COMBINATION THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 63/111,045, filed November 8, 2020, US Provisional Application No. 63/172,411, filed April 8, 2021, and US Provisional Application No. 63/208,179, filed June 8, 2021, each of which is incorporated by reference herein in its entirety for any purpose.

FIELD

[0002] Provided herein are methods of treating cancer with an antibody that binds an immune cell engager in combination with an antibody-drug conjugate.

BACKGROUND

[0003] Immuno-oncology therapeutics and antibody-drug conjugates (ADCs) have been used to treat cancer in patients. Neither class of therapeutics has been able to treat the full complement of patients in targeted indications. This disclosure solves this and other problems.

BRIEF SUMMARY

[0003a] In one aspect, the disclosure provides use of an antibody-drug conjugate (ADC) that comprises a first antibody that binds a tumor-associated antigen and a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter, in the manufacture of a first medicament; and use of a second antibody that binds to an immune cell engager, wherein the second antibody comprises an Fc with enhanced binding to one or more activating FcγRs, wherein the activating FcγRs include one or more of FcγRIIIa, FcγRIIa, and/or FcγRI, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer.

[0003b] In one aspect, the disclosure provides use of an antibody-drug conjugate (ADC), wherein the antibody-drug conjugate comprises a first antibody conjugated to a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter, in the manufacture of a first medicament; and use of a second antibody that binds an immune cell engager, wherein the second antibody is nonfucosylated, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer.

[0003c] In one aspect, the disclosure provides use of an antibody-drug conjugate (ADC), wherein the ADC comprises a first antibody that binds a tumor-associated antigen and a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter, in the manufacture of a first medicament; and use of a second antibody that binds an immune cell engager, wherein the second antibody comprises an Fc with enhanced ADCC activity relative to a corresponding wild-type Fc of the same isotype, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer.

[0004] ~~Embodiment~~Example 1. A method of treating cancer, comprising administering to a subject with cancer (1) an antibody-drug conjugate (ADC) that comprises a first antibody that binds a tumor-associated antigen and a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter; and (2) a second antibody that binds to an immune cell engager, wherein the second antibody comprises an Fc with enhanced binding to one or more activating FcγRs, wherein the activating FcγRs include one or more of FcγRIIIa, FcγRIIa, and/or FcγRI.

[0005] ~~Embodiment~~Example 2. The method of ~~embodiment~~example 1, wherein the second antibody comprises an Fc with enhanced binding to at least FcγRIIIa.

[0006] ~~Embodiment~~Example 3. The method of ~~embodiment~~example 1, wherein second antibody comprises an Fc with enhanced binding to at least FcγRIIIa and FcγRIIa.

[0007] ~~Embodiment~~Example 4. The method of ~~embodiment~~example 1, wherein the second antibody comprises an Fc with enhanced binding to at least FcγRIIIa and FcγRI.

[0008] ~~Embodiment~~Example 5. The method of ~~embodiment~~example 1, wherein the second antibody comprises an Fc with enhanced binding to FcγRIIIa, FcγRIIa, and FcγRI.

[0009] ~~Embodiment~~Example 6. The method of any one of ~~embodiment~~examples 1-5, wherein the Fc of the second antibody has reduced binding to one or more inhibitory FcγRs.

[0010] ~~Embodiment~~Example 7. The method of ~~embodiment~~example 6, wherein the Fc of the second antibody has reduced binding to FcγRIIb.

[0011] ~~Embodiment~~Example 8. The method of any one of ~~embodiment~~examples 1-7, wherein the Fc of the second antibody has reduced fucose levels and/or has been engineered to comprise one or more mutations such that the Fc has enhanced binding to the one or more activating FcγRs.

[0012] ~~Embodiment~~Example 9. The method of ~~embodiment~~example 8, wherein the second antibody is nonfucosylated.

[0013] ~~Embodiment~~Example 10. The method of ~~embodiment~~example 8, wherein the second antibody comprises substitutions S293D, A330L, and I332E in the heavy chain constant region.

[0014] ~~Embodiment~~Example 11. A method of treating cancer, comprising administering to a subject with cancer an antibody-drug conjugate, wherein the antibody-drug conjugate comprises a first antibody conjugated to a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter; and a second antibody that binds an immune cell engager, wherein the second antibody is nonfucosylated.

[0015] ~~Embodiment~~Example 12. The method of any one of ~~embodiment~~examples 1-11, wherein the first antibody binds a tumor-associated antigen.

[0016] ~~Embodiment~~Example 13. A method of treating cancer, comprising administering to a subject with cancer (1) an antibody-drug conjugate (ADC), wherein the ADC comprises a first antibody that binds a tumor-associated antigen and a cytotoxic agent, wherein the cytotoxic agent is a tubulin disrupter, and (2) a second antibody that binds an immune cell engager, wherein the second antibody comprises an Fc with enhanced ADCC activity relative to a corresponding wild-type Fc of the same isotype.

