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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2024 (28.03.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/064668 A1

(51) International Patent Classification:
C07K 16/28 (2006.01)

(21) International Application Number:
PCT/US2023/074560

(22) International Filing Date:
19 September 2023 (19.09.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/376,484 21 September 2022 (21.09.2022) US

(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) Inventors: **ASSI, Hikmat H.**; 1625 15th Street, San Pablo, California 94806 (US). **BATES, Jamie G.**; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(74) Agent: **WAHLSTEN, Jennifer L.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (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).

(54) Title: FOCAL IONIZING RADIATION AND CD47/SIRPα DISRUPTION ANTICANCER COMBINATION THERAPY

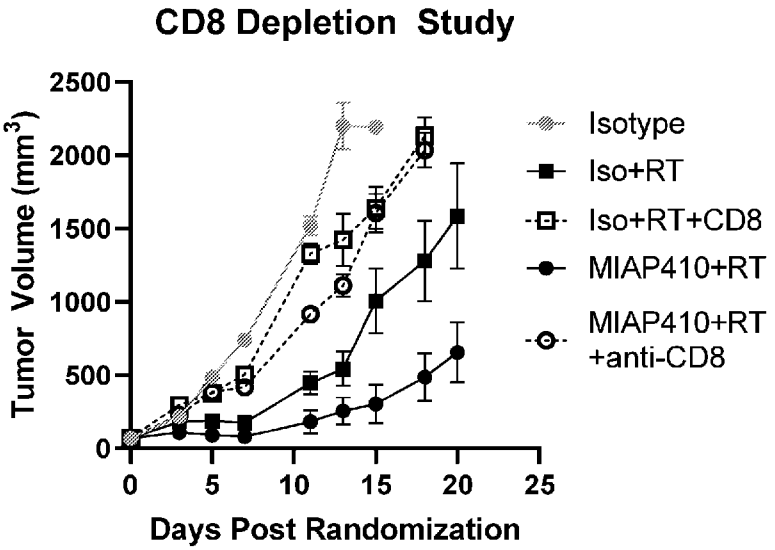

Fig. 4

(57) **Abstract:** Provided are methods of treating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of a solid cancer in a mammalian subject in need thereof comprising co-administering to the subject an effective amount of radiation therapy (RT) focally-delivered to the solid cancer; and an agent that inhibits binding between CD47 and SIRPα.

WO 2024/064668 A1

[Continued on next page]

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))*

— *with sequence listing part of description (Rule 5.2(a))*

FOCAL IONIZING RADIATION AND CD47/SIRPα DISRUPTION ANTICANCER COMBINATION THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 63/376,484, filed on September 21, 2022, which is hereby incorporated herein by reference in its entirety for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in .XML format and is hereby incorporated by reference in its entirety. Said .XML copy, created on August 14, 2023, is named 1450-WO-PCT_SL.xml and is 234,566 bytes in size.

BACKGROUND

[0003] Cluster of differentiation 47 (CD47) is a molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic "eat me" signals (Jaiswal, *et al.*, *Cell* (2009) 138(2):271-85; Majeti, *et al.*, *Cell* (2009) 138(2):286-99). The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal (Chao, *et al.*, *Nat Rev Cancer.* (2012) 12(1):58-67). Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint (Chao, *et al.*, 2012, *supra*). Increased CD47 expression was identified first on leukemic stem cells in human acute myeloid leukemia (AML) (Majeti, *et al.*, 2009, *supra*), and since then it has been found that CD47 expression is increased on the surface of cancer cells in a diverse set of human tumor types.

[0004] In mouse xenograft models, CD47-blocking monoclonal antibodies (mAbs) inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors (Chao, *et al.*, *Cancer Res* (2011) 71(4):1374-84; Chao, *et al.*, *Cell* (2010) 142:699-713; Chao, *et al.*, *Blood* (2011) 118 (18):4890-901; Edris, *et al.*, *Proc Natl Acad Sci U S A* (2012) 109(17):6656-61; Kim, *et al.*, *Proc Natl Acad Sci U S A* (2012) 109(17):6656-61; Majeti, *et al.*, *supra*; Willingham, *et al.*, *Proc Natl Acad Sci U S A* (2012) 109(17):6662-7). Binding of CD47

expressed by cancer cells to its ligand, signal regulatory protein alpha (SIRPα), expressed on phagocytes leads to inhibition of tumor cell phagocytosis. Thus, blockade of the CD47 SIRPα-signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of prophagocytic signals expressed mainly on tumor cells and not on normal cell counterparts (Chao, *et al.*, *Sci Transl Med* (2010) 2(63):63ra94). In addition, the anti-CD47 antibody can induce an anticancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis (Liu, *et al.*, *Nat Med* (2015) 21(10):1209-15, Tseng, *et al.*, *Proc Natl Acad Sci U S A* (2013) 110(27):11103-8).

[0005] Magrolimab is a humanized anti-CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells (Liu, *et al.*, *PLoS One.* (2015) 10 (9):e0137345). The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of fragment crystallizable (Fc) dependent effector functions, although the presence of the immunoglobulin G4 (IgG4) Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells (Liu, *et al.*, *PLoS One.* (2015), *supra*). Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a therapeutic candidate for solid tumors and hematologic malignancies.

SUMMARY

[0006] In one aspect, provided is a method of treating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of a solid cancer in a mammalian subject in need thereof comprising co-administering to the subject an effective amount of: (a) radiation therapy (RT) focally-delivered to the solid cancer; and (b) an agent that inhibits binding between CD47 and SIRPα. In some embodiments, the solid cancer is a non-irradiated tumor. In some embodiments, the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT. In some embodiments, the RT is focally-delivered via a technique selected from microbeam radiation therapy (MRT), external beam radiation therapy (EBRT), internal radiotherapy (brachytherapy), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic ablative radiation

therapy (SABR), low-dose stereotactic body radiation (SBRT), preoperative RT, intra-operative radiation therapy (IORT), postoperative RT (PORT), pulsed low-dose rate radiation therapy, and combinations thereof. In some embodiments, the RT dose is a dose sufficient to induce abscopal effect (i.e., reduction or elimination of non-irradiated tumors). In some embodiments, the RT dose is a maximum dose tolerated by the subject. In some embodiments, the RT dose is fractionated over multiple administrations. In some embodiments, the RT dose is hypofractionated or ultrahypofractionated. In some embodiments, administration of the RT and the agent that inhibits binding between CD47 and SIRPα are alternated over multiple administrations. In some embodiments, the RT and the agent that inhibits binding between CD47 and SIRPα are administered according to a regimen that entails first administering the agent that inhibits binding between CD47 and SIRPα. In some embodiments, the solid cancer is selected from an epithelial carcinoma, a squamous cell carcinoma, a sarcoma and a brain cancer. In some embodiments, the cancer is selected from lung cancer, colorectal cancer, head and neck cancer, glioblastoma, prostate cancer, pancreatic cancer, breast cancer, liver cancer, testicular cancer, nasopharyngeal cancer, stomach cancer, urinary tract cancer, urothelial cancer, bladder cancer, renal cancer, ovarian cancer, uterine cancer and esophageal cancer. In some embodiments, the cancer is (i) unresectable, locally advanced or (ii) metastatic. In some embodiments, the cancer has progressed after the subject has received a course of an immune checkpoint inhibitor. In some embodiments, the cancer has progressed after administration of the subject has received a course of a platinum coordination complex therapy. In some embodiments, the cancer is unresectable, locally advanced and the subject is treatment naïve. In some embodiments, the cancer is a lung cancer selected from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In some embodiments, the cancer is a colorectal cancer. In some embodiments, the treatment results in a reduction in overall tumor burden of at least 15%, at least 20%, at least 30%, or at least 40%, as determined using linear dimensional methods (*e.g.*, RECIST v1.1). In some embodiments, the method comprises reducing in size or eliminating the metastases. In some embodiments, the cancer has cell surface expression of CD47. In some embodiments, the agent that inhibits binding between CD47 and SIRPα comprises an antibody that binds to CD47. In some embodiments, the antibody that binds to CD47 is selected from magrolimab, lemzoparlimab, letaplimab, ligufalimab, gentulizumab, AO-176, simridarlimab (IBI-322), zeripatamig, ZL-1201, IMC-002, SRF-231, CC-90002 (*a.k.a.*, INBRX-103), NI-1701 (*a.k.a.*, TG-1801) and STI-6643. In some embodiments, the agent that inhibits binding between CD47 and SIRPα comprises an antibody that binds to SIRPα. In some embodiments, the antibody that binds to SIRPα is selected from anzurstobart (*a.k.a.*, BMS-

