CLAIMS

1. ~~An antibody-drug conjugate~~ A compound of Formula (~~I):~~ III):

~~Ab-(L-D)$_p$ (I)~~

~~wherein~~

~~Ab is an antibody or antigen binding fragment which targets a neoplastic cell;~~

~~D is a splicing modulator;~~

~~L is a linker which covalently attaches Ab to D; and~~

~~*p* is an integer from 1 to 15.~~

~~2. The antibody-drug conjugate of claim 1, wherein the antibody or antigen binding fragment targets a neoplastic cell derived from a hematological malignancy or a solid tumor.~~

~~3. The antibody-drug conjugate of claim 1 or claim 2, wherein the antibody or antigen binding fragment targets a neoplastic cell derived from a hematological malignancy.~~

~~4. The antibody-drug conjugate of claim 3, wherein the hematological malignancy is selected from a B-cell malignancy, a leukemia, a lymphoma, and a myeloma.~~

~~5. The antibody-drug conjugate of claim 3 or claim 4, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.~~

~~6. The antibody-drug conjugate of claim 1 or claim 2, wherein the antibody or antigen binding fragment targets a neoplastic cell derived from a solid tumor.~~

~~7. The antibody-drug conjugate of claim 6, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.~~

~~8. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.~~

~~9. The antibody-drug conjugate of claim 8, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.~~

10. The antibody-drug conjugate of claim 8 or claim 9, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

11. The antibody-drug conjugate of any one of claims 8 to 10, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

12. The antibody-drug conjugate of any one of claims 8 to 11, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

13. The antibody-drug conjugate of any one of claims 8 to 12, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

14. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a CD138-expressing cell.

15. The antibody-drug conjugate of claim 14, wherein the antibody or antigen binding fragment is an anti-CD138 antibody or antigen binding fragment.

16. The antibody-drug conjugate of claim 14 or claim 15, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:7 (HCDR1), SEQ ID NO:8 (HCDR2), and SEQ ID NO:9 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:10 (LCDR1), SEQ ID NO:11 (LCDR2), and SEQ ID NO:12 (LCDR3).

17. The antibody-drug conjugate of any one of claims 14 to 16, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of

~~SEQ ID NO:21, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22.~~

~~18. The antibody-drug conjugate of any one of claims 14 to 17, wherein the antibody or antigen binding fragment comprises a human IgG2a heavy chain constant region.~~

~~19. The antibody-drug conjugate of any one of claims 14 to 18, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~

~~20. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets an EPHA2-expressing cell.~~

~~21. The antibody-drug conjugate of claim 20, wherein the antibody or antigen binding fragment is an anti-EPHA2 antibody or antigen binding fragment.~~

~~22. The antibody-drug conjugate of claim 20 or claim 21, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:13 (HCDR1), SEQ ID NO:14 (HCDR2), and SEQ ID NO:15 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:16 (LCDR1), SEQ ID NO:17 (LCDR2), and SEQ ID NO:18 (LCDR3).~~

~~23. The antibody-drug conjugate of any one of claims 20 to 22, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24.~~

~~24. The antibody-drug conjugate of any one of claims 20 to 23, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.~~

~~25. The antibody-drug conjugate of any one of claims 20 to 24, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~

~~26. The antibody-drug conjugate of any one of claims 1 to 25, wherein the linker is a cleavable linker.~~

~~27. The antibody-drug conjugate of claim 26, wherein the linker comprises a cleavable peptide moiety.~~

~~28. The antibody-drug conjugate of claim 27, wherein the cleavable peptide moiety is cleavable by an enzyme.~~

~~29. The antibody-drug conjugate of any one of claims 26 to 28, wherein the cleavable peptide moiety or linker comprises an amino acid unit.~~

~~30. The antibody-drug conjugate of claim 29, wherein the amino acid unit comprises valine-citrulline (Val-Cit).~~

~~31. The antibody-drug conjugate of claim 29, wherein the amino acid unit comprises valine-alanine (Val-Ala).~~

~~32. The antibody-drug conjugate of claim 26, wherein the linker comprises a cleavable glucuronide moiety.~~

~~33. The antibody-drug conjugate of claim 32, wherein the cleavable glucuronide moiety is cleavable by an enzyme.~~

~~34. The antibody-drug conjugate of claim 32 or claim 33, wherein the cleavable glucuronide moiety is cleavable by a glucuronidase.~~

~~35. The antibody-drug conjugate of any one of claims 32 to 34, wherein the cleavable glucuronide moiety is cleavable by β-glucuronidase.~~

~~36. The antibody-drug conjugate of any one of claims 1 to 35, wherein the linker comprises at least one spacer unit.~~

~~37. The antibody-drug conjugate of claim 36, wherein the spacer unit or linker comprises a polyethylene glycol (PEG) moiety.~~

~~38. The antibody-drug conjugate of claim 37, wherein the PEG moiety comprises -$(PEG)_m$- and *m* is an integer from 1 to 10.~~

~~39. The antibody-drug conjugate of claim 38, wherein *m* is 2.~~

~~40. The antibody-drug conjugate of claim 36, wherein the spacer unit or linker comprises an alkyl moiety.~~

~~41. The antibody-drug conjugate of claim 40, wherein the alkyl moiety comprises -$(CH_2)_n$- and *n* is an integer from 1 to 10.~~

~~42. The antibody-drug conjugate of claim 41, wherein n is 2.~~

~~43. The antibody-drug conjugate of claim 41, wherein *n* is 5.~~

~~44. The antibody-drug conjugate of claim 41, wherein n is 6.~~

~~45. The antibody-drug conjugate of any one of claims 36 to 44, wherein the spacer unit attaches to the antibody or antigen binding fragment via a maleimide (Mal) moiety ("Mal-spacer unit").~~

~~46. The antibody-drug conjugate of claim 45, wherein the Mal-spacer unit is reactive with a cysteine residue on the antibody or antigen binding fragment.~~

~~47. The antibody-drug conjugate of claim 45 or claim 46, wherein the Mal-spacer unit is joined to the antibody or antigen binding fragment via a cysteine residue on the antibody or antigen binding fragment.~~

~~48. The antibody-drug conjugate of any one of claims 45 to 47, wherein the linker comprises the Mal-spacer unit and a cleavable peptide moiety.~~

~~49. The antibody-drug conjugate of claim 48, wherein the cleavable peptide moiety comprises an amino acid unit.~~

~~50. The antibody-drug conjugate of claim 48 or claim 49, wherein the cleavable peptide moiety or amino acid unit comprises Val-Cit.~~

~~51. The antibody-drug conjugate of claim 48 or claim 49, wherein the cleavable peptide moiety or amino acid unit comprises Val-Ala.~~

~~52. The antibody-drug conjugate of any one of claims 45 to 51, wherein the Mal-spacer unit comprises an alkyl moiety.~~

~~53. The antibody-drug conjugate of any one of claims 45 to 51, wherein the Mal-spacer unit comprises a PEG moiety.~~

~~54. The antibody-drug conjugate of any one of claims 45 to 52, wherein the Mal-spacer unit comprises a maleimidocaproyl (MC).~~

~~55. The antibody-drug conjugate of any one of claims 45 to 54, wherein the Mal-spacer unit attaches the antibody or antigen binding fragment to the cleavable moiety in the linker.~~

~~56. The antibody-drug conjugate of claim 55, wherein the cleavable moiety in the linker comprises a cleavable peptide moiety.~~

~~57. The antibody-drug conjugate of claim 56, wherein the cleavable peptide moiety comprises an amino acid unit.~~

~~58. The antibody-drug conjugate of claim 56 or claim 57, wherein the cleavable peptide moiety or amino acid unit comprises Val-Cit, Val-Ala, Glu-Val-Cit, or Ala-Ala-Asn.~~

~~59. The antibody-drug conjugate of any one of claims 55 to 58, wherein the linker comprises MC-Val-Cit.~~

~~60. The antibody-drug conjugate of any one of claims 55 to 58, wherein the linker comprises MC-Val-Ala.~~

~~61. The antibody-drug conjugate of any one of claims 55 to 60, wherein the Mal-spacer unit comprises an alkyl moiety.~~

~~62. The antibody-drug conjugate of any one of claims 55 to 60, wherein the Mal-spacer unit comprises a PEG moiety.~~

~~63. The antibody-drug conjugate of any one of claims 55 to 61, wherein the Mal-spacer unit comprises a maleimidocaproyl (MC).~~

~~64. The antibody-drug conjugate of any one of claims 36 to 63, wherein the cleavable moiety in the linker is directly joined to the splicing modulator, or wherein a spacer unit attaches the cleavable moiety in the linker to the splicing modulator.~~

~~65. The antibody-drug conjugate of claim 64, wherein cleavage of the conjugate releases the splicing modulator from the antibody or antigen binding fragment and linker.~~

~~66. The antibody-drug conjugate of claim 64 or claim 65, wherein the spacer unit attaching the cleavable moiety in the linker to the splicing modulator is self-immolative.~~

~~67. The antibody-drug conjugate of any one of claims 64 to 66, wherein the spacer unit attaching the cleavable moiety in the linker to the splicing modulator comprises a p-aminobenzyloxycarbonyl (pABC).~~

~~68. The antibody-drug conjugate of claim 67, wherein the pABC attaches the cleavable moiety in the linker to the splicing modulator.~~

~~69. The antibody-drug conjugate of claim 67 or claim 68, wherein the cleavable moiety in the linker comprises a cleavable peptide moiety.~~

~~70. The antibody-drug conjugate of claim 69, wherein the cleavable peptide moiety comprises an amino acid unit.~~

~~71. The antibody-drug conjugate of claim 69 or claim 70, wherein the cleavable peptide moiety or amino acid unit comprises Val-Cit, Val-Ala, Glu-Val-Cit, or Ala-Ala-Asn.~~

~~72. The antibody-drug conjugate of any one of claims 67 to 71, wherein the linker comprises Val-Cit-pABC.~~

~~73. The antibody-drug conjugate of any one of claims 67 to 71, wherein the linker comprises Val-Ala-pABC.~~

~~74. The antibody-drug conjugate of any one of claims 64 to 66, wherein the spacer unit attaching the cleavable moiety in the linker to the splicing modulator comprises a p-aminobenzyl (pAB).~~

~~75. The antibody-drug conjugate of claim 74, wherein the pAB attaches the cleavable moiety in the linker to the splicing modulator.~~

~~76. The antibody-drug conjugate of claim 74 or claim 75, wherein the cleavable moiety in the linker comprises a cleavable peptide moiety.~~

~~77. The antibody-drug conjugate of claim 76, wherein the cleavable peptide moiety comprises an amino acid unit.~~

~~78. The antibody-drug conjugate of claim 76 or claim 77, wherein the cleavable peptide moiety or amino acid unit comprises Val-Cit, Val-Ala, Glu-Val-Cit, or Ala-Ala-Asn.~~

~~79. The antibody-drug conjugate of any one of claims 74 to 78, wherein the linker comprises Val-Cit-pAB.~~

~~80. The antibody-drug conjugate of any one of claims 74 to 78, wherein the linker comprises Val-Ala-pAB.~~

~~81. The antibody-drug conjugate of any one of claims 1 to 25, wherein the linker is a non-cleavable linker.~~

~~82. The antibody-drug conjugate of claim 81, wherein the linker comprises at least one spacer unit.~~

~~83. The antibody-drug conjugate of claim 81 or claim 82, wherein the spacer unit or linker comprises a polyethylene glycol (PEG) moiety.~~

~~84. The antibody-drug conjugate of claim 83, wherein the PEG moiety comprises -$(PEG)_m$- and *m* is an integer from 1 to 10.~~

~~85. The antibody-drug conjugate of claim 84, wherein *m* is 2.~~

~~86. The antibody-drug conjugate of claim 81 or claim 82, wherein the spacer unit or linker comprises an alkyl moiety.~~

~~87. The antibody-drug conjugate of claim 86, wherein the alkyl moiety comprises -$(CH_2)_n$- and *n* is an integer from 1 to 10.~~

~~88. The antibody-drug conjugate of claim 87, wherein *n* is 2.~~

~~89. The antibody-drug conjugate of claim 87, wherein *n* is 5.~~

~~90. The antibody-drug conjugate of claim 87, wherein *n* is 6.~~

~~91. The antibody-drug conjugate of any one of claims 81 to 90, wherein the spacer unit attaches to the antibody or antigen binding fragment via a maleimide (Mal) moiety ("Mal-spacer unit").~~

~~92. The antibody-drug conjugate of claim 91, wherein the Mal-spacer unit is reactive with a cysteine residue on the antibody or antigen binding fragment.~~

~~93. The antibody-drug conjugate of claim 91 or claim 92, wherein the Mal-spacer unit is joined to the antibody or antigen binding fragment via a cysteine residue on the antibody or antigen binding fragment.~~

~~94. The antibody-drug conjugate of any one of claims 91 to 93, wherein the Mal-spacer unit comprises an alkyl moiety.~~

~~95. The antibody-drug conjugate of any one of claims 91 to 93, wherein the Mal-spacer unit comprises a PEG moiety.~~

~~96. The antibody-drug conjugate of any one of claims 91 to 95, wherein the linker or Mal-spacer unit comprises a maleimidocaproyl (MC).~~

~~97. The antibody-drug conjugate of claim 96, wherein the linker or Mal-spacer unit comprises a maleimidocaproyl (MC) and at least one additional spacer unit.~~

~~98. The antibody-drug conjugate of any one of claims 91 to 95, wherein the linker or Mal-spacer unit comprises MC-$(PEG)_2$.~~

~~99. The antibody-drug conjugate of claim 98, wherein the linker or Mal-spacer unit comprises MC-$(PEG)_2$ and at least one additional spacer unit.~~

~~100. The antibody-drug conjugate of any one of claims 91 to 95, wherein the linker or Mal-spacer unit comprises Mal-Hex.~~

~~101. The antibody-drug conjugate of claim 100, wherein the linker or Mal-spacer unit comprises Mal-Hex and at least one additional spacer unit.~~

~~102. The antibody-drug conjugate of any one of claims 91 to 95, wherein the linker or Mal-spacer unit comprises Mal-Et.~~

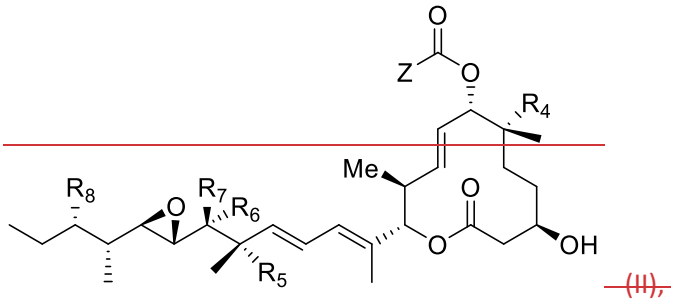
~~103. The antibody-drug conjugate of claim 102, wherein the linker or Mal-spacer unit comprises Mal-Et and at least one additional spacer unit.~~

~~104. The antibody-drug conjugate of any one of claims 91 to 95, wherein the linker or Mal-spacer unit comprises Mal-Et-O-Et.~~

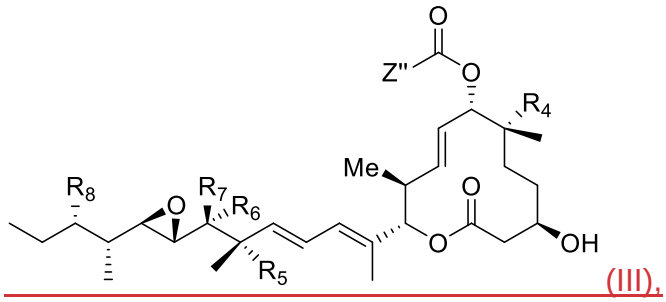
~~105. The antibody-drug conjugate of claim 104, wherein the linker or Mal-spacer unit comprises Mal-Et-O-Et and at least one additional spacer unit.~~

~~106. The antibody-drug conjugate of any one of claims 91 to 105, wherein the Mal-spacer unit attaches the antibody or antigen binding fragment to the splicing modulator.~~

~~107. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises a splicing modulator of Formula (II):~~



~~(II),~~



(III),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^2 is a linker L comprising at least one cleavable peptide moiety;

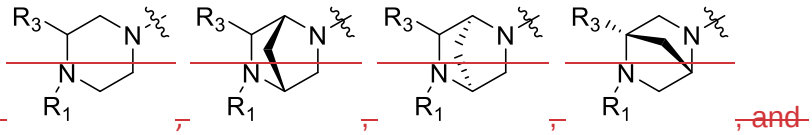
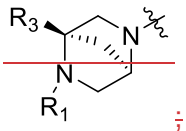
R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; ~~and~~

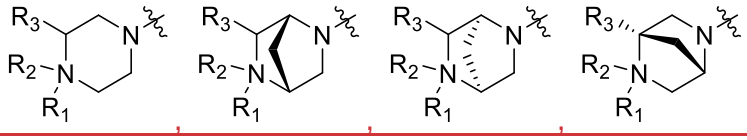
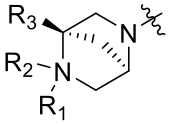
R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, and -$NR^{15}R^{16}$;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

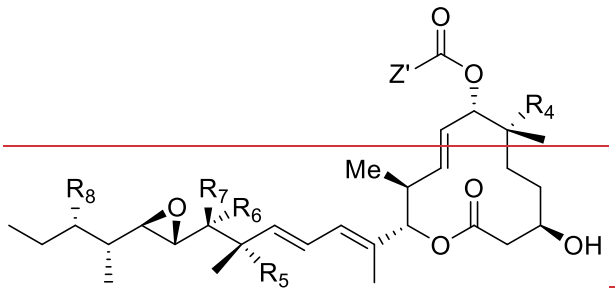
Z is chosen from , and ;

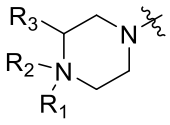
Z'' is chosen from , and ;