[0017] ~~Embodiment~~Example 14. The method of ~~embodiment~~example 13, wherein the second antibody comprises an Fc with enhanced ADCC and ADCP activity relative to a corresponding wild-type Fc of the same isotype.

[0018] ~~Embodiment~~Example 15. The method of ~~embodiment~~example 13 or 14, wherein the second antibody is nonfucosylated.

[0019] ~~Embodiment~~Example 16. The method of any one of ~~embodiment~~examples 13-15, wherein the second antibody comprises an Fc with enhanced binding to one or more activating FcγRs, wherein the activating FcγRs include one or more of FcγRIIIa, FcγRIIa, and/or FcγRI.

[0020] ~~Embodiment~~Example 17. The method of ~~embodiment~~example 16, wherein the second antibody comprise an Fc with enhanced binding to at least FcγRIIIa.

[0021] ~~Embodiment~~Example 18. The method of ~~embodiment~~example 16, wherein second antibody comprises an Fc with enhanced binding to at least FcγRIIIa and FcγRIIa.

[0022] ~~Embodiment~~Example 19. The method of ~~embodiment~~example 16, wherein the second antibody comprises an Fc with enhanced binding to at least FcγRIIIa and FcγRI.

[0023] ~~Embodiment~~Example 20. The method of ~~embodiment~~example 16, wherein the second antibody comprises an Fc with enhanced binding to FcγRIIIa, FcγRIIa, and FcγRI.

[0024] ~~Embodiment~~Example 21. The method of any one of ~~embodiment~~examples 13-20, wherein the Fc of the second antibody has reduced binding to one or more inhibitory FcγRs.

[0025] ~~Embodiment~~Example 22. The method of ~~embodiment~~example 21, wherein the Fc of the second antibody has reduced binding to FcγRIIb.

[0026] ~~Embodiment~~Example 23. The method of any one of ~~embodiment~~examples 1-22, wherein the first antibody binds an antigen selected from 5T4 (TPBG), ADAM-9 , AG-7, ALK, ALP, AMHRII, APLP2, ASCT2, AVB6, AXL (UFO), B7-H3 (CD276), B7-H4, BCMA, C3a, C3b, C4.4a (LYPD3), C5, C5a, CA6, CA9, CanAg, carbonic anhydrase IX (CAIX), Cathepsin D, CCR7, CD1, CD10, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107a, CD107b, CD108, CD109, CD111, CD112, CD113, CD116, CD117, CD118, CD119, CD11A, CD11b, CD11c, CD120a, CD121a, CD121b, CD122, CD123, CD124, CD125, CD126, CD127, CD13, CD130, CD131, CD132, CD133, CD135, CD136, CD137, CD138, CD14, CD140a, CD140b, CD141, CD142, CD143, CD144, CD146, CD147, CD148, CD15, CD150, CD151, CD154, CD155, CD156a, CD156b, CD156c, CD157, CD158b2, CD158e, CD158f1, CD158h, CD158i, CD159a, CD16, CD160, CD161, CD162, CD163, CD164, CD166, CD167b, CD169, CD16a, CD16b, CD170, CD171, CD172a, CD172b, CD172g, CD18, CD180, CD181, CD183, CD184, CD185, CD19, CD194, CD197, CD1a, CD1b, CD1c, CD1d, CD2, CD20, CD200, CD201, CD202b, CD203c, CD204, CD205, CD206, CD208, CD21, CD213a1, CD213a2, CD217, CD218a, CD22, CD220, CD221, CD222, CD224, CD226, CD228, CD229, CD23, CD230, CD232, CD239, CD243, CD244, CD248, CD249, CD25, CD26, CD265, CD267, CD269, CD27, CD272, CD273, CD274, CD275, CD279, CD28, CD280, CD281, CD282, CD283, CD284, CD289, CD29, CD294, CD295, CD298, CD3, CD3 epsilon, CD30, CD300f, CD302, CD304, CD305, CD307, CD31, CD312, CD315, CD316, CD317, CD318, CD319, CD32, CD321, CD322, CD324, CD325, CD326, CD327, CD328, CD32b, CD33, CD331, CD332, CD333, CD334, CD337, CD339, CD34, CD340, CD344, CD35, CD352, CD36, CD37, CD38, CD39, CD3d, CD3g, CD4, CD41, CD42d, CD44, CD44v6, CD45, CD46, CD47, CD48, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD5, CD50, CD51, CD51 (integrin alpha-V), CD52, CD53, CD54, CD55, CD56, CD58, CD59, CD6, CD61, CD62L, CD62P, CD63, CD64, CD66a-e, CD67, CD68, CD69, CD7, CD70, CD70L, CD71, CD71 (TfR), CD72, CD73, CD74, CD79a, CD79b, CD8, CD80, CD82, CD83, CD84, CD85f, CD85i, CD85j, CD86, CD87, CD89, CD90, CD91, CD92, CD95, CD96, CD97, CD98, CDH6, CDH6 (cadherin 6), CDw210a, CDw210b,