986351; CC-95251), GS-0189 (a.k.a., FSI-189), BI-765063 and APX-700. In some embodiments, the agent that inhibits binding between CD47 and SIRPα comprises a SIRPα-Fc fusion protein. In some embodiments, the SIRPα-Fc fusion protein is selected from evorpacept (ALX-148), timdarpacept, TTI-621, maplirpacept (TTI-622), JMT601 (CPO107) and SL-172154. In some embodiments, the agent that inhibits binding between CD47 and SIRPα is administered before the focally-delivered RT. In some embodiments, the subject is a human. In some embodiments, the method does not comprise further co-administering an immune checkpoint inhibitor. In some embodiments, an anti-PD-1 antibody is not co-administered.

[0007] In another aspect, provided is a method of treating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of a solid cancer in a mammalian subject in need thereof comprising co-administering to the subject an effective amount of: (a) radiation therapy (RT) focally-delivered to the solid cancer; and (b) magrolimab. In some embodiments, the solid cancer is a non-irradiated tumor. In some embodiments, the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT. In some embodiments, the RT is focally-delivered via a technique selected from microbeam radiation therapy (MRT), external beam radiation therapy (EBRT), internal radiotherapy (brachytherapy), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic ablative radiation therapy (SABR), low-dose stereotactic body radiation (SBRT), preoperative RT, intra-operative radiation therapy (IORT), postoperative RT (PORT), pulsed low-dose rate radiation therapy, and combinations thereof. In some embodiments, the RT dose is a dose sufficient to induce abscopal effect (i.e., reduction or elimination of non-irradiated tumors). In some embodiments, the RT dose is a maximum dose tolerated by the subject. In some embodiments, the RT dose is fractionated over multiple administrations. In some embodiments, the RT dose is hypofractionated or ultrahypofractionated. In some embodiments, administration of the RT and the agent that inhibits binding between CD47 and SIRPα are alternated over multiple administrations. In some embodiments, the RT and the agent that inhibits binding between CD47 and SIRPα are administered according to a regimen that entails first administering the agent that inhibits binding between CD47 and SIRPα. In some embodiments, the solid cancer is selected from an epithelial carcinoma, a squamous cell carcinoma, a sarcoma and a brain cancer. In some embodiments, the cancer is selected from lung cancer, colorectal cancer, head and neck cancer, glioblastoma, prostate cancer, pancreatic cancer, breast cancer, liver cancer, testicular cancer, nasopharyngeal cancer, stomach cancer, urinary tract cancer, urothelial cancer, bladder cancer, renal cancer, ovarian cancer, uterine cancer and esophageal cancer. In some embodiments, the

cancer is (i) unresectable, locally advanced or (ii) metastatic. In some embodiments, the cancer has progressed after the subject has received a course of an immune checkpoint inhibitor. In some embodiments, the cancer has progressed after administration of the subject has received a course of a platinum coordination complex therapy. In some embodiments, the cancer is unresectable, locally advanced and the subject is treatment naïve. In some embodiments, the cancer is a lung cancer selected from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In some embodiments, the cancer is a colorectal cancer. In some embodiments, the treatment results in a reduction in overall tumor burden of at least 15%, at least 20%, at least 30%, or at least 40%, as determined using linear dimensional methods (*e.g.*, RECIST v1.1). In some embodiments, the method comprises reducing in size or eliminating the metastases. In some embodiments, the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT. In some embodiments, the cancer has cell surface expression of CD47. In some embodiments, the magrolimab and the focally-delivered RT are administered in a combined synergistic amount. In some embodiments, administration of the magrolimab and the focally-delivered RT provides a synergistic effect. In some embodiments, the synergistic effect is increased cancer cell death and/or decreased cancer cell growth when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone. In some embodiments, the synergistic effect is increased phagocytosis of cancer cells by macrophages when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone. In some embodiments, the synergistic effect is increased or enhanced tumor burden reduction when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone. In some embodiments, the magrolimab is administered before the focally-delivered RT. In some embodiments, the magrolimab is first administered at a priming dose of 0.5 mg/kg to 10 mg/kg and then administered at one or more therapeutic doses of at least 15 mg/kg, e.g., at least 20 mg/kg, 30 mg/kg, 45 mg/kg, 60 mg/kg. In some embodiments, the magrolimab is first administered at a priming dose of 0.5 mg/kg to 5 mg/kg and then administered at one or more therapeutic doses of at least 20 mg/kg, e.g., 30 mg/kg, 45 mg/kg, 60 mg/kg. In some embodiments, the magrolimab is first administered at a priming dose of 1 mg/kg and then administered at one or more therapeutic doses of at least 20 mg/kg, e.g., 30 mg/kg, 45 mg/kg, 60 mg/kg. In some embodiments, the magrolimab is (1) administered at a priming dose of 1 mg/kg at week 1, (2) administered weekly (Q1W) at a dose of 30 mg/kg from week 2 to week 5, and (3) administered every 3 weeks (Q3W) at a dose of 60 mg/kg for week 6 and thereafter. In some embodiments, the magrolimab is (1) administered at a priming dose of 1 mg/kg at week 1, (2) administered weekly (Q1W) at a dose of 20 mg/kg from

week 2 to week 5, and (3) administered every 3 weeks (Q3W) at a dose of 45 mg/kg for week 6 and thereafter. In some embodiments, the subject is a human. In some embodiments, the method does not comprise further co-administering an immune checkpoint inhibitor. In some embodiments, an anti-PD-1 antibody is not co-administered.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Figures 1A-1B illustrate that focal radiotherapy combined with CD47 blockade induces tumor regression in mice bearing MC38 tumors. Subcutaneous MC38 tumors were generated on both flanks of C57BL6 and treated with isotype, anti-CD47 mAb (MIAP410), focal radiotherapy (2 Gray QD x3), or the combination as outlined in the diagram. The tumor height and width were recorded by a hand caliper and used to calculate mean tumor volume (n=8 group).

[0009] Figures 2A-2B illustrate that significant growth inhibition and regression was observed when CD47/SIRPα blockade was combined with focal radiotherapy (Figure 2A). Low dose fractionated radiotherapy did not impede the growth of non-irradiated tumors (Figure 2B).

[0010] Figures 3A-3D illustrate individual growth curves of the irradiated tumors are depicted and the number of tumor free (T.F.) mice is indicated.

