(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2024 (13.06.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/123765 A1

(51) International Patent Classification:
A61P 35/00 (2006.01) *C07K 16/28* (2006.01)
A61K 39/395 (2006.01) *C07K 16/46* (2006.01)
A61K 47/68 (2017.01)

(21) International Application Number:
PCT/US2023/082499

(22) International Filing Date:
05 December 2023 (05.12.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/386,627 08 December 2022 (08.12.2022) US

(71) Applicants: **IMMUNOGEN, INC.** [US/US]; 830 Winter Street, Waltham, Massachusetts 02451 (US). **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) Inventors: **ZWEIDLER-MCKAY, Patrick**; 111 Old Country Road, Lincoln, Massachusetts 01773 (US). **RAMSINGH, Giridharan**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(74) Agent: **GASZNER, Miklos**; Nixon & Vanderhye P.C., 901 North Glebe Road, 11th Floor, Arlington, Virginia 22203-1808 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

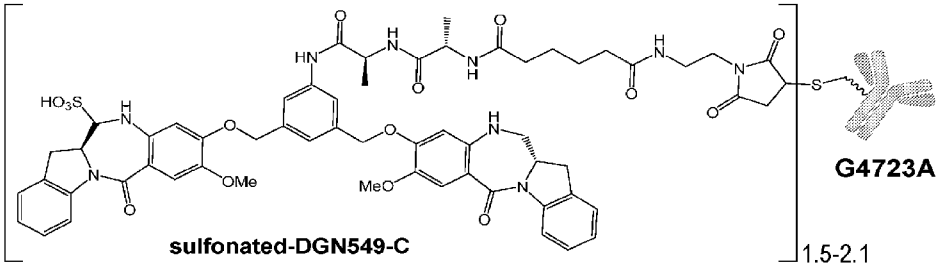
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: THERAPEUTIC COMBINATIONS COMPRISING ANTI-CD123 ANTIBODY-DRUG CONJUGATES AND ANTI-CD47 ANTIBODIES

FIG. 1A

Chemical Structure	 Note: The sulfur adjacent to the G4723A antibody is derived from the site specific engineered cysteine residues on the antibody

(57) Abstract: Therapeutic combinations of ADCs that bind to CD123 (e.g., IMGN632/PVEK) with an ant-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) are provided. Methods of administering the combinations to treat hematological malignancies, such as acute myeloid leukemia (AML), with improved clinical efficacy and/or a lack of increased toxicity are also provided.

WO 2024/123765 A1

THERAPEUTIC COMBINATIONS COMPRISING ANTI-CD123 ANTIBODY-DRUG CONJUGATES AND ANTI-CD47 ANTIBODIES

Field of the Invention

[0001] The field of the invention generally relates to combinations of an anti-CD123 antibody-drug conjugates (ADCs) and anti-CD47 antibodies or antigen-binding fragments thereof use in the treatment of hematologic malignancies.

Cross-refrence to Related Applications

[0002] This application claims the benefit of U.S. Application No. 63/386,627, filed December 8, 2022, which is incorporated herein by reference in its entirety.

Background

[0003] Cancer is one of the leading causes of death in the developed world, with over one million people diagnosed with cancer and 500,000 deaths per year in the United States alone. Overall it is estimated that more than 1 in 3 people will develop some form of cancer during their lifetime.

[0004] Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and accounts for the largest number of deaths from leukemias in the United States. In 2017, an estimated 21,380 people will be diagnosed with AML per year and 10,590 patients will die of the disease (Siegel *et al.*, *CA Cancer J Clin.* 2017;67(1):7-30 (2017)). The median age of diagnosis is 66 years. Frontline chemotherapy in AML is reported to induce complete response (CR) in 70%-80% of patients who are 60 years of age or younger and in approximately 50% of older patients. "Fit" patients are judged to be able to tolerate intensive treatment, are often younger (< 60 years), and typically receive one to two cycles of induction with "7 + 3," a combination of cytarabine and anthracycline, typically daunorubicin. Following this, these fit patients may receive high-dose cytarabine for one or more cycles and may receive a stem cell transplant. Standard induction and post-induction therapies result in a median duration of remission of approximately one year and potential cures in 25%-35% of the patients. "Unfit" patients, often older, typically receive venetoclax, azacitidine, a hypomethylating agent. The majority of AML patients will eventually relapse, and AML salvage regimens offer poor outcomes with significant toxicity.

[0005] Blastic plasmacytoid dendritic cell neoplasm is a rare, aggressive hematologic malignancy derived from myeloid dendritic cell precursors, which often manifests with skin lesions in addition to lymph node, blood, and bone marrow involvement. Characterized by CD4, CD56, and CD123 expression among other markers, BPDCN blasts express high levels of CD123. Unfortunately, there is no standard of care for BPDCN, with both acute lymphoblastic

leukemia (ALL) and AML regimens used in frontline treatment. Despite CR rates of 47%-86% in frontline disease, median overall survival is approximately 12-16 months. The majority of BPDCN patients will eventually relapse with no standard treatment options.

[0006] Acute lymphoblastic leukemia (ALL) is a rare, aggressive hematologic malignancy derived from lymphoid precursors, which often manifests with lymph node, blood, and bone marrow involvement. B-cell acute lymphoblastic leukemia and some T-cell acute lymphoblastic leukemia blasts express CD123 at levels similar to AML blasts. Although initial remission rates are high, long-term survival rates are 35%-40% in patients less than 60 years of age, and less than 10% for older patients (Goldstone 2008). Patients with relapsed ALL have several chemotherapeutic options, as well as immunotherapy with United States Food and Drug Administration-approved anti-CD19 bispecific blinatumomab. However, long-term survival remains poor for these patients.

[0007] CD123 has been proposed as a potential target for the treatment of some hematological malignancies. CD123 is the alpha-subunit of the interleukin-3 receptor (IL-3Rα). CD123 expression is low on normal hematopoietic stem cells (Testa *et al.*, *Biomark Res.*, 10;2(1):4.(2014), Jordan *et al.*, *Leukemia*, 14(10):1777-84 (2000)). However, CD123 is overexpressed in multiple hematological malignancies of both myeloid and lymphoid origins, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), chronic myeloid leukemia in blast crisis/phase (BP-CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN) (Testa 2014). IMGN632 (also known as pivekimab sunirine or PVEK) is an antibody-drug conjugate (ADC) that contains a DNA-alkylating IGN payload.

[0008] Cluster of differentiation 47 (CD47) also been proposed as a potential target for the treatment of some hematological malignancies. CD47 is a macrophage-signaling human cell surface antigen that is overexpressed on the surface of many types of cancer cells, enabling the escape of these cancer cells from macrophage-mediated phagocytosis. Magrolimab is a monoclonal antibody against CD47 and thus a macrophage checkpoint inhibitor that is designed to interfere with recognition of CD47 by the SIRPα receptor on macrophages, thereby allowing the activation of macrophages, resulting in specific tumor cell phagocytosis.

[0009] Given the inability of currently available therapeutics to treat many hematological malignancies, there is a need for more effective interventions that maximize efficacy without intolerable side effects.

BRIEF SUMMARY OF THE INVENTION

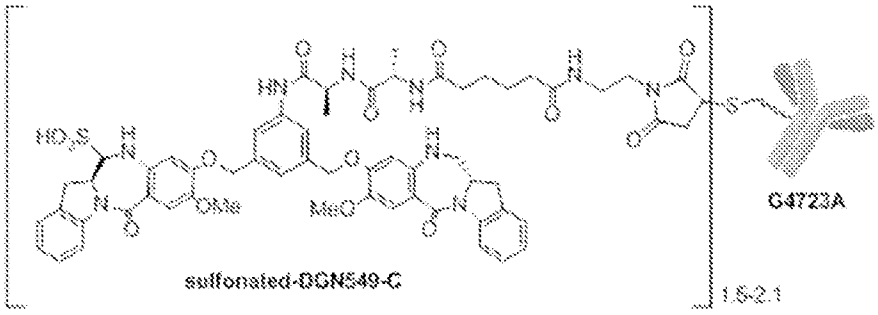
[0010] Combinations of an anti-CD123 ADCs and anti-CD47 antibodies or antigen-binding fragments thereof are provided herein. Also provided herein are methods of treating a patient with cancer using such a combination.

[0011] Provided herein is a method for treating in a subject comprising administering to said subject (a) an antibody drug conjugate (ADC) that binds to CD123, wherein said ADC comprises a DNA-alklyating agent conjugated to an anti-CD123 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 5; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 6; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 10, and (b) an anti-CD47 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 15; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 17; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 18; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 19; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 20.

[0012] In some aspects, the anti-CD123 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1 or a VL comprising the amino acid sequence set forth in SEQ ID NO: 2. In some aspects, the anti-CD123 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 2. In some aspects, the anti-CD123 antibody or antigen-binding fragment thereof is an antibody. In some aspects, the anti-CD123 antibody or antigen-binding fragment thereof is a human IgG antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a human IgG1 antibody or antigen-binding fragment thereof. In some aspects, the anti-CD123 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4. In some aspects, the anti-CD123 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4.

[0013] In some aspects, the DNA-alkylating agent is indolino-benzodiazepine (IGN) DNA-alkylator.

[0014] In some aspects, the ADC is IMGN632/PVEK. In some aspects, the ADC is administered in a pharmaceutical composition comprising ADCs with the following structure:



,wherein G4723A comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4.

[0015] In some aspects, the ADC is administered intravenously.

[0016] In some aspects, the ADC is administered once every 28 days.

[0017] In some aspects, the ADC is administered at a dose of 0.045 mg/kg. In some aspects, the ADC is administered at a dose of 0.045 mg/kg for two doses. In some aspects, the ADC is administered at a dose of 0.03 mg/kg. In some aspects, the ADC is administered at a dose of 0.03 mg/kg for two doses.

[0018] In some aspects, the anti-CD123 ADC and the anti-CD47 antibody or antigen-binding fragment thereof are administered in separate pharmaceutical compositions.

[0019] In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 13 or a VL comprising the amino acid sequence set forth in SEQ ID NO: 14. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 13 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 14. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is an antibody. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is a human IgG antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a human IgG4 antibody or antigen-binding fragment thereof. In some aspects, the anti-CD47 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 21 or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 22. In some aspects, the anti-CD47 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:

21 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 22. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab.

[0020] In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered intravenously.

[0021] In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered once every week. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered once every two weeks. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered once every week and once every two weeks (e.g., once every week and then once every two weeks).

[0022] In some aspects, administering the anti-CD47 antibody or antigen-binding fragment thereof comprises administering a priming regimen and administering a maintenance regimen.

[0023] In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered once every two weeks in the maintenance regimen. In some aspects,the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 30 mg/kg in the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 25 mg/kg in the maintenance regimen. In some aspects,the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 20 mg/kg in the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg in the maintenance regimen.

[0024] In some aspects,the anti-CD47 antibody or antigen-binding fragment thereof is administered once every 3 or 4 days. In some aspects,the anti-CD47 antibody or antigen-binding fragment thereof is administered once every week in the priming regimen. In some aspects,the anti-CD47 antibody or antigen-binding fragment thereof is administered once every 3 or 4 days and/or once every week in the priming regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered in at least two increasing doses in the priming regimen. In some aspects, the at least two increasing doses in the priming regimen are from 1 mg/kg to 30 mg/kg. In some aspects, the at least two increasing doses in the priming regimen are selected from the group consisting of 1 mg/kg, 15 mg/kg, and 30 mg/kg doses. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof is administered in three increasing doses in the priming regimen. In some aspects the three increasing doses in the priming regimen are from 1 mg/kg to 30 mg/kg. In some aspects, the at least three increasing doses in the priming regimen are 1 mg/kg, 15 mg/kg, and 30 mg/kg doses. In some aspects, the three increasing doses comprise a first dose administered on Days 1 and 4, a second dose administered on Day 8, and a third dose administered on Days 11, 15 and then once every week for 5 doses. In some aspects,in the priming regimen, the anti-CD47 antibody or antigen-binding fragment thereof is administered

at 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses.

[0025] In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks. In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

[0026] In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 25 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 25 mg/kg once every two weeks. In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 25 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 25 mg/kg once every two weeks.

[0027] In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 20 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 20 mg/kg once every two weeks. In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 20 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 20 mg/kg once every two weeks.

[0028] In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Days 8, 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 15 mg/kg once every two weeks. In some aspects, the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in

a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Days 8, 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 15 mg/kg once every two weeks.

[0029] In some aspects, the ADC is further administered as a maintenance therapy. In some aspects, the ADC is administered once every two weeks during the maintenance therapy. In some aspects, the ADC is administered once every four weeks during the maintenance therapy. In some aspects, the ADC is administered at 0.045 mg/kg during the maintenance therapy. In some aspects, the ADC is administered at 0.03 mg/kg during the maintenance therapy.

[0030] In some aspects, the hematological malignancy is a relapsed or refractory hematological malignancy. In some aspects, the hematological malignancy is a relapsed hematological malignancy. In some aspects, the hematological malignancy is a refractory hematological malignancy. In some aspects, the hematological malignancy is acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), chronic myeloid leukemia in blast crisis/phase (BP-CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN). In some aspects, the hematological malignancy is a CD123+ hematological malignancy. In some aspects, , the hematological malignancy has an FLT3-ITD mutation. In some aspects, the hematological malignancy expresses multidrug resistance 1 (MDR1). In some aspects, the hematological malignancy expresses P-glycoprotein (P-gp).

[0031] In some aspects, the administration is a first-line therapy. In some aspects, the subject received one prior line of therapy. In some aspects, the subject received two prior lines of therapy.

[0032] In some aspects, the cancer has not previously been treated with IMGN632/PVEK. In some aspects, the cancer has not previously been treated with magrolimab. In some aspects, the cancer has not previously been treated with an SIRPα-targeting agent.

[0033] In some aspects, administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof produces a synergistic effect. In some aspects, administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof does not produce more toxicity than administration of the ADC alone. In some aspects, administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof does not produce more toxicity than administration of the anti-CD47 antibody or antigen-binding fragment thereof alone.

[0034] In some aspects, the subject received dexamethasone on the day prior to the administration of the ADC. In some aspects, the subject received 8 mg dexamethasone twice on the day prior to the administration of the ADC. In some aspects, the method further comprises administering dexamethasone to the subject on the day prior to the administration of the ADC. In some aspects, the method further comprises administering 8 mg dexamethasone to the subject twice on the day prior to the administration of the ADC.

[0035] In some aspects, the subject received diphenhydramine prior to the administration of the ADC. In some aspects, the subject received 25 mg to 50 mg diphenhydramine prior to the administration of the ADC. In some aspects, the method further comprises administering diphenhydramine to the subject prior the administration of the ADC. In some aspects, the method further comprises method further comprises administering 25 mg to 50 mg diphenhydramine, to the subject prior the administration of the ADC.

[0036] In some aspects, the subject received acetaminophen or paracetamol prior to the administration of the ADC. In some aspects, the subject received 325 mg to 650 mg acetaminophen or paracetamol prior to the administration of the ADC. In some aspects, the method further comprises administering acetaminophen or paracetamol, optionally 325 mg to 650 mg acetaminophen or paracetamol, to the subject prior to the administration of the ADC.

[0037] In some aspects, the subject received dexamethasone prior to the administration of the ADC. In some aspects, the subject received 8 mg dexamethasone prior to the administration of the ADC. In some aspects, the method further comprises administering dexamethasone to the subject prior to the administration of the ADC. In some aspects, the method further comprises administering 8 mg dexamethasone to the subject prior to the administration of the ADC.

[0038] In some aspects, the the subject received acetaminophen (optionally 650 mg to 1000 mg acetaminophen), diphenhydramine (optionally 35 mg to 50 mg diphenhydramine), or comparable regimen prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof. In some aspects, the method further comprises administering acetaminophen (optionally 650 mg to 1000 mg acetaminophen), diphenhydramine (optionally 35 mg to 50 mg diphenhydramine), or comparable regimen to the subject prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof.