CEA, CEACAM5, CEACAM6, CFC1B, cKIT, CLDN18.2 (claudin 18.2), CLDN6, CLDN9, CLL-1, c-MET, complement factors C3, Cripto, CSP-1, CXCR5, DCLK1, DLK-1, DLL3, DPEP3, DR5 (Death receptor 5), Dysadherin, EFNA4 , EGFR, EGFR wild type, EGFRviii, EGP-1 (TROP-2), EGP-2, EMP2, ENPP3, EpCAM, EphA2, EphA3, Ephrin-A4 (EFNA4), ETBR, FAP, FcRH5, FGFR2, FGFR3, FLT3, FOLR, FOLR1, FOLR-alpha, FSH, GCC, GD2, GD3, globo H, GPC1, GPC-1, GPC3, GPNMB, GPR20, HER2, HER-2, HER3, HER-3, HGFR (c-Met), HLA-DR, HM1.24, HSP90, Ia, IGF-1R, IL-13R, IL-15, IL1RAP, IL-2, IL-3, IL-4, IL7R, integrin alphaVbeta3 (integrin αVβ3), integrin beta-6, Interleukin-4 Receptor (IL4R), KAAG-1, KLK2, LAMP-1, Le(y), Lewis Y antigen, LGALS3BP, LGR5, LH/hCG, LHRH, Lipid raft, LIV-1 (SLC39A6 or ZIP6), LRP-1, LRRC15, LY6E, Macrophage mannose receptor 1, MAGE, Mesothelin (MSLN), MET, MHC class I chain-related protein A and B (MICA and MICB), MN/CA IX, MRC2, MT1-MMP, MTX3, MTX5, MUC1, MUC16, MUC2, MUC3, MUC4, MUC5, MUC5ac, NaPi2b, NCA-90, NCA-95, Nectin-4, Notch3, Nucleolin, OAcGD2, OT-MUC1 (onco-tethered-MUC1), OX001L, P1GF, PAM4 antigen, p-cadherin (cadherin 3), PD-L1, Phosphatidyl Serine(PS), PRLR, Prolactin Receptor (PRLR), Pseudomonas, PSMA, PTK4, PTK7, Receptor tyrosine kinase (RTK), RNF43, ROR1, ROR2, SAIL, SEZ6, SLAMF7, SLC44A4, SLITRK6, SLMAMF7 (CS1), SLTRK6, Sortilin (SORT1), SSEA-4, SSTR2, Staphylococcus aureus (antibiotic agent), STEAP-1, STING, STn, T101, TAA, TAC, TDGF1, tenascin, TENB2, TGF-B, Thomson-Friedenreich antigens, Thy1.1, TIM-1, tissue factor (TF; CD142), TM4SF1, Tn antigen, TNF-alpha (TNFα), TRA-1-60, TRAIL receptor (R1 and R2), TROP-2, Tumor-associated glycoprotein 72 (TAG-72), uPAR, VEGFR, VEGFR-2, and xCT.

[0027] ~~Embodiment~~Example 24. The method of any one of ~~embodiment~~examples 1-23, wherein the first antibody does not bind Nectin-4.

[0028] ~~Embodiment~~Example 25. The method of any one of ~~embodiment~~examples 1-24, wherein the method does not comprise administering an antibody-drug conjugate comprising an antibody that binds Nectin-4.

[0029] ~~Embodiment~~Example 26. The method of any one of ~~embodiment~~examples 1-25, wherein the first antibody binds an antigen selected from CD71, Axl, AMHRII, and LGR5, Axl, CA9, CD142, CD20, CD22, CD228, CD248, CD30, CD33, CD37, CD48, CD7, CD71, CD79b, CLDN18.2, CLDN6, c-MET, EGFR, EphA2, ETBR, FCRH5, GCC, Globo H, gpNMB, HER-2, IL7R, Integrin beta-6, KAAG-1, LGR5, LIV-1, LRRC15, Ly6E, Mesothelin (MSLN), MET, MRC2, MUC16, NaPi2b, Nectin-4, OT-MUC1 (onco-tethered-MUC1), PSMA, ROR1, SLAMF7, SLC44A4, SLITRK6, STEAP-1, STn, TIM-1, TRA-1-60, and Tumor-associated glycoprotein 72 (TAG-72).

[0030] ~~Embodiment~~Example 27. The method of any one of ~~embodiment~~examples 1-25, wherein the first antibody binds an antigen selected from BCMA, GPC1, CD30, cMET, SAIL, HER3, CD70, CD46, CD48, HER2, 5T4, ENPP3, CD19, EGFR, and EphA2.