[0011] Figure 4 illustrates the cytotoxic CD8+ lymphocytes are required for therapeutic efficacy. On the day of MC38 cell inoculation, CD8+ T cells were depleted by intraperitoneal administration of 25 mg/kg anti-CD8 antibody (clone 2.43) for three consecutive days. A 5 mg/kg dose was administered once a week to maintain low CD8 levels. Mice were treated with radiotherapy alone or combined with CD47-blockade as previously shown. Tumor growth was monitored for 3 weeks and a dependency of CD8+ T cells was evident as mice depleted for cytotoxic T cells failed to inhibit tumor growth.

[0012] Figures 5A-5F illustrate that high dose radiotherapy can induce abscopal immunity when combined with CD47-blockade. Subcutaneous MC38 tumors were generated on both flanks of C57BL6 and treated when the mean tumor volume reached 50-80 mm^3 with isotype, anti-CD47 mAb (MIAP410), focal radiotherapy (10 Gy, single dose) or the combination. The tumor height and width or the irradiated and non-irradiated tumors were recorded by a hand caliper and used to calculate mean tumor volume (n=8 group). The body weight was also recorded. Individual growth curves of the un-irradiated tumors are depicted in the bottom panel.

[0013] Figure 6 illustrates that an increase in draining lymph T-cell frequency and dendritic cell maturation in response to anti-CD47 and RT combination treatment. Draining lymph nodes from treated, tumor-bearing mice were isolated 7-days post-treatment and processed into a single-cell suspension. Cells were stained for markers for T-cell activation using fluorophore-conjugated antibodies and analyzed by flow cytometry. Each dot represents an induvial mouse. Significance test: Kruskal-Wallis one-way ANOVA. The bottom panel displays the expression of MHC-II in dendritic cells (DCs) across various treatments (n=5 mice).

[0014] Figure 7 illustrates that tumor-infiltrating myeloid cells are abundant and undergo polarization in response to anti-CD47 and RT combination treatment. Subcutaneous MC38 tumors were excised from mice 7-days post-treatment and were mechanically and enzymatically digested into single-cell suspensions. Cells were then stained for various myeloid markers using fluorophore-conjugated antibodies and analyzed by flow cytometry. Each dot represents an individual mouse. Significance test: Kruskal-Wallis one-way ANOVA.

[0015] Figure 8 illustrates a volcano plot displaying differentially expressed genes in combo-treated mice relative to radiotherapy. Volcano plot displays each gene's –log10(p-value) and log2 fold change with the selected covariate (combo vs RT). The log ratio of the fold change is on the X axis, and the negative log of the p-value is on the Y axis. Each dot represents a gene within the comparison performed.

DETAILED DESCRIPTION

1. Introduction

[0016] Provided are methods of treating, ameliorating, mitigating, or preventing or delaying the growth, proliferation, recurrence or metastasis of, a cancer in a subject comprising administering: (a) an agent that inhibits binding between CD47 and SIRPα; and (b) focally delivered ionizing radiation therapy to the subject. Surprisingly, it has been found that co-administering an agent that inhibits binding between CD47 and SIRPα; and focally delivered ionizing radiation therapy to a subject in need thereof results in more than additive (*i.e.*, synergistic) reduction of solid tumor growth in the subject.

2. Agent that Inhibits Binding Between CD47 and SIRPα

a. Antibody or Antigen-Binding Fragment Thereof that Binds to CD47

[0017] In various embodiments, the agent that inhibits binding between CD47 and SIRPα is an antibody or antigen-binding fragment thereof that binds to CD47 (*a.k.a.*, IAP,

MER6, OA3; NCBI Gene ID: 961; UniProt Q08722). In various embodiments, an antibody that binds to CD47 has an Fc having effector function. In various embodiments, an antibody that binds to CD47 is an IgG4 or an IgG1. Examples of anti-CD47 antibodies of use include without limitation magrolimab, lemzoparlimab, letaplimab, ligufalimab (AK117), zeripatamig, gentulizumab, AO-176, IBI-322, ZL-1201, IMC-002, SRF-231, CC-90002 (*a.k.a.*, INBRX-103), NI-1701 (*a.k.a.*, TG-1801), STI-6643 (Vx-1004), CNTO-7108, RCT-1938, RRx-001, DSP-107, VT-1021 and SGN-CD47M.

[0018] In various embodiments, the antibody targeting CD47 is a bi-specific antibody. Examples bi-specific antibodies targeting CD47, include without limitation zeripatamig (CD47/CD19), IBI-322 (CD47/PD-L1), IMM-0306 (CD47/CD20), TJ-L1C4 (CD47/PD-L1), HX-009 (CD47/PD-1), PMC-122 (CD47/PD-L1), PT-217, (CD47/DLL3), IMM-26011 (CD47/FLT3), IMM-0207 (CD47/VEGF), IMM-2902 (CD47/HER2), BH29xx (CD47/PD-L1), IMM-03 (CD47/CD20), IMM-2502 (CD47/PD-L1), HMBD-004B (CD47/BCMA), HMBD-004A (CD47/CD33). Examples of anti-CD47antibodies, such as IBI-188, TJC-4, SHR-1603, HLX-24, LQ-001, IMC-002, ZL-1201, IMM-01, B6H12, GenSci-059, TAY-018, PT-240, 1F8-GMCSF, SY-102 and KD-015.

[0019] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Kabat), respectively:

- SEQ ID NOs: 1, 2, 3, 4, 5 and 6;
- SEQ ID NOs: 7, 8, 9, 10, 11 and 12;
- SEQ ID NOs: 13, 14, 15, 16, 17, and 18;
- SEQ ID NOs: 19, 20, 21, 22, 23 and 24;
- SEQ ID NOs: 25, 20, 21, 22, 23 and 24;
- SEQ ID NOs: 26, 27, 28, 29, 30 and 31;
- SEQ ID NOs: 32, 33, 34, 35, 36 and 37 or
- SEQ ID NOs: 38, 39, 40, 41, 23 and 42.

[0020] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to IMGT), respectively:

- SEQ ID NOs: 43, 44, 45, 46, 47 and 6;
- SEQ ID NOs: 48, 49, 50, 51, 52 and 12;
- SEQ ID NOs: 53, 54, 55, 56, 57 and 18;

- SEQ ID NOs: 58, 59, 60, 61, 62 and 24;
- SEQ ID NOs: 63, 59, 60, 61, 62 and 24;
- SEQ ID NOs: 64, 65, 66, 67, 68 and 31;
- SEQ ID NOs: 69, 70, 71, 72, 73 and 37; or
- SEQ ID NOs: 74, 75, 76, 77, 62 and 42.

[0021] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Chothia), respectively:

- SEQ ID NOs: 78, 79, 80, 81, 47 and 82;
- SEQ ID NOs: 83, 84, 85, 86, 52 and 87;
- SEQ ID NOs: 88, 89, 90, 91, 57 and 92;
- SEQ ID NOs: 93, 94, 95, 96, 62 and 97;
- SEQ ID NOs: 98, 94, 95, 96, 62 and 97;
- SEQ ID NOs: 99, 100, 101, 102, 68 and 103;
- SEQ ID NOs: 99, 104, 105, 106, 73 and 107; or
- SEQ ID NOs: 108, 109, 110, 111, 62 and 112.

[0022] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Honegger), respectively:

- SEQ ID NOs: 113, 114, 115, 116, 117 and 82;
- SEQ ID NOs: 118, 119, 120, 121, 122 and 87;
- SEQ ID NOs: 123, 124, 125, 126, 127 and 92;
- SEQ ID NOs: 128, 129, 130, 131, 132 and 97;
- SEQ ID NOs: 133, 129, 130, 131, 132 and 97;
- SEQ ID NOs: 134, 135, 136, 137, 138 and 103;
- SEQ ID NOs: 139, 140, 141, 142, 143 and 144; or
- SEQ ID NOs: 145, 146, 147, 148, 132 and 149.