[0039] In some aspects, the ADC is IMGN632/PVEK, the ADC is administered intravenously at a dose of 0.045 mg/kg once every 28 days, the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab, and the magrolimab is administered intravenously in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

[0040] In some aspects, the ADC is IMGN632/PVEK, the ADC is administered intravenously at a dose of 0.03 mg/kg once every 28 days, the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab, and the magrolimab is administered intravenously in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

[0041] In some aspects, the ADC is administered twice.

[0042] In some aspects, the subject is human.

[0043] Provided herein is a composition comprising an ADC that binds to CD123 for use in combination with an anti-CD47 antibody or antigen-binding fragment thereof for treating a hematologic malignancy in any method provided herein.

[0044] Provided herein is a composition comprising an ADC that binds to CD123, wherein the composition is to be administered with an anti-CD47 antibody or antigen-binding fragment thereof for treating a hematologic malignancy in any method provided herein.

[0045] Provided herein is a composition comprising an anti-CD47 antibody or antigen-binding fragment thereof for use in combination with an ADC that binds to CD123 for treating a hematologic malignancy in any method provided herein.

[0046] Provided herein is a composition comprising an anti-CD47 antibody or antigen-binding fragment thereof, wherein the composition is to be administered with an ADC that binds to CD123 for treating a hematologic malignancy any method provided herein.

BRIEF DESCRIPTION OF THE FIGURES

[0047] FIG. 1A shows the chemical structure for IMGN632 (PVEK). IMGN632 is composition comprising ADCs containing the anti-CD123 G4723A antibody linked to the cytotoxic payload DGN549-C in sodium bisulfite. The majority of the ADC in the composition is in the sulfonated version shown in FIG. 1A.

[0048] FIG. 1B shows an unsulfonated form of the ADC containing the anti-CD123 G4723A antibody linked to the cytotoxic payload DGN549-C (the mono-imine structure), which can also be present in an IMGN632 composition.

[0049] FIG. 2 shows the study schema for a trial demonstrating the efficacy of the combination of IMGN632 and magrolimab. After acceptable safety and sufficient efficacy are observed in the Safety Phase, and futility is passed (Stage 1), up to an additional 14 efficacy-evaluable patients are enrolled in the Full Expansion Phase to allow further demonstration of repeated dosing safety and efficacy (Stage 2).

DETAILED DESCRIPTION OF THE INVENTION

[0050] The present invention provides combinations of an anti-CD123 antibody drug conjugate (ADC) with an anti-CD47 antibody or antigen-binding fragment thereof and the use of the combinations in the treatment of hematologic malignancies.

I. Definitions

[0051] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0052] The terms "IL-3Rα," "Interleukine-3 Receptor alpha," "CD-123," and "CD123," as used interchangeably herein, refer to mammalian CD123 polypeptides, including, but not limited to, native CD123 polypeptides and isoforms of CD123 polypeptides, unless otherwise indicated. The terms encompass "full-length," unprocessed CD123 polypeptides as well as any form of CD123 polypeptide that results from processing within the cell. The term also encompasses naturally occurring variants of CD123, e.g., those encoded by splice variants and allelic variants. The CD123 polypeptides described herein can be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. Where specifically indicated, "CD123" can be used to refer to a nucleic acid that encodes a CD123 polypeptide. Human CD123 sequences are known and include, for example, those sequences associated with NCBI reference numbers NP_002174 & NM_002183 (protein and nucleic acid sequences for human CD123 variant 1), and NP_001254642 & NM_001267713 (protein and nucleic acid sequences for human CD123 variant 2). As used herein, the term "human CD123" refers to CD123 comprising the sequence of SEQ ID NO: 25 or SEQ ID NO: 26.
MVLLWLTLLLIALPCLLQTKEDPNPPITNLRMKAKAQQLTWDLNRNVTDIECVKDADYS
MPAVNNSYCQFGAISLCEVTNYTVRVANPPFSTWILFPENSGKPWAGAENLTCWIHDVD
FLSCSWAVGPGAPADVQYDLYLNVANRRQQYECLHYKTDAQGTRIGCRFDDISRLSSGS
QSSHILVRGRSAAFGIPCTDKFVVFSQIEILTPPNMTAKCNKTHSFMHWKMRSHFNRKFR
YELQIQKRMQPVITEQVRDRTSFQLLNPGTYTVQIRARERVYEFLSAWSTPQRFECDQEE
GANTRAWRTSLLIALGTLLALVCVFVICRRYLVMQRLFPRIPHMKDPIGDSFQNDKLVV
WEAGKAGLEECLVTEVQVVQKT (SEQ ID NO: 25)

MVLLWLTLLLIALPCLLQTKEGGKPWAGAENLTCWIHDVDFLSCSWAVGPGAPADVQY
DLYLNVANRRQQYECLHYKTDAQGTRIGCRFDDISRLSSGSQSSHILVRGRSAAFGIPCTD
KFVVFSQIEILTPPNMTAKCNKTHSFMHWKMRSHFNRKFRYELQIQKRMQPVITEQVRD
RTSFQLLNPGTYTVQIRARERVYEFLSAWSTPQRFECDQEEGANTRAWRTSLLIALGTLL
ALVCVFVICRRYLVMQRLFPRIPHMKDPIGDSFQNDKLVVWEAGKAGLEECLVTEVQVV
QKT (SEQ ID NO: 26)

[0053] The terms "leukocyte surface antigen CD47," "CD-47," and "CD47," as used interchangeably herein, refer to mammalian CD47 polypeptides, including, but not limited to, native CD47 polypeptides and isoforms of CD47 polypeptides, unless otherwise indicated. The

terms encompass "full-length," unprocessed CD47 polypeptides as well as any form of CD47 polypeptide that results from processing within the cell. The term also encompasses naturally occurring variants of CD47, e.g., those encoded by splice variants and allelic variants. The CD47 polypeptides described herein can be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. Where specifically indicated, "CD47" can be used to refer to a nucleic acid that encodes a CD47 polypeptide. Human CD47 sequences are known and include, for example, those sequences associated with UniProt reference number Q08722. As used herein, the term "human CD47" refers to CD47 comprising the sequence of SEQ ID NO: 27.

QLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKWKFKGRDIYTFDGALNKSTV
PTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTELTREGETIIELKYRVVSWFS
PNENILIVIFPIFAILLFWGQFGIKTLKYRSGGMDEKTIALLVAGLVITVIVIVGAILFVPGEY
SLKNATGLGLIVTSTGILILLHYYVFSTAIGLTSFVIAILVIQVIAYILAVVGLSLCIAACIPM
HGPLLISGLSILALAQLLGLVYMKFVASNQKTIQPPRKAVEEPLNAFKESKGMMNDE
(SEQ ID NO: 27)

[0054] In some aspects, "human CD47" can comprise the leader sequence MWPLVAALLLGSACCGSA (SEQ ID NO: 28) at the N-terminus of SEQ ID NO: 27, e.g., the complete sequence of SEQ ID NO: 29.
MWPLVAALLLGSACCGSAQLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKW
KFKGRDIYTFDGALNKSTVPTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTE
LTREGETIIELKYRVVSWFSPNENILIVIFPIFAILLFWGQFGIKTLKYRSGGMDEKTIALLV
AGLVITVIVIVGAILFVPGEYSLKNATGLGLIVTSTGILILLHYYVFSTAIGLTSFVIAILVIQ
VIAYILAVVGLSLCIAACIPMHGPLLISGLSILALAQLLGLVYMKFVASNQKTIQPPRKAVE
EPLNAFKESKGMMNDE (SEQ ID NO: 29)

[0055] The term "antibody" means an immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antibody, and any other modified immunoglobulin molecule so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM,

or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules such as toxins, radioisotopes, etc.

[0056] The term "anti-CD123 antibody" or "an antibody that binds to CD123" refers to an antibody that is capable of binding CD123 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CD123 (e.g., the antibody in IMGN632/PVEK). The extent of binding of an anti-CD123 antibody to an unrelated, non-CD123 protein can be less than about 10% of the binding of the antibody to CD123 measured, e.g., by a radioimmunoassay (RIA).

[0057] The term "anti-CD47 antibody" or "an antibody that binds to CD47" refers to an antibody that is capable of binding CD47 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CD47 (e.g., the antibody magrolimab). The extent of binding of an anti-CD47 antibody to an unrelated, non-CD47 protein can be less than about 10% of the binding of the antibody to CD47 measured, e.g., by a radioimmunoassay (RIA).

[0058] The term "antibody fragment" refers to a portion of an intact antibody with a sufficient positive charge to bind to a cation exchange resin. An "antigen-binding fragment" refers to a portion of an intact antibody that binds to an antigen and has a sufficient positive charge to bind to a cation exchange resin. An antigen-binding fragment can contain the antigenic determining variable regions of an intact antibody. Examples of antibody fragments include, but are not limited to Fab, Fab', F(ab')2, and Fv fragments, linear antibodies, and single chain antibodies.

[0059] The term "cysteine engineered" antibody or antigen-binding fragment thereof includes an antibody or antigen-binding fragment thereof with at least one cysteine ("Cys") that is not normally present at a given residue of the antibody or antigen-binding fragment thereof light chain or heavy chain. Such Cys, which may also be referred to as "engineered Cys," can be engineered using any conventional molecular biology or recombinant technology (e.g. , by replacing the coding sequence for a non-Cys residue at the target residue with a coding sequence for Cys). For example, if the original residue is Ser with a coding sequence of 5'-UCU-3', the coding sequence can be mutated (e.g., by site-directed mutagenesis) to 5'-UGU-3', which encodes Cys. In certain aspects, the Cys engineered antibody or antigen-binding fragment thereof has an engineered Cys in the heavy chain. In certain aspects, the engineered Cys is in or near the CH3 domain of the heavy chain. In certain aspects, the engineered Cys is at residue 442 of the heavy chain (EU/OU numbering; EU index, Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed., NIH publication No. 91-3242, 1991, the entire contents of which are

incorporated herein by reference). In certain aspects, the Fc region comprises a cysteine at one or more of positions 239, 282, 289, 297, 312, 324, 330, 335, 337, 339, 356, 359, 361, 383, 384, 398, 400, 440, 422, and 442, as numbered by the EU index. In certain aspects, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. In certain aspects, the variable light chain domain, e.g., of an scFv, has a cysteine at Kabat position 100. In certain aspects, the variable heavy chain domain ,e.g. of an scFv, has a cysteine at Kabat position 44. Cysteine engineered antibodies may be generated as described, e.g., in U.S. Pat. No. 7,521,541, U.S. Pat. No. 7,855,275, U.S. Published Application No. 20110033378 and WO 2011/005481.

[0060] A "monoclonal" antibody or antigen-binding fragment thereof refers to a homogeneous antibody or antigen-binding fragment population involved in the highly specific recognition and binding of a single antigenic determinant, or epitope. This is in contrast to polyclonal antibodies that typically include different antibodies directed against different antigenic determinants. The term "monoclonal" antibody or antigen-binding fragment thereof encompasses both intact and full-length monoclonal antibodies as well as antibody fragments (such as Fab, Fab', F(ab')2, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, "monoclonal" antibody or antigen-binding fragment thereof refers to such antibodies and antigen-binding fragments thereof made in any number of manners including but not limited to by hybridoma, phage selection, recombinant expression, and transgenic animals.

[0061] The term "humanized" antibody or antigen-binding fragment thereof refers to forms of non-human (e.g. murine) antibodies or antigen-binding fragments that are specific immunoglobulin chains, chimeric immunoglobulins, or fragments thereof that contain minimal non-human (e.g., murine) sequences. Typically, humanized antibodies or antigen-binding fragments thereof are human immunoglobulins in which residues from the complementary determining region (CDR) are replaced by residues from the CDR of a non-human species (e.g. mouse, rat, rabbit, hamster) that have the desired specificity, affinity, and capability ("CDR grafted") (Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Verhoeyen et al., Science 239:1534-1536 (1988)). In some instances, the Fv framework region (FR) residues of a human immunoglobulin are replaced with the corresponding residues in an antibody or fragment from a non-human species that has the desired specificity, affinity, and capability. The humanized antibody or antigen-binding fragment thereof can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody or antigen-binding fragment thereof

specificity, affinity, and/or capability. In general, the humanized antibody or antigen-binding fragment thereof will comprise substantially all of at least one, and typically two or three, variable domains containing all or substantially all of the CDR regions that correspond to the non-human immunoglobulin whereas all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody or antigen-binding fragment thereof can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Examples of methods used to generate humanized antibodies are described in U.S. Pat. 5,225,539; Roguska et al., Proc. Natl. Acad. Sci., USA, 91(3):969-973 (1994), and Roguska et al., Protein Eng. 9(10):895-904 (1996). In some aspects, a "humanized antibody" is a resurfaced antibody.

[0062] A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al., Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda Md.), "Kabat"); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-lazikani et al, J. Molec. Biol. 273:927-948 (1997)). In addition, combinations of these two approaches are sometimes used in the art to determine CDRs.

[0063] The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (e.g., Kabat et al., Sequences of Immunological Interest. (5th Ed., 1991, National Institutes of Health, Bethesda, Md.) ("Kabat").

[0064] The amino acid position numbering as in Kabat, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat et al. (Sequences of Immunological Interest. (5th Ed., 1991, National Institutes of Health, Bethesda, Md.), "Kabat"). Using this numbering system, the actual linear amino acid sequence can contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or CDR of the variable domain. For example, a heavy chain variable domain can include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (e.g. residues 82a, 82b, and 82c, etc. according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues can be determined for a given antibody by alignment at

regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. Chothia refers instead to the location of the structural loops (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software.

Loop	Kabat	AbM	Chothia
L1	L24-L34	L24-L34	L24-L34
L2	L50-L56	L50-L56	L50-L56
L3	L89-L97	L89-L97	L89-L97
H1	H31-H35B	H26-H35B	H26-H32..34
		(Kabat Numbering)	
H1	H31-H35	H26-H35	H26-H32
		(Chothia Numbering)	
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[0065] The term "human" antibody or antigen-binding fragment thereof means an antibody or antigen-binding fragment thereof produced by a human or an antibody or antigen-binding fragment thereof having an amino acid sequence corresponding to an antibody or antigen-binding fragment thereof produced by a human made using any technique known in the art. This definition of a human antibody or antigen-binding fragment thereof includes intact or full-length antibodies and fragments thereof.

[0066] The term "chimeric" antibodies or antigen-binding fragments thereof refers to antibodies or antigen-binding fragments thereof wherein the amino acid sequence is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies or antigen-binding fragments thereof derived from one species of mammals (e.g. mouse, rat, rabbit, etc.) with the desired specificity, affinity, and capability while the constant regions are homologous to the sequences in antibodies or antigen-binding fragments thereof derived from another (usually human) to avoid eliciting an immune response in that species.

[0067] The term "epitope" or "antigenic determinant" are used interchangeably herein and refer to that portion of an antigen capable of being recognized and specifically bound by a particular antibody. When the antigen is a polypeptide, epitopes can be formed both from contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed

from contiguous amino acids are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0068] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present disclosure. Specific illustrative aspects are described in the following.

[0069] "Or better" when used herein to refer to binding affinity refers to a stronger binding between a molecule and its binding partner. "Or better" when used herein refers to a stronger binding, represented by a smaller numerical Kd value. For example, an antibody which has an affinity for an antigen of "0.6 nM or better", the antibody's affinity for the antigen is <0.6 nM, i.e. 0.59 nM, 0.58 nM, 0.57 nM etc. or any value less than 0.6 nM.

[0070] By "specifically binds," it is generally meant that an antibody binds to an epitope via its antigen binding domain, and that the binding entails some complementarity between the antigen binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen binding domain more readily than it would bind to a random, unrelated epitope. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D."

[0071] By "preferentially binds," it is meant that the antibody specifically binds to an epitope more readily than it would bind to a related, similar, homologous, or analogous epitope. Thus, an antibody which "preferentially binds" to a given epitope would more likely bind to that epitope than to a related epitope, even though such an antibody may cross-react with the related epitope.

[0072] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer can be linear or branched, it can comprise

modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this disclosure are based upon antibodies, in certain aspects, the polypeptides can occur as single chains or associated chains.