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

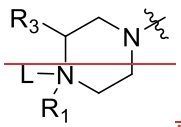
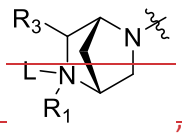
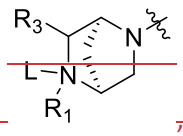
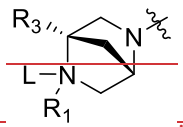
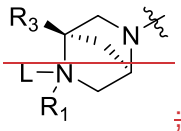
wherein at least one of R^6 and R^7 is hydrogen; and

~~108. The antibody-drug conjugate of claim 107, wherein the linker covalently attaches to the splicing modulator ("L-D"), and L-D has a structure of Formula (II-A):~~



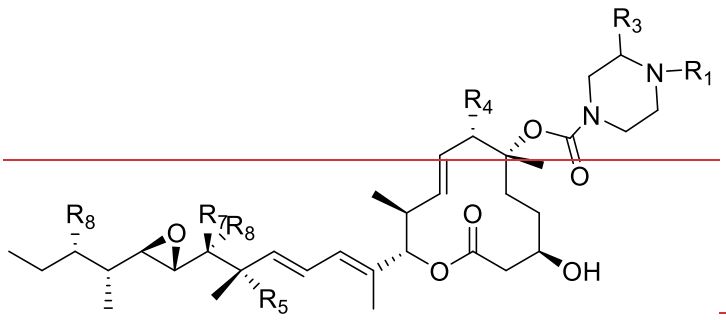
~~(II-A),~~ wherein if Z'' is  and R^3, R^6, and R^7 are H and R^4 is methoxy and R^5 is hydroxyl, then R^1 is neither absent nor methyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein ~~Z'~~:

R^1 is chosen from , , , , ~~and~~  ~~; and~~

~~wherein all other variables are as defined for Formula (II).~~

~~109. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator is a splicing modulator of Formula (IV):~~



~~(IV), or a pharmaceutically acceptable salt thereof, wherein:~~

~~R^1 is chosen from~~absent, hydrogen, C_1-~~C_6~~C_4 alkyl groups, C_1-~~C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6~~C_4 alkylcarboxylic acid groups, C_1-~~C_6~~C_4 alkylhydroxy groups, and

C_3-C_8 cycloalkyl groups~~, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and -CD_3~~;

R^2 is a linker L comprising at least one cleavable peptide moiety;

R^3 is chosen from hydrogen, C_1-~~C_6~~C_4 alkyl groups, C_1-~~C_6~~C_4 alkylalkoxy groups, C_1-~~C_6 alkylamino groups, C_1-C_6~~C_4 alkylcarboxylic acid groups, and C_1-~~C_6~~C_4 alkylhydroxy groups~~, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; and~~;

~~R^4, R^5, and R^8 are each independently~~ R^4 is chosen from hydrogen, hydroxyl groups, -O-(C_1-C_4 alkyl) groups, -O-C(=O)-(C_1-C_4 alkyl) groups, and C_1-C_4 alkyl groups;

R^5 is chosen from hydrogen, hydroxyl groups, -O-(C_1-~~C_6 alkyl) groups, -O-C(=O)-(C_1-C_6~~C_4 alkyl) groups, and C_1-~~C_6~~C_4 alkyl groups;

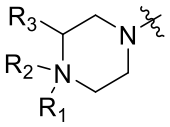
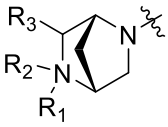
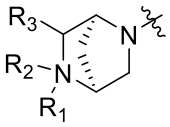
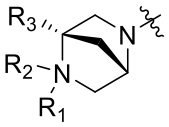
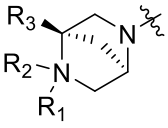
R^6 ~~and R^7 are each independently~~is chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, and C_1-C_4 alkyl groups~~, and a linker~~;

R^7 is chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, and -$NR^{15}R^{16}$;

R^8 is chosen from hydrogen, hydroxyl groups, -O-(C_1-C_4 alkyl) groups, and C_1-C_4 alkyl groups;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};~~ and~~

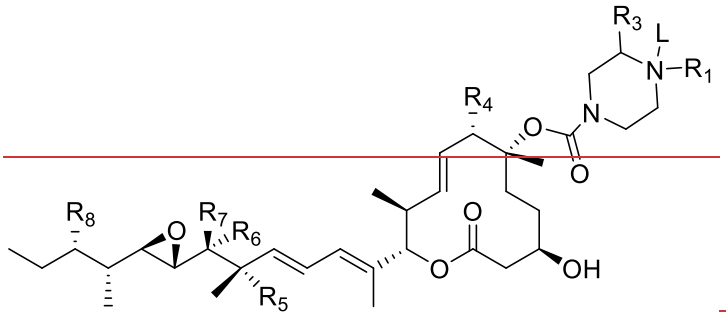
R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

Z'' is chosen from , , , , and ;

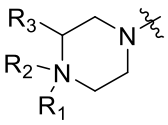
wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups~~,~~;

wherein at least one of R^6 and R^7 is hydrogen.

110. The antibody-drug conjugate of claim 109, wherein the linker covalently attaches to the splicing modulator ("L-D"), and L-D has a structure of Formula (IV-A):



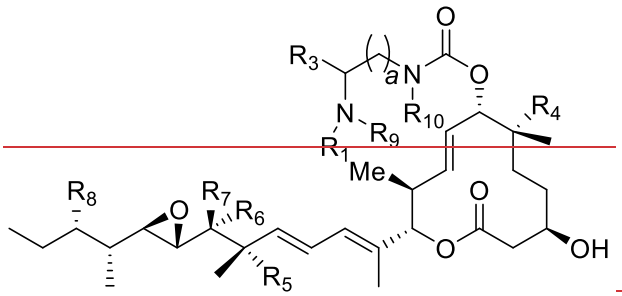
(IV-A), wherein if Z'' is



and R^3, R^6, and R^7 are H and R^4 is methoxy and R^5 is hydroxyl, then R^1 is neither absent nor methyl.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:

111. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator is a splicing modulator of Formula (VI):



(VI), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^9 are each independently R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 methyl, and C_1-C_4 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^2 is a linker L comprising at least one cleavable peptide moiety;

R^3 is chosen from hydrogen~~, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6~~ and C_1-C_4 alkylcarboxylic acid groups~~, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;~~;

~~R^4, R^5, and R^8 are each independently~~ R^4 is chosen from hydrogen, hydroxyl groups, -O-(C_1-~~C_6~~C_4 alkyl) groups, -O-C(=O)-(C_1-~~C_6~~C_4 alkyl) groups, and C_1-~~C_6~~C_4 alkyl groups;

~~R^6 and R^7 are each independently~~ R^5 is chosen from hydrogen~~, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, -$NR^{15}R^{16}$, and a linker~~ and hydroxyl groups;

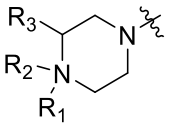
~~R^{10}~~R^6 is hydrogen;

R^7 is hydrogen;

R^8 is chosen from hydrogen~~, C_1-C_6 alkyl groups, -C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;~~

~~R^{15}~~ and ~~R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};~~ hydroxyl groups; and

~~R^{17}~~Z'' is chosen from ~~hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and~~

~~a is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10~~ 

;

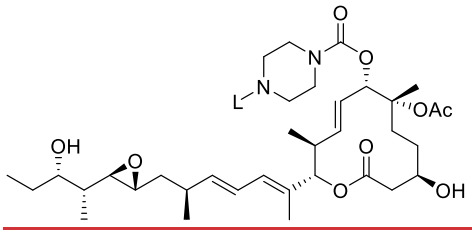
wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8~~, R^9, R^{10}, R^{15}, R^{16}, and R^{17}~~ are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, ~~-$NR^{15}R^{16}$,~~ C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

wherein if R^3, R^6, and R^7 are H and ~~C_3-C_8 heterocyclyl groups;~~R^4 is methoxy and R_5 is hydroxyl, then R^1 is neither absent nor methyl.

~~wherein at least one of R^6 and R^7 is hydrogen; and~~

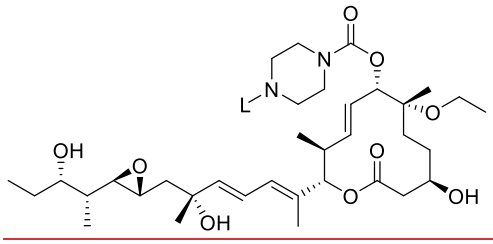
~~wherein R^1 and R^9 cannot both be absent.~~

~~112.~~ 4. The ~~antibody-drug conjugate~~ compound of claim ~~111~~1, wherein the compound is chosen from a compound of formula



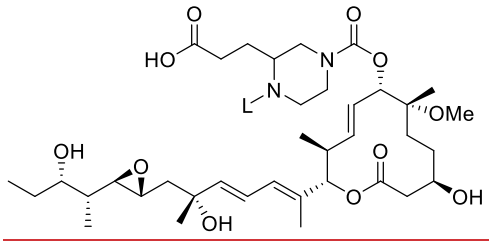
and pharmaceutically acceptable salts thereof.

5. The compound of claim 1, wherein the compound is chosen from a compound of formula



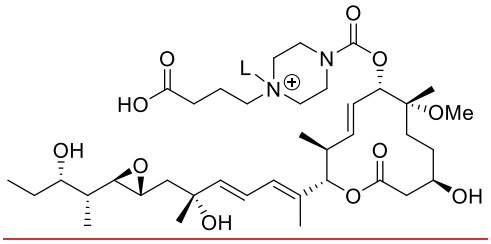
and pharmaceutically acceptable salts thereof.

6. The compound of claim 1, wherein the ~~linker covalently attaches to the splicing modulator ("L-D"),~~compound is chosen from a compound of formula



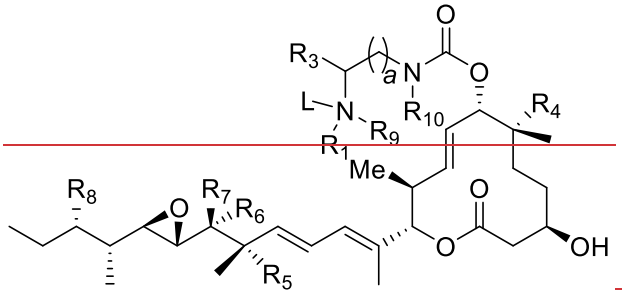
and pharmaceutically acceptable salts thereof.

7. The compound of claim 1, wherein the compound is chosen from a compound of formula



and ~~L-D has a structure of Formula (VI-~~ pharmaceutically acceptable salts thereof.

8. A~~):~~ pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

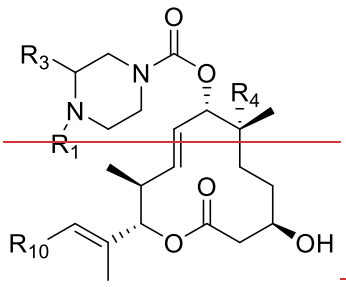


~~(VI-A),~~

9. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject having or suspected of having a neoplastic disorder, comprising a therapeutically effective amount of the compound to be administered to the subject.

~~113.~~ 10. The ~~antibody-drug conjugate~~use of ~~any one~~the compound of ~~claims 1 to 106~~claim 9, wherein the ~~splicing modulator~~neoplastic disorder is a ~~splicing modulator~~leukemia, a lymphoma, or a myeloma.

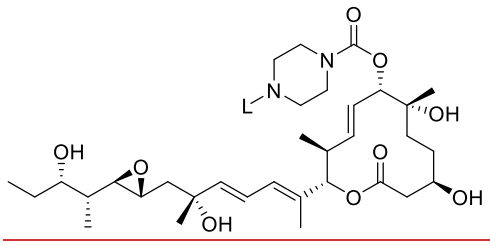
11. The use of ~~Formula (VIII):~~the compound of claim 10, wherein the myeloma is multiple myeloma.



~~(VIII),~~

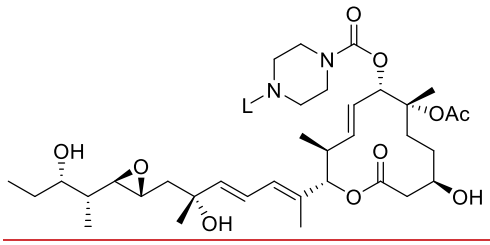
12. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof, ~~wherein~~ in the manufacture of a medicament for reducing or inhibiting growth of a tumor in a subject having or suspected of having a neoplastic disorder, comprising a therapeutically effective amount of the compound to be administered to the subject.

13. The compound of claim 1, wherein the compound is chosen from a compound of formula



and pharmaceutically acceptable salts thereof.

14. The compound of claim 1, wherein the compound is chosen from a compound of formula



and pharmaceutically acceptable salts thereof.

15. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety further comprises at least one spacer unit.

16. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the at least one cleavable peptide moiety comprises valine-alanine (Val-Ala).

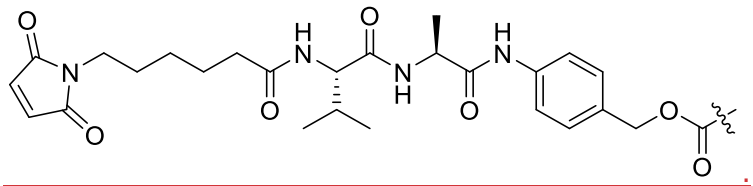
17. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the at least one cleavable peptide moiety comprises valine-citrulline (Val-Cit), glutamic acid-valine-citrulline (Glu-Val-Cit), or alanine-alanine-asparagine (Ala-Ala-Asn).

18. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety comprises p-aminobenzyloxycarbonyl.

19. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety further comprises a polyethylene glycol moiety and/or an alkyl moiety.

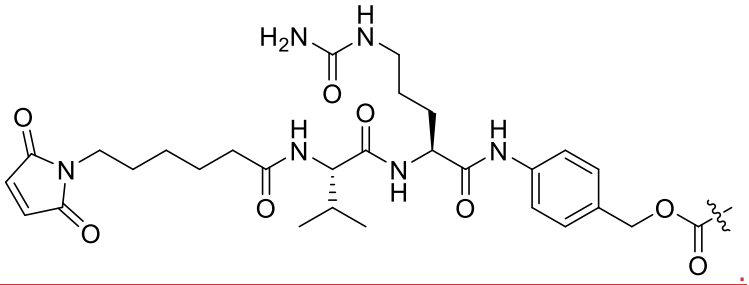
20. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety further comprises maleimidocaproyl (MC).

21. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety is a compound of formula:



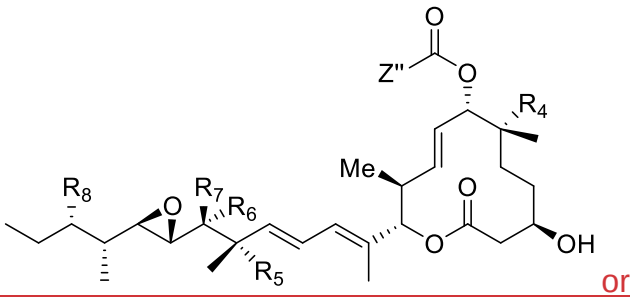
.

22. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the linker L comprising at least one cleavable peptide moiety is a compound of formula:



.

23. A compound of formula:



or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^2 is a linker L comprising at least one cleavable peptide moiety;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;

R^4 is chosen from hydrogen, hydroxyl groups, -O~~-(C_1-C_6 alkyl) groups, -O~~-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;~~ ~~and~~

~~R^{10} is chosen from 3 to 10 membered carbocycles and 3 to 10 membered heterocycles, each of which is substituted with 0 to 3 R^a, wherein each R^a is independently chosen from halogens,~~

C_1-C_6 alkyl groups, -O-(C_1-C_6)alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylhydroxy groups, -S(=O)$_w$-(4 to 7 membered heterocycles), 4 to 7 membered carbocycles, and 4 to 7 membered heterocycles;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17}; and

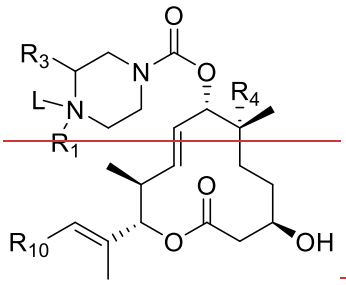
R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein R^1, R^3, R^4, R^{10}, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

wherein each R^a is independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, -$NR^{15}R^{16}$, C_1-C_6 alkyl groups, -(C=O)-(C_1-C_6 alkyl) groups, -(C=O)-(C_1-C_6 alkyl)-(C_3-C_{10} heterocyclyl) groups, -S(=O)$_w$-(C_3-C_8 heterocyclyl groups), and C_1-C_6 alkylcarboxylic acid groups, each of which is substituted with 0, 1, or 2 groups independently chosen from halogens, hydroxyl groups, -$NR^{15}R^{16}$, and C_1-C_3 alkyl groups; and

w is 0, 1, or 2.

114. The antibody-drug conjugate of claim 113, wherein the linker covalently attaches to the splicing modulator ("L-D"), and L-D has a structure of Formula (VIII-A):



(VIII-A), or a pharmaceutically acceptable salt thereof.

115. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises a modulator of the SF3b complex.

116. The antibody-drug conjugate of claim 115, wherein the splicing modulator comprises a pladienolide or a pladienolide derivative.

117. The antibody-drug conjugate of claim 115 or claim 116, wherein the splicing modulator comprises pladienolide D or a pladienolide D derivative.