[0023] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 1, 2, 3, 4, 5 and 6 (according to Kabat);
- SEQ ID NOs: 43, 44, 45, 46, 47 and 6 (according to IMGT);

- SEQ ID NOs: 78, 79, 80, 81, 47 and 82 (according to Chothia); or
- SEQ ID NOs: 113, 114, 115, 116, 117 and 82 (according to Honegger).

[0024] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 7, 8, 9, 10, 11 and 12 (according to Kabat);
- SEQ ID NOs: 48, 49, 50, 51, 52 and 12 (according to IMGT);
- SEQ ID NOs: 83, 84, 85, 86, 52 and 87 (according to Chothia); or
- SEQ ID NOs: 118, 119, 120, 121, 122 and 87 (according to Honegger).

[0025] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 13, 14, 15, 16, 17, and 18 (according to Kabat);
- SEQ ID NOs: 53, 54, 55, 56, 57 and 18 (according to IMGT);
- SEQ ID NOs: 88, 89, 90, 91, 57 and 92 (according to Chothia); or
- SEQ ID NOs: 123, 124, 125, 126, 127 and 92 (according to Honegger).

[0026] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 19, 20, 21, 22, 23 and 24 (according to Kabat);
- SEQ ID NOs: 58, 59, 60, 61, 62 and 24 (according to IMGT);
- SEQ ID NOs: 93, 94, 95, 96, 62 and 97 (according to Chothia); or
- SEQ ID NOs: 128, 129, 130, 131, 132 and 97 (according to Honegger).

[0027] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 25, 20, 21, 22, 23 and 24 (according to Kabat);
- SEQ ID NOs: 63, 59, 60, 61, 62 and 24 (according to IMGT);
- SEQ ID NOs: 98, 94, 95, 96, 62 and 97 (according to Chothia); or
- SEQ ID NOs: 133, 129, 130, 131, 132 and 97 (according to Honegger).

[0028] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 26, 27, 28, 29, 30 and 31 (according to Kabat);
- SEQ ID NOs: 64, 65, 66, 67, 68 and 31 (according to IMGT);
- SEQ ID NOs: 99, 100, 101, 102, 68 and 103 (according to Chothia); or
- SEQ ID NOs: 139, 140, 141, 142, 143 and 144 (according to Honegger).

[0029] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 32, 33, 34, 35, 36 and 37 (according to Kabat);
- SEQ ID NOs: 69, 70, 71, 72, 73 and 37 (according to IMGT);
- SEQ ID NOs: 99, 104, 105, 106, 73 and 107 (according to Chothia); or
- SEQ ID NOs: 247, 248, 249, 239, 250 and 251 (according to Honegger).

[0030] In various embodiments, the antibody targeting CD47 comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 38, 39, 40, 41, 23 and 42 (according to Kabat);
- SEQ ID NOs: 74, 75, 76, 77, 62 and 42 (according to IMGT);
- SEQ ID NOs: 108, 109, 110, 111, 62 and 112 (according to Chothia); or
- SEQ ID NOs: 145, 146, 147, 148, 132 and 149 (according to Honegger).

[0031] In various embodiments, the antibody targeting CD47 comprises a VH and a VL comprising the amino acid sequences set forth, respectively, or comprise amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively, in:

- SEQ ID NOs: 150 and 151;
- SEQ ID NOs: 152 and 153;
- SEQ ID NOs: 154 and 155;
- SEQ ID NOs: 156 and 157;
- SEQ ID NOs: 158 and 159;
- SEQ ID NOs: 160 and 161;

- SEQ ID NOs: 162 and 163; or
- SEQ ID NOs: 164 and 165. Sequence identity can be determined according to the BLAST algorithm (blast.ncbi.nlm.nih.gov/Blast.cgi), using default settings.

[0032] Amino acid sequences of CDRs and variable regions (VH/VL) of illustrative anti-CD47 antibodies that can be used in the present methods are described in Tables A1, A2, A3, A4 and B.

TABLE A1 – CDRs for illustrative anti-CD47 binding antibodies (Kabat)

Ab Name	VH – CDR1	VH – CDR2	VH – CDR3	VL – CDR1	VL – CDR2	VL – CDR3
1	NYNMH SEQ ID NO:1	TIYPGNDDTSYNQKFKD SEQ ID NO:2	GGYRAMDY SEQ ID NO:3	RSSQSIVYSNGNTYLG SEQ ID NO:4	KVSNRFS SEQ ID NO:5	FQGSHVPYT SEQ ID NO:6
2	DYYIN SEQ ID NO:7	RIYPGIGNTYYNKKFKG SEQ ID NO:8	GHYGRGMDY SEQ ID NO:9	KSSQSLLNSIDQKNYLA SEQ ID NO:10	FASTKES SEQ ID NO:11	QQHYSTPWT SEQ ID NO:12
3	RAWMN SEQ ID NO:13	RIKRKTDGETTDYAAPV KG SEQ ID NO:14	SNRAFDI SEQ ID NO:15	KSSQSVLYAGNNRNYLA SEQ ID NO:16	QASTRAS SEQ ID NO:17	QQYYTPPLA SEQ ID NO:18
4	SYYWSW SEQ ID NO:19	YIYYSGSTNYNPSLKS SEQ ID NO:20	GKTGSAA SEQ ID NO:21	RASQGISRWLA SEQ ID NO:22	AASSLQS SEQ ID NO:23	QQTVSFPIT SEQ ID NO:24
5	HYYWS SEQ ID NO:25	YIYYSGSTNYNPSLKS SEQ ID NO:20	GKTGSAA SEQ ID NO:21	RASQGISRWLA SEQ ID NO:22	AASSLQS SEQ ID NO:23	QQTVSFPIT SEQ ID NO:24
6	SYWMN SEQ ID NO:26	MIDPSDSETHNAQKFQG SEQ ID NO:27	LYRWYFDV SEQ ID NO:28	RASEIVGTYVS SEQ ID NO:29	GASNRYT SEQ ID NO:30	GQSYNFPYT SEQ ID NO:31
7	SYYMH SEQ ID NO:32	IINPSGGSTSYAQKFQG SEQ ID NO:33	STLWFSEFDY SEQ ID NO:34	SGTSSDVGGHNYVS SEQ ID NO:35	DVTKRPS SEQ ID NO:36	LSYAGSRVY SEQ ID NO:37
8	SYAMS SEQ ID NO:38	AISGSGGSTYYADSVKG SEQ ID NO:39	SYGAFDY SEQ ID NO:40	RASQSISSYLN SEQ ID NO:41	AASSLQS SEQ ID NO:23	QQMHPRAPKT SEQ ID NO:42