[0031] ~~Embodiment~~Example 28. The method of any one of ~~embodiment~~examples 1-25, wherein the first antibody binds an antigen selected from Her2, TROP2, BCMA, cMet, integrin alphVbeta6 (integrin αVβ6), CD22, CD79b, CD30, CD19, CD70, CD228, CD47, and CD48.

[0032] ~~Embodiment~~Example 29. The method of any one of ~~embodiment~~examples 1-25, wherein the first antibody binds an antigen selected from CD142, Integrin beta-6, integrin alphaVbeta6, ENPP3, CD19, Ly6E, cMET, C4.4a, CD37, MUC16, STEAP-1, LRRC15, SLITRK6, ETBR, FCRH5, Axl, EGFR, CD79b, BCMA, CD70, PSMA, CD79b, CD228, CD48, LIV-1, EphA2, SLC44A4, CD30, and sTn.

[0033] ~~Embodiment~~Example 30. The method of any one of ~~embodiment~~examples 1-26, wherein the tubulin disrupter is an auristatins, a tubulysin, a colchicine, a vinca alkaloid, a taxane, a cryptophycin, a maytansinoid, or a hemiasterlin.

[0034] ~~Embodiment~~Example 31. The method of ~~embodiment~~example 30, wherein the tubulin disrupter is an auristatin.

[0035] ~~Embodiment~~Example 32. The method of any one of ~~embodiment~~examples 1-31, wherein tubulin disrupter is dolostatin-10, MMAE (N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine), MMAF (N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine), auristatin F, AEB, AEVB, or AFP (auristatin phenylalanine phenylenediamine).

[0036] ~~Embodiment~~Example 33. The method of any one of ~~embodiment~~examples 1-32, wherein the tubulin disrupter is MMAE.

[0037] ~~Embodiment~~Example 33-1. The method of ~~embodiment~~example 33, wherein the antibody-drug conjugate comprises MMAE and is selected from: DP303c, also known as SYSA1501, targeting HER-2 (CSPC Pharmaceutical; Dophen Biomed), SIA01-ADC, also known as ST1, targeting STn (Siamab Therapeutics), Ladiratuzumab vedotin, also known as SGN-LIV1A, targeting LIV-1 (Merck & Co., Inc.; Seagen (Seattle Genetics) Inc.), ABBV-085, also known as Samrotamab vedotin, targeting LRRC15 (Abbvie; Seagen (Seattle Genetics) Inc.), DMOT4039A, also known as RG7600; αMSLN-MMAE, targeting Mesothelin (MSLN) (Roche-Genentech), RC68, also known as Remegen EGFR ADC, targeting EGFR (RemeGen (Rongchang Biopharmaceutical (Yantai) Co., Ltd.)), RC108, also known as RC108-ADC, targeting c-MET (RemeGen (Rongchang Biopharmaceutical (Yantai) Co., Ltd.)), CMG901, also known as MRG005, targeting CLDN18.2 (Keymed Biosciences; Lepu biotech; Shanghai Miracogen Inc. (Shanghai Meiya Biotechnology Co., Ltd)), YBL-001, also known as LCB67, targeting DLK-1 (Lego Chem Biosciences; Pyxis Oncology; Y-Biologics), DCDS0780A, also

Therapeutics), BVX001 targeting CD33; CD7 (Bivictrix therapeutics), SGN-B6A targeting Integrin beta-6 (Seagen (Seattle Genetics) Inc.), MRG003 targeting EGFR (Lepu biotech; Shanghai Miracogen Inc. (Shanghai Meiya Biotechnology Co., Ltd)), and PYX-202 targeting DLK-1 (Pyxis Oncology; Lego Chem Biosciences).

[0038] ~~Embodiment~~Example 34. The method of ~~embodiment~~example 33, wherein the MMAE is conjugated to the first antibody through a linker that comprises valine and citrulline.

[0039] ~~Embodiment~~Example 35. The method of ~~embodiment~~example 34, wherein the linker-MMAE is vcMMAE.

[0040] ~~Embodiment~~Example 36. The method of ~~embodiment~~example 33, wherein the MMAE is conjugated to the first antibody through a linker that comprises leucine, alanine, and glutamic acid.

[0041] ~~Embodiment~~Example 37. The method of ~~embodiment~~example 36, wherein the linker-MMAE is dLAE-MMAE.

[0042] ~~Embodiment~~Example 38. The method of any one of ~~embodiment~~examples 1-32, wherein the tubulin disrupter is MMAF.