~~118. The antibody-drug conjugate of claim 117, wherein the pladienolide D or derivative comprises D2, D1, D4, D8, D10, D11 (E7107), D20, D21, D22, D12, or D25.~~

~~119. The antibody-drug conjugate of claim 117 or claim 118, wherein the pladienolide D or derivative comprises D2.~~

~~120. The antibody-drug conjugate of claim 117 or claim 118, wherein the pladienolide D or derivative comprises D1.~~

~~121. The antibody-drug conjugate of claim 117 or claim 118, wherein the pladienolide D or derivative is a zwitterionic pladienolide D or derivative.~~

~~122. The antibody-drug conjugate of claim 121, wherein the zwitterionic pladienolide D or derivative comprises D22 or D25.~~

~~123. The antibody-drug conjugate of claim 115 or claim 116, wherein the splicing modulator comprises pladienolide B or a pladienolide B derivative.~~

~~124. The antibody-drug conjugate of claim 123, wherein the pladienolide B or derivative comprises D9, D18, D19, or D13.~~

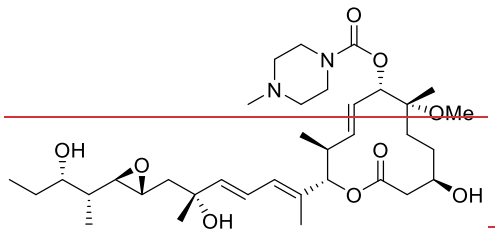
~~125. The antibody-drug conjugate of claim 115 or claim 116, wherein the splicing modulator comprises an aryl pladienolide.~~

~~126. The antibody-drug conjugate of claim 125, wherein the aryl pladienolide comprises D15, D14, D16, D17, D26, or D33.~~

~~127. The antibody-drug conjugate of claim 125 or claim 126, wherein the aryl pladienolide is a zwitterionic aryl pladienolide.~~

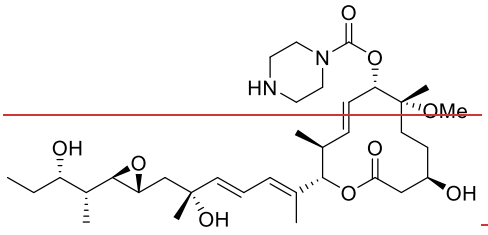
~~128. The antibody-drug conjugate of claim 127, wherein the zwitterionic aryl pladienolide comprises D33.~~

~~129. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D2:~~



~~(D2).~~

~~130. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D1:~~



~~(D1).~~

~~131. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D4, D12, D15, D8, D9, D10, D13, D18, D19, D20, D21, D22, D25, or D33.~~

~~132. The antibody-drug conjugate of any one of claims 1 to 131, wherein *p* is from 1 to 10.~~

~~133. The antibody-drug conjugate of any one of claims 1 to 132, wherein *p* is from 2 to 8.~~

~~134. The antibody-drug conjugate of any one of claims 1 to 133, wherein *p* is from 4 to 8.~~

~~135. The antibody-drug conjugate of any one of claims 1 to 134, wherein *p* is 4.~~

~~136. The antibody-drug conjugate of any one of claims 1 to 134, wherein *p* is 8.~~

137. An antibody-drug conjugate of Formula (I):

$$Ab-(L-D)_p \quad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

D is D2;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

138. The antibody-drug conjugate of claim 137, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.

139. The antibody-drug conjugate of claim 138, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.

140. The antibody-drug conjugate of claim 138 or claim 139, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

141. The antibody-drug conjugate of any one of claims 138 to 140, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

142. The antibody-drug conjugate of any one of claims 138 to 141, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

143. The antibody-drug conjugate of any one of claims 138 to 142, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

144. The antibody-drug conjugate of claim 137, wherein the antibody or antigen binding fragment targets a CD138-expressing cell.

~~145. The antibody-drug conjugate of claim 144, wherein the antibody or antigen binding fragment is an anti-CD138 antibody or antigen binding fragment.~~

~~146. The antibody-drug conjugate of claim 144 or claim 145, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:7 (HCDR1), SEQ ID NO:8 (HCDR2), and SEQ ID NO:9 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:10 (LCDR1), SEQ ID NO:11 (LCDR2), and SEQ ID NO:12 (LCDR3).~~

~~147. The antibody-drug conjugate of any one of claims 144 to 146, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22.~~

~~148. The antibody-drug conjugate of any one of claims 144 to 147, wherein the antibody or antigen binding fragment comprises a human IgG2a heavy chain constant region.~~

~~149. The antibody-drug conjugate of any one of claims 144 to 148, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~

~~150. The antibody-drug conjugate of claim 137, wherein the antibody or antigen binding fragment targets an EPHA2-expressing cell.~~

~~151. The antibody-drug conjugate of claim 150, wherein the antibody or antigen binding fragment is an anti-EPHA2 antibody or antigen binding fragment.~~

~~152. The antibody-drug conjugate of claim 150 or claim 151, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:13 (HCDR1), SEQ ID NO:14 (HCDR2), and SEQ ID NO:15 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:16 (LCDR1), SEQ ID NO:17 (LCDR2), and SEQ ID NO:18 (LCDR3).~~

153. The antibody-drug conjugate of any one of claims 150 to 152, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24.

154. The antibody-drug conjugate of any one of claims 150 to 153, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

155. The antibody-drug conjugate of any one of claims 150 to 154, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

156. An antibody-drug conjugate of Formula (I):

$$Ab-(L-D)_p \qquad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

D is D1;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

157. The antibody-drug conjugate of claim 156, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.

158. The antibody-drug conjugate of claim 157, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.

159. The antibody-drug conjugate of claim 157 or claim 158, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

~~160. The antibody-drug conjugate of any one of claims 157 to 159, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.~~

~~161. The antibody-drug conjugate of any one of claims 157 to 160, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.~~

~~162. The antibody-drug conjugate of any one of claims 157 to 161, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~

~~163. The antibody-drug conjugate of claim 156, wherein the antibody or antigen binding fragment targets a CD138-expressing cell.~~

~~164. The antibody-drug conjugate of claim 163, wherein the antibody or antigen binding fragment is an anti-CD138 antibody or antigen binding fragment.~~

~~165. The antibody-drug conjugate of claim 163 or claim 164, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:7 (HCDR1), SEQ ID NO:8 (HCDR2), and SEQ ID NO:9 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:10 (LCDR1), SEQ ID NO:11 (LCDR2), and SEQ ID NO:12 (LCDR3).~~

~~166. The antibody-drug conjugate of any one of claims 163 to 165, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22.~~

~~167. The antibody-drug conjugate of any one of claims 163 to 166, wherein the antibody or antigen binding fragment comprises a human IgG2a heavy chain constant region.~~

~~168. The antibody-drug conjugate of any one of claims 163 to 167, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~

169. The antibody-drug conjugate of claim 156, wherein the antibody or antigen binding fragment targets an EPHA2-expressing cell.

170. The antibody-drug conjugate of claim 169, wherein the antibody or antigen binding fragment is an anti-EPHA2 antibody or antigen binding fragment.

171. The antibody-drug conjugate of claim 169 or claim 170, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:13 (HCDR1), SEQ ID NO:14 (HCDR2), and SEQ ID NO:15 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:16 (LCDR1), SEQ ID NO:17 (LCDR2), and SEQ ID NO:18 (LCDR3).

172. The antibody-drug conjugate of any one of claims 169 to 171, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24.

173. The antibody-drug conjugate of any one of claims 169 to 172, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

174. The antibody-drug conjugate of any one of claims 169 to 173, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

175. An antibody-drug conjugate of Formula (I):

$$Ab\text{-}(L\text{-}D)_p \qquad (I)$$

wherein

Ab is an anti-HER2 antibody or antigen binding fragment comprising three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3);

D is D2, D1, D4, D12, or D15;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

176. The antibody-drug conjugate of claim 175, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

177. An antibody-drug conjugate of Formula (I):

$$Ab-(L-D)_p \quad (I)$$

wherein

Ab is an anti-CD138 antibody or antigen binding fragment comprising three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:7 (HCDR1), SEQ ID NO:8 (HCDR2), and SEQ ID NO:9 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:10 (LCDR1), SEQ ID NO:11 (LCDR2), and SEQ ID NO:12 (LCDR3);

D is D2, D1, D4, D12, or D15;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

178. The antibody-drug conjugate of claim 177, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22.

179. An antibody-drug conjugate of Formula (I):

$$Ab-(L-D)_p \quad (I)$$

wherein

Ab is an anti-EPHA2 antibody or antigen binding fragment comprising three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:13 (HCDR1), SEQ ID NO:14 (HCDR2), and SEQ ID NO:15 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:16 (LCDR1), SEQ ID NO:17 (LCDR2), and SEQ ID NO:18 (LCDR3);

D is D2, D1, D4, D12, or D15;

L is a linker that covalently attaches Ab to D; and

~~p is an integer from 1 to 15.~~

~~180. The antibody-drug conjugate of claim 179, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24.~~

~~181. The antibody-drug conjugate of any one of claims 156 to 180, wherein the linker is a cleavable linker.~~

~~182. The antibody-drug conjugate of claim 181, wherein the cleavable linker comprises MC-Val-Cit-pABC.~~

~~183. The antibody-drug conjugate of claim 181, wherein the cleavable linker comprises MC-Val-Ala-pABC.~~

~~184. The antibody-drug conjugate of claim 181, wherein the cleavable linker comprises MC-Val-Ala-pAB.~~

~~185. The antibody-drug conjugate of any one of claims 156 to 180, wherein the linker is a non-cleavable linker.~~

~~186. The antibody-drug conjugate of claim 185, wherein the non-cleavable linker comprises Mal-Hex.~~

~~187. The antibody-drug conjugate of claim 185, wherein the non-cleavable linker comprises Mal-Et.~~

~~188. The antibody-drug conjugate of claim 185, wherein the non-cleavable linker comprises Mal-Et-O-Et.~~

~~189. The antibody-drug conjugate of any one of claims 156 to 188, wherein *p* is from 1 to 10.~~

~~190. The antibody-drug conjugate of any one of claims 156 to 189, wherein *p* is from 2 to 8.~~

~~191. The antibody-drug conjugate of any one of claims 156 to 190, wherein *p* is from 4 to 8.~~

~~192. The antibody-drug conjugate of any one of claims 156 to 191, wherein *p* is 4.~~

~~193. The antibody-drug conjugate of any one of claims 156 to 191, wherein *p* is 8.~~

~~194. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 1 to 193, wherein the average *p* of the antibody-drug conjugates in the composition is from about 3.5 to about 5.5.~~

~~195. The composition of claim 194, wherein the average *p* of the antibody-drug conjugates in the composition is about 4.~~

~~196. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 1 to 193, wherein the average *p* of the antibody-drug conjugates in the composition is from about 7 to about 9.~~

~~197. The composition of claim 196, wherein the average *p* of the antibody-drug conjugates in the composition is about 8.~~

~~198. A method of treating a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197.~~

~~199. The method of claim 198, wherein the neoplastic disorder is a hematological malignancy or a solid tumor.~~

~~200. The method of claim 198 or claim 199, wherein the neoplastic disorder is a hematological malignancy.~~

~~201. The method of claim 199 or claim 200, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.~~

~~202. The method of claim 198 or claim 199, wherein the neoplastic disorder is a solid tumor.~~

~~203. The method of claim 199 or claim 202, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.~~

~~204. The method of any one of claims 198 to 203, wherein treatment with the antibody-drug conjugate or composition induces bystander killing of neoplastic cells which do not express a target antigen but are adjacent to neoplastic cells which express a target antigen.~~

~~205. The method of any one of claims 198 to 204, wherein the subject has one or more neoplastic cells which express a target antigen.~~

~~206. The method of claim 205, wherein the target antigen is HER2.~~

~~207. The method of claim 206, wherein the one or more neoplastic cells are derived from a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.~~

~~208. The method of claim 207, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.~~

~~209. The method of any one of claims 206 to 208, wherein the subject is non-responsive or poorly responsive to treatment with (a) an anti-HER2 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~210. The method of any one of claims 206 to 209, wherein the subject is intolerant, non-responsive, or poorly responsive to treatment with a splicing modulator when administered alone.~~

~~211. The method of claim 205, wherein the target antigen is CD138.~~

~~212. The method of claim 211, wherein the one or more neoplastic cells are derived from a CD138-expressing multiple myeloma.~~

~~213. The method of claim 211 or claim 212, wherein the subject is non-responsive or poorly responsive to treatment with (a) an anti-CD138 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~214. The method of any one of claims 211 to 213, wherein the subject is intolerant, non-responsive, or poorly responsive to treatment with a splicing modulator when administered alone.~~

~~215. The method of claim 205, wherein the target antigen is EPHA2.~~

~~216. The method of claim 215, wherein the one or more neoplastic cells are derived from an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.~~

~~217. The method of claim 215 or claim 216, wherein the subject is non-responsive or poorly responsive to treatment with (a) an anti-EPHA2 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~218. The method of any one of claims 215 to 217, wherein the subject is intolerant, non-responsive, or poorly responsive to treatment with a splicing modulator when administered alone.~~

~~219. A method of reducing or inhibiting growth of a tumor in a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197.~~

~~220. The method of claim 219, wherein treatment with the antibody-drug conjugate or composition induces bystander killing of neoplastic tumor cells which do not express a target antigen but are adjacent to neoplastic tumor cells which express a target antigen.~~

~~221. The method of claim 219 or claim 220, wherein the tumor comprises one or more neoplastic cells which express a target antigen.~~

~~222. The method of claim 221, wherein the target antigen is HER2.~~

~~223. The method of claim 222, wherein the one or more neoplastic cells are derived from a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.~~

~~224. The method of claim 223, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.~~

~~225. The method of any one of claims 222 to 224, wherein the tumor is resistant or refractory to treatment with (a) an anti-HER2 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~226. The method of claim 221, wherein the target antigen is CD138.~~

~~227. The method of claim 226, wherein the one or more neoplastic cells are derived from a CD138-expressing multiple myeloma.~~

~~228. The method of claim 226 or claim 227, wherein the tumor is resistant or refractory to treatment with (a) an anti-CD138 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~229. The method of claim 221, wherein the target antigen is EPHA2.~~

~~230. The method of claim 229, wherein the one or more neoplastic cells are derived from an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.~~

~~231. The method of claim 229 or claim 230, wherein the tumor is resistant or refractory to treatment with (a) an anti-EPHA2 antibody when administered alone and/or (b) a splicing modulator when administered alone.~~

~~232. A method of determining whether a subject having or suspected of having a neoplastic disorder will be responsive to treatment with the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197, comprising providing a biological sample~~

from the subject and contacting the biological sample with the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197.

233. The method of claim 232, wherein the biological sample is a tumor sample.

234. The method of claim 233, wherein the tumor sample is a tumor biopsy or blood sample.

235. The method of claim 234, wherein the blood sample is selected from blood, a blood fraction, or a cell obtained from the blood or blood fraction.

236. The method of any one of claims 232 to 235, wherein the subject has one or more neoplastic cells which express a target antigen.

237. The method of claim 236, wherein the target antigen is HER2.

238. The method of claim 237, wherein the one or more neoplastic cells are derived from a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.

239. The method of claim 238, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.

240. The method of claim 236, wherein the target antigen is CD138.

241. The method of claim 240, wherein the one or more neoplastic cells are derived from a CD138-expressing multiple myeloma.

242. The method of claim 236, wherein the target antigen is EPHA2.

243. The method of claim 242, wherein the one or more neoplastic cells are derived from an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.

~~244. An antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197 for use in the treatment of a neoplastic disorder.~~

~~245. The antibody-drug conjugate for use of claim 244, wherein the neoplastic disorder is characterized by having one or more neoplastic cells which express a target antigen.~~

~~246. The antibody-drug conjugate for use of claim 245, wherein the target antigen is HER2.~~

~~247. The antibody-drug conjugate for use of claim 246, wherein the neoplastic disorder is a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.~~

~~248. The antibody-drug conjugate of claim 247, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.~~

~~249. The antibody-drug conjugate for use of claim 245, wherein the target antigen is CD138.~~

~~250. The antibody-drug conjugate for use of claim 249, wherein the neoplastic disorder is a CD138-expressing multiple myeloma.~~

~~251. The antibody-drug conjugate for use of claim 245, wherein the target antigen is EPHA2.~~

~~252. The antibody-drug conjugate for use of claim 251, wherein the neoplastic disorder is an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.~~

~~253. Use of an antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197 in the treatment of a neoplastic disorder.~~

~~254. The use of claim 253, wherein the neoplastic disorder is characterized by having one or more neoplastic cells which express a target antigen.~~

~~255. The use of claim 254, wherein the target antigen is HER2.~~

~~256. The use of claim 255, wherein the neoplastic disorder is a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.~~

~~257. The use of claim 256, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.~~

~~258. The use of claim 254, wherein the target antigen is CD138.~~

~~259. The use of claim 258, wherein the neoplastic disorder is a CD138-expressing multiple myeloma.~~

~~260. The use of claim 254, wherein the target antigen is EPHA2.~~

~~261. The use of claim 260, wherein the neoplastic disorder is an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.~~

~~262. Use of an antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197 in a method of manufacturing a medicament for the treatment of a neoplastic disorder.~~

~~263. The use of claim 262, wherein the neoplastic disorder is characterized by having one or more neoplastic cells which express a target antigen.~~

~~264. The use of claim 263, wherein the target antigen is HER2.~~

~~265. The use of claim 264, wherein the neoplastic disorder is a HER2-expressing breast cancer, ovarian cancer, gastric cancer, lung cancer, uterine cancer, osteosarcoma, or salivary duct carcinoma.~~

~~266. The use of claim 265, wherein the lung cancer is lung adenocarcinoma and/or the uterine cancer is uterine serous endometrial carcinoma.~~

~~267. The use of claim 263, wherein the target antigen is CD138.~~

268. The use of claim 267, wherein the neoplastic disorder is a CD138-expressing multiple myeloma.

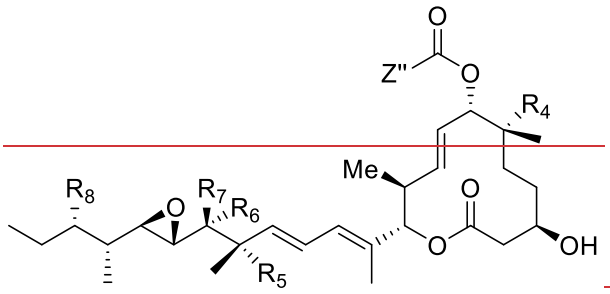
269. The use of claim 263, wherein the target antigen is EPHA2.

270. The use of claim 269, wherein the neoplastic disorder is an EPHA2-expressing breast cancer, prostate cancer, ovarian cancer, lung cancer, melanoma, colon cancer, or esophageal cancer.

271. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197, and a pharmaceutically acceptable carrier.

272. A method of producing the antibody-drug conjugate of any one of claims 1 to 193, comprising reacting an antibody or antigen binding fragment with a linker joined to a splicing modulator under conditions that allow conjugation.