[0073] The term "antibody-drug conjugate," "ADC," or "conjugate" as used herein refers to a conjugate comprising a drug that is linked to a cell binding agent (e.g., an anti-CD123 antibody or fragment thereof) and is defined by a generic formula: C-A, wherein C = cytotoxin (e.g., such as an indolino-benzodiazepine (IGN) DNA-alkylator (e.g., DGN549-C)) and A = antibody or antigen-binding fragment thereof, e.g., an anti-CD123 antibody or antibody fragment. An ADC can optionally contain a linker and be defined by the generic formula C-L-A, wherein C = cytotoxin, L = linker, and A = antibody or antigen-binding fragment thereof, e.g., an anti-CD123 antibody or antibody fragment. ADCs can also be defined by the generic formula in reverse order: C-A or A-L-C. ADCs can contain multiple cytotoxins (C) per antibody or antigen-binding fragment thereof (A) or multiple cytotoxins (C) and linkers (L) per antibody or antigen-binding fragment thereof (A).

[0074] A "linker" is any chemical moiety that is capable of linking a compound, usually a drug (such as IGN DNA-alkylators), to a cell-binding agent (such as an anti-CD123 antibody or a fragment thereof) in a stable, covalent manner. Linkers can be susceptible to or be substantially resistant to acid-induced cleavage, light-induced cleavage, peptidase-induced cleavage, esterase-induced cleavage, and disulfide bond cleavage, at conditions under which the compound or the antibody remains active. Suitable linkers are well known in the art and include, for example, disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups and esterase labile groups. Linkers also include charged linkers, and hydrophilic forms thereof as described herein and know in the art. In some aspects disclosed herein, the linker is a peptide linker.

[0075] The term "IMGN632" (also known as pivekimab sunirine or PVEK) refers to the ADC composition shown in FIGs. 1A and 1B. The composition comprises ADCs with an average of 1.5 to 2.1 DGN549-C cytotoxic agents per huCD123-6Gv4.7 ("G4723A") antibody in a sulfonated version (Figure 1A). The composition can also comprise the unsulfonated ADC (the mono-imine structure shown in Figure 1B).

[0076] The term "magrolimab" (also known as Hu5F9-G4) refers to an anti-CD47 antibody comprising a heavy chain comprising SEQ ID NO: 21 and a light chain comprising SEQ ID NO: 22.

[0077] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals in which a population of cells are characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. "Tumor" and "neoplasm" refer to one or more cells that result from excessive cell growth or proliferation, either benign (noncancerous) or malignant (cancerous) including pre-cancerous lesions. A cancer as disclosed herein can be a hematological malignancy. Examples of hematological malignancies include, for example, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL) such as B-cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T ALL), mixed-lineage leukemia ALL (MLL-ALL), B-cell precursor ALL (BCP-ALL), Ph+ ALL, Ph-like ALL, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia in blast crisis/phase (BP-CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN). Additional examples of "cancer" include, B-cell lymphomas including NHL, precursor B-cell lymphoblastic leukemia/lymphoma and mature B-cell neoplasms, such as B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low- grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B-cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B-cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenstrom's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).The cancer can be a CD123-positive cancer.

[0078] A "CD123-positive" cancer is a caner that has CD123-positive blasts as determined by flow cytometry or immunohistochemistry (IHC).

[0079] The terms "cancer cell," "tumor cell," and grammatical equivalents refer to the total population of cells derived from a tumor or a pre-cancerous lesion, including both non-tumorigenic cells, which comprise the bulk of the tumor cell population, and tumorigenic stem cells (cancer stem cells). As used herein, the term "tumor cell" will be modified by the term "non-tumorigenic" when referring solely to those tumor cells lacking the capacity to renew and differentiate to distinguish those tumor cells from cancer stem cells.

[0080] A "refractory" cancer is one that progresses even though an anti-cancer treatment, such as a chemotherapy, is administered to the cancer patient. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.

[0081] A “primary refractory” cancer is one that does not achieve complete remission (CR) or complete remission with incomplete recovery (CRi) after a patient has received 2 cycles of intense chemotherapy.

[0082] A "relapsed" cancer is one in which the cancer or the signs and symptoms of a cancer returns after a period of improvement.

[0083] The term "fit AML" as used herein refers to a subject having AML who is eligible for intensive therapy. The measures for determining a subject with fit AML include, e.g., physical performance (as determined by e.g., the Eastern Cooperative Oncology Group performance status (ECOG PS), the Karnofsky performance status (KPS), and the short physical performance battery (SPPB)), comorbid conditions (as determined by the Charlson comorbidity index (CCI) or the hematopoietic cell transplantation-specific comorbidity index (HCT-CI)), cognitive function, and prognostic models (including but not limited to, cytogenetic group, age, white blood cell count, LDH, type of AML). In some cases, a fit AML subject is a subject at the age of 60 or under the age of 60.

[0084] The term "unfit AML" as used herein refers to a subject having AML who is ineligible for intensive therapy. The measures for determining a subject with unfit AML include, e.g., physical performance (as determined by e.g., the Eastern Cooperative Oncology Group performance status (ECOG PS), the Karnofsky performance status (KPS), and the short physical performance battery (SPPB)), comorbid conditions (as determined by the Charlson comorbidity index (CCI) or the hematopoietic cell transplantation-specific comorbidity index (HCT-CI)), cognitive function, and prognostic models (including but not limited to, cytogenetic group, age, white blood cell count, LDH, type of AML). In some cases, an unfit AML subject is a subject over the age of 60.

[0085] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder.

[0086] The term "therapeutically effective amount" refers to an amount of an antibody, antigen-binding fragment thereof, ADC, or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug can reduce the number of cancer cells; reduce the tumor size or burden; inhibit (i.e., slow to some extent and in a certain aspect, stop) cancer cell infiltration into peripheral organs; relieve to some extent one or more of the symptoms associated with the cancer; and/or result in a favorable response such as complete remission (CR), complete remission with incomplete recovery (CRi); complete remission with incomplete platelet recovery (CRp), complete remission with partial hematologic recovery (CRh); CR without minimal residual disease (CRMRD-); complete remission clinical

(CRc); morphologic leukemia-free state (MLFS); partial remission (PR); increased duration of response (DOR); and decrease in progressive disease (PD).

[0087] The term "respond favorably" generally refers to causing a beneficial state in a subject. With respect to cancer treatment, the term refers to providing a therapeutic effect on the subject. Positive therapeutic effects in cancer can be measured in a number of ways (See, W.A. Weber, J. Nucl. Med. 50:1S-10S (2009)). A favorable response can be assessed, for example, by complete remission (CR), complete remission with incomplete recovery (CRi); CR without minimal residual disease (CRMRD-); complete remission clinical (CRc); morphologic leukemia-free state; partial remission (PR); a decrease in progressive disease (PD), or any combination thereof.

[0088] A "complete response" or "complete remission" or "CR" indicates the disappearance of all signs of tumor or cancer in response to treatment. This does not always mean the cancer has been cured. A "CRi" refers to a morphologically complete remissions with an incomplete hematological (blood count) recovery. A "CRMRD-" refers to a complete recovery without measurable residual disease.

[0089] "Minimal residual disease," "MRD" or "MRD+" refers to post-therapy persistence of cancerous (e.g., leukemic) cells at levels below morphological detection. MRD can be assessed using, for example, central flow cytometry. MRD+ status is a predictor of relapse, and it is associated with decrease survival in AML patients.

[0090] A "partial response" or "PR" refers to a decrease in the size or volume of one or more tumors or lesions, or in the extent of cancer in the body, in response to treatment.

[0091] "Progressive disease" refers to the appearance of one more new lesions or tumors and/or the unequivocal progression of existing non-target lesions. Progressive disease can also refer to a tumor growth of more than 20% since treatment began, either due to an increases in mass or in spread of the tumor.

[0092] The terms "line of treatment" or "line of therapy" refer to a therapeutic regimen that can include but is not limited to surgery, radiation therapy, chemotherapy, differentiating therapy, biotherapy, immune therapy, induction therapy, consolidation therapy, transplant, maintenance therapy, or the administration of one or more anti-cancer agents (e.g., a cytotoxic agent and/or an anti-proliferative compound).

[0093] The terms "first-line treatment," "first-line therapy," "front-line treatment," and "front-line therapy" refer to the preferred and standard initial treatment for a particular condition, e.g., induction therapy, consolidation therapy, transplant, maintenance therapy. These treatments differ from "second-line" therapies, which are tried when a first-line therapy does not work adequately. "Third-line" therapies are tried when a first-line therapy and a second-line therapy do

not work adequately. "Salvage therapy" or "salvage regimen" is a treatment that is tried when the cancer has not responded to other treatments.

[0094] For example, the combination of an anti-CD123 ADC (e.g. IMGN632/PVEK) with anti-CD47 antibody or antigen-binding fragment thereof provided herein can be given as first-line therapy. The combination of an anti-CD123 ADC (e.g. IMGN632/PVEK) with anti-CD47 antibody or antigen-binding fragment thereof provided herein can be given as a second-line therapy, or a third-line therapy. The combination of an anti-CD123 ADC (e.g. IMGN632/PVEK) with anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) provided herein can be given as a line of therapy in patients who have received at least 1, at least 2, (e.g., front-line therapy and one salvage therapy), or at least 3 lines of therapy prior to treatment with the combination of an anti-CD123 ADC (e.g. IMGN632/PVEK) with anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) provided herein. In some aspects, the combination of an anti-CD123 ADC (e.g. IMGN632/PVEK) with anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) provided herein can be given as a line of therapy in patients having received no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, or no more than 6 lines of therapy.

[0095] The term "maintenance therapy" refers to therapy that is given to help keep cancer from coming back after it has disappeared following the initial therapy.

[0096] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0097] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. The formulation can be sterile.

[0098] The term "subject" refers to any animal (e.g., a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

[0099] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) or consecutive administration in any order.

[0100] The combination therapy can provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect can be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined,

unit dosage formulation; (2) delivered serially, by alternation, or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect can be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes.

[0101] The term "instructing" means providing directions for applicable therapy, medication, treatment, treatment regimens, and the like, by any means, for example, in writing, such as in the form of package inserts or other written promotional material.

[0102] An "effective amount" of an antibody, ADC, or other drug as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

[0103] A polypeptide, antibody, polynucleotide, vector, cell, or composition which is "isolated" is a polypeptide, antibody, polynucleotide, vector, cell, or composition which is in a form not found in nature. Isolated polypeptides, antibodies, polynucleotides, vectors, cell or compositions include those which have been purified to a degree that they are no longer in a form in which they are found in nature. In some aspects, an antibody, polynucleotide, vector, cell, or composition which is isolated is substantially pure.

[0104] As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure.

[0105] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0106] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0107] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11. As is understood by one skilled in the art, reference to "about" a value or parameter herein includes (and describes) aspects that are directed to that value or parameter per se. For example, description referring to "about X" includes a description of "X."

[0108] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

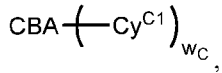
II. Anti-CD123 Antibody-Drug Conjugates (ADCs)

[0109] Described herein are methods of administering ADCs that specifically bind CD123 (e.g., IMGN632/PVEK) in combination with other agents. ADCs that specifically bind to CD123 are referred to herein as "CD123 ADCs" or "anti-CD123 ADCs." Such ADCs comprise an anti-

CD123 antibody or antigen-binding fragment thereof and a cytotoxin. The cytotoxin can be attached to the anti-CD123 antibody or antigen-binding fragment thereof by a linker.

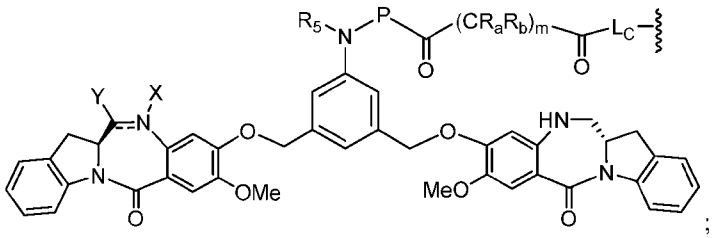
[0110] In some aspects, the anti-CD123 antibodies or antigen-binding fragments thereof are humanized antibodies or antigen-binding fragments thereof. In some aspects, the humanized antibody or fragment is a resurfaced antibody or antigen-binding fragment thereof. In some aspects, the antibodies or antigen-binding fragments thereof is a fully human antibody or antigen-binding fragment thereof.

[0111] In some aspects, an ADC is represented by the following formula:

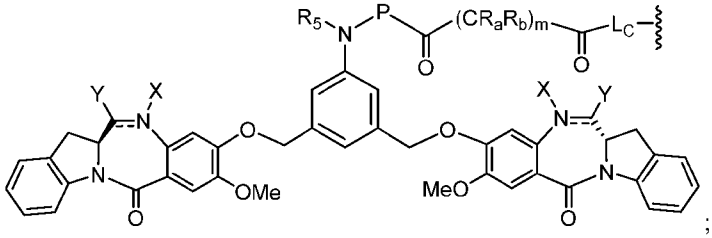


wherein CBA is an anti-CD123 antibody or antigen-binding fragment or polypeptide, covalently linked to CyC1 through a cysteine residue; and WC is 1 or 2.

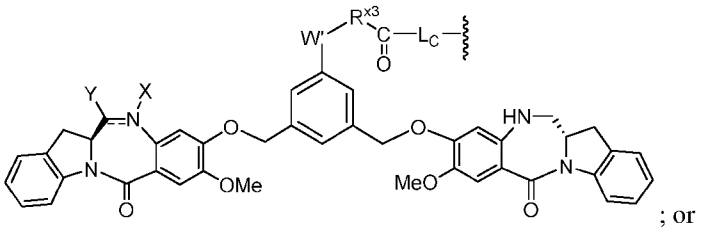
[0112] In the above formula, Cy^{C1} is represented by the following formulae:



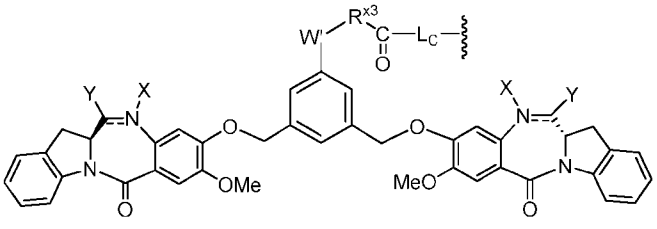
;



;



; or



,

or a pharmaceutically acceptable salt thereof, wherein the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond, X is absent and Y is -H or a (C1-C4)alkyl; and when it is a single bond, X is -H or an amine protecting moiety, Y is -OH or -SO3M, and M is H+ or a cation;

[0113] R_5 is -H or a (C_1-C_3)alkyl;

[0114] P is an amino acid residue or a peptide containing 2 to 20 amino acid residues;

[0115] R_a and R_b, for each occurrence, are independently -H, (C_1-C_3)alkyl, or a charged substituent or an ionizable group Q;

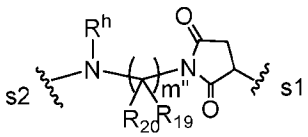
[0116] W' is -$NR^{e'}$,

[0117] $R^{e'}$ is -$(CH_2$-CH_2-$O)_n$-R^k;

[0118] n is an integer from 2 to 6;

[0119] R^k is -H or -Me;

[0120] R^{x3} is a (C_1-C_6)alkyl; and,

[0121] L_C is represented by 

, s1 is the site covalently linked to CBA, and s2 is the site covalently linked to the -C(=O)- group on Cy^{C1}; wherein:

[0122] R_{19} and R_{20}, for each occurrence, are independently -H or a (C_1-C_3)alkyl;

[0123] m'' is an integer between 1 and 10; and

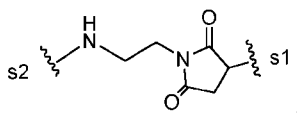
[0124] R^h is -H or a (C_1-C_3)alkyl.

[0125] In certain aspects, R_a and R_b are both H; and R_5 is H or Me.