TABLE A2 – CDRs for illustrative anti-CD47 binding antibodies (IMGT)						
Ab Name	**VH – CDR1**	**VH – CDR2**	**VH – CDR3**	**VL – CDR1**	**VL – CDR2**	**VL – CDR3**
9	GYTFTNYN SEQ ID NO:43	IYPGNDDT SEQ ID NO:44	ARGGYRAMDY SEQ ID NO:45	QSIVYSNGNTY SEQ ID NO:46	KVS SEQ ID NO:47	FQGSHVPYT SEQ ID NO:6
10	GYSFTDYY SEQ ID NO:48	IYPGIGNT SEQ ID NO:49	ARGHYGRGMDY SEQ ID NO:50	QSLLNSIDQKNY SEQ ID NO:51	FAS SEQ ID NO:52	QQHYSTPWT SEQ ID NO:12
11	GLTFERAW SEQ ID NO:53	IKRKTDGETT SEQ ID NO:54	AGSNRAFDI SEQ ID NO:55	QSVLYAGNNRNY SEQ ID NO:56	QAS SEQ ID NO:57	QQYYTPPLA SEQ ID NO:18
12	GGSISSYY SEQ ID NO:58	IYYSGST SEQ ID NO:59	ARGKTGSAA SEQ ID NO:60	QGISRW SEQ ID NO:61	AAS SEQ ID NO:62	QQTVSFPIT SEQ ID NO:24
13	GGSIEHYY SEQ ID NO:63	IYYSGST SEQ ID NO:59	ARGKTGSAA SEQ ID NO:60	QGISRW SEQ ID NO:61	AAS SEQ ID NO:62	QQTVSFPIT SEQ ID NO:24
14	GYTFTSYW SEQ ID NO:64	IDPSDSET SEQ ID NO:65	ARLYRWYFDV SEQ ID NO:66	EIVGTY SEQ ID NO:67	GAS SEQ ID NO:68	GQSYNFPYT SEQ ID NO:31
15	GYTFTSYY SEQ ID NO:69	INPSGGST SEQ ID NO:70	ARSTLWFSEFDY SEQ ID NO:71	SSDVGGHNY SEQ ID NO:72	DVT SEQ ID NO:73	LSYAGSRVY SEQ ID NO:37
16	GFTFSSYA SEQ ID NO:74	ISGSGGST SEQ ID NO:75	AKSYGAFDY SEQ ID NO:76	QSISSY SEQ ID NO:77	AAS SEQ ID NO:62	QQMHPRAPKT SEQ ID NO:42

TABLE A3 – CDRs for illustrative anti-CD47 binding antibodies (Chothia)						
Ab Name	**VH – CDR1**	**VH – CDR2**	**VH – CDR3**	**VL – CDR1**	**VL – CDR2**	**VL – CDR3**
17	GYTFTNY SEQ ID NO:78	PGND SEQ ID NO:79	GYRAMD SEQ ID NO:80	SQSIVYSNGNTY SEQ ID NO:81	KVS SEQ ID NO:47	GSHVPY SEQ ID NO:82
18	GYSFTDY SEQ ID NO:83	PGIG SEQ ID NO:84	HYGRGMD SEQ ID NO:85	SQSLLNSIDQKNY SEQ ID NO:86	FAS SEQ ID NO:52	HYSTPW SEQ ID NO:87
19	GLTFERA SEQ ID NO:88	RKTDGE SEQ ID NO:89	NRAFD SEQ ID NO:90	SQSVLYAGNNRNY SEQ ID NO:91	QAS SEQ ID NO:57	YYTPPL SEQ ID NO:92
20	GGSISSY SEQ ID NO:93	YSG SEQ ID NO:94	KTGSA SEQ ID NO:95	SQGISRW SEQ ID NO:96	AAS SEQ ID NO:62	TVSFPI SEQ ID NO:97
21	GGSIEHY	YSG	KTGSA	SQGISRW	AAS	TVSFPI

TABLE A3 – CDRs for illustrative anti-CD47 binding antibodies (Chothia)						
Ab Name	**VH – CDR1**	**VH – CDR2**	**VH – CDR3**	**VL – CDR1**	**VL – CDR2**	**VL – CDR3**
	SEQ ID NO:98	SEQ ID NO:94	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:62	SEQ ID NO:97
22	GYTFTSY SEQ ID NO:99	PSDS SEQ ID NO:100	YRWYFD SEQ ID NO:101	SEIVGTY SEQ ID NO:102	GAS SEQ ID NO:68	SYNFPY SEQ ID NO:103
23	GYTFTSY SEQ ID NO:99	PSGG SEQ ID NO:104	TLWFSEFD SEQ ID NO:105	GTSSDVGGHNY SEQ ID NO:106	DVT SEQ ID NO:73	YAGSRV SEQ ID NO:107
24	GFTFSSY SEQ ID NO:108	GSGG SEQ ID NO:109	YGAFD SEQ ID NO:110	SQSISSY SEQ ID NO:111	AAS SEQ ID NO:62	MHPRAPK SEQ ID NO:112

TABLE A4 – CDRs for illustrative anti-CD47 binding antibodies (Honegger)						
Ab Name	**VH – CDR1**	**VH – CDR2**	**VH – CDR3**	**VL – CDR1**	**VL – CDR2**	**VL – CDR3**
25	ASGYTFTNYN SEQ ID NO:113	IYPGNDDTSYNQKFKDR SEQ ID NO:114	GGYRAMD SEQ ID NO:115	SSQSIVYSNGNTY SEQ ID NO:116	KVSNRFSGVPDR SEQ ID NO:117	GSHVPY SEQ ID NO:82
26	ASGYSFTDYY SEQ ID NO:118	IYPGIGNTYYNKKFKGR SEQ ID NO:119	GHYGRGMD SEQ ID NO:120	SSQSLLNSIDQKNY SEQ ID NO:121	FASTKESGVPDR SEQ ID NO:122	HYSTPW SEQ ID NO:87
27	ASGLTFERAW SEQ ID NO:123	IKRKTDGETTDYAAPVKGR SEQ ID NO:124	SNRAFD SEQ ID NO:125	SSQSVLYAGNNRNY SEQ ID NO:126	QASTRASGVPDR SEQ ID NO:127	YYTPPL SEQ ID NO:92
28	VSGGSISSYY SEQ ID NO:128	IYYSGSTNYNPSLKSR SEQ ID NO:129	GKTGSA SEQ ID NO:130	ASQGISRW SEQ ID NO:131	AASSLQSGVPSR SEQ ID NO:132	TVSFPI SEQ ID NO:97
29	VSGGSIEHYY SEQ ID NO:133	IYYSGSTNYNPSLKSR SEQ ID NO:129	GKTGSA SEQ ID NO:130	ASQGISRW SEQ ID NO:131	AASSLQSGVPSR SEQ ID NO:132	TVSFPI SEQ ID NO:97
30	ASGYTFTSYW SEQ ID NO:134	IDPSDSETHNAQKFQGK SEQ ID NO:135	LYRWYFD SEQ ID NO:136	ASEIVGTY SEQ ID NO:137	GASNRYTGVPAR SEQ ID NO:138	SYNFPY SEQ ID NO:103
31	ASGYTFTSYY SEQ ID NO:139	INPSGGSTSYAQKFQGR SEQ ID NO:140	STLWFSEFD SEQ ID NO:141	GTSSDVGGHNY SEQ ID NO:142	DVTKRPSGVPDR SEQ ID NO:143	YAGSRVY SEQ ID NO:144
32	ASGFTFSSYA SEQ ID NO:145	ISGSGGSTYYADSVKGR SEQ ID NO:146	SYGAFD SEQ ID NO:147	ASQSISSY SEQ ID NO:148	AASSLQSGVPSR SEQ ID NO:132	MHPRAPK SEQ ID NO:149