273. A compound of Formula (III):



(III), or a pharmaceutically acceptable salt thereof, wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^2 is absent or a linker;

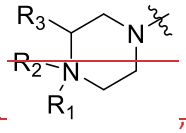
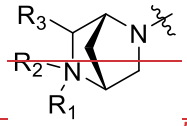
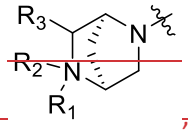
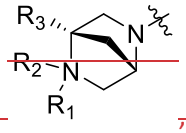
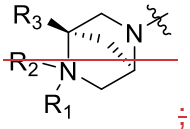
R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; and

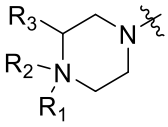
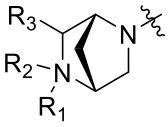
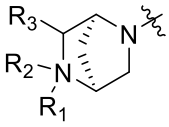
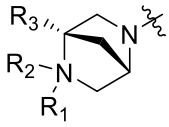
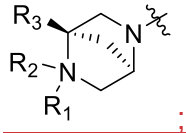
~~R⁴,~~ R^5~~,~~ and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, and -$NR^{15}R^{16}$~~, and a linker~~;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

~~Z'' is chosen from~~  ~~,~~  ~~,~~  ~~,~~  ~~, and~~  ~~;~~

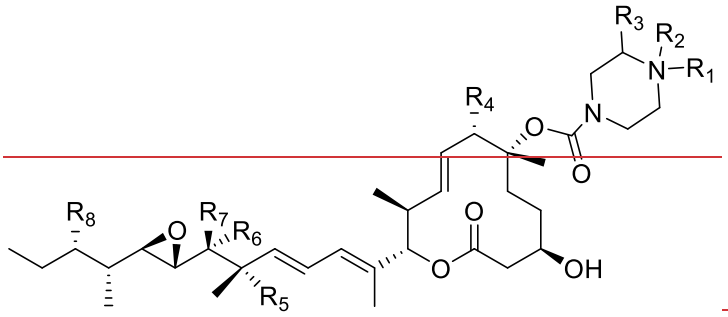
Z'' is chosen from  ,  ,  ,  , and  ;

wherein R^1~~, R^2~~, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein at least one of R^6 and R^7 is hydrogen~~; and.~~

~~wherein if R^2 is a linker, then neither R^6 or R^7 is a linker, and if R^6 or R^7 is a linker, then R^2 is absent.~~

274. A compound of Formula (V):



(V), or a pharmaceutically acceptable salt thereof, wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^2 is absent or a linker;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; and

R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, -$NR^{15}R^{16}$, and a linker;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17}; and

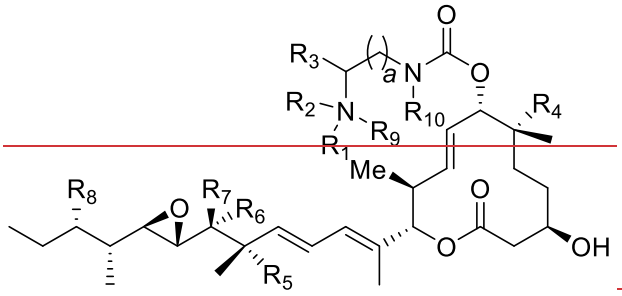
R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein at least one of R^6 and R^7 is hydrogen; and

wherein if R^2 is a linker, then neither R^6 or R^7 is a linker, and if R^6 or R^7 is a linker, then R^2 is absent.

275. A compound of Formula (VII):



(VII), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^9 are each independently chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^2 is absent or a linker;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;

R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, -$NR^{15}R^{16}$, and a linker;

R^{10} is chosen from hydrogen, C_1-C_6 alkyl groups, -C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

a is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

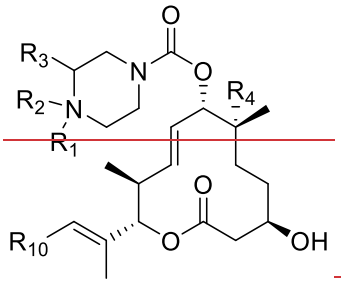
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein at least one of R^6 and R^7 is hydrogen;

wherein if R^2 is a linker, then neither R^6 or R^7 is a linker, and if R^6 or R^7 is a linker, then R^2 is absent; and

wherein R^1 and R^9 cannot both be absent.

276. A compound of Formula (IX):



(IX), or a pharmaceutically acceptable salt thereof, wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^2 is a linker;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;

R^4 is chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^{10} is chosen from 3 to 10 membered carbocycles and 3 to 10 membered heterocycles, each of which is substituted with 0 to 3 R^a, wherein each R^a is independently chosen from halogens, C_1-C_6 alkyl groups, -O-(C_1-C_6)alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylhydroxy groups, $-S(=O)_w$-(4 to 7 membered heterocycles), 4 to 7 membered carbocycles, and 4 to 7 membered heterocycles;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17}; and

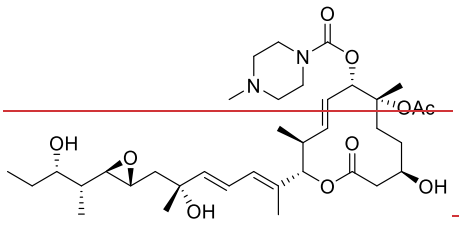
R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein R^1, R^2, R^3, R^4, R^{10}, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, $-NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

wherein each R^a is independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, $-NR^{15}R^{16}$, C_1-C_6 alkyl groups, -(C=O)-(C_1-C_6 alkyl) groups, -(C=O)-(C_1-C_6 alkyl)-(C_3-C_{10} heterocyclyl) groups, $-S(=O)_w$-(C_3-C_8 heterocyclyl groups, and C_1-C_6 alkylcarboxylic acid groups,

each of which is substituted with 0, 1, or 2 groups independently chosen from halogens, hydroxyl groups, $NR^{15}R^{16}$, and C_1-C_3 alkyl groups.

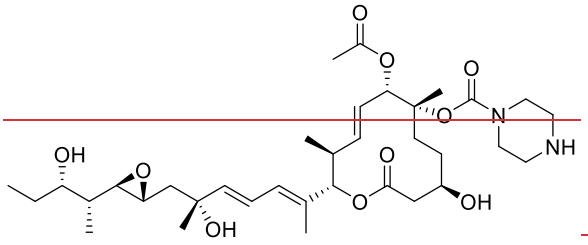
277. A compound chosen from a compound of formula



(D4), and pharmaceutically acceptable salts thereof.

278. A pharmaceutical composition comprising the compound of claim 277, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

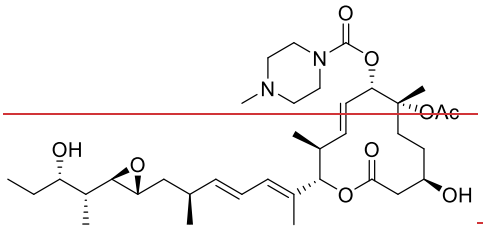
279. A compound chosen from a compound of formula



(D8), and pharmaceutically acceptable salts thereof.

280. A pharmaceutical composition comprising the compound of claim 279, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

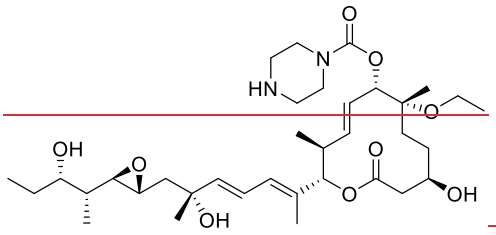
281. A compound chosen from a compound of formula



(D9), and pharmaceutically acceptable salts thereof.

282. A pharmaceutical composition comprising the compound of claim 281, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

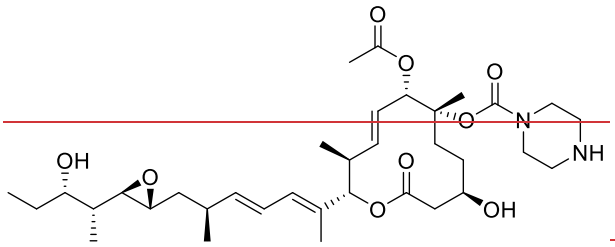
283. A compound chosen from a compound of formula



(D10), and pharmaceutically acceptable salts thereof.

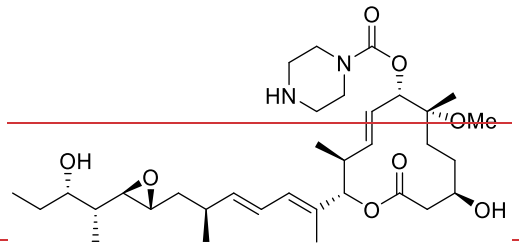
284. A pharmaceutical composition comprising the compound of claim 283, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

285. A compound chosen from a compound of formula



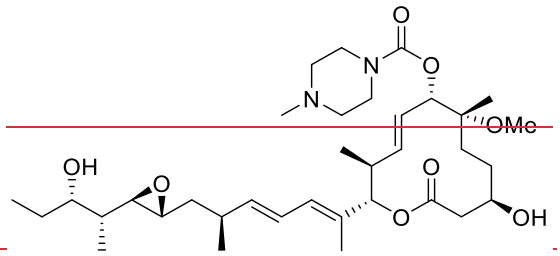
(D13), and pharmaceutically acceptable salts thereof.

286. A pharmaceutical composition comprising the compound of claim 285, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

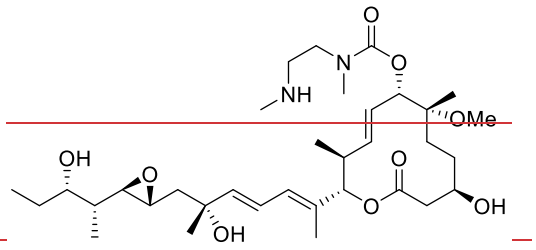


287. A compound chosen from a compound of formula (D18), and pharmaceutically acceptable salts thereof.

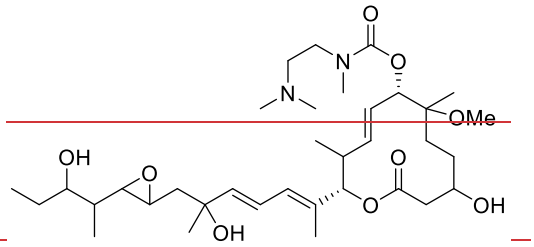
288. A pharmaceutical composition comprising the compound of claim 287, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

289. A compound chosen from a compound of formula  (D19), and pharmaceutically acceptable salts thereof.

290. A pharmaceutical composition comprising the compound of claim 289, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

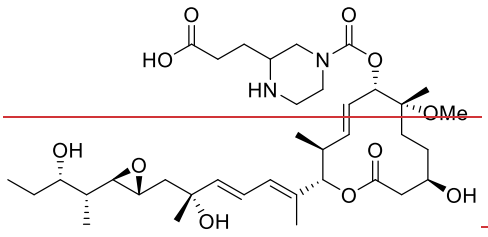
291. A compound chosen from a compound of formula  (D20), and pharmaceutically acceptable salts thereof.

292. A pharmaceutical composition comprising the compound of claim 291, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

293. A compound chosen from a compound of formula  (D21), and pharmaceutically acceptable salts thereof.

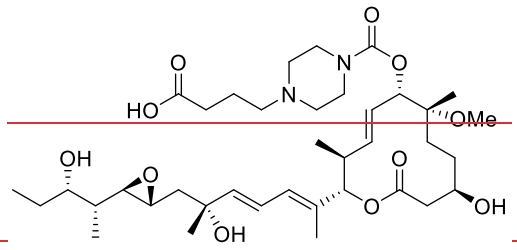
294. A pharmaceutical composition comprising the compound of claim 293, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

295. A compound chosen from a compound of formula



(D22), and pharmaceutically acceptable salts thereof.

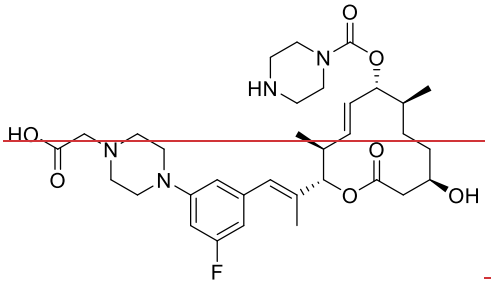
296. A pharmaceutical composition comprising the compound of claim 295, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

297. A compound chosen from a compound of formula 

(D25), and pharmaceutically acceptable salts thereof.

298. A pharmaceutical composition comprising the compound of claim 297, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

299. A compound chosen from a compound of formula



(D33), and pharmaceutically acceptable salts thereof.

300. A pharmaceutical composition comprising the compound of claim 299, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

301. A method of treating a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the compound or pharmaceutical composition of any one of claims 273 to 300.

302. A method of reducing or inhibiting growth of a tumor in a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the compound or pharmaceutical composition of any one of claims 273 to 300.

303. A method of inducing at least one neoantigen, comprising contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197, thereby inducing production of at least one neoantigen.

304. The method of claim 303, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

305. The method of claim 304, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 37.

306. The method of claim 304, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 39.

307. The method of claim 304, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

308. The method of any one of claims 303 to 307, wherein the neoplastic cell is present in an in vitro cell culture.

309. The method of claim 308, wherein the neoplastic cell is obtained from a subject.

310. The method of any one of claims 303 to 307, wherein the neoplastic cell is present in a subject.

311. The method of any one of claims 303 to 310, wherein the neoplastic cell is derived from a hematological malignancy or a solid tumor.

312. The method of claim 311, wherein the hematological malignancy is selected from a B-cell malignancy, a leukemia, a lymphoma, and a myeloma.

313. The method of claim 311 or claim 312, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.

~~314. The method of claim 311, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.~~

~~315. A method of inducing at least one neoantigen and/or a T-cell response in a subject having or suspected of having a neoplastic disorder, comprising administering to the subject an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197.~~

~~316. A method of treating a subject having or suspected of having a neoplastic disorder, comprising administering to the subject an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197, wherein administration of the splicing modulator, antibody-drug conjugate, or composition induces at least one neoantigen and/or a T-cell response.~~

~~317. The method of claim 315 or claim 316, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.~~

~~318. The method of claim 317, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 37.~~

~~319. The method of claim 317, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 39.~~

~~320. The method of claim 317, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.~~

~~321. The method of any one of claims 315 to 320, wherein the administered amount of the splicing modulator, antibody-drug conjugate, or composition is reduced due to induction of at least one neoantigen and/or a T-cell response, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.~~

~~322. The method of any one of claims 315 to 321, wherein the administered amount of the splicing modulator, antibody-drug conjugate, or composition is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.~~

323. The method of any one of claims 315 to 322, wherein the splicing modulator, antibody-drug conjugate, or composition is administered at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90% less frequently, as compared to a standard dosing regimen of the splicing modulator, antibody-drug conjugate, or composition.

324. The method of any one of claims 315 to 323, wherein the administered amount and/or dosage of the splicing modulator, antibody-drug conjugate, or composition results in lower systemic toxicity and/or improved tolerance.

325. The method of any one of claims 315 to 324, further comprising administering at least one additional therapy.

326. The method of claim 325, wherein the administered amount of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy is reduced due to induction of at least one neoantigen and/or a T-cell response, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy.

327. The method of claim 325 or claim 326, wherein the administered amount of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy.

328. The method of any one of claims 325 to 327, wherein the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy is administered at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90% less frequently, as compared to a standard dosing regimen of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy.

329. The method of any one of claims 325 to 328, wherein the administered amount and/or dosage of the splicing modulator, antibody-drug conjugate, composition, and/or the at least one additional therapy results in lower systemic toxicity and/or improved tolerance.

330. The method of any one of claims 325 to 329, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated before administration of the at least one additional therapy.

331. The method of any one of claims 325 to 329, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated after administration of the at least one additional therapy.

332. The method of any one of claims 325 to 329, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated concurrently with administration of the at least one additional therapy.

333. The method of any one of claims 315 to 332, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is repeated at least once after initial administration.

334. The method of claim 333, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to the amount used for initial administration.

335. The method of claim 333 or claim 334, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

336. The method of any one of claims 333 to 335, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

337. The method of any one of claims 325 to 336, wherein administration of the at least one additional therapy is repeated at least once after initial administration.

338. The method of claim 337, wherein the amount of the at least one additional therapy used for repeated administration is reduced as compared to the amount used for initial administration.

339. The method of claim 337 or claim 338, wherein the amount of the at least one additional therapy used for repeated administration is reduced as compared to a standard dosage of the at least one additional therapy.

340. The method of any one of claims 337 to 339, wherein the amount of the at least one additional therapy used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%,

35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the at least one additional therapy.

341. The method of any one of claims 337 to 340, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is concurrent with repeated administration of the at least one additional therapy.

342. The method of any one of claims 337 to 340, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is sequential or staggered with repeated administration of the at least one additional therapy.

343. The method of any one of claims 325 to 342, wherein the at least one additional therapy comprises administering a checkpoint inhibitor.

344. The method of claim 343, wherein the subject is intolerant, non-responsive, or poorly responsive to the checkpoint inhibitor when administered alone.

345. The method of claim 343 or claim 344, wherein the checkpoint inhibitor targets CTLA4, PD1, PDL1, OX40, CD40, GITR, LAG3, TIM3, and/or KIR.

346. The method of any one of claims 343 to 345, wherein the checkpoint inhibitor targets CTLA4, OX40, CD40, and/or GITR.

347. The method of any one of claims 343 to 346, wherein the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated antigen 4 pathway (CTLA4) inhibitor.

348. The method of claim 347, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.

349. The method of claim 348, wherein the anti-CTLA4 antibody is ipilimumab.

350. The method of any one of claims 343 to 346, wherein the checkpoint inhibitor comprises a programmed death-1 pathway (PD1) inhibitor.