[0126] In certain aspects, P is a peptide containing 2 to 5 amino acid residues. For example, P may be selected from Gly-Gly-Gly, Ala-Val, Val-Ala, Val-Cit, Val-Lys, Phe-Lys, Lys-Lys, Ala-Lys, Phe-Cit, Leu-Cit, Ile-Cit, Trp, Cit, Phe-Ala, Phe-N^9-tosyl-Arg, Phe-N^9-nitro-Arg, Phe-Phe-Lys, D-Phe-Phe-Lys, Gly-Phe-Lys, Leu-Ala-Leu, Ile-Ala-Leu, Val-Ala-Val, Ala-Leu-Ala-Leu, β-Ala-Leu-Ala-Leu, Gly-Phe-Leu-Gly, Val-Arg, Arg-Val, Arg-Arg, Val-D-Cit, Val-D-Lys, Val-D-Arg, D-Val-Cit, D-Val-Lys, D-Val-Arg, D-Val-D-Cit, D-Val-D-Lys, D-Val-D-Arg, D-Arg-D-Arg, Ala-Ala, Ala-D-Ala, D-Ala-Ala, D-Ala-D-Ala, Ala-Met, and Met-Ala. In certain aspects, P is Gly-Gly-Gly, Ala-Val, Ala-Ala, Ala-D-Ala, D-Ala-Ala, or D-Ala-D-Ala. In certain aspects, Q is -SO_3M.

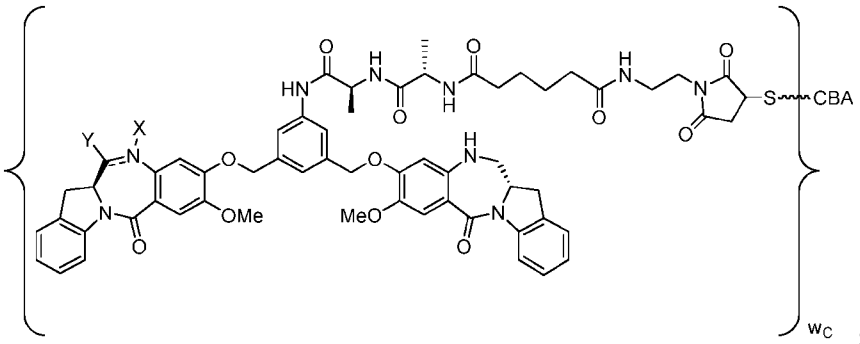
[0127] In certain aspects, R_{19} and R_{20} are both H; and m'' is an integer from 1 to 6.

[0128] In certain aspects, -L_C- is represented by the following formula:

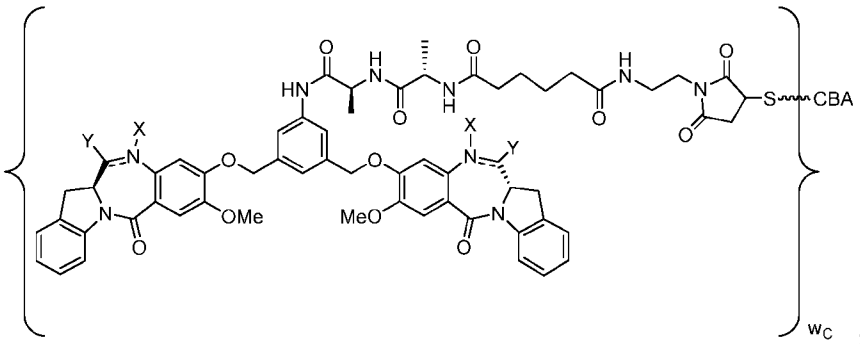


.

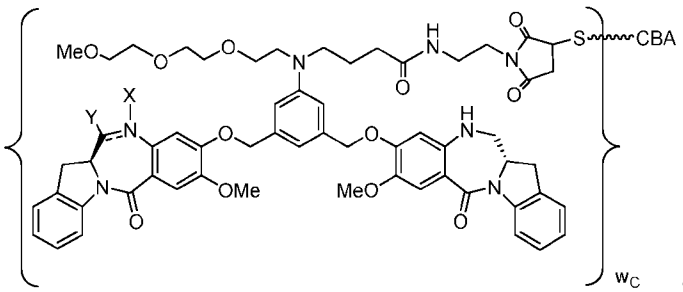
[0129] In certain aspects, the ADC is represented by one of the following formulae:



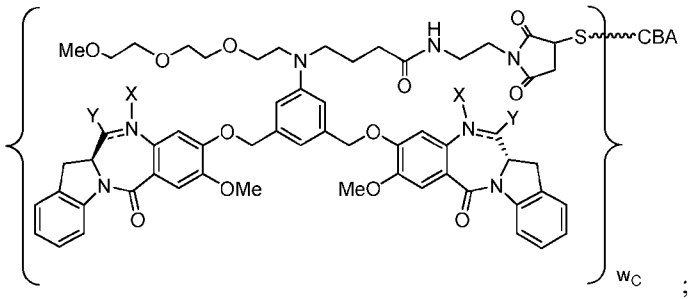
;



;



; or



;

or a pharmaceutically acceptable salt thereof, wherein the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond, X is absent and Y is -H, and when it is a single bond, X is -H, and Y is -OH or -SO3M.

[0130] An anti-CD123 ADC for use in the present methods can comprise an anti-CD123 antibody or antigen-binding fragment thereof. Anti-CD123 antibodies or antigen-binding

fragments thereof have been described (see e.g., US Patent No. 10,077,313 B2, the contents of which are herein incorporated by reference in their entirety). The anti-CD123 antibody or antigen-binding fragment thereof can be the huCD123-6Gv4.7 ("G4723A") antibody (see WO 2017/004025, WO 2017/004026, and PCT/US2018/052212, each of which is herein incorporated by reference in its entirety) or can comprise sequences of the G4723A antibody, e.g., as shown below in Tables 1-3. For example, an anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively and/or variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1 and a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a heavy chain comprising the sequence set forth in SEQ ID NO: 3. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a light chain comprising the sequence set forth in SEQ ID NO: 4. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a heavy chain comprising the sequence set forth in SEQ ID NO: 3 and a light chain comprising the sequence set forth in SEQ ID NO: 4.

Table 1. huCD123-6Gv4.7 Heavy and Light Chain Variable Regions

Name	**Sequence**
huCD123-6Gv7 Heavy Chain Variable Region	QVQLVQSGAEVKKPGASVKVSCKASGYIFT**SSIMH**WVR QAPGQGLEWIG**YIKPYNDGTKYNEKFKG**RATLTSDRST STAYMELSSLRSEDTAVYYCAR**EGGNDYYDTMDY**WG QGTLVTVSS (SEQ ID NO: 1)
huCD123-6Gv4 Light Chain Variable Region	DIQMTQSPSSLSASVGDRVTITC**RASQDINSYLS**WFQQK PGKAPKTLIY**RVNRLVD**GVPSRFSGSGSGNDYTLTISSLQ PEDFATYYC**LQYDAFPYT**FGQGTKVEIKR (SEQ ID NO: 2)

Table 2. huCD123-6Gv4.7-C442 Full Length Heavy and Light Chain

Name	Sequence
huCD123-6Gv7-C442 Full Length Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYIFT**SSIMH**WVR QAPGQGLEWIG**YIKPYNDGTKYNEKFKG**RATLTSDRST STAYMELSSLRSEDTAVYYCAR**EGGNDYYDTMDY**WG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLCLSPG (SEQ ID NO: 3)
huCD123-6Gv4 Full Length Light Chain	DIQMTQSPSSLSASVGDRVTITC**RASQDINSYLS**WFQQK PGKAPKTLIY**RVNRLVD**GVPSRFSGSGSGNDYTLTISSLQ PEDFATYYC**LQYDAFPYT**FGQGTKVEIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC (SEQ ID NO: 4)

Table 3. huCD123-6Gv4.7 Variable Heavy and Light Chain Complementary Determining Regions

Name	Sequence
huCD123-6Gv7 Variable Heavy Chain CDR1	SSIMH (SEQ ID NO: 5)
huCD123-6Gv7 Variable Heavy Chain CDR2	YIKPYNDGTKYNEKFKG (SEQ ID NO: 6)
huCD123-6Gv7 Variable Heavy Chain CDR3	EGGNDYYDTMDY (SEQ ID NO: 7)
huCD123-6Gv4 Variable Light Chain CDR1	RASQDINSYLS (SEQ ID NO: 8)
huCD123-6Gv4 Variable Light Chain CDR2	RVNRLVD (SEQ ID NO: 9)
huCD123-6Gv4 Variable Light Chain CDR3	LQYDAFPYT (SEQ ID NO: 10)

[0131] In some aspects provided herein, an anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; variable light

chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and an IgG constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and a human IgG constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and an IgG1 constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and a human IgG1 constant region.

[0132] An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 11. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 12. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 5, 6, and 7, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 8, 9, and 10, respectively; a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 11; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 12.
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLCLSPG (SEQ ID NO: 11)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 12)

[0133] An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and an IgG constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and a human IgG constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and an IgG1 constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and a human IgG1 constant region.

[0134] An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 11. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 12. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 1; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 2; a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 11; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 12.

[0135] An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can bind to an epitope within amino acids 205 to 346 of human CD123.

[0136] An anti-CD123 antibody or antigen-binding fragment thereof for use in methods provided herein can be recombinantly produced. For example, an anti-CD123 antibody or antigen-binding

fragment thereof for use in the methods provided herein can be produced in a mammalian cell line, e.g., a CHO cell.

[0137] An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can be a cysteine-engineered antibody or fragment. Cysteine-engineered antibodies can be covalently conjugated to cytotoxic agents of interest to generate ADCs.

[0138] As used herein, the expression "linked to a cell-binding agent" or "linked to an anti-CD123 antibody or fragment" refers to a conjugate molecule comprising at least one cytotoxic agent bound to a cell-binding agent, e.g., anti-CD123 antibody or fragment, via a suitable linking group, or a precursor thereof. Linkers include, for example, peptide linkers.

[0139] An ADC can contain multiple cytotoxic agents bound to an antibody or antigen-binding fragment thereof. As provided herein, in certain instances, about 1 to about 3 drug molecules e.g., cytotoxic agents, are linked to an anti-CD123 antibody or antigen-binding fragment thereof. In one aspect, an ADC comprises 1, 2, or 3, cytotoxic agents per antibody or antigen-binding fragment thereof.

[0140] A composition comprising ADCs can contain ADCs with varying numbers of cytotoxic agents bound per antibody or antigen-binding fragment thereof. Thus, compositions comprising ADCs can contain an average number of cytotoxic agents bound per antibody or antigen-binding fragment thereof. In one aspect, a pharmaceutical composition comprising anti-CD123 ADCs comprises about 1 to about 3 cytotoxic agents per anti-CD123 antibody or antigen-binding fragment thereof, about 1.5 to about 2.5 cytotoxic agents per anti-CD123 antibody or antigen-binding fragment thereof, about 1.5 to about 2.1 cytotoxic agents per anti-CD123 antibody or antigen-binding fragment thereof, or about 1.5 to about 2.0 cytotoxic agents cytotoxic agents per anti-CD123 antibody or antigen-binding fragment thereof.

[0141] In certain instances, a pharmaceutical composition for use in the methods provided herein comprises anti-CD123 ADCs comprising about 1 to about 3 cytotoxic agents per antibody or antigen-binding fragment thereof, for example, wherein the average number of cytotoxic agents per antibody or antigen-binding fragment thereof is from about 1 to about 3 (e.g., 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0).

[0142] In some aspects, a pharmaceutical composition for use in the methods provided herein comprises anti-CD123 ADCs with an average of about 1 ± 0.2, about 1.1 ± 0.2, about 1.2 ± 0.2, about 1.3 ± 0.2, about 1.4 ± 0.2, about 1.5 ± 0.2, about 1.6 ± 0.2, about 1.7 ± 0.2, about 1.8 ± 0.2, about 1.9 ± 0.2, about 2.0 ± 0.2, about 2.1 ± 0.2, 2.2 ± 0.2, 2.3 ± 0.2, 2.4 ± 0.2, 2.5 ± 0.2, or 2.6 ± 0.2 drug molecules (e.g., cytotoxic agents) attached per antibody or antigen-binding fragment thereof. In certain aspects, a pharmaceutical composition provided herein comprises anti-CD123 ADCs with an average of about 1.5 to 2.1 drug molecules (e.g., cytotoxic agents) per antibody.

[0143] The antibodies or antigen-binding fragments thereof for use in the present disclosure may be linked to cytotoxic agents, for example, through linkage with the Lys side chain amino group, the Cys side chain thiol group, or an oxidized N-terminal Ser/Thr. Cytotoxic agents include, for example, DNA alkylating agents such as indolino-benzodiazepene (IGN) DNA alkylators. In certain instances, a cytotoxic agent is a indolino-benzodiazepine pseudodimer. In certain instances, an anti-CD123 ADC for use in the present disclosure comprises DGN549-C.

III. Anti-CD47 Antibodies and Antigen-Binding Fragments Thereof

[0144] Described herein are methods of administering anti-CD123 ADCs such as IMGN632/PVEK in combination with anti-CD47 antibodies or antigen-binding fragments thereof. The anti-CD47 antibody can be magrolimab (see WO 2011/143624, which is herein incorporated by reference in its entirety; see in particular discussion of humanized "5F9"; see also Liu J.. *et al.*, (2015) Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS ONE 10(9): e0137345. doi:10.1371/journal.pone.0137345, which is herein incorporated by reference in its entirety) or can comprise sequences of the magrolimab antibody, e.g., as shown below in Tables 4-6. Magrolimab is a recombinant humanized monoclonal antibody of the immunoglobulin G4 kappa (IgG4) isotype that binds to CD47. The primary mechanism of action of magrolimab is to block the inhibitory CD47-signal regulatory protein alpha (SIRPα) interaction, enhancing the ability of macrophages and other phagocytes to identify and destroy foreign and malignant cells. Magrolimab is a novel immunotherapy based on its ability to enhance immune response to cancer by blocking inhibitory signals on phagocytic cells. Magrolimab was specifically engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions to minimize any deleterious effects on CD47-expressing normal cells. Consequently, magrolimab has been shown to lack antibody-dependent cellular cytotoxicity (ADCC) activity in vitro. While Fc-dependent effector functions may theoretically contribute to the efficacy, the primary mechanism is blockade of the "don't eat me," CD47/SIRPα interaction, which preferentially induces the phagocytosis of tumor cells that express pro-phagocytic "eat me" signals that are absent on most normal cells.

[0145] Amino acid sequences of magrolimab are provided in Tables 4-6.

Table 4. Magrolimab Heavy and Light Chain Variable Regions

Name	**Sequence**
Magrolimab Heavy Chain Variable Region	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWV RQAPGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTS ASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTL VTVSS (SEQ ID NO: 13)

Magrolimab Light Chain Variable Region	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGW YLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIK (SEQ ID NO: 14)

Table 5. Magrolimab Full Length Heavy and Light Chain

Name	**Sequence**
Magrolimab Full Length Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWV RQAPGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTS ASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTL VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE FLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK (SEQ ID NO: 21)
Magrolimab Full Length Light Chain	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGW YLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 22)

Table 6. Magrolimab Variable Heavy and Light Chain Complementary Determining Regions

Name	**Sequence**
Magrolimab Variable Heavy Chain CDR1	NYNMH (SEQ ID NO: 15)
Magrolimab Variable Heavy Chain CDR2	TIYPGNDDTSYNQKFKD (SEQ ID NO: 16)
Magrolimab Variable Heavy Chain CDR3	GGYRAMDY (SEQ ID NO: 17)
Magrolimab Variable Light Chain CDR1	RSSQSIVYSNGNTYLG (SEQ ID NO: 18)
Magrolimab Variable Light Chain CDR2	KVSNRFS (SEQ ID NO: 19)
Magrolimab Variable Light Chain CDR3	FQGSHVPYT (SEQ ID NO: 20)

[0146] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively and/or variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively. An anti- CD47 antibody or antigen-binding fragment thereof for use in the methods

provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13. An anti- CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14. An anti- CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13 and a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14.

[0147] In some aspects provided herein, an anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and an IgG constant region. An anti- CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and a human IgG constant region. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and an IgG4 constant region, optionally wherein the IgG4 constant region comprises a Ser228Pro substitution. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and a human IgG4 constant region, optionally wherein the human IgG4 constant region comprises a Ser228Pro substitution.