TABLE B - VH/VL for illustrative anti-CD47 binding antibodies

Ab Name	VH	VL
33	**SEQ ID NO:150** QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWVRQA PGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTSASTAY MELSSLRSEDTAVYYCARGGYRAMDYWGQGTLVTVSS	**SEQ ID NO:151** DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYL GWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIK
34	**SEQ ID NO:152** QVQLVQSGAEVKKPGASVKVSCKASGYSFTDYYINWVRQA PGQGLEWMGRIYPGIGNTYYNKKFKGRVTITRDTSASTAY MELSSLRSEDTAVYYCARGHYGRGMDYWGQGTLVTVSS	**SEQ ID NO:153** DIVMTQSPDSLAVSLGERATINCKSSQSLLNSIDQKNY LAWYQQKPGQPPKLLIYFASTKESGVPDRFSGSGSGTD FTLTISGLQAEDVAVYFCQQHYSTPWTFGGGTKVEIR
35	**SEQ ID NO:154** EVQLVESGGGLVKPGGSLRLSCAASGLTFERAWMNWVRQA PGKGLEWVGRIKRKTDGETTDYAAPVKGRFSISRDDSKNT LYLQMNSLKTEDTAVYYCAGSNRAFDIWGQGTMVTVSS	**SEQ ID NO:155** DIVMTQSPDSLAVSLGERATINCKSSQSVLYAGNNRNY LAWYQQKPGQPPKLLINQASTRASGVPDRFSGSGSGTE FTLIISSLQAEDVAIYYCQQYYTPPLAFGGGTKLEIK
36	**SEQ ID NO:156** QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQP PGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYCARGKTGSAAWGQGTLVTVSS	**SEQ ID NO:157** DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQTVSFPITFGGGTKVEIK
37	**SEQ ID NO:158** QVQLQESGPGLVKPSETLSLTCTVSGGSIEHYYWSWIRQP PGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYCARGKTGSAAWGQGTLVTVSS	**SEQ ID NO:159** DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQTVSFPITFGGGTKVEIK
38	**SEQ ID NO:160** QVQLVQSGAEVVKPGASVKLSCKASGYTFTSYWMNWVRQR PGQGLEWIGMIDPSDSETHNAQKFQGKATLTVDKSTSTAY MHLSSLRSEDTAVYYCARLYRWYFDVWGAGTTVTVSS	**SEQ ID NO:161** NIVMTQSPATMSMSPGERVTLSCRASEIVGTYVSWFQQ KPGQAPRLLIYGASNRYTGVPARFSGSGSGTDFTLTIS SVQPEDLADYHCGQSYNFPYTFGGGTKLEIK
39	**SEQ ID NO:162** QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQA PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARSTLWFSEFDYWGQGTLVTVSS	**SEQ ID NO:163** QSVLTQPSSVSASPGQSITISCSGTSSDVGGHNYVSWY QQHPGKAPKLMIYDVTKRPSGVPDRFSGSKSGNTASLT VSGLQAEDEADYYCLSYAGSRVYVFGTGTKLTVL
40	**SEQ ID NO:164**	**SEQ ID NO:165**

TABLE B - VH/VL for illustrative anti-CD47 binding antibodies

Ab Name	VH	VL
	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[0033] Additional anti-CD47 antibodies of use in the present methods include those described in WO199727873, WO199940940, WO2002092784, WO2005044857, WO2009046541, WO2010070047, WO2011143624, WO2012170250, WO2013109752, WO2013119714, WO2014087248, WO2015191861, WO2016022971, WO2016023040, WO2016024021, WO2016081423, WO2016109415, WO2016141328, WO2016188449, WO2017027422, WO2017049251, WO2017053423, WO2017121771, WO2017194634, WO2017196793, WO2017215585, WO2018075857, WO2018075960, WO2018089508, WO2018095428, WO2018137705, WO2018233575, WO2019027903, WO2019034895, WO2019042119, WO2019042285, WO2019042470, WO2019086573, WO2019108733, WO2019138367, WO2019144895, WO2019157843, WO2019179366, WO2019184912, WO2019185717, WO2019201236, WO2019238012, WO2019241732, WO2020019135, WO2020036977, WO2020043188 and WO2020009725.

b. Antibody or Antigen-Binding Fragment Thereof that Binds to SIRPα

[0034] In various embodiments, the agent that inhibits binding between CD47 and SIRPα CD47 is an antibody or antigen-binding fragment thereof that binds to signal regulatory protein alpha (SIRPα) (NCBI Gene ID: 140885; UniProt P78324). Illustrative antibodies that bind to SIRPα include without limitation anzurstobart (*a.k.a.*, BMS-986351; CC-95251), GS-0189 (*a.k.a.*, FSI-189), BI-765063, APX-700, ES-004, BI765063 and ADU1805.

[0035] In certain embodiments, an antibody can comprise one or more CDRs of 1H9. In some embodiments, an antibody can comprise all CDRs of 1H9. In some embodiments, an antibody can comprise one or more variable sequences of 1H9. In some embodiments, an antibody can comprise each variable sequence of 1H9. In some embodiments, an antibody can comprise the heavy chain of 1H9. In some embodiments, an antibody can comprise the light chain of 1H9. In some embodiments, an antibody can comprise the heavy chain and the light chain of 1H9. In some embodiments, an antibody is 1H9.

[0036] In certain embodiments, an antibody can comprise one or more CDRs of 3C2. In some embodiments, an antibody can comprise all CDRs of 3C2. In some embodiments, an antibody can comprise one or more variable sequences of 3C2. In some embodiments, an antibody can comprise each variable sequence of 3C2. In some embodiments, an antibody can comprise the heavy chain of 3C2. In some embodiments, an antibody can comprise the light chain of 3C2. In some embodiments, an antibody can comprise the heavy chain and the light chain of 3C2. In some embodiments, an antibody is 3C2.

[0037] In some embodiments, an antibody can comprise one or more CDRs of 9B11. In some embodiments, an antibody can comprise all CDRs of 9B11. In some embodiments, an antibody can comprise one or more variable sequences of 9B11. In some embodiments, an antibody can comprise each variable sequence of 9B11. In some embodiments, an antibody can comprise the heavy chain of 9B11. In some embodiments, an antibody can comprise the light chain of 9B11. In some embodiments, an antibody can comprise the heavy chain and the light chain of 9B11. In some embodiments, an antibody is 9B11.

[0038] In some embodiments, an antibody can comprise one or more CDRs of 7E11. In some embodiments, an antibody can comprise all CDRs of 7E11. In some embodiments, an antibody can comprise one or more variable sequences of 7E11. In some embodiments, an antibody can comprise each variable sequence of 7E11. In some embodiments, an antibody can comprise the heavy chain of 7E11. In some embodiments, an antibody can comprise the light chain of 7E11. In some embodiments, an antibody can comprise the heavy chain and the light chain of 7E11. In some embodiments, an antibody is 7E11.

[0039] Additional anti-SIRPα antibodies of use in the present methods include those described in WO200140307, WO2002092784, WO2007133811, WO2009046541, WO2010083253, WO2011076781, WO2013056352, WO2015138600, WO2016179399, WO2016205042, WO2017178653, WO2018026600, WO2018057669, WO2018107058, WO2018190719, WO2018210793, WO2019023347, WO2019042470, WO2019175218, WO2019183266, WO2020013170, WO2020068752 and WO2020088580.

[0040] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Kabat), respectively:

- SEQ ID NOs: 166, 167, 168, 169, 170 and 171;
- SEQ ID NOs: 172, 173, 174, 175, 5 and 6;
- SEQ ID NOs: 172, 173, 176, 175, 5 and 177;
- SEQ ID NOs: 178, 179, 180, 181, 182 and 183;
- SEQ ID NOs: 184, 185, 186, 187, 188 and 189; or
- SEQ ID NOs: 190, 191, 192, 193, 194 and 195.