351. The method of claim 350, wherein the PD1 inhibitor is an anti-PD1 antibody.

352. The method of claim 351, wherein the anti-PD1 antibody is nivolumab.

353. The method of claim 350, wherein the PD1 inhibitor is an anti-PDL1 antibody.

354. The method of claim 353, wherein the anti-PDL1 antibody is atezolizumab.

~~355. The method of any one of claims 343 to 346, wherein the checkpoint inhibitor comprises a CTLA4 inhibitor and a PD1 inhibitor.~~

~~356. The method of claim 355, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.~~

~~357. The method of claim 356, wherein the anti-CTLA4 antibody is ipilimumab.~~

~~358. The method of claim 355, wherein the PD1 inhibitor is an anti-PD1 antibody.~~

~~359. The method of claim 358, wherein the anti-PD1 antibody is nivolumab.~~

~~360. The method of claim 355, wherein the PD1 inhibitor is an anti-PDL1 antibody.~~

~~361. The method of claim 360, wherein the anti-PDL1 antibody is atezolizumab.~~

~~362. The method of any one of claims 325 to 342, wherein the at least one additional therapy comprises administering a neoantigen vaccine.~~

~~363. The method of claim 362, wherein the splicing modulator, antibody-drug conjugate, or composition is administered before administration of the neoantigen vaccine.~~

~~364. The method of claim 362, wherein the splicing modulator, antibody-drug conjugate, or composition is administered after administration of the neoantigen vaccine.~~

~~365. The method of claim 362, wherein the splicing modulator, antibody-drug conjugate, or composition is administered concurrently with administration of the neoantigen vaccine.~~

~~366. The method of any one of claims 362 to 365, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is repeated at least once after initial administration.~~

~~367. The method of claim 366, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to the amount used for initial administration.~~

~~368. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen peptide.~~

~~369. The method of claim 368, wherein the at least one neoantigen peptide ranges from about 10 to about 50 or about 10 to about 35 amino acids in length.~~

~~370. The method of claim 368 or claim 369, wherein the at least one neoantigen peptide ranges from about 15 to about 25 amino acids in length.~~

~~371. The method of any one of claims 368 to 370, wherein the at least one neoantigen peptide comprises one or more than one neoantigen sequence.~~

~~372. The method of claim 371, wherein the neoantigen sequence is a neoantigen sequence specific to the subject.~~

~~373. The method of claim 371, wherein the neoantigen sequence is a universal neoantigen sequence.~~

~~374. The method of any one of claims 371 to 373, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.~~

~~375. The method of claim 374, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.~~

~~376. The method of claim 374, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.~~

~~377. The method of claim 374, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.~~

~~378. The method of any one of claims 371 to 373, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.~~

~~379. The method of claim 378, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.~~

~~380. The method of claim 378, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.~~

~~381. The method of any one of claims 374 to 380, wherein the neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.~~

382. The method of any one of claims 374 to 381, wherein the neoantigen sequence and/or antigenic portion is a personalized neoantigen vaccine for the subject.

383. The method of claim 382, wherein the neoantigen sequence and/or antigenic portion has been identified by sequencing at least one neoantigen induced in the subject by administering an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

384. The method of claim 382 or claim 383, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in the subject.

385. The method of any one of claims 374 to 381, wherein the neoantigen sequence and/or antigenic portion is a universal neoantigen vaccine.

386. The method of claim 385, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

387. The method of claim 385 or claim 386, wherein the neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

388. The method of any one of claims 385 to 387, wherein the at least one neoantigen peptide comprises a neoantigen sequence induced by contacting a neoplastic cell with an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

389. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable carrier.

390. The method of claim 389, wherein the at least one neoantigen peptide is linked to the pharmaceutically acceptable carrier.

391. The method of claim 389 or claim 390, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

392. The method of any one of claims 389 to 391, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are covalently attached via a linker.

393. The method of any one of claims 389 to 391, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are expressed as a fusion protein.

394. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable diluent.

395. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable adjuvant.

396. The method of claim 388, wherein the neoplastic cell is present in an in vitro cell culture.

397. The method of claim 396, wherein the neoplastic cell is obtained from the subject.

398. The method of claim 388, wherein the neoplastic cell is present in the subject.

399. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen mRNA.

400. The method of claim 399, wherein the at least one neoantigen mRNA encodes one or more than one neoantigen sequence.

401. The method of claim 400, wherein the neoantigen sequence is a neoantigen sequence specific to the subject.

402. The method of claim 400, wherein the neoantigen sequence is a universal neoantigen sequence.

403. The method of any one of claims 400 to 402, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

404. The method of claim 403, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.

405. The method of claim 403, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

406. The method of claim 403, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

407. The method of any one of claims 400 to 402, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

408. The method of claim 407, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

409. The method of claim 407, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

410. The method of any one of claims 403 to 409, wherein the neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

411. The method of any one of claims 403 to 410, wherein the neoantigen sequence and/or antigenic portion is a personalized neoantigen vaccine for the subject.

412. The method of claim 411, wherein the neoantigen sequence and/or antigenic portion has been identified by sequencing at least one neoantigen induced in the subject by administering an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

413. The method of claim 411 or claim 412, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in the subject.

414. The method of any one of claims 403 to 410, wherein the neoantigen sequence and/or antigenic portion is a universal neoantigen vaccine.

415. The method of claim 414, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

416. The method of claim 414 or claim 415, wherein the neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

417. The method of any one of claims 414 to 416, wherein the at least one neoantigen mRNA encodes a neoantigen sequence induced by contacting a neoplastic cell with an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

418. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable carrier.

419. The method of claim 418, wherein the at least one neoantigen mRNA is linked to the pharmaceutically acceptable carrier.

420. The method of claim 418 or claim 419, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

421. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable diluent.

422. The method of any one of claims 362 to 367, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable adjuvant.

423. The method of any one of claims 399 to 422, wherein the neoantigen mRNA is encapsulated by an encapsulating agent.

424. The method of claim 423, wherein the encapsulating agent is a liposome.

425. The method of claim 423, wherein the encapsulating agent is a nanoparticle.

426. The method of claim 417, wherein the neoplastic cell is present in an in vitro cell culture.

427. The method of claim 426, wherein the neoplastic cell is obtained from the subject.

428. The method of claim 417, wherein the neoplastic cell is present in the subject.

429. The method of any one of claims 325 to 342, wherein the at least one additional therapy comprises administering a cytokine or cytokine analog.

430. The method of claim 429, wherein the subject is intolerant, non-responsive, or poorly responsive to the cytokine or cytokine analog when administered alone.

431. The method of claim 429 or claim 430, wherein the cytokine or cytokine analog comprises a T-cell enhancer.

432. The method of any one of claims 429 to 431, wherein the cytokine or cytokine analog comprises IL-2, IL-10, IL-12, IL-15, IFNγ, and/or TNFα.

433. The method of any one of claims 325 to 342, wherein the at least one additional therapy comprises administering engineered tumor-targeting T-cells.

434. The method of any one of claims 315 to 433, further comprising detecting one or more neoantigens and/or a T-cell response in the subject after administration of the splicing modulator, antibody-drug conjugate, or composition.

435. The method of claim 434, further comprising continuing administration of the splicing modulator, antibody-drug conjugate, or composition if one or more neoantigens and/or a T-cell response is detected.

436. The method of claim 434 or claim 435, further comprising continuing administration of the splicing modulator, antibody-drug conjugate, or composition less frequently and/or at a reduced dosage if one or more neoantigens and/or a T-cell response is detected.

437. The method of any one of claims 434 to 436, wherein detecting one or more neoantigens and/or a T-cell response in the subject indicates efficacy of treatment with the splicing modulator, antibody-drug conjugate, or composition.

438. The method of any one of claims 315 to 437, wherein the subject has a non-synonymous mutational burden of about 150 mutations or less.

439. The method of any one of claims 315 to 438, wherein the subject has a non-synonymous mutational burden of about 100 mutations or less.

440. The method of any one of claims 315 to 439, wherein the subject has a non-synonymous mutational burden of about 50 mutations or less.

441. The method of any one of claims 315 to 440, wherein the neoplastic disorder is a hematological malignancy or a solid tumor.

442. The method of claim 441, wherein the hematological malignancy is selected from a B-cell malignancy, a leukemia, a lymphoma, and a myeloma.

443. The method of claim 441 or claim 442, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.

444. The method of claim 441, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.

445. A method of treating a subject having or suspected of having a neoplastic disorder, comprising:

(a) administering to the subject an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197, wherein administration of the splicing modulator, antibody-drug conjugate, or composition induces at least one neoantigen and/or a T-cell response;

(b) detecting one or more neoantigens and/or a T-cell response in the subject after administration of the splicing modulator, antibody-drug conjugate, or composition; and

(c) continuing administration of the splicing modulator, antibody-drug conjugate, or composition if one or more neoantigens and/or a T-cell response is detected.

446. The method of claim 445, wherein detecting one or more neoantigens and/or a T-cell response in the subject indicates efficacy of treatment with the splicing modulator, antibody-drug conjugate, or composition.

447. The method of claim 445 or claim 446, wherein the one or more neoantigens comprise an amino acid sequence of any one of SEQ ID NOs: 37-65.

448. The method of claim 447, wherein the one or more neoantigens comprise an amino acid sequence of SEQ ID NO: 37.

449. The method of claim 447, wherein the one or more neoantigens comprise an amino acid sequence of SEQ ID NO: 39.

450. The method of claim 447, wherein the one or more neoantigens comprise an amino acid sequence of any one of SEQ ID NOs: 46-49.

451. A method of treating a subject having or suspected of having a neoplastic disorder, comprising administering to the subject an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197; and at least one additional therapy.

452. The method of claim 451, wherein the at least one additional therapy comprises at least one, at least two, at least three, at least four, or at least five additional therapies.

453. The method of claim 451 or claim 452, wherein administration of the splicing modulator, antibody-drug conjugate, or composition induces at least one neoantigen and/or a T-cell response.

454. The method of any one of claims 451 to 453, wherein the administered amount of the splicing modulator, antibody-drug conjugate, or composition and/or the at least one additional therapy is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition and/or the at least one additional therapy.

455. The method of any one of claims 451 to 454, wherein the splicing modulator, antibody-drug conjugate, or composition and/or the at least one additional therapy is administered at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90% less frequently, as compared to a standard dosing regimen of the splicing modulator, antibody-drug conjugate, or composition and/or the at least one additional therapy.

456. The method of any one of claims 451 to 455, wherein the administered amount and/or dosage of the splicing modulator, antibody-drug conjugate, or composition and/or the at least one additional therapy results in lower systemic toxicity and/or improved tolerance.

457. The method of any one of claims 451 to 456, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated before administration of the at least one additional therapy.

458. The method of any one of claims 451 to 456, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated after administration of the at least one additional therapy.

459. The method of any one of claims 451 to 456, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is initiated concurrently with administration of the at least one additional therapy.

460. The method of any one of claims 451 to 460, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is repeated at least once after initial administration.

461. The method of claim 460, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to the amount used for initial administration.

462. The method of claim 460 or claim 461, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

463. The method of any one of claims 460 to 462, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

464. The method of any one of claims 451 to 463, wherein administration of the at least one additional therapy is repeated at least once after initial administration.

465. The method of claim 464, wherein the amount of the at least one additional therapy used for repeated administration is reduced as compared to the amount used for initial administration.

466. The method of claim 464 or claim 465, wherein the amount of the at least one additional therapy used for repeated administration is reduced as compared to a standard dosage of the at least one additional therapy.

467. The method of any one of claims 464 to 466, wherein the amount of the at least one additional therapy used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%,

35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the at least one additional therapy.

468. The method of any one of claims 464 to 467, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is concurrent with repeated administration of the at least one additional therapy.

469. The method of any one of claims 464 to 467, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is sequential or staggered with repeated administration of the at least one additional therapy.

470. The method of any one of claims 451 to 469, wherein the at least one additional therapy comprises administering a checkpoint inhibitor.

471. The method of claim 470, wherein the subject is intolerant, non-responsive, or poorly responsive to the checkpoint inhibitor when administered alone.

472. The method of claim 470 or claim 471, wherein the checkpoint inhibitor targets CTLA4, PD1, PDL1, OX40, CD40, GITR, LAG3, TIM3, and/or KIR.

473. The method of any one of claims 470 to 472, wherein the checkpoint inhibitor targets CTLA4, OX40, CD40, and/or GITR.

474. The method of any one of claims 470 to 473, wherein the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated antigen 4 pathway (CTLA4) inhibitor.

475. The method of claim 474, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.

476. The method of claim 475, wherein the anti-CTLA4 antibody is ipilimumab.

477. The method of any one of claims 470 to 473, wherein the checkpoint inhibitor comprises a programmed death-1 pathway (PD1) inhibitor.

478. The method of claim 477, wherein the PD1 inhibitor is an anti-PD1 antibody.

479. The method of claim 478, wherein the anti-PD1 antibody is nivolumab.

480. The method of claim 477, wherein the PD1 inhibitor is an anti-PDL1 antibody.

481. The method of claim 480, wherein the anti-PDL1 antibody is atezolizumab.

482. The method of any one of claims 470 to 473, wherein the checkpoint inhibitor comprises a CTLA4 inhibitor and a PD1 inhibitor.

483. The method of claim 482, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.

484. The method of claim 483, wherein the anti-CTLA4 antibody is ipilimumab.

485. The method of claim 482, wherein the PD1 inhibitor is an anti-PD1 antibody.

486. The method of claim 485, wherein the anti-PD1 antibody is nivolumab.

487. The method of claim 482, wherein the PD1 inhibitor is an anti-PDL1 antibody.

488. The method of claim 487, wherein the anti-PDL1 antibody is atezolizumab.

489. The method of any one of claims 451 to 469, wherein the at least one additional therapy comprises administering a neoantigen vaccine.

490. The method of claim 489, wherein the splicing modulator, antibody-drug conjugate, or composition is administered before administration of the neoantigen vaccine.

491. The method of claim 489, wherein the splicing modulator, antibody-drug conjugate, or composition is administered after administration of the neoantigen vaccine.

492. The method of claim 489, wherein the splicing modulator, antibody-drug conjugate, or composition is administered concurrently with administration of the neoantigen vaccine.

493. The method of any one of claims 489 to 492, wherein administration of the splicing modulator, antibody-drug conjugate, or composition is repeated at least once after initial administration.

494. The method of claim 493, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to the amount used for initial administration.

495. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen peptide.

496. The method of claim 495, wherein the at least one neoantigen peptide ranges from about 10 to about 50 or about 10 to about 35 amino acids in length.

497. The method of claim 495 or claim 496, wherein the at least one neoantigen peptide ranges from about 15 to about 25 amino acids in length.

498. The method of any one of claims 495 to 497, wherein the at least one neoantigen peptide comprises one or more than one neoantigen sequence.

499. The method of claim 498, wherein the neoantigen sequence is a neoantigen sequence specific to the subject.

500. The method of claim 498, wherein the neoantigen sequence is a universal neoantigen sequence.

501. The method of any one of claims 498 to 500, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

502. The method of claim 501, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.

503. The method of claim 501, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

504. The method of claim 501, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

505. The method of any one of claims 498 to 500, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

506. The method of claim 505, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

507. The method of claim 505, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

508. The method of any one of claims 501 to 507, wherein the neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

509. The method of any one of claims 501 to 508, wherein the neoantigen sequence and/or antigenic portion is a personalized neoantigen vaccine for the subject.

510. The method of claim 509, wherein the neoantigen sequence and/or antigenic portion has been identified by sequencing at least one neoantigen induced in the subject by administering an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

511. The method of claim 509 or claim 510, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in the subject.

512. The method of any one of claims 501 to 508, wherein the neoantigen sequence and/or antigenic portion is a universal neoantigen vaccine.

513. The method of claim 512, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

514. The method of claim 512 or claim 513, wherein the neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

515. The method of any one of claims 512 to 514, wherein the at least one neoantigen peptide comprises a neoantigen sequence induced by contacting a neoplastic cell with an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

516. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable carrier.

517. The method of claim 516, wherein the at least one neoantigen peptide is linked to the pharmaceutically acceptable carrier.

518. The method of claim 516 or claim 517, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin,

~~a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.~~

~~519. The method of any one of claims 516 to 518, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are covalently attached via a linker.~~

~~520. The method of any one of claims 516 to 518, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are expressed as a fusion protein.~~

~~521. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable diluent.~~

~~522. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable adjuvant.~~

~~523. The method of claim 515, wherein the neoplastic cell is present in an in vitro cell culture.~~

~~524. The method of claim 523, wherein the neoplastic cell is obtained from the subject.~~

~~525. The method of claim 515, wherein the neoplastic cell is present in the subject.~~

~~526. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen mRNA.~~

~~527. The method of claim 526, wherein the at least one neoantigen mRNA encodes one or more than one neoantigen sequence.~~

~~528. The method of claim 527, wherein the neoantigen sequence is a neoantigen sequence specific to the subject.~~

~~529. The method of claim 527, wherein the neoantigen sequence is a universal neoantigen sequence.~~

~~530. The method of any one of claims 527 to 529, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.~~

~~531. The method of claim 530, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.~~

532. The method of claim 530, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

533. The method of claim 530, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

534. The method of any one of claims 527 to 529, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

535. The method of claim 534, wherein the neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

536. The method of claim 534, wherein the neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

537. The method of any one of claims 530 to 536, wherein the neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

538. The method of any one of claims 530 to 537, wherein the neoantigen sequence and/or antigenic portion is a personalized neoantigen vaccine for the subject.

539. The method of claim 538, wherein the neoantigen sequence and/or antigenic portion has been identified by sequencing at least one neoantigen induced in the subject by administering an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

540. The method of claim 538 or claim 539, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in the subject.

541. The method of any one of claims 530 to 537, wherein the neoantigen sequence and/or antigenic portion is a universal neoantigen vaccine.

542. The method of claim 541, wherein the neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

543. The method of claim 541 or claim 542, wherein the neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

544. The method of any one of claims 541 to 543, wherein the at least one neoantigen mRNA encodes a neoantigen sequence induced by contacting a neoplastic cell with an effective amount of the splicing modulator, antibody-drug conjugate, or composition.

545. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable carrier.

546. The method of claim 545, wherein the at least one neoantigen mRNA is linked to the pharmaceutically acceptable carrier.

547. The method of claim 545 or claim 546, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

548. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable diluent.