[0043] ~~Embodiment~~Example 38-1. The method of ~~embodiment~~example 38, wherein the antibody-drug conjugate comprises MMAF and is selected from: CD70-ADC targeting CD70 (Kochi University; Osaka University), IGN786 targeting SAIL (AstraZeneca; Igenica Biotherapeutics), PF-06263507 targeting 5T4 (Pfizer), GPC1-ADC targeting GPC-1 (Kochi University), ADC-AVP10 targeting CD30 (Avipep), M290-MC-MMAF targeting CD103 (The Second Affiliated Hospital of Harbin Medical University), BVX001 targeting CD33; CD7 (Bivictrix therapeutics), Tanabe P3D12-vc-MMAF targeting c-MET (Tanabe Research Laboratories), LILRB4-Targeting ADC targeting LILRB4 (The University of Texas Health Science Center, Houston), TSD101, also known as ABL201, targeting BCMA (TSD Life Science; ABL Bio; Lego Chem Biosciences), Depatuxizumab mafodotin, also known as ABT-414, targeting EGFR (Abbvie; Seagen (Seattle Genetics) Inc.), AGS16F, also known as AGS-16C3F; AGS-16M8F, targeting ENPP3 (Astellas Pharma Inc.; Seagen (Seattle Genetics) Inc.), AVG-A11 BCMA ADC, also known as AVG-A11-mcMMAF, targeting BCMA (Avantgen), Belantamab mafodotin, also known as BLENREP; GSK2857916; J6M0-mcMMAF, targeting BCMA (GlaxoSmithKline; Seagen (Seattle Genetics) Inc.), MP-HER3-ADC, also known as HER3-ADC, targeting HER-3 (MediaPharma), FS-1502, also known as LCB14-0110, targeting HER-2 (Lego Chem Biosciences; Shanghai Fosun Pharmaceutical Development Co, Ltd.), MEDI-547, also known as MI-CP177, targeting EphA2 (AstraZeneca; Seagen (Seattle Genetics) Inc.), Vorsetuzumab mafodotin, also known as SGN-75, targeting CD70 (Seagen (Seattle Genetics) Inc.), Denintuzumab mafodotin, also known as SGN-CD19A, targeting CD19 (Seagen (Seattle

Genetics) Inc.), and HTI-1066, also known as SHR-A1403, targeting c-MET (Jiangsu HengRui Medicine Co., Ltd).

[0044] ~~Embodiment~~Example 39. The method of ~~embodiment~~example any one of ~~embodiment~~examples 1-30, wherein the tubulin disrupter is a tubulysin.

[0045] ~~Embodiment~~Example 40. The method of ~~embodiment~~example 39, wherein the tubulysin is selected from tubulysin D, tubulysin M, tubuphenylalanine, and tubutyrosine.

[0046] ~~Embodiment~~Example 41. The method of any one of ~~embodiment~~examples 1-32, wherein the antibody-drug conjugate is selected from AbGn-107 (Ab1-18Hr1), AGS62P1 (ASP1235), ALT-P7 (HM2-MMAE), BA3011 (CAB-AXL-ADC), belantamab mafodotin, brentuximab vedotin, cirmtuzumab vedotin (VLS-101, UC-961ADC3), cofetuzumab pelidotin (PF-06647020, PTK7-ADC, PF-7020, ABBV-647), CX-2029 (ABBV-2029), disitamab vedotin (RC48), enapotamab vedotin (HuMax-AXL-ADC, AXL-107-MMAE), enfortumab vedotin (EV), FS-1502 (LCB14-0110), gemtuzumab ozogamicin, HTI-1066 (SHR-A1403), inotuzumab ozogamicin, PF-06804103 (NG-HER2 ADC), polatuzumab vedotin, sacituzumab govitecan, SGN-B6A, SGN-CD228A , SGN-STNV, STI-6129 (CD38 ADC, LNDS1001, CD38-077 ADC), telisotuzumab vedotin (ABBV-399), tisotumab vedotin (Humax-TF-ADC, tf-011-mmae, TV), trastuzumab deruxtecan, trastuzumab emtansine, and vorsetuzumab mafodotin.

[0047] ~~Embodiment~~Example 42. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-claudin-18.2 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:61-66.

[0048] ~~Embodiment~~Example 43. The method of ~~embodiment~~example 42, wherein the anti-claudin-18.2 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:59 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:60.

[0049] ~~Embodiment~~Example 44. The method of ~~embodiment~~example 43, wherein the anti-claudin-18.2 antibody is zolbetuximab (175D10).

[0050] ~~Embodiment~~Example 45. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-claudin-18.2 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 69-74.

[0051] ~~Embodiment~~Example 46. The method of ~~embodiment~~example 45, wherein the anti-claudin-18.2 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:67 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:68.

[0052] ~~Embodiment~~Example 47. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-PD-L1 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:77-82.

[0053] ~~Embodiment~~Example 48. The method of ~~embodiment~~example 47, wherein the anti-PD-L1 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:75 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:76.

[0054] ~~Embodiment~~Example 49. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-ALP antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:85-90.

[0055] ~~Embodiment~~Example 50. The method of ~~embodiment~~example 49, wherein the anti-ALP antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:83 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:84.