[0041] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to IMGT), respectively:

- SEQ ID NOs: 196, 197, 198, 199, 200 and 171;
- SEQ ID NOs: 196, 201, 202, 203, 47 and 6;
- SEQ ID NOs: 196, 201, 204, 203, 47 and 177;
- SEQ ID NOs: 205, 206, 207, 208, 209 and 183;
- SEQ ID NOs: 210, 201, 211, 212, 213 and 189; or
- SEQ ID NOs: 214, 215, 216, 217, 62 and 195.

[0042] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Chothia), respectively:

- SEQ ID NOs: 99, 218, 219, 220, 200 and 221;
- SEQ ID NOs: 99, 100, 222, 223, 47 and 82;
- SEQ ID NOs: 99, 100, 224, 223, 47 and 225;
- SEQ ID NOs: 226, 227, 228, 229, 209 and 230;
- SEQ ID NOs: 231, 100, 232, 233, 213 and 234; or
- SEQ ID NOs: 235, 236, 237, 238, 62 and 239.

[0043] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences (according to Honegger), respectively:

- SEQ ID NOs: 134, 240, 241, 242, 243 and 221;
- SEQ ID NOs: 134, 244, 245, 246, 117 and 82;
- SEQ ID NOs: 134, 247, 248, 246, 117 and 225;
- SEQ ID NOs: 249, 250, 251, 252, 253 and 230;
- SEQ ID NOs: 254, 255, 256, 257, 258 and 234; or
- SEQ ID NOs: 259, 260, 261, 262, 263 and 239.

[0044] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 166, 167, 168, 169, 170 and 171 (according to Kabat);
- SEQ ID NOs: 196, 197, 198, 199, 200 and 171 (according to IMGT);
- SEQ ID NOs: 99, 218, 219, 220, 200 and 221 (according to Chothia); or
- SEQ ID NOs: 134, 240, 241, 242, 243 and 221 (according to Honegger).

[0045] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 172, 173, 174, 175, 5 and 6 (according to Kabat);
- SEQ ID NOs: 196, 201, 202, 203, 47 and 6 (according to IMGT);
- SEQ ID NOs: 99, 100, 222, 223, 47 and 82 (according to Chothia); or
- SEQ ID NOs: 134, 244, 245, 246, 117 and 82 (according to Honegger).

[0046] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 172, 173, 176, 175, 5 and 177 (according to Kabat);
- SEQ ID NOs: 196, 201, 204, 203, 47 and 177 (according to IMGT);
- SEQ ID NOs: 99, 100, 224, 223, 47 and 225 (according to Chothia); or
- SEQ ID NOs: 134, 247, 248, 246, 117 and 225 (according to Honegger).

[0047] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 178, 179, 180, 181, 182 and 183 (according to Kabat);
- SEQ ID NOs: 205, 206, 207, 208, 209 and 183 (according to IMGT);
- SEQ ID NOs: 226, 227, 228, 229, 209 and 230 (according to Chothia); or
- SEQ ID NOs: 249, 250, 251, 252, 253 and 230 (according to Honegger).

[0048] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 184, 185, 186, 187, 188 and 189 (according to Kabat);
- SEQ ID NOs: 210, 201, 211, 212, 213 and 189 (according to IMGT);
- SEQ ID NOs: 231, 100, 232, 233, 213 and 234 (according to Chothia); or
- SEQ ID NOs: 254, 255, 256, 257, 258 and 234 (according to Honegger).

[0049] In various embodiments, the antibody targeting SIRPα comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2 and a VL-CDR3 comprising the following amino acid sequences, respectively:

- SEQ ID NOs: 190, 191, 192, 193, 194 and 195 (according to Kabat);
- SEQ ID NOs: 214, 215, 216, 217, 62 and 195 (according to IMGT);
- SEQ ID NOs: 235, 236, 237, 238, 62 and 239 (according to Chothia); or
- SEQ ID NOs: 259, 260, 261, 262, 263 and 239 (according to Honegger).

[0050] In various embodiments, the antibody targeting SIRPα comprises a VH and a VL comprising the amino acid sequences set forth, respectively, or comprise amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively, in:

- SEQ ID NOs: 264 and 265;
- SEQ ID NOs: 266 and 267;
- SEQ ID NOs: 268 and 269;
- SEQ ID NOs: 270 and 271;
- SEQ ID NOs: 272 and 273; or
- SEQ ID NOs: 274 and 275. Sequence identity can be determined according to the BLAST algorithm (blast.ncbi.nlm.nih.gov/Blast.cgi), using default settings.

[0051] Amino acid sequences of CDRs and variable regions (VH/VL) of illustrative anti-SIRPα antibodies that can be used in the present methods are described in Tables C1, C2, C3, C4 and D.

TABLE C1 – CDRs for illustrative anti-SIRPα binding antibodies (Kabat)

Ab Name	VH – CDR1	VH – CDR2	VH – CDR3	VL – CDR1	VL – CDR2	VL – CDR3
41	SYWIT SEQ ID NO:166	DIYPGSGSTNHIEKFKS SEQ ID NO:167	GYGSSYGYFDY SEQ ID NO:168	RASENIYSYLA SEQ ID NO:169	TAKTLAE SEQ ID NO:170	QHQYGPPFT SEQ ID NO:171
42	SYWMH SEQ ID NO:172	NIDPSDSDTHYNQKFKD SEQ ID NO:173	GYSKYYAMDY SEQ ID NO:174	RSSQSIVHSYGNTYLE SEQ ID NO:175	KVSNRFS SEQ ID NO:5	FQGSHVPYT SEQ ID NO:6
43	SYWMH SEQ ID NO:172	NIDPSDSDTHYNQKFKD SEQ ID NO:173	YGNYGENAMDY SEQ ID NO:176	RSSQSIVHSYGNTYLE SEQ ID NO:175	KVSNRFS SEQ ID NO:5	FQGSHVPFT SEQ ID NO:177
44	DYYIH SEQ ID NO:178	RIDPEDGETKYAPKFQG SEQ ID NO:179	GGFAY SEQ ID NO:180	ASSSVSSSYLY SEQ ID NO:181	STSNLAS SEQ ID NO:182	HQWSSHPYT SEQ ID NO:183
45	SYWVH SEQ ID NO:184	NIDPSDSDTHYSPSFQG SEQ ID NO:185	GGTGTLAYFAY SEQ ID NO:186	RSSQSLVHSYGNTYLY SEQ ID NO:187	RVSNRFS SEQ ID NO:188	FQGTHVPYT SEQ ID NO:189
46	GYGIS SEQ ID NO:190	WISAYGGETNYAQKLQG SEQ ID NO:191	EAGSSWYDFDL SEQ ID NO:192	RASQGISSWLA SEQ ID NO:193	AASNLQS SEQ ID NO:194	QQGASFPIT SEQ ID NO:195

TABLE C2 – CDRs for illustrative anti-SIRPα binding antibodies (IMGT)

Ab Name	VH – CDR1	VH – CDR2	VH – CDR3	VL – CDR1	VL – CDR2	VL – CDR3
47	GYTFTSYW SEQ ID NO:196	IYPGSGST SEQ ID NO:197	ATGYGSSYGYFDY SEQ ID NO:198	ENIYSY SEQ ID NO:199	TAK SEQ ID NO:200	QHQYGPPFT SEQ ID NO:171
48	GYTFTSYW SEQ ID NO:196	IDPSDSDT SEQ ID NO:201	ARGYSKYYAMDY SEQ ID NO:202	QSIVHSYGNTY SEQ ID NO:203	KVS SEQ ID NO:47	FQGSHVPYT SEQ ID NO:6
49	GYTFTSYW	IDPSDSDT	ASYGNYGENAMDY	QSIVHSYGNTY	KVS	FQGSHVPFT