549. The method of any one of claims 489 to 494, wherein the neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable adjuvant.

550. The method of any one of claims 526 to 549, wherein the neoantigen mRNA is encapsulated by an encapsulating agent.

551. The method of claim 550, wherein the encapsulating agent is a liposome.

552. The method of claim 550, wherein the encapsulating agent is a nanoparticle.

553. The method of claim 544, wherein the neoplastic cell is present in an in vitro cell culture.

554. The method of claim 553, wherein the neoplastic cell is obtained from the subject.

555. The method of claim 544, wherein the neoplastic cell is present in the subject.

556. The method of any one of claims 451 to 469, wherein the at least one additional therapy comprises administering a cytokine or cytokine analog.

557. The method of claim 556, wherein the subject is intolerant, non-responsive, or poorly responsive to the cytokine or cytokine analog when administered alone.

558. The method of claim 556 or claim 557, wherein the cytokine or cytokine analog comprises a T-cell enhancer.

559. The method of any one of claims 556 to 558, wherein the cytokine or cytokine analog comprises IL-2, IL-10, IL-12, IL-15, IFNγ, and/or TNFα.

560. The method of any one of claims 451 to 469, wherein the at least one additional therapy comprises administering engineered tumor-targeting T-cells.

561. The method of any one of claims 451 to 560, wherein the subject has a non-synonymous mutational burden of about 150 mutations or less.

562. The method of any one of claims 451 to 561, wherein the subject has a non-synonymous mutational burden of about 100 mutations or less.

563. The method of any one of claims 451 to 562, wherein the subject has a non-synonymous mutational burden of about 50 mutations or less.

564. The method of any one of claims 451 to 563, wherein the neoplastic disorder is a hematological malignancy or a solid tumor.

565. The method of claim 564, wherein the hematological malignancy is selected from a B-cell malignancy, a leukemia, a lymphoma, and a myeloma.

566. The method of claim 564 or claim 565, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.

567. The method of claim 564, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.

568. A method of identifying at least one neoantigen, comprising:

(a) contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197;

(b) detecting at least one alternatively-spliced mRNA transcript after contacting the neoplastic cell with the splicing modulator, antibody-drug conjugate, or composition;

(c) predicting translation of the at least one alternatively-spliced mRNA transcript into at least one peptide; and

(d) comparing the at least one peptide to a reference proteome, wherein at least one neoantigen is identified if the at least one peptide does not match any peptides in the reference proteome.

569. The method of claim 568, wherein detecting at least one alternatively-spliced mRNA transcript comprises RNAseq.

570. The method of claim 568 or claim 569, wherein predicting translation of the at least one alternatively-spliced mRNA transcript comprises quantifying the change in percent spliced in (dPSI) value for the at least one transcript.

571. The method of any one of claims 568 to 570, wherein predicting translation of the at least one alternatively-spliced mRNA transcript comprises RiboSeq and/or ribosomal profiling.

572. The method of any one of claims 568 to 571, wherein the method further comprises evaluating the at least one peptide for predicted major histocompatibility complex (MHC) binding.

573. The method of claim 572, wherein predicted MHC binding is determined by measuring raw affinity predicted binding strength of the at least one peptide.

574. The method of claim 573, wherein a raw affinity predicted binding strength of about 500 nM or higher indicates MHC binding.

575. The method of claim 572, wherein predicted MHC binding is determined by identifying a distribution of predicted binding strengths for a series of random peptides; and comparing predicted binding strength of the at least one peptide to the distribution.

576. The method of claim 575, wherein a predicted binding strength in the top 2.0% of the distribution indicates weak MHC binding.

577. The method of claim 575, wherein a predicted binding strength in the top 0.5% of the distribution indicates strong MHC binding.

578. The method of any one of claims 568 to 577, wherein the neoplastic cell is present in an in vitro cell culture.

579. The method of claim 578, wherein the neoplastic cell is obtained from the subject.

580. The method of any one of claims 568 to 577, wherein the neoplastic cell is present in the subject.

581. The method of any one of claims 568 to 580, further comprising contacting one or more additional neoplastic cells to identify at least one universal neoantigen.

582. A method of identifying at least one neoantigen, comprising:

(a) contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197;

(b) detecting at least one peptide comprising a potential neoantigen sequence after contacting the neoplastic cell with the splicing modulator, antibody-drug conjugate, or composition; and

(c) comparing the at least one peptide to a reference proteome, wherein at least one neoantigen is identified if the at least one peptide does not match any peptides in the reference proteome.

583. The method of claim 582, wherein the method further comprises evaluating the at least one peptide for predicted major histocompatibility complex (MHC) binding.

584. The method of claim 583, wherein predicted MHC binding is determined by measuring raw affinity predicted binding strength of the at least one peptide.

585. The method of claim 584, wherein a raw affinity predicted binding strength of about 500 nM or higher indicates MHC binding.

586. The method of claim 583, wherein predicted MHC binding is determined by identifying a distribution of predicted binding strengths for a series of random peptides; and comparing predicted binding strength of the at least one peptide to the distribution.

587. The method of claim 586, wherein a predicted binding strength in the top 2.0% of the distribution indicates weak MHC binding.

588. The method of claim 586, wherein a predicted binding strength in the top 0.5% of the distribution indicates strong MHC binding.

589. The method of any one of claims 582 to 588, wherein the neoplastic cell is present in an in vitro cell culture.

590. The method of claim 589, wherein the neoplastic cell is obtained from the subject.

591. The method of any one of claims 582 to 588, wherein the neoplastic cell is present in the subject.

592. The method of any one of claims 582 to 591, further comprising contacting one or more additional neoplastic cells to identify at least one universal neoantigen.

593. A method of making a neoantigen vaccine, comprising:

(a) identifying at least one neoantigen using the method of any one of claims 568 to 592; and

(b) formulating the at least one neoantigen together with a pharmaceutically acceptable carrier, diluent, or adjuvant.

594. The method of claim 593, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

595. The method of claim 594, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 37.

596. The method of claim 594, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 39.

597. The method of claim 594, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

598. The method of claim 593, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

599. The method of claim 598, wherein the at least one neoantigen comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

600. The method of claim 598, wherein the at least one neoantigen comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

601. The method of any one of claims 593 to 600, wherein the at least one neoantigen and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

602. The method of any one of claims 593 to 601, wherein the at least one neoantigen and/or antigenic portion is linked to the pharmaceutically acceptable carrier.

603. The method of any one of claims 593 to 602, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

604. A method of treating a subject having or suspected of having a neoplastic disorder, comprising:

(a) administering to the subject an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193, or the composition of any one of claims 194 to 197;

(b) detecting one or more neoantigens in the subject after administration of the splicing modulator, antibody-drug conjugate, or composition;

(c) comparing the one or more neoantigens to a panel of universal neoantigens; and

(d) administering to the subject a universal neoantigen vaccine comprising at least one universal neoantigen present in the subject.

605. The method of claim 604, wherein the universal neoantigen vaccine is administered alone or in combination with at least one additional therapy.

606. The method of claim 605, wherein the at least one additional therapy comprises at least one, at least two, at least three, at least four, or at least five additional therapies.

607. The method of claim 605 or claim 606, wherein the at least one additional therapy comprises repeated administration of the splicing modulator, antibody-drug conjugate, or composition.

608. The method of claim 607, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is initiated before administration of the universal neoantigen vaccine.

609. The method of claim 607, wherein repeated of the splicing modulator, antibody-drug conjugate, or composition is initiated after administration of the universal neoantigen vaccine.

610. The method of claim 607, wherein repeated administration of the splicing modulator, antibody-drug conjugate, or composition is initiated concurrently with administration of the universal neoantigen vaccine.

611. The method of any one of claims 607 to 610, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to the amount used for initial administration.

612. The method of any one of claims 607 to 611, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

613. The method of any one of claims 607 to 612, wherein the amount of the splicing modulator, antibody-drug conjugate, or composition used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the splicing modulator, antibody-drug conjugate, or composition.

614. The method of any one of claims 605 to 613, wherein the at least one additional therapy comprises administering a checkpoint inhibitor.

615. The method of claim 614, wherein administration of the checkpoint inhibitor is initiated before administration of the universal neoantigen vaccine and/or repeated administration of the splicing modulator, antibody-drug conjugate, or composition.

616. The method of claim 614, wherein administration of the checkpoint inhibitor is initiated after administration of the universal neoantigen vaccine and/or repeated of the splicing modulator, antibody-drug conjugate, or composition.

617. The method of claim 614, wherein administration of the checkpoint inhibitor is initiated concurrently with administration of the universal neoantigen vaccine and/or repeated administration of the splicing modulator, antibody-drug conjugate, or composition.

618. The method of any one of claims 614 to 617, wherein administration of the checkpoint inhibitor is repeated at least once after initial administration.

619. The method of claim 618, wherein the amount of the checkpoint inhibitor used for repeated administration is reduced as compared to the amount used for initial administration.

620. The method of claim 618 or claim 619, wherein the amount of the checkpoint inhibitor used for repeated administration is reduced as compared to a standard dosage of the checkpoint inhibitor.

621. The method of any one of claims 618 to 620, wherein the amount of the checkpoint inhibitor used for repeated administration is reduced by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, or 90%, as compared to a standard dosage of the checkpoint inhibitor.

622. The method of any one of claims 614 to 621, wherein the subject is intolerant, non-responsive, or poorly responsive to the checkpoint inhibitor when administered alone.

623. The method of any one of claims 614 to 622, wherein the checkpoint inhibitor targets CTLA4, PD1, PDL1, OX40, CD40, GITR, LAG3, TIM3, and/or KIR.

624. The method of any one of claims 614 to 623, wherein the checkpoint inhibitor targets CTLA4, OX40, CD40, and/or GITR.

625. The method of any one of claims 614 to 624, wherein the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated antigen 4 pathway (CTLA4) inhibitor.

626. The method of claim 625, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.

627. The method of claim 626, wherein the anti-CTLA4 antibody is ipilimumab.

628. The method of any one of claims 614 to 624, wherein the checkpoint inhibitor comprises a programmed death-1 pathway (PD1) inhibitor.

629. The method of claim 628, wherein the PD1 inhibitor is an anti-PD1 antibody.

630. The method of claim 629, wherein the anti-PD1 antibody is nivolumab.

631. The method of claim 628, wherein the PD1 inhibitor is an anti-PDL1 antibody.

632. The method of claim 631, wherein the anti-PDL1 antibody is atezolizumab.

633. The method of any one of claims 614 to 624, wherein the checkpoint inhibitor comprises a CTLA4 inhibitor and a PD1 inhibitor.

634. The method of claim 633, wherein the CTLA4 inhibitor is an anti-CTLA4 antibody.

635. The method of claim 634, wherein the anti-CTLA4 antibody is ipilimumab.

636. The method of claim 633, wherein the PD1 inhibitor is an anti-PD1 antibody.

637. The method of claim 636, wherein the anti-PD1 antibody is nivolumab.

638. The method of claim 633, wherein the PD1 inhibitor is an anti-PDL1 antibody.

639. The method of claim 638, wherein the anti-PDL1 antibody is atezolizumab.

640. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen peptide.

641. The method of claim 640, wherein the at least one neoantigen peptide ranges from about 10 to about 50 or about 10 to about 35 amino acids in length.

642. The method of claim 640 or claim 641, wherein the at least one neoantigen peptide ranges from about 15 to about 25 amino acids in length.

643. The method of any one of claims 640 to 642, wherein the at least one neoantigen peptide comprises one or more than one universal neoantigen sequence.

644. The method of claim 643, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

645. The method of claim 644, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.

646. The method of claim 644, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

647. The method of claim 644, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

648. The method of claim 643, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

649. The method of claim 648, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

650. The method of claim 648, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

651. The method of any one of claims 643 to 650, wherein the universal neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

652. The method of any one of claims 643 to 651, wherein the universal neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

653. The method of any one of claims 643 to 652, wherein the universal neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

654. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable carrier.

655. The method of claim 654, wherein the at least one neoantigen peptide is linked to the pharmaceutically acceptable carrier.

656. The method of claim 654 or claim 655, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

657. The method of any one of claims 654 to 656, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are covalently attached via a linker.

658. The method of any one of claims 654 to 656, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are expressed as a fusion protein.

659. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable diluent.

660. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen peptide and a pharmaceutically acceptable adjuvant.

661. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen mRNA.

662. The method of claim 661, wherein the at least one neoantigen mRNA encodes one or more than one universal neoantigen sequence.

663. The method of claim 662, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

664. The method of claim 663, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.

665. The method of claim 663, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

666. The method of claim 663, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

667. The method of claim 662, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

668. The method of claim 667, wherein the universal neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

669. The method of claim 667, wherein the universal neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

670. The method of any one of claims 662 to 669, wherein the universal neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

671. The method of any one of claims 662 to 670, wherein the universal neoantigen sequence and/or antigenic portion is capable of binding to at least one HLA allele expressed in at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 45% of subjects in a population of subjects suffering from the neoplastic disorder.

672. The method of any one of claims 662 to 671, wherein the universal neoantigen sequence and/or antigenic portion is capable of eliciting a T-cell response against a tumor present in at least 1%, at least 5%, or at least 10% of a population of subjects suffering from the neoplastic disorder.

673. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable carrier.

674. The method of claim 673, wherein the at least one neoantigen mRNA is linked to the pharmaceutically acceptable carrier.

675. The method of claim 673 or claim 674, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

676. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable diluent.

677. The method of any one of claims 604 to 639, wherein the universal neoantigen vaccine comprises at least one neoantigen mRNA and a pharmaceutically acceptable adjuvant.

678. The method of any one of claims 661 to 677, wherein the neoantigen mRNA is encapsulated by an encapsulating agent.

679. The method of claim 678, wherein the encapsulating agent is a liposome.

680. The method of claim 678, wherein the encapsulating agent is a nanoparticle.

681. The method of any one of claims 604 to 680, wherein the subject has a non-synonymous mutational burden of about 150 mutations or less.

682. The method of any one of claims 604 to 681, wherein the subject has a non-synonymous mutational burden of about 100 mutations or less.

683. The method of any one of claims 604 to 682, wherein the subject has a non-synonymous mutational burden of about 50 mutations or less.

684. The method of any one of claims 604 to 683, wherein the neoplastic disorder is a hematological malignancy or a solid tumor.

685. The method of claim 684, wherein the hematological malignancy is selected from a B-cell malignancy, a leukemia, a lymphoma, and a myeloma.

686. The method of claim 684 or claim 685, wherein the hematological malignancy is selected from acute myeloid leukemia and multiple myeloma.

687. The method of claim 684, wherein the solid tumor is selected from breast cancer, gastric cancer, prostate cancer, ovarian cancer, lung cancer, uterine cancer, salivary duct carcinoma, melanoma, colon cancer, cervical cancer, pancreatic cancer, kidney cancer, colorectal cancer, and esophageal cancer.

688. The method of any one of claims 303 to 687, wherein the antibody-drug conjugate comprises an antibody-drug conjugate of Formula (I):

$$Ab\text{-}(L\text{-}D)_p \qquad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

~~D is D2, D1, D4, D12, or D15;~~

~~L is a linker that covalently attaches Ab to D; and~~

~~*p* is an integer from 1 to 15.~~

~~689. The method of claim 688, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.~~

~~690. The method of claim 689, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.~~

~~691. The method of claim 689 or claim 690, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).~~

~~692. The method of any one of claims 689 to 691, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.~~

~~693. The method of claim 688, wherein the antibody or antigen binding fragment targets a CD138-expressing cell.~~

~~694. The method of claim 693, wherein the antibody or antigen binding fragment is an anti-CD138 antibody or antigen binding fragment.~~

~~695. The method of claim 693 or claim 694, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:7 (HCDR1), SEQ ID NO:8 (HCDR2), and SEQ ID NO:9 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:10 (LCDR1), SEQ ID NO:11 (LCDR2), and SEQ ID NO:12 (LCDR3).~~

696. The method of any one of claims 693 to 695, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22.

697. The method of claim 688, wherein the antibody or antigen binding fragment targets an EPHA2-expressing cell.

698. The method of claim 697, wherein the antibody or antigen binding fragment is an anti-EPHA2 antibody or antigen binding fragment.

699. The method of claim 697 or claim 698, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:13 (HCDR1), SEQ ID NO:14 (HCDR2), and SEQ ID NO:15 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:16 (LCDR1), SEQ ID NO:17 (LCDR2), and SEQ ID NO:18 (LCDR3).

700. The method of any one of claims 697 to 699, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24.

701. The method of any one of claims 688 to 700, wherein the linker is a cleavable linker.

702. The method of claim 701, wherein the cleavable linker comprises MC-Val-Cit-pABC.

703. The method of claim 701, wherein the cleavable linker comprises MC-Val-Ala-pABC.

704. The method of claim 701, wherein the cleavable linker comprises MC-Val-Ala-pAB.

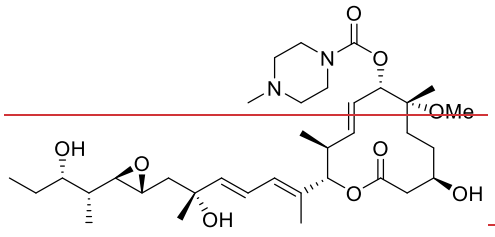
705. The method of any one of claims 688 to 700, wherein the linker is a non-cleavable linker.