[0148] An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 23. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; and a light chain constant region

comprising the amino acid sequence of SEQ ID NO: 24. An anti-CD123 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 15, 16, and 17, respectively; a variable light chain CDR-1, CDR-2, and CDR-3 comprising the sequences of SEQ ID NOs: 18, 19, and 20, respectively; a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 23; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 24.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
GNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 23)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 24)

[0149] An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; and an IgG constant region. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; and a human IgG constant region. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; and an IgG4 constant region, optionally wherein the IgG4 constant region comprises a Ser228Pro substitution. An anti- CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; and a human IgG4 constant region, optionally wherein the human IgG4 constant region comprises a Ser228Pro substitution.

[0150] An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO:

14; and a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 23. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 24. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a variable heavy chain domain comprising the sequence set forth in SEQ ID NO: 13; a variable light chain domain comprising the sequence set forth in SEQ ID NO: 14; a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 23; and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 24.

[0151] An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a heavy chain comprising the sequence set forth in SEQ ID NO: 21. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a light chain comprising the sequence set forth in SEQ ID NO: 22. An anti-CD47 antibody or antigen-binding fragment thereof for use in the methods provided herein can comprise a heavy chain comprising the sequence set forth in SEQ ID NO: 21 and a light chain comprising the sequence set forth in SEQ ID NO: 22.

[0152] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof provided herein is an IgG4 antibody. In some aspects, an IgG4 anti-CD47 antibody or antigen-binding fragment thereof comprises a Ser228Pro substitution, wherein the numbering of the residues in the heavy chain is that of the EU index (see Kabat et al., "Sequences of Proteins of Immunological Interest," 5.sup.th Ed., National Institutes of Health, Bethesda, Md. (1991)). Position 228 is naturally occupied by P in human IgG1 and IgG2 but is occupied by S in human IgG4 and R in human IgG3. A Ser228Pro substitution in an IgG4 antibody or antigen-binding fragment thereof is advantageous in stabilizing an IgG4 antibody or antigen-binding fragment thereof and reducing exchange of heavy chain light chain pairs between exogenous and endogenous antibodies and antigen-binding fragments thereof.

[0153] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof provided herein binds to monomeric human CD47 with a KD of about $8x10^{-9}$ M as measured using surface plasmon resonance. In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof provided herein blocks the interaction between CD47 and SIRPα. In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof enables human peripheral blood-derived macrophages to phagocytose HL-60 AML cells and primary human AML cells. Methods of determining (i) whether an anti-CD47 antibody or antigen-binding fragment thereof provided herein blocks the interaction between CD47 and SIRPα and (ii) whether an anti-CD47 antibody or

antigen-binding fragment thereof enables phagocytosis are provided in also Liu J.. *et al.*, (2015) Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS ONE 10(9): e0137345. doi:10.1371/journal.pone.0137345, which is herein incorporated by reference in its entirety.

IV. Antibodies and Antigen-Binding Fragments Thereof

[0154] Provided herein are combinations of anti-CD123 ADCs, which contain anti-CD123 antibodies or antigen-binding fragments thereof and anti-CD47 antibodies and antigen-binding fragments thereof.

[0155] An antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be a monoclonal antibody or antigen-binding fragment thereof. Monoclonal antibodies or antigen-binding fragments thereof can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, yeast-based presentation technologies, or a combination thereof. For example, monoclonal antibodies or antigen-binding fragments thereof can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow E & Lane D, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981), or as described in Kohler G & Milstein C (1975) Nature 256: 495. Examples of yeast-based presentation methods that can be employed to select and generate the antibodies described herein include those disclosed in, for example, WO2009/036379A2; WO2010/105256; and WO2012/009568, each of which is herein incorporated by reference in its entirety.

[0156] In some aspects, a monoclonal antibody or antigen-binding fragment is an antibody or antigen-binding fragment produced by a clonal cell (*e.g.*, hybridoma or host cell producing a recombinant antibody or antigen-binding fragment). In some aspects, a monoclonal antibody or antigen-binding fragment thereof can be a human antibody or antigen-binding fragment thereof. In some aspects, a monoclonal antibody or antigen-binding fragment thereof can be a Fab fragment or a $F(ab')_2$ fragment. Monoclonal antibodies or antigen-binding fragments thereof described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495 or can, *e.g.*, be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies and antigen-binding fragments thereof expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al., supra*).

[0157] An antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be a recombinant antibody. An antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be an isolated antibody or antigen-binding fragment thereof.

[0158] An antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be described by its VL domain alone, or its VH domain alone, or by its 3 VL CDRs alone, or its 3 VH CDRs alone. *See*, for example, Rader C *et al.*, (1998) PNAS 95: 8910-8915, which is incorporated herein by reference in its entirety, describing the humanization of the mouse anti-αvβ3 antibody by identifying a complementing light chain or heavy chain, respectively, from a human light chain or heavy chain library, resulting in humanized antibody variants having affinities as high or higher than the affinity of the original antibody. *See also* Clackson T *et al.*, (1991) Nature 352: 624-628, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VL domain (or VH domain) and screening a library for the complementary variable domains. The screen produced 14 new partners for a specific VH domain and 13 new partners for a specific VL domain, which were strong binders, as determined by ELISA. *See also* Kim SJ & Hong HJ, (2007) J Microbiol 45: 572-577, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VH domain and screening a library (*e.g.*, human VL library) for complementary VL domains; the selected VL domains in turn could be used to guide selection of additional complementary (*e.g.*, human) VH domains.

[0159] In some aspects, the CDRs of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see*, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol Biol 227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light

chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34).

[0160] In some aspects, an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) comprises the Chothia VH and VL CDRs of an antibody listed in Table 1, 2, 4, or 5. In some aspects, the antibodies or antigen-binding fragments comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In some aspects, provided herein are antibodies and antigen-binding fragments thereof that comprise combinations of Kabat CDRs and Chothia CDRs.

[0161] In some aspects, the CDRs of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) The Immunologist 7: 132-136 and Lefranc M-P *et al.*, (1999) Nucleic Acids Res 27: 209-212. According to the IMGT numbering scheme, VH-CDR1 is at positions 26 to 35, VH-CDR2 is at positions 51 to 57, VH-CDR3 is at positions 93 to 102, VL-CDR1 is at positions 27 to 32, VL-CDR2 is at positions 50 to 52, and VL-CDR3 is at positions 89 to 97. In some aspects, provided herein are antibodies and antigen-binding fragments thereof that comprise the IMGT VH and VL CDRs of an antibody listed in Table 1, 2, 4, or 5, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*).

[0162] In some aspects, the CDRs of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be determined according to MacCallum RM *et al.*, (1996) J Mol Biol 262: 732-745. *See also, e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in *Antibody Engineering*, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In some aspects, provided herein are antibodies or antigen-binding fragments thereof that comprise VH and VL CDRs of an antibody listed in Table 1, 2, 4, or 5 as determined by the method in MacCallum RM *et al.*

[0163] In some aspects, the CDRs of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be determined according to the AbM

numbering scheme, which refers AbM hypervariable regions which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.). In some aspects, provided herein are antibodies or antigen-binding fragments thereof that comprise VH and VL CDRs of an antibody listed in Table 1, 2, 4, or 5 as determined by the AbM numbering scheme.

[0164] In some aspects, provided herein are antibodies or antigen-binding fragments thereof (e.g., anti-CD123 antibodies or antigen-binding fragments thereof and/or anti-CD47 antibodies or antigen-binding fragments thereof) that comprise a heavy chain and/or a light chain. Non-limiting examples of human constant region sequences have been described in the art, *e.g.*, see U.S. Patent No. 5,693,780 and Kabat EA *et al.*, (1991) *supra*.

[0165] With respect to the heavy chain, in some aspects, the heavy chain of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) can be an alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In some aspects, the heavy chain of an antibody or antigen-binding fragment thereof provided can comprise a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In some aspects, an antibody or antigen-binding fragment thereof provided herein, comprises a heavy chain wherein the amino acid sequence of the VH domain comprises an amino acid sequence set forth in Table 1 or 4 and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region (e.g., a human IgG1 heavy chain constant region). In some aspects, an antibody or antigen-binding fragment thereof provided herein comprises a heavy chain wherein the amino acid sequence of the VH domain comprises a sequence set forth in Table 1 or 4, and wherein the constant region of the heavy chain comprises the amino acid of a human heavy chain described herein or known in the art.

[0166] In some aspects, the light chain of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) is a human kappa light chain or a human lambda light chain. In some aspects, an antibody described herein comprises a light chain wherein the amino acid sequence of the VL domain comprises a sequence set forth in Table 1 or 4 and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa or lambda light chain constant region.

[0167] In some aspects, an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) comprises a light chain wherein the amino acid sequence of the

VL domain comprises a sequence set forth in Table 1 or 4, and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region.

[0168] In some aspects, the light chain of an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) is a lambda light chain. In some aspects, an antibody described herein comprises a light chain wherein the amino acid sequence of the VL domain comprises a sequence set forth in Table 1 or 4 and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region.

[0169] In some aspects, an antibody or antigen-binding fragment thereof provided herein (e.g., an anti-CD123 antibody or antigen-binding fragment thereof and/or an anti-CD47 antibody or antigen-binding fragment thereof) comprises a VH domain and a VL domain comprising any amino acid sequence described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule. In some aspects, an antibody or antigen-binding fragment provided herein comprises a VH domain and a VL domain comprising any amino acid sequence described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), or any subclass (*e.g.*, IgG2a and IgG2b) of immunoglobulin molecule. In some aspects, the constant regions comprise the amino acid sequences of the constant regions of a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), or any subclass (*e.g.*, IgG2a and IgG2b) of immunoglobulin molecule.

[0170] Fc region engineering is used in the art, e.g., to extend the half-life of therapeutic antibodies and antigen-binding fragments thereof and protect from degradation *in vivo*.

[0171] In some aspects, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody or antigen-binding fragment thereof provided herein (*e.g.*, into the CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to alter one or more functional properties of the antibody or antigen-binding fragment thereof, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity.

[0172] In some aspects, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, *e.g.*, U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain

may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody or antigen-binding fragment thereof.

[0173] In some aspects, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody or antigen-binding fragment thereof provided herein (*e.g.*, CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to increase or decrease the affinity of the antibody or antigen-binding fragment thereof for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region that decrease or increase affinity for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor that can be made to alter the affinity of the antibody or antigen-binding fragment thereof for an Fc receptor are described in, *e.g.*, Smith P *et al.*, (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[0174] In some aspects, one, two, or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (e.g., an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of the antibody or antigen-binding fragment thereof *in vivo*. *See. e.g.*, International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody or antigen-binding fragment thereof *in vivo*. In some aspects, one, two or more amino acid mutations (*i.e.*, substitutions, insertions, or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the antibody or antigen-binding fragment thereof *in vivo*. In some aspects, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody or antigen-binding fragment thereof *in vivo*. In some aspects, the antibodies or antigen-binding fragments thereof may have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat EA *et al.*, (1991) *supra*).

[0175] In some aspects, one, two, or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the antibody or antigen-binding

fragment thereof. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody or antigen-binding fragment thereof has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody.

[0176] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Methods for generating engineered glycoforms in an antibody or antigen-binding fragment thereof described herein include but are not limited to those disclosed, *e.g.*, in Umaña P *et al.*, (1999) Nat Biotechnol 17: 176-180; Davies J *et al.*, (2001) Biotechnol Bioeng 74: 288-294; Shields RL *et al.*, (2002) J Biol Chem 277: 26733-26740; Shinkawa T *et al.*, (2003) J Biol Chem 278: 3466-3473; Niwa R *et al.*, (2004) Clin Cancer Res 1: 6248-6255; Presta LG *et al.*, (2002) Biochem Soc Trans 30: 487-490; Kanda Y *et al.*, (2007) Glycobiology 17: 104-118; U.S. Patent Nos. 6,602,684; 6,946,292; and 7,214,775; U.S. Patent Publication Nos. US 2007/0248600; 2007/0178551; 2008/0060092; and 2006/0253928; International Publication Nos. WO 00/61739; WO 01/292246; WO 02/311140; and WO 02/30954; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb® glycosylation engineering technology (Glycart biotechnology AG, Zurich, Switzerland). *See also*, *e.g.*, Ferrara C *et al.*, (2006) Biotechnol Bioeng 93: 851-861; International Publication Nos. WO 07/039818; WO 12/130831; WO 99/054342; WO 03/011878; and WO 04/065540.

[0177] In some aspects, any of the constant region mutations or modifications described herein can be introduced into one or both heavy chain constant regions of an antibody or antigen-binding fragment thereof described herein having two heavy chain constant regions.

[0178] Antigen-binding fragments of antibodies described herein can be generated by any technique known to those of skill in the art. For example, Fab and $F(ab')_2$ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). A Fab fragment corresponds to one of the two identical arms of a tetrameric antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A $F(ab')_2$ fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[0179] In some aspects, an antigen-binding fragment as described herein is selected from the group consisting of a Fab, Fab', $F(ab')_2$, and scFv, wherein the Fab, Fab', $F(ab')_2$, or scFv comprises a heavy chain variable region sequence and a light chain variable region sequence of an antibody or antigen-binding fragment thereof provided herein. A Fab, Fab', $F(ab')_2$, or scFv can be produced by any technique known to those of skill in the art. In some aspects, the Fab, Fab', $F(ab')_2$, or scFv further comprises a moiety that extends the half-life of the antibody *in vivo*. The moiety is also termed a "half-life extending moiety." Any moiety known to those of skill in the

art for extending the half-life of a Fab, Fab', $F(ab')_2$, or scFv *in vivo* can be used. For example, the half-life extending moiety can include a Fc region, a polymer, an albumin, or an albumin binding protein or compound. The polymer can include a natural or synthetic, optionally substituted straight or branched chain polyalkylene, polyalkenylene, polyoxylalkylene, polysaccharide, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, methoxypolyethylene glycol, lactose, amylose, dextran, glycogen, or derivative thereof. Substituents can include one or more hydroxy, methyl, or methoxy groups. In some aspects, the Fab, Fab', $F(ab')_2$, or scFv can be modified by the addition of one or more C-terminal amino acids for attachment of the half-life extending moiety. In some aspects the half-life extending moiety is polyethylene glycol or human serum albumin. In some aspects, the Fab, Fab', $F(ab')_2$, or scFv is fused to a Fc region.

V. Pharmaceutical Compositions and Kits

[0180] As provided herein, anti-CD123 ADCs (e.g., IMGN632/PVEK) can be used in combination with an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) to treat cancer.

[0181] In some aspects, an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) are contained within the same pharmaceutical composition. In some aspects, an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) are contained within two separate pharmaceutical compositions within a single kit. In some aspects, a kit comprises an anti-CD123 ADC (e.g., IMGN632/PVEK) and instructions to administer the anti-CD123 ADC (e.g., IMGN63/PVEK 2) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab). In some aspects, a kit comprises an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) and instructions to administer the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) and an anti-CD123 ADC (e.g., IMGN632/PVEK).

[0182] The pharmaceutical compositions for use as provided herein can have an anti-CD123 ADC (e.g., IMGN632/PVEK) and/or an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) having the desired degree of purity in a physiologically acceptable carrier, excipient, or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed. (See, e.g., Gennaro, Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus, 20th ed. (2003); Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippencott Williams and Wilkins (2004); Kibbe et al., Handbook of Pharmaceutical Excipients, 3rd ed., Pharmaceutical

Press (2000)). The compositions to be used for in vivo administration can be sterile. This is readily accomplished by filtration through, e.g., sterile filtration membranes.

[0183] In some aspects, a pharmaceutical composition comprising an anti-CD123 ADC (e.g., IMGN632/PVEK) and/or an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is formulated for parenteral (e.g., intravenous) administration.

VI. Methods of Use

[0184] As provided herein, anti-CD123 ADCs (e.g., IMGN632/PVEK) can be used in combination anti-CD47 antibody or antigen-binding fragments thereof to treat hematological cancers. In some aspects, the DNA-damaging effects of an anti-CD123 ADCs (e.g., IMGN632/PVEK) can trigger enhanced anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) macrophage activity towards apoptotic AML cells. In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is synergistic.