[0056] ~~Embodiment~~Example 51. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody comprises an anti-B7H4 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:93-98.

[0057] ~~Embodiment~~Example 52. The method of ~~embodiment~~example 51, wherein the anti-B7H4 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:91 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:92.

[0058] ~~Embodiment~~Example 53. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-HER2 antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:99 and a light chain comprising the amino acid sequence of SEQ ID NO:100.

[0059] ~~Embodiment~~Example 54. The method of ~~embodiment~~example 53, wherein the antibody-drug conjugate is disitamab vedotin.

[0060] ~~Embodiment~~Example 55. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-NaPi2B antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:101 and a light chain comprising the amino acid sequence of SEQ ID NO:102.

[0061] ~~Embodiment~~Example 56. The method of ~~embodiment~~example 55, wherein the antibody-drug conjugate is lifastuzumab vedotin.

[0062] ~~Embodiment~~Example 57. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-nectin-4 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:105-110.

[0063] ~~Embodiment~~Example 58. The method of ~~embodiment~~example 57, wherein the anti-nectin-4 antibody is an antibody that comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:103 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:104.

[0064] ~~Embodiment~~Example 59. The method of ~~embodiment~~example 58, wherein the antibody-drug conjugate is enfortumab vedotin.

[0065] ~~Embodiment~~Example 60. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-AVB6 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:113-118.

[0066] ~~Embodiment~~Example 61. The method of ~~embodiment~~example 60, wherein the anti-AVB6 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:111 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:112.

[0067] ~~Embodiment~~Example 62. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-AVB6 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:121-126.

[0068] ~~Embodiment~~Example 63. The method of ~~embodiment~~example 62, wherein the anti-AVB6 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:119 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:120.

[0069] ~~Embodiment~~Example 64. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-CD228 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:129-134.

[0070] ~~Embodiment~~Example 65. The method of ~~embodiment~~example 64, wherein the anti-CD228 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID

NO:127 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:128.

[0071] ~~Embodiment~~Example 66. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-LIV-1 antibody that comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:137-142.

[0072] ~~Embodiment~~Example 67. The method of ~~embodiment~~example 66, wherein the anti-LIV-1 antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:135 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:136.

[0073] ~~Embodiment~~Example 68. The method of any one of ~~embodiment~~examples 1-41, 33-1, and 38-1, wherein the first antibody is an anti-tissue factor antibody that comprises heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs:145-150.

[0074] ~~Embodiment~~Example 69. The method of ~~embodiment~~example 68, wherein the anti-tissue factor antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:143 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:144.

[0075] ~~Embodiment~~Example 70. The method of ~~embodiment~~example 69, wherein the antibody-drug conjugate is tisotumab vedotin.

[0076] ~~Embodiment~~Example 71. The method of any one of ~~embodiment~~examples 1-70, 33-1, and 38-1, wherein the second antibody binds an immune cell engager selected from anti-Mullerian Hormone Receptor II (AMHR2), B7, B7H1, B7H2, B7H3, B7H4, BAFF-R, BCMA (B-cell maturation antigen), Bst1/CD157, C5 complement, CC chemokine receptor 4 (CCR4), CD123, CD137, CD19, CD20, CD25 (IL2RA), CD276, CD278, CD3, CD32, CD33, CD37, CD38, CD4 and HIV-1 gp120-binding sites, CD40, CD70, CD70 (a member of the TNF receptor ligand family), CD80, CD86, Claudin 18.2, c-MET, CSF1R, CTLA-4, EGFR, EGFR MET proto-oncogene, EPHA3, ERBB2, ERBB3, FGFR2b, FLT3, GITR, glucocorticoid-induced TNF receptor (GITR), HER2, HER3, HLA, ICOS, IDO1, IFNAR1, IFNAR2, IGF-1R, IL-3Ralpha (CD123), IL-5R, IL-5Ralpha, LAG-3, MET proto-oncogene , OX40 (CD134), PD-1, PD-L1, PD-L2, PVRIG, respiratory syncytial virus (RSV) heavily glycosylated mucin-like domain of EBOV glycoprotein (GP), Rhesus (Rh) D, sialic acid immunoglobulin-like lectins 8 (Siglec-8), signaling lymphocyte activation molecule (SLAMF7/CS1), T-cell receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), TIGIT, TIM3 (HAVCR2), tumor specific glycoepitope of Muc1 (TA-Muc1), VSIR (VISTA), and VTCN1.

[0077] ~~Embodiment~~Example 72. The method of any one of ~~embodiment~~examples 1-71, 33-1, and 38-1, wherein the second antibody binds TIGIT.

[0078] ~~Embodiment~~Example 73. The method of ~~embodiment~~example 72, wherein the second antibody comprises: (a) a heavy chain CDR1 comprising an amino acid sequence selected from SEQ ID NOs: 7-9; (b) a heavy chain CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 10-13; (c) a heavy chain CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 14-16; (d) a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 17; (e) a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 18; and (f) a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 19.