706. The method of claim 705, wherein the non-cleavable linker comprises Mal-Hex.

707. The method of claim 705, wherein the non-cleavable linker comprises Mal-Et.

~~708. The method of claim 705, wherein the non-cleavable linker comprises Mal-Et-O-Et.~~

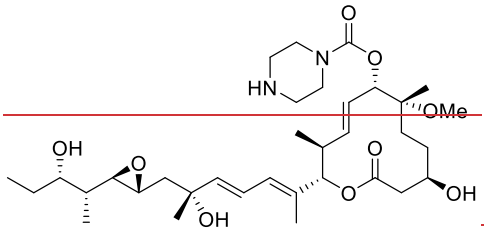
~~709. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D2:~~



~~(D2).~~

~~710. The method of claim 709, wherein the splicing modulator comprises D2 and the linker comprises MC-Val-Ala-pAB.~~

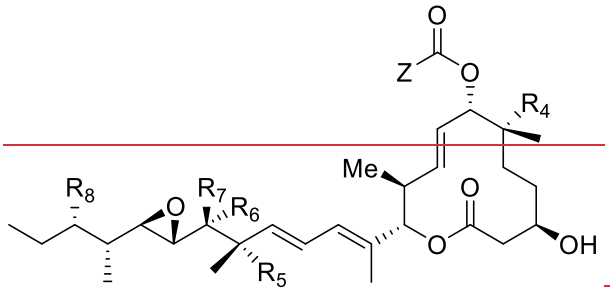
~~711. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D1:~~



~~(D1).~~

~~712. The method of claim 711, wherein the splicing modulator comprises D1 and the linker comprises MC-Val-Cit-pABC.~~

~~713. The method of any one of claims 688 to 708, wherein the splicing modulator comprises a splicing modulator of Formula (II):~~



~~(II), or a pharmaceutically acceptable salt thereof, wherein:~~

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

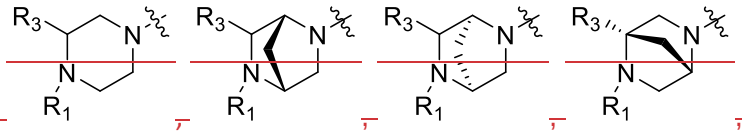
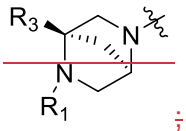
R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; and

R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, and $-NR^{15}R^{16}$;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};

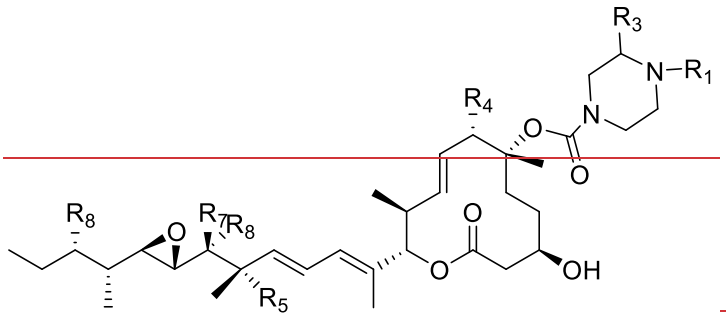
R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

Z is chosen from , and ;

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, $-NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups,

wherein at least one of R^6 and R^7 is hydrogen.

714. The method of any one of claims 688 to 708, wherein the splicing modulator comprises a splicing modulator of Formula (IV):



(IV), or a pharmaceutically acceptable salt thereof, wherein:

R^1 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups; and

R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, $-O-R^{17}$, $-O-C(=O)-R^{17}$, $-O-C(=O)-NR^{15}R^{16}$, C_1-C_6 alkyl groups, and $-NR^{15}R^{16}$;

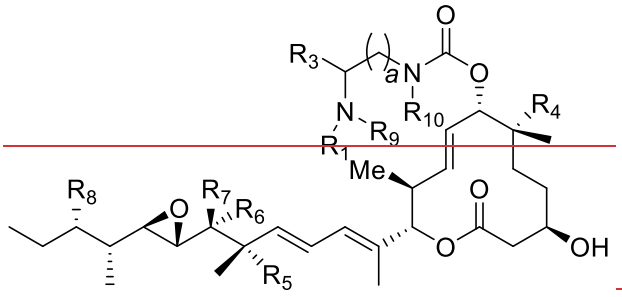
R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, $-C(=O)-R^{17}$, and $-C(=O)-O-R^{17}$; and

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, $-NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups,

wherein at least one of R^6 and R^7 is hydrogen.

715. The method of any one of claims 688 to 708, wherein the splicing modulator comprises a splicing modulator of Formula (VI):



(VI), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^9 are each independently chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;

R^4, R^5, and R^8 are each independently chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups;

R^6 and R^7 are each independently chosen from hydrogen, -O-R^{17}, -O-C(=O)-R^{17}, -O-C(=O)-$NR^{15}R^{16}$, C_1-C_6 alkyl groups, -$NR^{15}R^{16}$, and a linker;

R^{10} is chosen from hydrogen, C_1-C_6 alkyl groups, -C(=O)-(C_1-C_6 alkyl) groups, and -CD_3;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17};

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

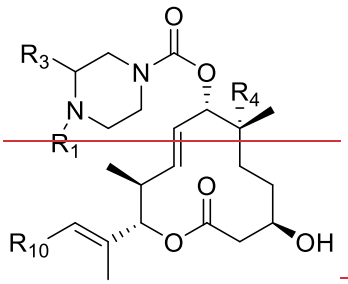
a is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, -$NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein at least one of R^6 and R^7 is hydrogen; and

wherein R^1 and R^9 cannot both be absent.

716. The method of any one of claims 688 to 708, wherein the splicing modulator comprises a splicing modulator of Formula (VIII):



(VIII), or a pharmaceutically acceptable salt thereof, wherein:

R^1 is chosen from absent, hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and $-CD_3$;

R^3 is chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylamino groups, C_1-C_6 alkylcarboxylic acid groups, C_1-C_6 alkylhydroxy groups, C_3-C_8 cycloalkyl groups, benzyl groups, C_3-C_8 heterocyclyl groups, and -O-C(=O)-(C_1-C_6 alkyl) groups;

R^4 is chosen from hydrogen, hydroxyl groups, -O-(C_1-C_6 alkyl) groups, -O-C(=O)-(C_1-C_6 alkyl) groups, and C_1-C_6 alkyl groups; and

R^{10} is chosen from 3 to 10 membered carbocycles and 3 to 10 membered heterocycles, each of which is substituted with 0 to 3 R^a, wherein each R^a is independently chosen from halogens, C_1-C_6 alkyl groups, -O-(C_1-C_6)alkyl groups, C_1-C_6 alkylalkoxy groups, C_1-C_6 alkylhydroxy groups, -S(=O)$_w$-(4 to 7 membered heterocycles), 4 to 7 membered carbocycles, and 4 to 7 membered heterocycles;

R^{15} and R^{16} are each independently chosen from hydrogen, R^{17}, -C(=O)-R^{17}, and -C(=O)-O-R^{17}; and

R^{17} is chosen from hydrogen, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, benzyl groups, and C_3-C_8 heterocyclyl groups;

wherein R^1, R^3, R^4, R^{10}, R^{15}, R^{16}, and R^{17} are each independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, C_1-C_6 alkyl groups, -O-(C_1-C_6 alkyl) groups, $-NR^{15}R^{16}$, C_3-C_8 cycloalkyl groups, C_1-C_6 alkylhydroxy groups, C_1-C_6 alkylalkoxy groups, benzyl groups, and C_3-C_8 heterocyclyl groups; and

wherein each R^a is independently substituted with 0 to 3 groups independently chosen from halogens, hydroxyl groups, $-NR^{15}R^{16}$, C_1-C_6 alkyl groups, -(C=O)-(C_1-C_6 alkyl) groups, -(C=O)-(C_1-C_6 alkyl)-(C_3-C_{10} heterocyclyl) groups, -S(=O)$_w$-(C_3-C_8 heterocyclyl groups), and C_1-C_6 alkylcarboxylic acid groups, each of which is substituted with 0, 1, or 2 groups independently chosen from halogens, hydroxyl groups, $-NR^{15}R^{16}$, and C_1-C_3 alkyl groups; and

w is 0, 1, or 2.

~~717. The method of any one of claims 688 to 708, wherein the splicing modulator comprises a modulator of the SF3b complex.~~

~~718. The method of claim 717, wherein the splicing modulator comprises a pladienolide or a pladienolide derivative.~~

~~719. The method of claim 717 or claim 718, wherein the splicing modulator comprises pladienolide D or a pladienolide D derivative.~~

~~720. The method of claim 719, wherein the pladienolide D or derivative comprises D2, D1, D4, D8, D10, D11 (E7107), D20, D21, D22, D12, or D25.~~

~~721. The method of claim 719 or claim 720, wherein the pladienolide D or derivative comprises D2.~~

~~722. The method of claim 719 or claim 720, wherein the pladienolide D or derivative comprises D1.~~

~~723. The method of claim 719 or claim 720, wherein the pladienolide D or derivative is a zwitterionic pladienolide D or derivative.~~

~~724. The method of claim 723, wherein the zwitterionic pladienolide D or derivative comprises D22 or D25.~~

~~725. The method of claim 717 or claim 718, wherein the splicing modulator comprises pladienolide B or a pladienolide B derivative.~~

~~726. The method of claim 725, wherein the pladienolide B or derivative comprises D9, D18, D19, or D13.~~

~~727. The method of claim 717 or claim 718, wherein the splicing modulator comprises an aryl pladienolide.~~

728. The method of claim 727, wherein the aryl pladienolide comprises D15, D14, D16, D17, D26, or D33.

729. The method of claim 727 or claim 728, wherein the aryl pladienolide is a zwitterionic aryl pladienolide.

730. The method of claim 729, wherein the zwitterionic aryl pladienolide comprises D33.

731. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D4, D12, D15, D8, D9, D10, D13, D18, D19, D20, D21, D22, D25, or D33.

732. The method of any one of claims 688 to 731, wherein *p* is from 2 to 8.

733. The method of any one of claims 688 to 732, wherein *p* is from 4 to 8.

734. The method of any one of claims 688 to 733, wherein *p* is 4 or 8.

735. A neoantigen vaccine comprising at least one neoantigen peptide, wherein the at least one neoantigen peptide comprises a modified or novel neoantigen sequence induced by contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197.

736. The neoantigen vaccine of claim 735, wherein the at least one neoantigen peptide ranges from about 10 to about 50 or about 10 to about 35 amino acids in length.

737. The neoantigen vaccine of claim 735 or claim 736, wherein the at least one neoantigen peptide ranges from about 15 to about 25 amino acids in length.

738. The neoantigen vaccine of any one of claims 735 to 737, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.

739. The neoantigen vaccine of claim 738, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.

740. The neoantigen vaccine of claim 738, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.

741. The neoantigen vaccine of claim 738, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.

742. The neoantigen vaccine of any one of claims 735 to 737, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.

743. The neoantigen vaccine of claim 742, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.

744. The neoantigen vaccine of claim 742, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

745. The neoantigen vaccine of any one of claims 735 to 744, wherein the modified or novel neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

746. The neoantigen vaccine of any one of claims 735 to 745, further comprising a pharmaceutically acceptable carrier.

747. The neoantigen vaccine of claim 746, wherein the at least one neoantigen peptide is linked to the pharmaceutically acceptable carrier.

748. The neoantigen vaccine of claim 746 or claim 747, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

749. The neoantigen vaccine of any one of claims 746 to 748, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are covalently attached via a linker.

750. The neoantigen vaccine of any one of claims 746 to 748, wherein the neoantigen peptide and the pharmaceutically acceptable carrier are expressed as a fusion protein.

751. The neoantigen vaccine of any one of claims 735 to 745, further comprising a pharmaceutically acceptable diluent.

~~752. The neoantigen vaccine of any one of claims 735 to 745, further comprising a pharmaceutically acceptable adjuvant.~~

~~753. The neoantigen vaccine of any one of claims 735 to 752, wherein the neoplastic cell is present in an in vitro cell culture.~~

~~754. The neoantigen vaccine of claim 753, wherein the neoplastic cell is obtained from a subject.~~

~~755. The neoantigen vaccine of any one of claims 735 to 752, wherein the neoplastic cell is present in a subject.~~

~~756. A neoantigen vaccine comprising at least one neoantigen mRNA, wherein the at least one neoantigen mRNA encodes a modified or novel neoantigen sequence induced by contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 1 to 193 or the composition of any one of claims 194 to 197.~~

~~757. The neoantigen vaccine of claim 756, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 37-65.~~

~~758. The neoantigen vaccine of claim 757, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 37.~~

~~759. The neoantigen vaccine of claim 757, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 39.~~

~~760. The neoantigen vaccine of claim 757, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 46-49.~~

~~761. The neoantigen vaccine of claim 756, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 66-93, or an antigenic portion of any one of SEQ ID NOs: 66-93.~~

~~762. The neoantigen vaccine of claim 761, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of SEQ ID NO: 66, or an antigenic portion of SEQ ID NO: 66.~~

763. The neoantigen vaccine of claim 761, wherein the modified or novel neoantigen sequence comprises an amino acid sequence of any one of SEQ ID NOs: 74-77, or an antigenic portion of any one of SEQ ID NOs: 74-77.

764. The neoantigen vaccine of any one of claims 756 to 763, wherein the modified or novel neoantigen sequence and/or antigenic portion ranges from about 10 to about 50, about 10 to about 35, about 15 to about 25, or about 10 to about 20 amino acids in length.

765. The neoantigen vaccine of any one of claims 756 to 764, further comprising a pharmaceutically acceptable carrier.

766. The neoantigen vaccine of claim 765, wherein the at least one neoantigen mRNA is linked to the pharmaceutically acceptable carrier.

767. The neoantigen vaccine of claim 765 or claim 766, wherein the pharmaceutically acceptable carrier is selected from a peptide, a serum albumin, a keyhole limpet hemocyanin, an immunoglobulin, a thyroglobulin, an ovalbumin, a toxoid or an attenuated toxoid derivative, a cytokine, and a chemokine.

768. The neoantigen vaccine of any one of claims 756 to 764, further comprising a pharmaceutically acceptable diluent.

769. The neoantigen vaccine of any one of claims 756 to 764, further comprising a pharmaceutically acceptable adjuvant.

770. The neoantigen vaccine of any one of claims 756 to 769, wherein the neoantigen mRNA is encapsulated by an encapsulating agent.

771. The neoantigen vaccine of claim 770, wherein the encapsulating agent is a liposome.

772. The neoantigen vaccine of claim 770, wherein the encapsulating agent is a nanoparticle.

773. The neoantigen vaccine of any one of claims 756 to 772, wherein the neoplastic cell is present in an in vitro cell culture.

774. The neoantigen vaccine of claim 773, wherein the neoplastic cell is obtained from a subject.

~~775. The neoantigen vaccine of any one of claims 756 to 772, wherein the neoplastic cell is present in a subject.~~

~~776. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a MSLN-expressing cell.~~

~~777. The antibody-drug conjugate of claim 776, wherein the antibody or antigen binding fragment is an anti-MSLN antibody or antigen binding fragment.~~

~~778. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a FOLH1-expressing cell.~~

~~779. The antibody-drug conjugate of claim 778, wherein the antibody or antigen binding fragment is an anti-FOLH1 antibody or antigen binding fragment.~~

~~780. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a CDH6-expressing cell.~~

~~781. The antibody-drug conjugate of claim 780, wherein the antibody or antigen binding fragment is an anti-CDH6 antibody or antigen binding fragment.~~

~~782. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a CEACAM5-expressing cell.~~

~~783. The antibody-drug conjugate of claim 782, wherein the antibody or antigen binding fragment is an anti-CEACAM5 antibody or antigen binding fragment.~~

~~784. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a CFC1B-expressing cell.~~

~~785. The antibody-drug conjugate of claim 784, wherein the antibody or antigen binding fragment is an anti-CFC1B antibody or antigen binding fragment.~~

~~786. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets an ENPP3-expressing cell.~~

~~787. The antibody-drug conjugate of claim 786, wherein the antibody or antigen binding fragment is an anti-ENPP3 antibody or antigen binding fragment.~~

~~788. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a FOLR1-expressing cell.~~

~~789. The antibody-drug conjugate of claim 788, wherein the antibody or antigen binding fragment is an anti-FOLR1 antibody or antigen binding fragment.~~

~~790. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a HAVCR1-expressing cell.~~

~~791. The antibody-drug conjugate of claim 790, wherein the antibody or antigen binding fragment is an anti-HAVCR1 antibody or antigen binding fragment.~~

~~792. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a KIT-expressing cell.~~

~~793. The antibody-drug conjugate of claim 792, wherein the antibody or antigen binding fragment is an anti-KIT antibody or antigen binding fragment.~~

~~794. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a MET-expressing cell.~~

~~795. The antibody-drug conjugate of claim 794, wherein the antibody or antigen binding fragment is an anti-MET antibody or antigen binding fragment.~~

~~796. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a MUC16-expressing cell.~~

~~797. The antibody-drug conjugate of claim 796, wherein the antibody or antigen binding fragment is an anti-MUC16 antibody or antigen binding fragment.~~

~~798. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a SLC39A6-expressing cell.~~

~~799. The antibody-drug conjugate of claim 798, wherein the antibody or antigen binding fragment is an anti-SLC39A6 antibody or antigen binding fragment.~~

800. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a SLC44A4-expressing cell.

801. The antibody-drug conjugate of claim 800, wherein the antibody or antigen binding fragment is an anti-SLC44A4 antibody or antigen binding fragment.

802. The antibody-drug conjugate of any one of claims 1 to 7, wherein the antibody or antigen binding fragment targets a STEAP1-expressing cell.

803. The antibody-drug conjugate of claim 802, wherein the antibody or antigen binding fragment is an anti-STEAP1 antibody or antigen binding fragment.

804. The antibody-drug conjugate of claim 29, wherein the amino acid unit comprises glutamine-valine-citrulline (Glu-Val-Cit).

805. The antibody-drug conjugate of claim 29, wherein the amino acid unit comprises alanine-alanine-asparagine (Ala-Ala-Asn).

806. The antibody-drug conjugate of claim 48 or claim 49, wherein the cleavable peptide moiety or amino acid unit comprises Glu-Val-Cit.

807. The antibody-drug conjugate of claim 48 or claim 49, wherein the cleavable peptide moiety or amino acid unit comprises Ala-Ala-Asn.