VI(A). Cancer Selection

[0185] Cancers that can be treated by the methods provided herein include hematological cancers. In some aspects, the hematological malignancy is of myeloid origin. In some aspects, the hematological malignancy is of lymphoid origin. In some aspects, the hematological malignancy is of both myeloid and lymphoid origins. In some aspects, the hematological malignancy is a B-cell malignancy. In some aspects, the hematological malignancy is a CD123-positive hematological malignancy.

[0186] In some aspects, the hematological malignancy is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL), B-cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T ALL), chronic myeloid leukemia in blast crisis/phase (BP-CML), blastic plasmacytoid dendritic cell neoplasm (BPDCN), (CMML), and malignancy is myelofibrosis (MF).

[0187] In some aspects, the hematological malignancy is a relapsed or refractory hematological malignancy. In some aspects, the hematological malignancy is a relapsed hematological malignancy. In some aspects, the hematological malignancy is a refractory hematological malignancy.

[0188] In some aspects, the hematological malignancy is AML. In some aspects, the AML is relapsed or refractory AML. In some aspects, the AML is relapsed AML. In some aspects, the AML is refractory AML. In some aspects, the AML is not secondary AML. In certain some, the AML is fit AML. In some aspects, the AML is unfit AML.

[0189] In some aspects, the hematological malignancy is BPDCN. In some aspects, the BPDCN is relapsed or refractory BPDCN. In some aspects, the BPDCN is relapsed BPDCN. In some aspects, the BPDCN is refractory BPDCN.

[0190] In some aspects, the hematological malignancy is ALL. In some aspects, the ALL is relapsed or refractory ALL. In some aspects, the ALL is relapsed ALL. In some aspects, the ALL is refractory ALL.

[0191] In some aspects, the hematological malignancy is MDS. In some aspects, the MDS is high risk MDS.

[0192] In some aspects, the hematological malignancy is chronic myelomonocytic leukemia (CMML).

[0193] In some aspects, the hematological malignancy is myelofibrosis (MF).

[0194] In some aspects, the hematological malignancy is chemotherapy resistant.

[0195] In some aspects, the hematological malignancy is chemotherapy sensitive.

[0196] In some aspects, the hematological malignancy expresses multidrug resistance 1 (MDR1). In some aspects, the hematological malignancy expresses the multidrug resistance (MDR)-related P-glycoprotein (P-gp). In some aspects, the hematological malignancy overexpresses MDR1 and P-gp.

[0197] In some aspects, the hematological malignancy is a CD123-positive hematological malignancy.

[0198] In some aspects, the hematological malignancy or the subject with the hematological malignancy has an FLT3-ITD mutation. In some aspects, the hematological malignancy or the subject with the hematological malignancy does not have an FLT3-ITD mutation.

[0199] In some aspects, the hematological malignancy is present in the subject as minimal residual disease (MRD). In some aspects, an MRD+ patient has fit AML. In some aspects, an MRD+ patient has unfit AML. The methods provided herein can covert MRD+ patients to MRD- patients. The methods provided herein can also increase the relapse-free survival time (e.g., the median relapse-free survival time) in MRD+ patients.

[0200] In some aspects, the human subject has received at least one prior treatment regimen for the cancer. In some aspects, the human subject has received one prior treatment regimen for the cancer. In some aspects, the human subject has received two prior treatment regimens for the cancer. In some aspects, the human subject has received two prior treatment regimens for the cancer. In some aspects, the human subject has received no more than six prior treatment regimens for the cancer. In some aspects, the human subject has received at least one prior treatment, but no more than six prior treatment regimens for the cancer.

[0201] In some aspects, the cancer has not previously been treated with IMGN632/PVEK.

[0202] In some aspects, the cancer has not previously been treated with magrolimab. In some aspects, the cancer has not previously been treated with an SIRPα-targeting agent.

[0203] In some aspects, the cancer has not previously been treated with IMGN632/PVEK and has not previously been treated with magrolimab. In some aspects, the cancer has not previously been treated with IMGN632/PVEK and has not previously been treated with an SIRPα-targeting agent.

[0204] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered as a first-line therapy.

VI(B). Dosing

[0205] As provided herein, an anti-CD123 ADC (e.g., IMGN632/PVEK) can be administered at a particular dose and/or at particular timing intervals. Administration of anti-CD123 ADCs (e.g., IMGN632) can be, for example, intravenous.

[0206] In some aspects, an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered once in a four-week (28-day) cycle. In some aspects, the anti-CD123 ADC (e.g., IMGN632) is administered on Day 1 of a 28-day cycle. ADC (e.g., IMGN632/PVEK) can be administered on Day 7, Day 10, and Day 14 of a 21-day cycle. In some aspects, one cycle of treatment with an anti-CD123 ADC (e.g., IMGN632/PVEK) is therapeutically effective. In some aspects, two cycles of treatment with an anti-CD123 ADC (e.g., IMGN632/PVEK) are therapeutically effective. In some aspects, one to four cycles of treatment with an anti-CD123 ADC (e.g., IMGN632/PVEK) are therapeutically effective. In some aspects, two to twelve cycles of treatment with an anti-CD123 ADC (e.g., IMGN632/PVEK) are therapeutically effective.

[0207] In some aspects, about 0.03 mg/kg to about 0.45 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered. In some aspects, about 0.03 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered. In some aspects, about 0.45 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered.

[0208] In some aspects, about 0.03 mg/kg to about 0.45 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered once in a four-week (28-day) cycle. In some aspects, about 0.03 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered once in a four-week (28-day) cycle. In some aspects, about 0.45 mg/kg of an anti-CD123 ADC (e.g., IMGN632/PVEK) is administered once in a four-week (28-day) cycle.

[0209] As provided herein, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) can be administered at a particular dose and/or at particular timing intervals. Administration of a an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) can be, for example, intravenous.

[0210] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered every 2 days to every 14 days. In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered every 3 or 4 days. In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered once every week. In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered once every two weeks.

[0211] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered once every three or four days for a first interval and then once every week for a second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about two to about twenty times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about four times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about six times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about two to about twenty times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about four times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about six times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the first interval and about five times in the second interval.

[0212] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered once every week for a first interval and then once every two weeks for a second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about two to about twenty times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about four times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about six times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least twice in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof

(e.g., magrolimab) is administered at least three times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least four times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least five times in the second interval.

[0213] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered once every three or four days for a first interval; then once every week for a second interval; then once every two weeks for a third interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about two to about twenty times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about four times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about six times in the first interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about two to about twenty times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about four times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about six times in the second interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least twice in the third interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least three times in the third interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least four times in the third interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at least five times in the third interval. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered about five times in the first interval, about five times in the second interval, and at least twice in the third interval.

[0214] In some aspects, about 1 mg/kg to about 30 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered.

[0215] In some aspects, about 1 mg/kg to about 10 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered. In some aspects, about 10 mg/kg to about 20 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab)

is administered. In some aspects, about 20 mg/kg to about 60 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered. In some aspects, about 1 mg/kg to about 10 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered; then about 10 mg/kg to about 20 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered; and then about 20 mg/kg to about 60 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof is administered.

[0216] In some aspects, about 1 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered. In some aspects, about 15 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered. In some aspects, about 30 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered. In some aspects, about 1 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered; then about 15 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered; and then about 30 mg/kg of an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered.

[0217] In some aspects, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered in a priming regimen and then a maintenance regimen.

[0218] A maintenance regimen, as provided herein, can comprise administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) about once every two weeks. The anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) can be administered at a dose of about 15 mg/kg to about 30 mg/kg during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 15 mg/kg during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 15 mg/kg during about once every two weeks during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 20 mg/kg during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 20 mg/kg during about once every two weeks during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 25 mg/kg during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 25 mg/kg during about once every two weeks during the maintenance regimen. In some aspects, the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 30 mg/kg during the maintenance regimen. In some aspects, the

anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at a dose of about 30 mg/kg during about once every two weeks during the maintenance regimen.

[0219] A priming regimen, as provided herein, can comprise administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a dose that is lower than the dose administered during a maintenance regimen and/or a dose that is administered more frequently than during a maintenance regimen. In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a multiple doses (e.g., increasing doses) that are less than the dose administered during a maintenance regimen. Accordingly, in some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a first dose of about 1 mg/kg to about 10 mg/kg and then a second, higher dose of about 10 mg/kg to about 20 mg/kg (e.g., wherein the maintenance regimen comprises administering the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at about 30 mg/kg to about 60 mg/kg). In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a first dose of about 1 mg/kg and then a second dose of about 15 mg/kg (e.g., wherein the maintenance regimen comprises administering the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at about 30 mg/kg. In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a first interval of about once every week (e.g., wherein the maintenance regiment comprises administering the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) about once every two weeks. In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at a first dose of about 1 mg/kg, then a second dose of about 15 mg/kg, and then a third dose of 30 mg/kg about once every week (e.g., wherein the maintenance regimen comprises administering the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) at about 30 mg/kg about once every two weeks).

[0220] In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) once every three or four days. In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) about once every week. In some aspects, a priming regimen comprises administering an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) once every three or four days and then about once every week.

[0221] In some aspects, a priming regimen comprises administering three increasing doses. In some aspects, the three increasing doses comprise a first dose administered on Days 1 and 4, a

second dose administered on Day 8, and a third dose administered on Days 11, 15 and then once every week for 5 doses.

[0222] In some aspects, in a priming regimen, an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is administered at 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses.

[0223] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.045 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 30 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 30 mg/kg once every two weeks.

[0224] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.03 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 30 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 30 mg/kg once every two weeks.

[0225] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.045 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 25 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 25 mg/kg once every two weeks.

[0226] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.03 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 25 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 25 mg/kg once every two weeks.

[0227] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.045 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 20 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 20 mg/kg once every two weeks.

[0228] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.03 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Day 8, and about 20 mg/kg on Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 20 mg/kg once every two weeks.

[0229] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.045 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Days 8, Days 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 15 mg/kg once every two weeks.

[0230] In some aspects provided herein, an anti-CD123 ADC is administered (e.g., intravenously) once every 28 days at a dose of 0.03 mg/kg and an anti-CD47 antibody or antigen-binding fragment thereof is administered (e.g., intravenously) in a priming regimen comprising about 1 mg/kg on Days 1 and 4, about 15 mg/kg on Days 8, 11, 15, and then once every week for five doses and then a maintenance regimen comprising about 15 mg/kg once every two weeks.

[0231] In some aspects provided herein, a method of treating a hematological malignancy in a patient comprises administering an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) and further comprises administering a corticosteroid, e.g., dexamethasone, to the patient on the day prior to the administration of the anti-CD123 ADC. In some aspects, 8 mg dexamethasone is administered to the patient twice on the day prior to the administration of the anti-CD123 ADC.

[0232] In some aspects provided herein, a method of treating a hematological malignancy in a patient comprises administering an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) and further comprises administering (i) diphenhydramine, (ii) acetaminophen or paracetamol, and/or (iii) dexamethasone to the patient prior to the administration of the anti-CD123 ADC on the day the anti-CD123 ADC is administered. In some aspects, (i) 25 to 50 mg diphenhydramine (IV), (ii) 325 to 650 mg acetaminophen or paracetamol (IV or PO), and (iii) 8 mg dexamethasone (IV) is administered to the patient prior to the administration of the anti-CD123 ADC on the day the anti-CD123 ADC is administered.

[0233] In some aspects provided herein, a method of treating a hematological malignancy in a patient comprises administering an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) and further comprises

administering acetaminophen and/or diphenhydramine to the patient prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof. In some aspects, oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg (or a comparable regimen) is administered to the patient prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof.

VI(C). Assessment and Efficacy

[0234] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is useful for treating a hematological cancer. In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) is useful for increasing survival.

[0235] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) increases a full complete response (CR) rate, e.g., as compared to monotherapy with the anti-CD123 ADC and/or monotherapy with the anti-CD47 antibody or antigen-binding fragment thereof. Full CR rate includes complete remission without minimal residual disease (CR_{MRD-}), complete remission (CR).

[0236] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) increases a f composite CR rate (CCR), e.g., as compared to monotherapy with the anti-CD123 ADC and/or monotherapy with the anti-CD47 antibody or antigen-binding fragment thereof. Composite CR rate (CCR) includes complete remission without minimal residual disease (CR_{MRD-}), complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete recovery (CRi).

[0237] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) increases an overall response rate (ORR), e.g., as compared to monotherapy with the anti-CD123 ADC and/or monotherapy with the anti-CD47 antibody or antigen-binding fragment thereof. ORR is defined as the proportion of patients with a best overall response of of complete remission without minimal residual disease (CR_{MRD-}), complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete recovery (CRi), morphologic leukemia-free state (MLFS), or partial remission (PR).

[0238] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) increases a duration of complete remission (DOCR), e.g., as compared to monotherapy with the anti-CD123 ADC and/or monotherapy with the anti-CD47 antibody or antigen-binding fragment thereof. DOCR is the date of achieving CR_{MRD-}/CR until the date of relapse or death from any cause, whichever occurs first.

[0239] In some aspects, the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) increases a duration of response (DOR), e.g., as compared to monotherapy with the anti-CD123 ADC and/or monotherapy with the anti-CD47 antibody or antigen-binding fragment thereof. DOR is defined for patients who have achieved a complete or partial remission (CRMRD-, CR, CRh, CRp, and CRi) and is measured from the date of the first specific response until the date of relapse or death from any cause, whichever comes first.

[0240] In certain aspects, the combination of combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) produces a synergistic effect.

[0241] In some aspects, administration of the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) does not produce more toxicity than administration of the anti-CD123 ADC (e.g., IMGN632/PVEK) as a monotherapy. In some aspects, administration of the combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof does not produce more toxicity than administration of the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) as a monotherapy. In some aspects, administration of combination of an anti-CD123 ADC (e.g., IMGN632/PVEK) and an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) does not produce more toxicity than administration of the anti-CD123 ADC (e.g., IMGN632/PVEK) as a monotherapy and does not produce more toxicity than the anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) as a monotherapy.

VI(D). Additional Therapies

[0242] In some aspects, patients receiving therapy with anti-CD123 ADC (e.g., IMGN632/PVEK) in combination with an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) have received pretreatment with a corticosteroid. In some aspects, the corticosteroid can be selected from the group consisting of prednisone, prednisolone, methylprednisolone, beclamethasone, betamethasone, dexamethasone, fludrocortisone,

hydrocortisone, and triamcinolone. In some aspects, the corticosteroid is dexamethasone. In some aspects, the corticosteroid (e.g., dexamethasone) was administered orally (PO) or intravenously (IV). In some aspects, dexamethasone is given orally. In some aspects, dexamethasone is given intravenously. In some aspects, the corticosteroid (e.g., dexamethasone) was administered on the day prior to the administration of the anti-CD123 ADC. In some aspects, the patient received 8 mg dexamethasone (PO or IV) BID on the day prior to the administration of the anti-CD123 ADC.

[0243] In some aspects, patients receiving therapy with anti-CD123 ADC (e.g., IMGN632/PVEK) in combination with an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) have received pretreatment prior to the administration of the anti-CD123 ADC on the day of administration of the anti-CD123 ADC. In some aspects, the patient was pretreated with (i) diphenhydramine, (ii) acetaminophen or paracetamol, and/or (iii) dexamethasone. In some aspects, the patient was pretreated with (i) diphenhydramine, (ii) acetaminophen or paracetamol, and (iii) dexamethasone. In some aspects, acetaminophen is given intravenously. In some aspects, acetaminophen is given orally. In some aspects, paracetamol is given intravenously. In some aspects, paracetamol is given orally. In some aspects, diphenhydramine is given intravenously. In some aspects, diphenhydramine is given orally. In some aspects, the patient was pretreated with (i) 25 to 50 mg diphenhydramine (IV), (ii) 325 to 650 mg acetaminophen or paracetamol (IV or PO), and (iii) 8 mg dexamethasone (IV) prior to the administration of the anti-CD123 ADC on the day of administration of the anti-CD123 ADC.

[0244] In some aspects, patients receiving therapy with anti-CD123 ADC (e.g., IMGN632/PVEK) in combination with an anti-CD47 antibody or antigen-binding fragment thereof (e.g., magrolimab) have received pretreatment prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof. In some aspects, the patient was pretreated with acetaminophen and/or diphenhydramine prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof. In some aspects, diphenhydramine is given intravenously. In some aspects, diphenhydramine is given orally. In some aspects, the patient received oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg (or a comparable regimen prior) to the administration of the anti-CD47 antibody or antigen-binding fragment thereof.