[0079] ~~Embodiment~~Example 74. The method of ~~embodiment~~example 72, wherein the second antibody comprises a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR, and CDR3 comprising the sequences of: (a) SEQ ID NOs: 7, 10, 14, 17, 18, and 19, respectively; or (b) SEQ ID NOs: 8, 11, 14, 17, 18, and 19, respectively; or (c) SEQ ID NOs: 9, 12, 15, 17, 18, and 19, respectively; or (d) SEQ ID NOs: 8, 13, 16, 17, 18, and 19, respectively; or (e) SEQ ID NOs: 8, 12, 16, 17, 18, and 19, respectively.

[0080] ~~Embodiment~~Example 75. The method of ~~embodiment~~example 72, wherein the second antibody comprises a heavy chain variable region comprising an amino acid sequence selected from SEQ ID NOs: 1-5 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6.

[0081] ~~Embodiment~~Example 76. The method of ~~embodiment~~example 72, wherein the second antibody comprises a heavy chain comprising an amino acid sequence selected from SEQ ID NOs: 20-24 and a light chain comprising the amino acid sequence of SEQ ID NO: 25.

[0082] ~~Embodiment~~Example 77. The method of any one of ~~embodiment~~examples 1-71, wherein the second antibody binds CD40.

[0083] ~~Embodiment~~Example 78. The method of ~~embodiment~~example 77, wherein the second antibody comprises a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR, and CDR3 comprising the sequences of: (a) SEQ ID NOs: 30, 31, 32, 33, 34, and 35, respectively; or (b) SEQ ID NOs: 30, 36, 32, 33, 34, and 35, respectively.

[0084] ~~Embodiment~~Example 79. The method of ~~embodiment~~example 77, wherein the second antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

[0085] ~~Embodiment~~Example 80. The method of ~~embodiment~~example 77, wherein the second antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 27.

[0086] ~~Embodiment~~Example 81. The method of any one of ~~embodiment~~examples 1-71, 33-1, and 38-1, wherein the second antibody binds CD70.

[0087] ~~Embodiment~~Example 82. The method of ~~embodiment~~example 81, wherein the second antibody comprises a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR, and CDR3 comprising the sequences of SEQ ID NOs: 53-58, respectively.

[0088] ~~Embodiment~~Example 83. The method of ~~embodiment~~example 81, wherein the second antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 41 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 42.

[0089] ~~Embodiment~~Example 84. The method of any one of ~~embodiment~~examples 1-71, 33-1, and 38-1, wherein the second antibody binds BCMA.

[0090] ~~Embodiment~~Example 85. The method of ~~embodiment~~example 84, wherein the second antibody comprises a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR, and CDR3 comprising the sequences of SEQ ID NOs: 47-52, respectively.

[0091] ~~Embodiment~~Example 86. The method of ~~embodiment~~example 84, wherein the second antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 45 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 46.

[0092] ~~Embodiment~~Example 87. The method of any one of ~~embodiment~~examples 1-86, 33-1, and 38-1, wherein the second antibody is an IgG1 or IgG3 antibody.

[0093] ~~Embodiment~~Example 88. The method of any one of ~~embodiment~~examples 1-87, 33-1, and 38-1, wherein the second antibody is comprised in a composition of antibodies, wherein at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the antibodies in the composition are nonfucosylated.

[0094] ~~Embodiment~~Example 89. The method of ~~embodiment~~example 88, wherein each antibody in the composition comprises the same heavy chain and light chain amino acid sequences as the second antibody.

[0095] ~~Embodiment~~Example 90. The method of any one of ~~embodiment~~examples 1-89, 33-1, and 38-1, wherein the Fc of the second antibody has enhanced binding to one or more activating FcγRs as compared to a corresponding wild-type Fc of the same isotype, wherein the activating FcγRs include one or more of FcγRIIIa, FcγRIIa, and/or FcγRI.

[0096] ~~Embodiment~~Example 91. The method of ~~embodiment~~example 90, wherein the Fc of the second antibody has enhanced binding to FcγRIIIa.

[0097] ~~Embodiment~~Example 92. The method of any one of ~~embodiment~~examples 1-91, 33-1, and 38-1, wherein the Fc of the second antibody has reduced binding to one or more inhibitory FcγRs as compared to a corresponding wild-type Fc of the same isotype.

[0098] ~~Embodiment~~Example 93. The method of ~~embodiment~~example 92, wherein the Fc of the second antibody has reduced binding to FcγRIIb.

[0099] ~~Embodiment~~Example 94. The method of any one of ~~embodiment~~examples 1-93, 33-1, and 38-1, wherein the Fc of the second antibody has enhanced binding to FcγRIIIa and reduced binding to FcγRIIb.