808. The antibody-drug conjugate of any one of claims 55 to 58, wherein the linker comprises MC-Glu-Val-Cit.

809. The antibody-drug conjugate of any one of claims 55 to 58, wherein the linker comprises MC-Ala-Ala-Asn.

810. The antibody-drug conjugate of any one of claims 67 to 71, wherein the linker comprises Glu-Val-Cit-pABC.

811. The antibody-drug conjugate of any one of claims 67 to 71, wherein the linker comprises Ala-Ala-Asn-pABC.

812. The antibody-drug conjugate of any one of claims 74 to 78, wherein the linker comprises Glu-Val-Cit-pAB.

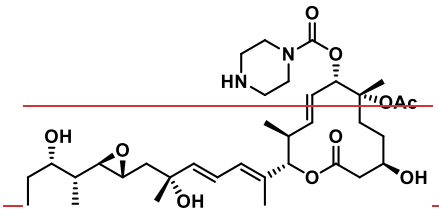
813. The antibody-drug conjugate of any one of claims 74 to 78, wherein the linker comprises Ala-Ala-Asn-pAB.

814. The antibody-drug conjugate of claim 117 or claim 118, wherein the pladienolide D or derivative comprises D4.

815. The antibody-drug conjugate of claim 117 or claim 118, wherein the pladienolide D or derivative comprises D12.

816. The antibody-drug conjugate of claim 125 or claim 126, wherein the aryl pladienolide comprises D15.

817. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D4:

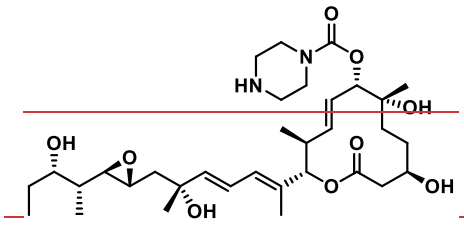


(D4).

818. The antibody-drug conjugate of claim 817, wherein the splicing modulator comprises D4 and the linker comprises MC-Val-Cit-pABC.

819. The antibody-drug conjugate of claim 817, wherein the splicing modulator comprises D4 and the linker comprises MC-β-glucuronide.

820. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D12:

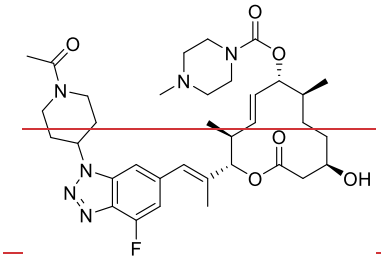


(D12).

821. The antibody-drug conjugate of 820, wherein the splicing modulator comprises D12 and the linker comprises MC-Val-Cit-pABC.

822. The antibody-drug conjugate of claim 820, wherein the splicing modulator comprises D12 and the linker comprises MC-β-glucuronide.

823. The antibody-drug conjugate of any one of claims 1 to 106, wherein the splicing modulator comprises D15:



(D15).

824. The antibody-drug conjugate of 823, wherein the splicing modulator comprises D15 and the linker comprises MC-Val-Ala-pAB.

825. The antibody-drug conjugate of claim 137, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

826. The antibody-drug conjugate of claim 156, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

827. An antibody-drug conjugate of Formula (I):

$$Ab\text{-}(L\text{-}D)_p \quad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

D is D4;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

828. The antibody-drug conjugate of claim 827, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.

829. The antibody-drug conjugate of claim 828, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.

830. The antibody-drug conjugate of claim 828 or claim 829, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

831. The antibody-drug conjugate of any one of claims 828 to 830, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

832. The antibody-drug conjugate of any one of claims 828 to 831, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

833. The antibody-drug conjugate of any one of claims 828 to 832, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

834. The antibody-drug conjugate of claim 827, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

835. An antibody-drug conjugate of Formula (I):

$$Ab\text{-}(L\text{-}D)_p \qquad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

D is D12;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

836. The antibody-drug conjugate of claim 835, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.

837. The antibody-drug conjugate of claim 836, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.

838. The antibody-drug conjugate of claim 836 or claim 837, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

839. The antibody-drug conjugate of any one of claims 836 to 838, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

840. The antibody-drug conjugate of any one of claims 836 to 839, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

841. The antibody-drug conjugate of any one of claims 836 to 840, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

842. The antibody-drug conjugate of claim 835, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

843. An antibody-drug conjugate of Formula (I):

$$Ab\text{-}(L\text{-}D)_p \qquad (I)$$

wherein

Ab is an antibody or antigen binding fragment which targets a neoplastic cell;

D is D15;

L is a linker that covalently attaches Ab to D; and

p is an integer from 1 to 15.

844. The antibody-drug conjugate of claim 843, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.

845. The antibody-drug conjugate of claim 844, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.

846. The antibody-drug conjugate of claim 844 or claim 845, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).

847. The antibody-drug conjugate of any one of claims 844 to 846, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.

848. The antibody-drug conjugate of any one of claims 844 to 847, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.

849. The antibody-drug conjugate of any one of claims 844 to 848, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.

850. The antibody-drug conjugate of claim 843, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

851. The antibody-drug conjugate of any one of claims 827 to 850, wherein the linker is a cleavable linker.

852. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-Val-Cit-pABC.

853. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-Val-Ala-pABC.

854. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-Val-Ala-pAB.

855. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-Glu-Val-Cit-pABC.

856. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-Ala-Ala-Asn-pABC.

857. The antibody-drug conjugate of claim 851, wherein the cleavable linker comprises MC-β-glucuronide.

858. The antibody-drug conjugate of any one of claims 827 to 850, wherein the linker is a non-cleavable linker.

~~859. The antibody-drug conjugate of claim 858, wherein the non-cleavable linker comprises Mal-Hex.~~

~~860. The antibody-drug conjugate of claim 858, wherein the non-cleavable linker comprises Mal-Et.~~

~~861. The antibody-drug conjugate of claim 858, wherein the non-cleavable linker comprises Mal-Et-O-Et.~~

~~862. The antibody-drug conjugate of any one of claims 827 to 861, wherein *p* is from 1 to 10.~~

~~863. The antibody-drug conjugate of any one of claims 827 to 862, wherein *p* is from 2 to 8.~~

~~864. The antibody-drug conjugate of any one of claims 827 to 863, wherein *p* is from 4 to 8.~~

~~865. The antibody-drug conjugate of any one of claims 827 to 864, wherein *p* is 4.~~

~~866. The antibody-drug conjugate of any one of claims 827 to 864, wherein *p* is 8.~~

~~867. The antibody-drug conjugate of claim 181, wherein the cleavable linker comprises MC-Glu-Val-Cit-pABC.~~

~~868. The antibody-drug conjugate of claim 181, wherein the cleavable linker comprises MC-Ala-Ala-Asn-pABC.~~

~~869. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 776 to 868, wherein the average *p* of the antibody-drug conjugates in the composition is from about 3.5 to about 5.5.~~

~~870. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 776 to 868, wherein the average *p* of the antibody-drug conjugates in the composition is from about 7 to about 9.~~

~~871. A method of treating a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870.~~

~~872. A method of reducing or inhibiting growth of a tumor in a subject having or suspected of having a neoplastic disorder, comprising administering to the subject a therapeutically effective amount of the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870.~~

~~873. A method of determining whether a subject having or suspected of having a neoplastic disorder will be responsive to treatment with the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870, comprising providing a biological sample from the subject and contacting the biological sample with the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870.~~

~~874. An antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870 for use in the treatment of a neoplastic disorder.~~

~~875. Use of an antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870 in the treatment of a neoplastic disorder.~~

~~876. Use of an antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870 in a method of manufacturing a medicament for the treatment of a neoplastic disorder.~~

~~877. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870, and a pharmaceutically acceptable carrier.~~

~~878. A method of producing the antibody-drug conjugate of any one of claims 776 to 868, comprising reacting an antibody or antigen binding fragment with a linker joined to a splicing modulator under conditions that allow conjugation.~~

~~879. The method of any one of claims 303 to 687, wherein the antibody-drug conjugate comprises an antibody-drug conjugate of any one of claims 776 to 868.~~

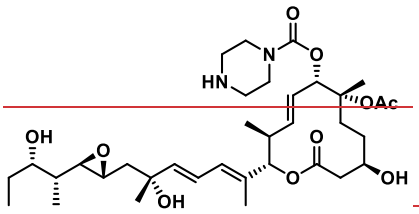
880. The method of claim 688, wherein the antibody or antigen binding fragment targets a cell expressing HER2, CD138, EPHA2, MSLN, FOLH1, CDH6, CEACAM5, CFC1B, ENPP3, FOLR1, HAVCR1, KIT, MET, MUC16, SLC39A6, SLC44A4, and/or STEAP1.

881. The method of claim 701, wherein the cleavable linker comprises MC-Glu-Val-Cit-pABC.

882. The method of claim 701, wherein the cleavable linker comprises MC-Ala-Ala-Asn-pABC.

883. The method of claim 701, wherein the cleavable linker comprises MC-β-glucuronide.

884. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D4:

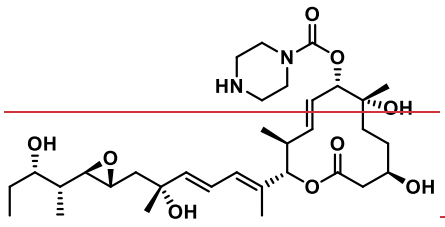


(D4).

885. The method of claim 884, wherein the splicing modulator comprises D4 and the linker comprises MC-Val-Cit-pABC.

886. The method of claim 884, wherein the splicing modulator comprises D4 and the linker comprises MC-β-glucuronide.

887. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D12:

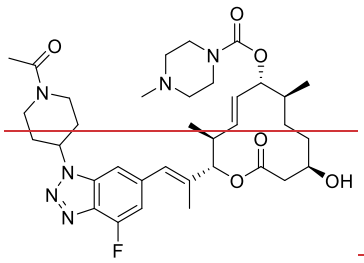


(D12).

888. The method of claim 887, wherein the splicing modulator comprises D12 and the linker comprises MC-Val-Cit-pABC.

889. The method of claim 887, wherein the splicing modulator comprises D12 and the linker comprises MC-β-glucuronide.

890. The method of any one of claims 688 to 708, wherein the splicing modulator comprises D15:



(D15).

891. The method of claim 890, wherein the splicing modulator comprises D15 and the linker comprises MC-Val-Ala-pAB.

892. The method of claim 719 or claim 720, wherein the pladienolide D or derivative comprises D4.

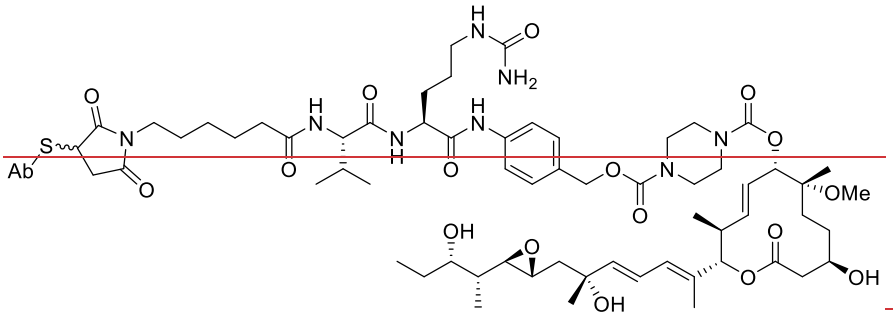
893. The method of claim 719 or claim 720, wherein the pladienolide D or derivative comprises D12.

894. The method of claim 727 or claim 728, wherein the aryl pladienolide comprises D15.

895. A neoantigen vaccine comprising at least one neoantigen peptide, wherein the at least one neoantigen peptide comprises a modified or novel neoantigen sequence induced by contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870.

896. A neoantigen vaccine comprising at least one neoantigen mRNA, wherein the at least one neoantigen mRNA encodes a modified or novel neoantigen sequence induced by contacting a neoplastic cell with an effective amount of a splicing modulator, the antibody-drug conjugate of any one of claims 776 to 868 or the composition of claim 869 or claim 870.

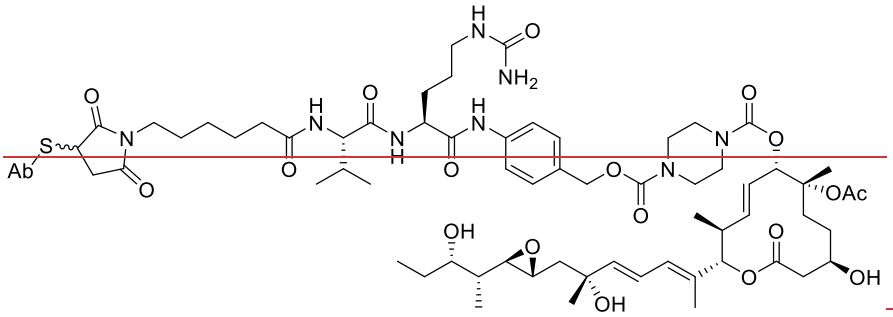
~~897. An antibody-drug conjugate having the structure~~



~~(Ab-ADL1-D1),~~

~~wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL1-D1 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.~~

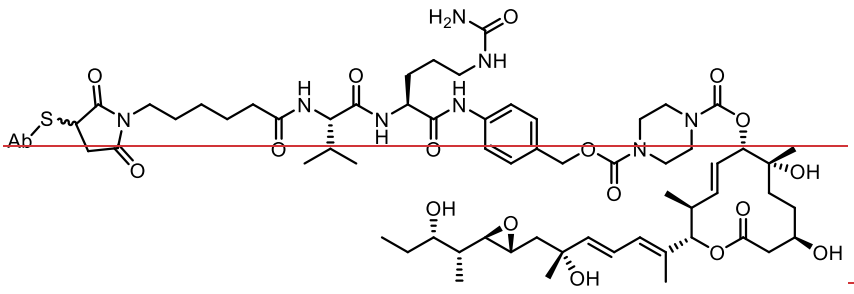
~~898. An antibody-drug conjugate having the structure~~



~~(Ab-ADL1-D4),~~

~~wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL1-D4 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.~~

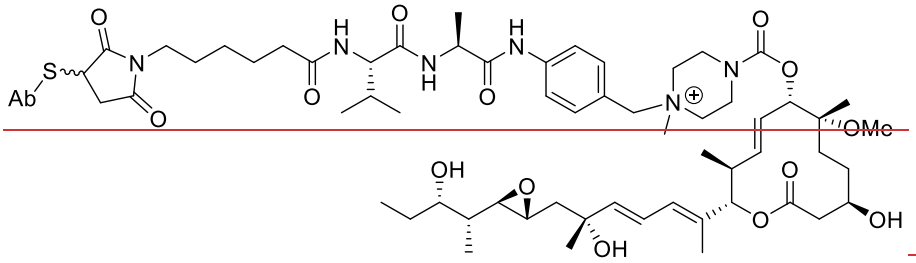
~~899. An antibody-drug conjugate having the structure~~



~~(Ab-ADL1-D12),~~

~~wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL1-D12 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.~~

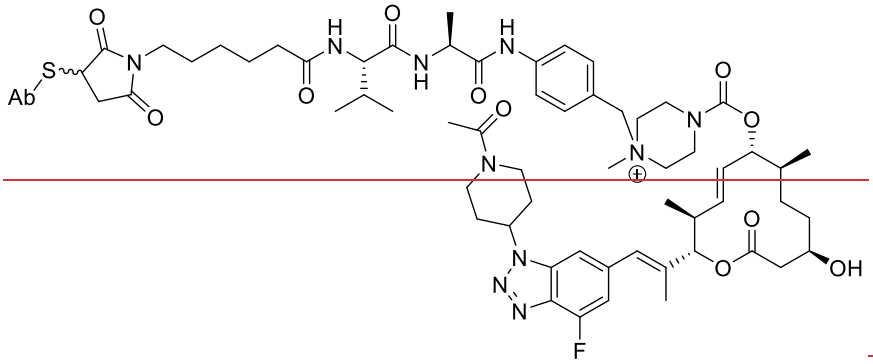
900. An antibody-drug conjugate having the structure



(Ab-ADL5-D2),

wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL5-D2 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.

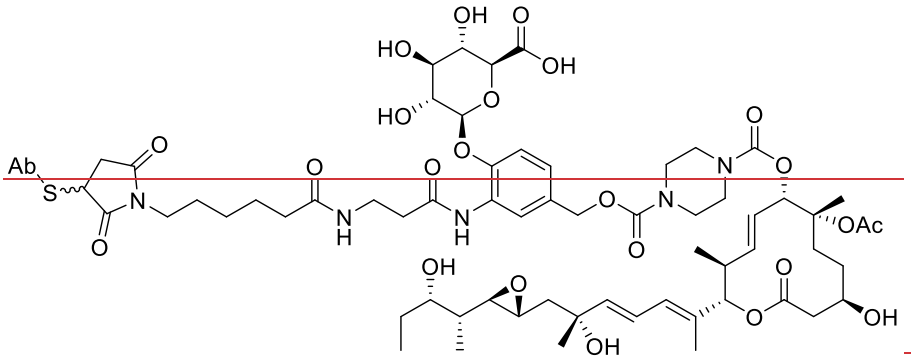
901. An antibody-drug conjugate having the structure



(Ab-ADL5-D15),

wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL5-D15 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.

902. An antibody-drug conjugate having the structure



(Ab-ADL13-D4),

wherein Ab is an antibody or antigen binding fragment covalently bound to a maleimide group of ADL13-D4 through the sulfur atom of a thiol group on the antibody or antigen binding fragment.

~~903. The antibody-drug conjugate of any one of claims 897 to 902, wherein the antibody or antigen binding fragment targets a HER2-expressing cell.~~

~~904. The antibody-drug conjugate of claim 903, wherein the antibody or antigen binding fragment is an anti-HER2 antibody or antigen binding fragment.~~

~~905. The antibody-drug conjugate of claim 903 or claim 904, wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO:1 (HCDR1), SEQ ID NO:2 (HCDR2), and SEQ ID NO:3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO:4 (LCDR1), SEQ ID NO:5 (LCDR2), and SEQ ID NO:6 (LCDR3).~~

~~906. The antibody-drug conjugate of any one of claims 903 to 905, wherein the antibody or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19, and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20.~~

~~907. The antibody-drug conjugate of any one of claims 903 to 906, wherein the antibody or antigen binding fragment comprises a human IgG1 heavy chain constant region.~~

~~908. The antibody-drug conjugate of any one of claims 903 to 907, wherein the antibody or antigen binding fragment comprises a human Ig kappa light chain constant region.~~