[0245] Additional aspects of the present disclosure can be further defined by reference to the following non-limiting examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of the present disclosure.

Examples

[0246] It is understood that the examples and aspects described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application

Example 1

The combination of IMGN632/PVEK and magrolimab for the treatment of relapsed or refractor CD123-positive acute myeloid leukemia (AML)

[0247] An open-label, multicenter, Phase 1b/2 study of the combination of IMGN632/PVEK and magrolimab is performed to demonstrate the safety of the combination and its efficacy in treating relapsed or refractory CD123-positive acute myeloid leukemia (AML).

[0248] The study comprises a Phase 1b Safety Phase and by Phase 2 Expansion Phase. The Safety and Expansion Phases include an antileukemia activity futility assessment using a Simon's 2-stage design. The Expansion Phase occurs after acceptable safety and sufficient efficacy are demonstrated in the Safety Phase. The schema for the study is provided in Figure 2.

[0249] Patients are enrolled in a 3 + 3 design with 3, then 3 additional, then up to 16 additional patients, for a total of up to 22 efficacy-evaluable patients treated at the same dose to assess safety and signal findings for anti-leukemia activity.

Patient Inclusion Criteria

[0250] Patients are adults ((≥ 18 years of age) and are evaluated for any available standard of care therapies (including induction, consolidation chemotherapy and/or transplant) and are deemed appropriate for this experimental therapy. Patients meet all of the following inclusion criteria:

- confirmed diagnosis of AML (excluding acute promyelocytic leukemia) based on World Health Organization classification (Arber DA, et al., The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405 (2016)).
- have qualitative CD123-positive AML blasts as confirmed by local flow cytometry (or immunohistochemistry (IHC));
- may have received prior CD123-targeted therapies, except IMGN632/PVEK, as long as CD123 remains detectable during screening;
- relapsed or refractory CD123-positive AML with up to 2 prior lines of therapy (Prior lines of therapy may include multiple regimens, e.g., frontline treatment may include induction, consolidation [including transplant], and maintenance as one line of therapy);

- Eastern Cooperative Oncology Group performance status ≤ 1. If nonambulatory due to a chronic disability, must be Karnofsky performance status ≥ 70;
- Previous treatment-related toxicities must have resolved to Grade 1 or baseline (excluding alopecia);
- Total white blood cell (WBC) count must be less than or equal to $20x10^9$ cells/L. Leukapheresis and/or hydroxyurea may be used to control blood counts before Cycle 1 Day 1;
- Hemoglobin must be ≥9 g/dL prior to initial dose of magrolimab (transfusions are allowed to meet hemoglobin eligibility);
- Liver enzymes (AST and ALT) ≤ 3 × the upper limit of normal (ULN);
- Total bilirubin ≤ 1.5 × the ULN;
- An estimated glomerular filtration rate (eGFR) of > 30 mL/min/1.73 m^2 or creatinine clearance of > 30 mL/min; and
- Left ventricular ejection fraction (LVEF) ≥ 50% based on locally available assessment, e.g., echocardiogram or other modality.

Patient Exclusion Criteria

[0251] Patients who have received prior treatment with either IMGN632/PVEK, magrolimab, or other SIRPα-targeting agents are excluded. Patients are also excluded based on the following criteria:

- Patients who have received any anticancer therapy, including investigational agents, within 14 days (or within 28 days for checkpoint inhibitors) before drug administration on this study (hydroxyurea is allowed before beginning study treatment). Patients must have recovered to baseline from all acute toxicity from this prior therapy;
- Patients with active central nervous system (CNS) AML are excluded.

Dosing and Administration

[0252] IMGN632/PVEK is administered intravenously on Day 1 of a 28-day cycle at doses of 0.045 mg/kg or 0.03 mg/kg. Patients receive 8 mg dexamethasone (PO or IV) BID on the day prior to any IMGN632/PVEK dose. Patients receive the following premedication regimen before each IMGN632/PVEK infusion: (i) 25 to 50 mg diphenhydramine (IV), (ii) 325 to 650 mg acetaminophen or paracetamol (IV or PO), and (iii) 8 mg dexamethasone (IV).

[0253] The dose for magrolimab ramps up in each patient to maximum dose of 30 mg/kg given every 2 weeks. The dosing schedule for magrolimab is presented in Table 7.

Table 7: Magrolimab Dose and Schedule

Magrolimab 1 mg/kg IV (over 30 hours ± 30 minutes)	Days 1 and 4
Magrolimab 15 mg/kg IV (over 30 hours ± 30 minutes)	Day 8
Magrolimab 30 mg/kg IV (over 30 hours ± 30 minutes)	Days 11, 15, and then QW x 5 doses
Magrolimab 30 mg/kg IV (over 30 hours ± 30 minutes)	Q2W beginning 1 week after the fifth weekly 30 mg/kg dose

IV = intravenous; QW = once weekly; Q2W = once every two weeks.

[0254] The magrolimab given at 1 mg/kg IV over 3 hours (± 30 minutes) on Days 1 and 4; at 15 mg/kg IV over 3 hours (± 30 minutes) on Day 8; and at 30 mg/kg IV over 2 hours (± 30 minutes) on Days 11, 15, and then weekly for 5 doses is referred to as "magrolimab priming." Magrolimab given at 30 mg/kg IV over 2 hours (± 30 minutes) every 2 weeks beginning 1 week after the fifth weekly 30 mg/kg dose is referred to as "magrolimab maintenance dose."

[0255] Premedication is required prior to the administration of the first 4 doses of magrolimab. Required premedications for magrolimab are oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg or comparable regimen. If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted.

[0256] Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. The repriming guidelines presented in Table 8 are followed for patients with dose delays. Premedication for magrolimab is required prior to the administration of the first 4 doses in case of reintroduction with repriming.

Table 8: Magrolimab Repriming

Dose of Magrolimab	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	2 weeks
15 mg/kg	2 weeks
30 mg/kg	4 weeks

[0257] If both IMGN632/PVEK and magrolimab are given on the same day, IMGN632/PVEK is administered first. The magrolimab infusion starts at least 1 hour after the end of IMGN632/PVEK infusion.

[0258] Up to 22 patients are evaluated (Phase 1b), and then IMGN632/PVEK in combination with magrolimab will be evaluated with up to 14 efficacy-evaluable patients (Phase 2).

[0259] The initial treatment consists of 2 cycles of IMGN632/PVEK in combination with magrolimab. Additional treatments may be administered until progression for patients deriving benefit from the treatment regimen.

Results

[0260] Blood samples are taken to assess the pharmacokinetic (PK) properties of IMGN632/PVEK concentrations when administered in combination with magrolimab. Assessment of safety is performed via reports of adverse events (AE) and laboratory assessments including hematology and serum chemistry, vital signs, physical examination, and left ventricular ejection fraction assessment (LVEF) to demonstrate that the combination of IMGN632/PVEK and magrolimab is safe. Assessment of anti-leukemia activity is performed via response assessments, comprising primarily bone marrow aspirates (BMAs) and/or biopsies assessed by morphology and minimal residual disease (MRD) testing at the end of IMGN632/PVEK Cycle 1 and Cycle 2 and every other subsequent cycle to demonstrate that the combination of IMGN632/PVEK and magrolimab is effective. Response assessments used to demonstrate the efficacy of the combination include the overall response rate (ORR), duration of complete remission (DOCR), and duration of response (DOR).

[0261] ORR is defined as the proportion of patients with a best overall response of complete remission without minimal residual disease (CR_{MRD-}), complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete recovery (CRi), morphologic leukemia-free state (MLFS), or partial remission (PR). Full CR rate (CR) includes CR_{MRD-} and CR, and composite CR rate (CCR) includes CR_{MRD-}, CR, CRh, CRp, and CR.

[0262] DOCR is defined from the date of achieving CR_{MRD-}/CR until the date of relapse or death from any cause, whichever occurs first. For a patient who is not known to have relapsed or died by the end of study follow-up, observation of DOCR is censored on the date of his or her last bone marrow disease assessment.

[0263] DOR is defined for patients who have achieved a complete or partial remission (CR_{MRD-}, CR, CRh, CRp, and CRi) and is be measured from the date of the first specific response until the date of relapse or death from any cause, whichever comes first. For a patient with no report of relapse or death by the end of the follow-up data collection, observation is censored on the date of his or her last bone marrow disease assessment.

* * *

[0264] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections sets forth one or more, but not all, exemplary aspects of the present invention as contemplated by the inventors, and thus, are not intended to limit the present invention and the appended claims in any way.

[0265] The foregoing description of the specific aspects will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0266] The breadth and scope of the present invention should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating in a subject comprising administering to said subject

(a) an antibody drug conjugate (ADC) that binds to CD123, wherein said ADC comprises a DNA-alklyating agent conjugated to an anti-CD123 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 5; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 6; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 10, and

(b) an anti-CD47 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 15; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 17; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 18; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 19; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 20.

2. The method of claim 1, wherein the anti-CD123 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1 and/or a VL comprising the amino acid sequence set forth in SEQ ID NO: 2.

3. The method of claim 1 or 2, wherein the anti-CD123 antibody or antigen-binding fragment thereof is an antibody.

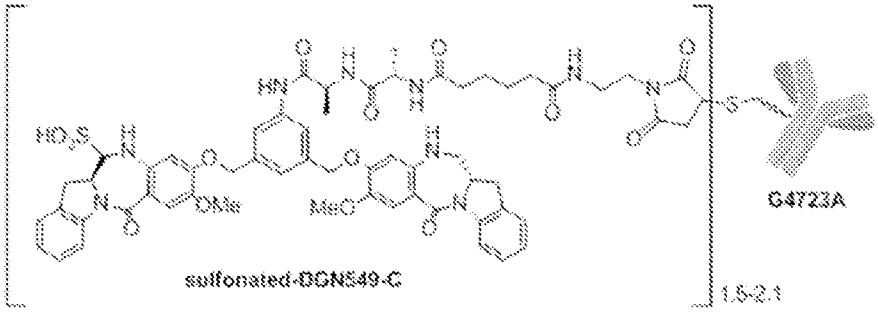
4. The method of any one of claims 1-3, wherein the anti-CD123 antibody or antigen-binding fragment thereof is a human IgG antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a human IgG1 antibody or antigen-binding fragment thereof.

5. The method of any one of claims 1-4, wherein the anti-CD123 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 and/or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4.

6. The method of any one of claims 1-5, wherein the DNA-alkylating agent is indolino-benzodiazepine (IGN) DNA-alkylator.

7. The method of any one of claims 1-6, wherein the ADC is IMGN632/PVEK.

8. The method of any one of claims 1-6, wherein the ADC is administered in a pharmaceutical composition comprising ADCs with the following structure:



,wherein G4723A comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4.

9. The method of any one of claims 1-8, wherein the ADC is administered intravenously.

10. The method of any one of claims 1-9, wherein the ADC is administered once every 28 days.

11. The method of any one of claims 1-10, wherein the ADC is administered at a dose of 0.045 mg/kg, optionally for two doses.

12. The method of any one of claims 1-10, wherein the ADC is administered at a dose of 0.03 mg/kg, optionally for two doses.

13. The method of any one of claims 1-12, wherein the anti-CD123 ADC and the anti-CD47 antibody or antigen-binding fragment thereof are administered in separate pharmaceutical compositions.

14. The method of any one of claims 1-13, wherein the anti-CD47 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 13 and/or a VL comprising the amino acid sequence set forth in SEQ ID NO: 14.

15. The method of any one of claims 1-14, wherein the anti-CD47 antibody or antigen-binding fragment thereof is an antibody.

16. The method of any one of claims 1-15, wherein the anti-CD47 antibody or antigen-binding fragment thereof is a human IgG antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a human IgG4 antibody or antigen-binding fragment thereof.

17. The method of any one of claims 1-16, wherein the anti-CD47 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 21 and/or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 22.

18. The method of any one of claims 1-17, wherein the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab.

19. The method of any one of claims 1-18, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered intravenously.

20. The method of any one of claims 1-19, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered once every week and/or once every two weeks.

21. The method of any one of claims 1-20, wherein administering the anti-CD47 antibody or antigen-binding fragment thereof comprises administering a priming regimen and administering a maintenance regimen.

22. The method of claim 21, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered once every two weeks in the maintenance regimen.

23. The method of claim 21 or 22, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 30 mg/kg in the maintenance regimen.

24. The method of claim 21 or 22, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 25 mg/kg in the maintenance regimen.

25. The method of claim 21 or 22, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 20 mg/kg in the maintenance regimen.

26. The method of claim 21 or 22, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg in the maintenance regimen

27. The method of any one of claims 21-26, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered once every 3 or 4 days and/or once every week in the priming regimen.

28. The method of any one of claims 21-27, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered in at least two increasing doses in the priming regimen.

29. The method of claim 28, wherein the at least two increasing doses in the priming regimen are from 1 mg/kg to 30 mg/kg, optionally wherein the at least two increasing doses are selected from the group consisting of 1 mg/kg, 15 mg/kg, and 30 mg/kg doses.

30. The method of any one of claims 1-29, wherein the anti-CD47 antibody or antigen-binding fragment thereof is administered in three increasing doses in the priming regimen.

31. The method of claim 30, wherein the three increasing doses in the priming regimen are from 1 mg/kg to 30 mg/kg, optionally wherein the three increasing doses are 1 mg/kg, 15 mg/kg, and 30 mg/kg doses.

32. The method of claim 30 or 31, wherein the three increasing doses comprise a first dose administered on Days 1 and 4, a second dose administered on Day 8, and a third dose administered on Days 11, 15 and then once every week for 5 doses.

33. The method of any one of claims 21-32, wherein in the priming regimen, the anti-CD47 antibody or antigen-binding fragment thereof is administered at 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses.

34. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

35. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

36. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg

on Day 8, and at 25 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 25 mg/kg once every two weeks.

37. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 25 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 25 mg/kg once every two weeks.

38. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 20 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 20 mg/kg once every two weeks.

39. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 20 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 20 mg/kg once every two weeks.

40. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.045 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Days 8, 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 15 mg/kg once every two weeks.

41. The method of any one of claims 1-33, wherein the ADC is administered intravenously once every 28 days at a dose of 0.03 mg/kg and the anti-CD47 antibody or antigen-binding fragment thereof is administered in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Days 8, 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 15 mg/kg once every two weeks

42. The method of any one of claims 1-41, wherein the ADC is further administered as a maintenance therapy.

43. The method of claim 42, wherein the ADC is administered once every two weeks during the maintenance therapy.

44. The method of claim 42, wherein the ADC is administered once every four weeks during the maintenance therapy.

45. The method of any one of claims 42-44, wherein the ADC is administered at 0.045 mg/kg during the maintenance therapy.

46. The method of any one of claims 42-44, wherein the ADC is administered at 0.03 mg/kg during the maintenance therapy.

47. The method of any one of claims 1-46, wherein the hematological malignancy is a relapsed or refractory hematological malignancy.

48. The method of claim 47, wherein the hematological malignancy is a relapsed hematological malignancy.

49. The method of claim 47, wherein the hematological malignancy is a refractory hematological malignancy.

50. The method of any one of claims 1-49, wherein the hematological malignancy is acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), chronic myeloid leukemia in blast crisis/phase (BP-CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN).

51. The method of any one of claims 1-50, wherein the hematological malignancy is a CD123+ hematological malignancy.

52. The method of any one of claims 1-51, the hematological malignancy has an FLT3-ITD mutation.

53. The method of any one of claims 1-85, wherein the hematological malignancy expresses multidrug resistance 1 (MDR1).

54. The method of any one of claims 1-53, wherein the hematological malignancy expresses P-glycoprotein (P-gp).

55. The method of any one of claims 1-54, wherein the subject received one prior line of therapy.

56. The method of any one of claims 1-54, wherein the subject received two prior lines of therapy.

57. The method of any one of claims 1-56, wherein the cancer has not previously been treated with IMGN632/PVEK.

58. The method of any one of claims 1-57, wherein the cancer has not previously been treated with magrolimab.

59. The method of any one of claims 1-58, wherein the cancer has not previously been treated with an SIRPα-targeting agent.