[00100] ~~Embodiment~~Example 95. The method of any one of ~~embodiment~~examples 1-94, 33-1, and 38-1, wherein the second antibody is a monoclonal antibody.

[00101] ~~Embodiment~~Example 96. The method of any one of ~~embodiment~~examples 1-95, 33-1, and 38-1, wherein the second antibody is a humanized antibody or a human antibody.

[00102] ~~Embodiment~~Example 97. The method of any one of ~~embodiment~~examples 1-96, 33-1, and 38-1, wherein the cancer is bladder cancer, breast cancer, uterine cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, colorectal cancer, colon cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, lung cancer, lung adenocarcinoma, stomach cancer, germ cell cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, melanoma, neoplasm of the central nervous system, mesothelioma, lymphoma, leukemia, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, or sarcoma.

[00103] ~~Embodiment~~Example 98. The method of any one of ~~embodiment~~examples 1-97, 33-1, and 38-1, wherein the cancer is lymphoma, leukemia, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, or Hodgkin lymphoma.

[00104] ~~Embodiment~~Example 99. The method of any one of ~~embodiment~~examples 1-98, 33-1, and 38-1, wherein the antibody-drug conjugate and the second antibody are administered concurrently.

[00105] ~~Embodiment~~Example 100. The method of ~~embodiment~~example 99, 33-1, and 38-1, wherein the antibody-drug conjugate and the second antibody are administered in a single pharmaceutical composition.

[00106] ~~Embodiment~~Example 101. The method of any one of ~~embodiment~~examples 1-98, 33-1, and 38-1, wherein the antibody-drug conjugate and the second antibody are administered sequentially.

[00107] ~~Embodiment~~Example 102. The method of ~~embodiment~~example 101, wherein at least a first dose of the antibody-drug conjugate is administered prior to a first dose of the second antibody; or wherein at least a first dose of the second antibody is administered prior to a first dose of the antibody-drug conjugate.

[00108] ~~Embodiment~~Example 103. The method of any one of ~~embodiment~~examples 1-102, 33-1, and 38-1, wherein the second antibody depletes T regulatory cells (Tregs).

[00109] ~~Embodiment~~Example 104. The method of any one of ~~embodiment~~examples 1-103, 33-1, and 38-1, wherein the antibody-drug conjugate induces immune memory against cells expressing the antigen bound by the antibody-drug conjugate.

[00110] ~~Embodiment~~Example 105. The method of ~~embodiment~~example 104, wherein the induction of immune memory comprises induction of memory T cells.

[00111] ~~Embodiment~~Example 106. The method of any one of ~~embodiment~~examples 1-105, 33-1, and 38-1, wherein the second antibody activates antigen presenting cells (APCs).

[00112] ~~Embodiment~~Example 107. The method of any one of ~~embodiment~~examples 1-106, 33-1, and 38-1, wherein the second antibody enhances CD8 T cell responses.

[00113] ~~Embodiment~~Example 108. The method of any one of ~~embodiment~~examples 1-107, 33-1, and 38-1, wherein the second antibody upregulates co-stimulatory receptors.

[00114] ~~Embodiment~~Example 109. The method of any one of ~~embodiment~~examples 1-108, 33-1, and 38-1, wherein administration of the ADC and the second antibody promotes release of an immune activating cytokine.

[00115] ~~Embodiment~~Example 110. The method of ~~embodiment~~example 109, wherein the immune activating cytokine is CXCL10 or IFNγ.

[00116] ~~Embodiment~~Example 111. The method of any one of ~~embodiment~~examples 1-110, 33-1, and 38-1, wherein the ADC and the second antibody act synergistically.

[00117] ~~Embodiment~~Example 112. The method of any one of ~~embodiment~~examples 1-111, 33-1, and 38-1, wherein administration of the ADC and the second antibody in combination has a toxicity profile comparable to that of the ADC or the second antibody when either is administered as monotherapy.

[00118] ~~Embodiment~~Example 113. The method of any one of ~~embodiment~~examples 1-112, 33-1, and 38-1, wherein the effective dose of the ADC and/or the second antibody when dosed in combination is less than when administered as monotherapy.

[00119] ~~Embodiment~~Example 114. The method of any one of ~~embodiment~~examples 1-113, 33-1, and 38-1, wherein the cancer has high tumor mutation burden.

[00120] ~~Embodiment~~Example 115. The method of any one of ~~embodiment~~examples 1-114, 33-1, and 38-1, wherein the cancer has microsatellite instability.

BRIEF DESCRIPTION OF THE DRAWINGS

[00121] **FIG. 1** shows that non-directed chemotherapeutic agents impair T cell responses.

[00122] **FIG. 2** shows brentuximab vedotin (BV) treatment of CD30+ CD8 T cells. Vedotin ADCs that have directed delivery to T cells do not inhibit proliferation.