 184, and a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO 175, SEQ ID NO: 176, SEQ ID NO: 177, and SEQ ID NO: 178.

29. A pharmaceutical composition comprising the ADC of claim 16, and a pharmaceutically acceptable carrier.

30. An isolated anti-CD117 antibody, or antigen-binding fragment thereof, comprising (i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 153, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 154, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 151, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 152;

(iii) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 157, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 5, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(iv) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 156;

(v) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 159, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region

comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 157, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 5, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(vi) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 158, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 156;

(vii) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 2, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 154, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(viii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 160, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 152;

(ix) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 102;

(x) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 186, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 2, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 187; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 188, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 189;

(xi) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 99;

(xii) a heavy chain variable region comprising the amino acid sequence as set forth in

SEQ ID NO: 7, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 99;

(xiii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 7, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 100; or (xiv) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 101.

31. An antibody drug conjugate (ADC) comprising an isolated anti-CD117 antibody conjugated to a cytotoxin via a linker, wherein the antibody comprises

(i) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 153, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 154, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(ii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 151, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 152;

(iii) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 146, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 147; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 157, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 5, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(iv) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 143, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 156;

(v) a heavy chain variable region comprising a CDR1 domain comprising the amino

acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 159, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 157, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 5, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(vi) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 158, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 156;

(vii) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 145, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 2, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 3; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 154, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 155;

(viii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 160, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 152;

(ix) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 102;

(x) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 186, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 2, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 187; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO: 188, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO: 149, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO: 189;

(xi) a heavy chain variable region comprising the amino acid sequence as set forth in

SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 99;

(xii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 7, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 99;

(xiii) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 7, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 100; or

(xiv) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 98, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 101.

32. The antibody drug conjugate of claim 31, wherein the cytotoxin is selected from the group consisting of an amatoxin, a pseudomonas exotoxin A, deBouganin, a diphtheria toxin, saporin, a maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, and an indolinobenzodiazepine dimer.

33. A pharmaceutical composition comprising the intact anti-CD117 antibody of claim 11 or 12, and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising the ADC of claim 18, 24, or 31, and a pharmaceutically acceptable carrier.