60. The method of any one of claims 1-59, wherein administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof produces a synergistic effect.

61. The method of any one of claims 1-60, wherein administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof does not produce more toxicity than administration of the ADC alone.

62. The method of any one of claims 1-61, wherein administration of the ADC and the anti-CD47 antibody or antigen-binding fragment thereof does not produce more toxicity than administration of the anti-CD47 antibody or antigen-binding fragment thereof alone.

63. The method of any one of claims 1-62, wherein the subject received dexamethasone on the day prior to the administration of the ADC.

64. The method of any one of claims 1-62, wherein the subject received 8 mg dexamethasone twice on the day prior to the administration of the ADC.

65. The method of any one of claims 1-62, further comprising administering dexamethasone to the subject on the day prior to the administration of the ADC.

66. The method of any one of claims 1-62, further comprising administering 8 mg dexamethasone to the subject twice on the day prior to the administration of the ADC.

67. The method of any one of claims 166, wherein the subject received diphenhydramine prior to the administration of the ADC, optionally wherein the subject received 25 mg to 50 mg diphenhydramine prior to the administration of the ADC.

68. The method of any one of claims 1-66, further comprising administering diphenhydramine, optionally 25 mg to 50 mg diphenhydramine, to the subject prior the administration of the ADC.

69. The method of any one of claims 1-68, wherein the subject received acetaminophen or paracetamol prior to the administration of the ADC, optionally wherein the subject received 325 mg to 650 mg acetaminophen or paracetamol prior to the administration of the ADC.

70. The method of any one of claims 1-68, further comprising administering acetaminophen or paracetamol, optionally 325 mg to 650 mg acetaminophen or paracetamol, to the subject prior to the administration of the ADC.

71. The method of any one of claims 1-70, wherein the subject received dexamethasone prior to the administration of the ADC, optionally wherein the subject received 8 mg dexamethasone prior to the administration of the ADC.

72. The method of any one of claims 1-70, further comprising administering dexamethasone, optionally 8 mg dexamethasone, to the subject prior to the administration of the ADC.

73. The method of any one of claims 1-72, wherein the subject received acetaminophen (optionally 650 mg to 1000 mg acetaminophen), diphenhydramine (optionally 35 mg to 50 mg diphenhydramine), or comparable regimen prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof.

74. The method of any one of claims 1-72, further comprising administering acetaminophen (optionally 650 mg to 1000 mg acetaminophen), diphenhydramine (optionally 35 mg to 50 mg diphenhydramine), or comparable regimen to the subject prior to the administration of the anti-CD47 antibody or antigen-binding fragment thereof.

75. The method of any one of claims 1-74, wherein the ADC is IMGN632/PVEK, the ADC is administered intravenously at a dose of 0.045 mg/kg once every 28 days, the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab, and the magrolimab is administered intravenously in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

76. The method of any one of claims 1-74, wherein the ADC is IMGN632/PVEK, the ADC is administered intravenously at a dose of 0.03 mg/kg once every 28 days, the anti-CD47 antibody or antigen-binding fragment thereof is magrolimab, and the magrolimab is administered intravenously in a priming regimen comprising 1 mg/kg on Days 1 and 4, at 15 mg/kg on Day 8, and at 30 mg/kg on Days 11, 15, and then once every week for 5 doses and then a maintenance regimen comprising 30 mg/kg once every two weeks.

77. The method of any one of claims 1-76, wherein the ADC is administered twice.

78. The method of any one of claims 1-77, wherein the subject is human.

79. A composition comprising an ADC that binds to CD123 for use in combination with an anti-CD47 antibody or antigen-binding fragment thereof for treating a hematologic malignancy in the method of any one of claims 1-78.

80. A composition comprising an ADC that binds to CD123, wherein the composition is to be administered with an anti-CD47 antibody or antigen-binding fragment thereof for treating a hematologic malignancy in the method of any one of claims 1-78.

81. A composition comprising an anti-CD47 antibody or antigen-binding fragment thereof for use in combination with an ADC that binds to CD123 for treating a hematologic malignancy in the method of any one of claims 1-78.

82. A composition comprising an anti-CD47 antibody or antigen-binding fragment thereof, wherein the composition is to be administered with an ADC that binds to CD123 for treating a hematologic malignancy in the method of any one of claims 1-78.

FIG. 1A

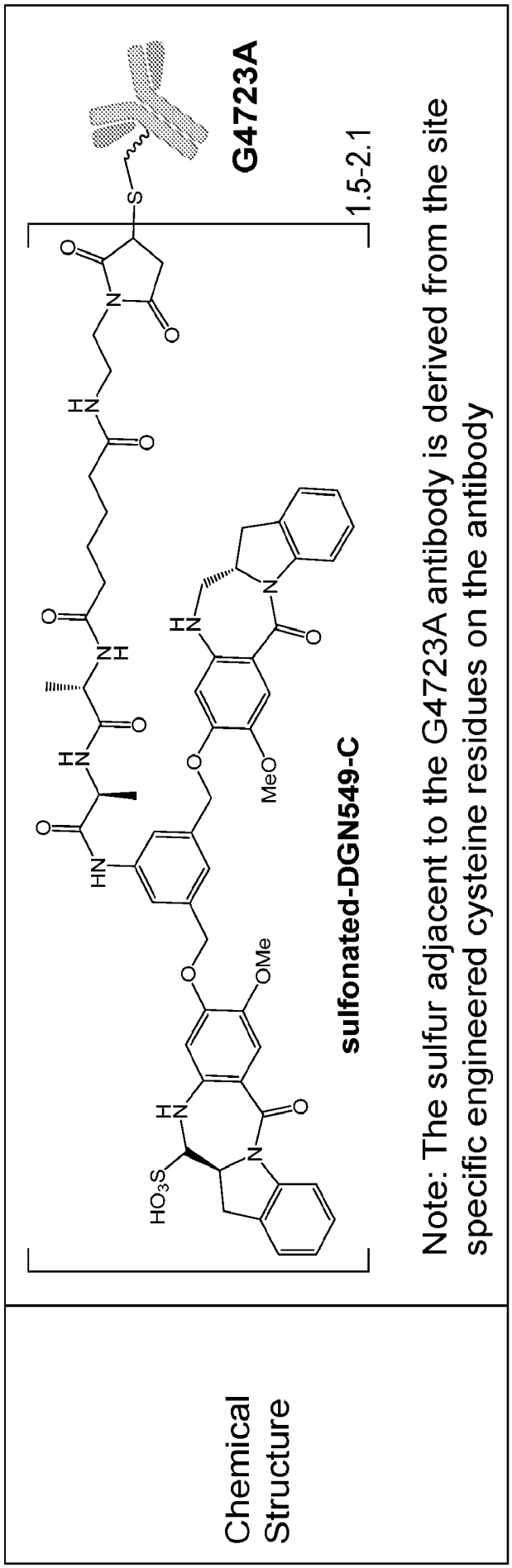

Chemical Structure
G4723A
1.5-2.1
sulfonated-DGN549-C
Note: The sulfur adjacent to the G4723A antibody is derived from the site specific engineered cysteine residues on the antibody

FIG. 1B

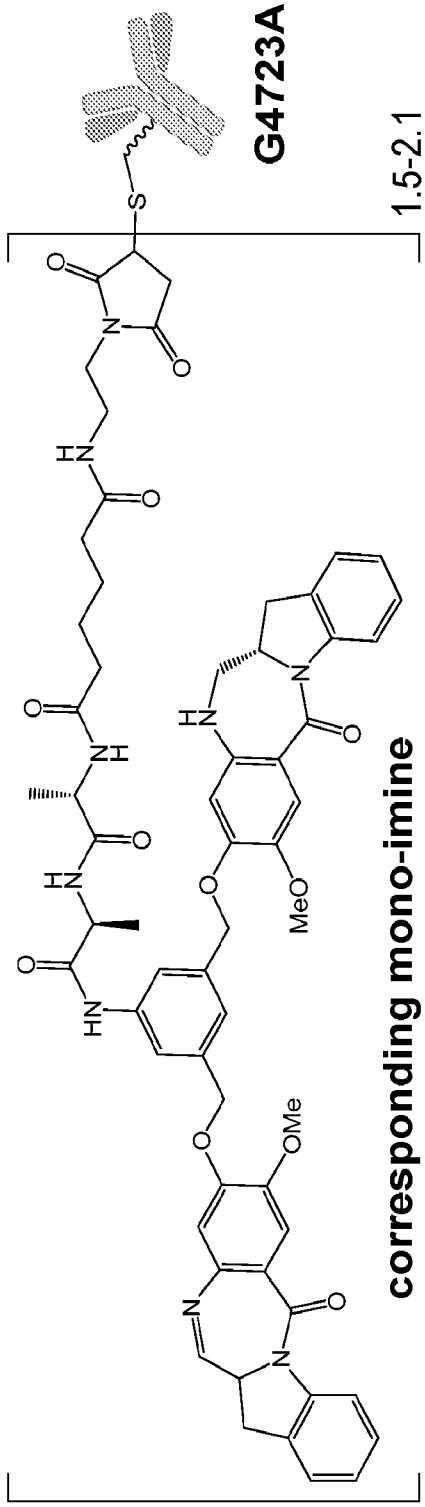
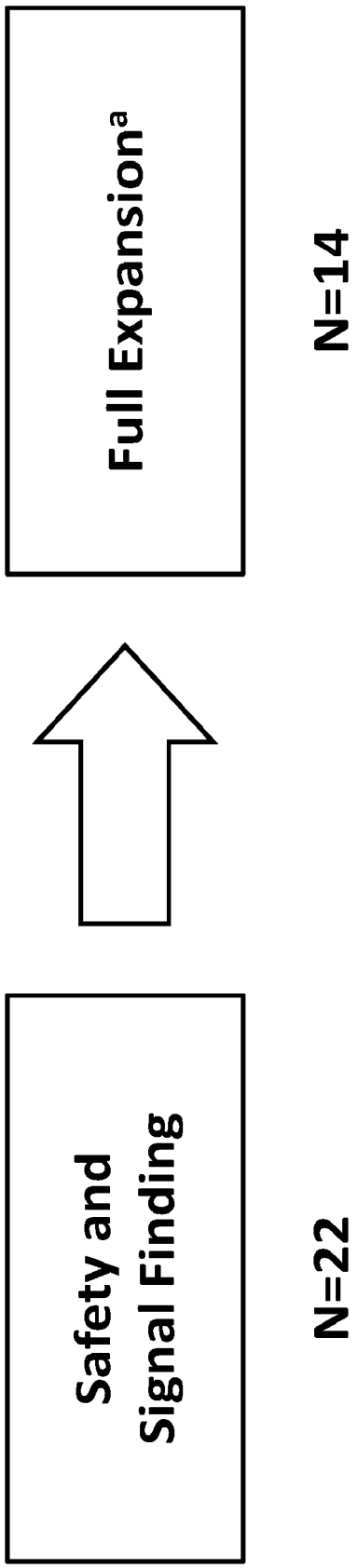

G4723A
1.5-2.1
corresponding mono-imine

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/082499

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61P 35/00*** (2023.01); ***A61K 39/395*** (2023.01); ***A61K 47/68*** (2023.01); ***C07K 16/28*** (2023.01); ***C07K 16/46*** (2023.01)

CPC: ***A61P 35/00; A61K 39/3955; A61K 47/6803; A61K 47/6849; C07K 16/2803; C07K 16/2866; C07K 16/2896; C07K 16/468;*** *A61K 2039/507; C07K 2317/76*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2021/0023237 A1 (IMMUNOGEN INC.) 28 January 2021 (28.01.2021) entire document	1-3
Y	WO 2021/206965 A1 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY et al.) 14 October 2021 (14.10.2021) entire document	1-3
A	US 2020/0147117 A1 (BIOSIGHT LTD.) 14 May 2020 (14.05.2020) entire document	1-3
A	US 2020/0283536 A1 (PFIZER INC.) 10 September 2020 (10.09.2020) entire document	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 February 2024 (29.02.2024)	**24 April 2024 (24.04.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/082499

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☐ forming part of the international application as filed.
   b. ☑ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☑ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/082499

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **4-82**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3 are drawn to methods for treating in a subject.

The first invention of Group I+ is restricted to an anti-CD123 antibody comprising a heavy chain variable region comprising SEQ ID NO: 1 and a light chain variable region comprising SEQ ID NO: 2, and an anti-CD47 antibody comprising a heavy chain variable region comprising SEQ ID NO: 13 and a light chain variable region comprising SEQ ID NO: 14, and methods for treating in a subject comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claims 1, 2, and 14). It is believed that claims 1-3 read on this first named invention and thus these claims will be searched without fee to the extent that they read on anti-CD123 antibody comprising a heavy chain variable region comprising SEQ ID NO: 1 and a light chain variable region comprising SEQ ID NO: 2, and an anti-CD47 antibody comprising a heavy chain variable region comprising SEQ ID NO: 13 and a light chain variable region comprising SEQ ID NO: 14, and methods for treating in a subject comprising the same.

Applicant is invited to elect additional anti-CD123 and anti-CD47 antibodies to be searched in a specific combination by paying an additional fee for each election. An exemplary election would be an anti-CD123 antibody comprising a heavy chain variable region comprising SEQ ID NO: 3 and a light chain variable region comprising SEQ ID NO: 4, and an anti-CD47 antibody comprising a heavy chain variable region comprising SEQ ID NO: 21 and a light chain variable region comprising SEQ ID NO: 22, and methods for treating in a subject comprising the same. Additional anti-CD123 and anti-CD47 antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The Groups I+ formulas do not share a significant structural element responsible for binding to CD123 and CD47 requiring the selection of alternative antibody sequences where "an anti-CD123 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 5; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 6; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 10, and (b) an anti-CD47 antibody or antigen-binding fragment thereof comprising a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 15; a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 17; and a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 18; a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 19; and a light chain variable region CDR3 comprising the amino acid sequence of: SEQ ID NO: 20" "wherein the anti-CD123 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1 and/or a VL comprising the amino acid sequence set forth in SEQ ID NO: 2," or "wherein the anti-CD123 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 3 and/or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 4," and "wherein the anti-CD47 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 13 and/or a VL comprising the amino acid sequence set forth in SEQ ID NO: 14" or "wherein the anti-CD47 antibody or antigen-binding fragment comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 21 and/or a light chain comprising the amino acid sequence set forth in SEQ ID NO: 22."

Additionally, even if Groups I+ were considered to share the technical features of a method for treating in a subject comprising administering to said subject (a) an antibody drug conjugate (ADC) that binds to CD123, wherein said ADC comprises a DNA-alklyating agent conjugated to an anti-CD123 antibody or antigen-binding fragment thereof, and (b) an anti-CD47 antibody or antigen-binding fragment thereof, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2020/0283536 to Pfizer Inc. teaches a method for treating in a subject (methods of treating a condition associated with cells expressing CD123 in a subject, Para. [0027]) comprising administering to said subject (a) an antibody drug conjugate (ADC) that binds to CD123, wherein said ADC comprises a DNA-alklyating agent conjugated to an anti-CD123 antibody or antigen-binding fragment thereof (comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising any of the CD123 antibodies described herein, or the conjugate of any of the antibodies, Para. [0027]; Also provided are conjugates that comprise a CD123 antibody as described herein conjugated to an agent…. In some embodiments, the agent can be a cytotoxic agent. In some embodiments, the cytotoxic agent can be… a duocarmycin, Para. [0020]), and (b) a CD47-targeting agent (a CD123 antibody is used in conjunction with one or more other therapeutic agents targeting an immune checkpoint modulator, such as, for example without limitation, an agent targeting … CD47, Para. [0174]).

Further, WO 2021/206965 to The Board Of Trustees of The Leland Stanford Junior University et al. teaches an anti-CD47 antibody (Formulations of anti-CD47 antibodies are provided, Para. [0008]; the antibody is magrolimab, and comprises the heavy chain variable region sequence of SEQ ID NO: 8 and the light chain variable region sequence of SEQ ID NO: 11, Para. [0074]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/082499

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-3**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.