TABLE C2 - CDRs for illustrative anti-SIRPα binding antibodies (IMGT)

Ab Name	VH - CDR1	VH - CDR2	VH - CDR3	VL - CDR1	VL - CDR2	VL - CDR3
	SEQ ID NO:196	SEQ ID NO:201	SEQ ID NO:204	SEQ ID NO:203	SEQ ID NO:47	SEQ ID NO:177
50	GFNIKDYY SEQ ID NO:205	IDPEDGET SEQ ID NO:206	AKGGFAY SEQ ID NO:207	SSVSSSY SEQ ID NO:208	STS SEQ ID NO:209	HQWSSHPYT SEQ ID NO:183
51	GYSFTSYW SEQ ID NO:210	IDPSDSDT SEQ ID NO:201	VRGGTGTLAYFAY SEQ ID NO:211	QSLVHSYGNTY SEQ ID NO:212	RVS SEQ ID NO:213	FQGTHVPYT SEQ ID NO:189
52	GYTFRGYG SEQ ID NO:214	ISAYGGET SEQ ID NO:215	AREAGSSWYDFDL SEQ ID NO:216	QGISSW SEQ ID NO:217	AAS SEQ ID NO:62	QQGASFPIT SEQ ID NO:195

TABLE C3 - CDRs for illustrative anti-SIRPα binding antibodies (Chothia)

Ab Name	VH - CDR1	VH - CDR2	VH - CDR3	VL - CDR1	VL - CDR2	VL - CDR3
53	GYTFTSY SEQ ID NO:99	PGSG SEQ ID NO:218	YGSSYGYFD SEQ ID NO:219	SENIYSY SEQ ID NO:220	TAK SEQ ID NO:200	QYGPPF SEQ ID NO:221
54	GYTFTSY SEQ ID NO:99	PSDS SEQ ID NO:100	YSKYYAMD SEQ ID NO:222	SQSIVHSYGNTY SEQ ID NO:223	KVS SEQ ID NO:47	GSHVPY SEQ ID NO:82
55	GYTFTSY SEQ ID NO:99	PSDS SEQ ID NO:100	GNYGENAMD SEQ ID NO:224	SQSIVHSYGNTY SEQ ID NO:223	KVS SEQ ID NO:47	GSHVPF SEQ ID NO:225
56	GFNIKDY SEQ ID NO:226	PEDG SEQ ID NO:227	GFA SEQ ID NO:228	SSSVSSSY SEQ ID NO:229	STS SEQ ID NO:209	WSSHPY SEQ ID NO:230
57	GYSFTSY SEQ ID NO:231	PSDS SEQ ID NO:100	GTGTLAYFA SEQ ID NO:232	SQSLVHSYGNTY SEQ ID NO:233	RVS	GTHVPY SEQ ID NO:234

TABLE C3 - CDRs for illustrative anti-SIRPα binding antibodies (Chothia)

Ab Name	VH - CDR1	VH - CDR2	VH - CDR3	VL - CDR1	VL - CDR2	VL - CDR3
					SEQ ID NO:213	
58	GYTFRGY SEQ ID NO:235	AYGG SEQ ID NO:236	AGSSWYDFD SEQ ID NO:237	SQGISSW SEQ ID NO:238	AAS SEQ ID NO:62	GASFPI SEQ ID NO:239

TABLE C4 - CDRs for illustrative anti-SIRPα binding antibodies (Honegger)

Ab Name	VH - CDR1	VH - CDR2	VH - CDR3	VL - CDR1	VL - CDR2	VL - CDR3
59	ASGYTFTSYW SEQ ID NO:134	IYPGSGSTNHIEKFKSK SEQ ID NO:240	GYGSSYGYFD SEQ ID NO:241	ASENIYSY SEQ ID NO:242	TAKTLAEGVPSR SEQ ID NO:243	QYGPPF SEQ ID NO:221
60	ASGYTFTSYW SEQ ID NO:134	IDPSDSDTHYNQKFKDR SEQ ID NO:244	GYSKYYAMD SEQ ID NO:245	SSQSIVHSYGNTY SEQ ID NO:246	KVSNRFSGVPDR SEQ ID NO:117	GSHVPY SEQ ID NO:82
61	ASGYTFTSYW SEQ ID NO:134	IDPSDSDTHYNQKFKDK SEQ ID NO:247	YGNYGENAMD SEQ ID NO:248	SSQSIVHSYGNTY SEQ ID NO:246	KVSNRFSGVPDR SEQ ID NO:117	GSHVPF SEQ ID NO:225
62	ASGFNIKDYY SEQ ID NO:249	IDPEDGETKYAPKFQGK SEQ ID NO:250	GGFA SEQ ID NO:251	ASSSVSSSY SEQ ID NO:252	STSNLASGVPAR SEQ ID NO:253	WSSHPY SEQ ID NO:230
63	ASGYSFTSYW SEQ ID NO:254	IDPSDSDTHYSPSFQGH SEQ ID NO:255	GGTGTLAYFA SEQ ID NO:256	SSQSLVHSYGNTY SEQ ID NO:257	RVSNRFSGVPDR SEQ ID NO:258	GTHVPY SEQ ID NO:234
64	ASGYTFRGYG SEQ ID NO:259	ISAYGGETNYAQKLQGR SEQ ID NO:260	EAGSSWYDFD SEQ ID NO:261	ASQGISSW SEQ ID NO:262	AASNLQSGVPSR SEQ ID NO:263	GASFPI SEQ ID NO:239

TABLE D – VH/VL for illustrative anti-SIRPα binding antibodies

Ab Name	VH	VL
65	**SEQ ID NO:264** QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWITWVKQAP GQGLEWIGDIYPGSGSTNHIEKFKSKATLTVDTSISTAYME LSRLRSDDTAVYYCATGYGSSYGYFDYWGQGTLVTVSS	**SEQ ID NO:265** DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQ KPGKAPKLLIYTAKTLAEGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQHQYGPPFTFGQGTKLEIK
66	**SEQ ID NO:266** QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAP GQGLEWMGNIDPSDSDTHYNQKFKDRVTMTRDTSTSTVYME LSSLRSEDTAVYYCARGYSKYYAMDYWGQGTLVTVSS	**SEQ ID NO:267** DIVMTQTPLSLSVTPGQPASISCRSSQSIVHSYGNTYL EWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIK
67	**SEQ ID NO:268** QVKLQESGAELVRPGSSVKLSCKASGYTFTSYWMHWVKQRP IQGLEWIGNIDPSDSDTHYNQKFKDKATLTVDNSSSTAYMQ LSSLTSEDSAVYYCASYGNYGENAMDYWGQGTSVTVSS	**SEQ ID NO:269** DILMTQTPLSLPVSLGDQASISCRSSQSIVHSYGNTYL EWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDLGVYYCFQGSHVPFTFGSGTKLEIK
68	**SEQ ID NO:270** EVQLQQSGAELVKPGASVKLSCTASGFNIKDYYIHWVKQRT EQGLEWIGRIDPEDGETKYAPKFQGKATITADTSSNTAYLQ LNSLTSEDTAVYSCAKGGFAYWGQGTLVTVSA	**SEQ ID NO:271** QIVLTQSPAIMSASPGEKVTLTCSASSSVSSSYLYWYQ QKPGSSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTI SSMEAEDAASYFCHQWSSHPYTFGGGTKLEIK
69	**SEQ ID NO:272** EVQLVQSGAEVKKPGESLRISCKASGYSFTSYWVHWVRQMP GKGLEWMGNIDPSDSDTHYSPSFQGHVTLSVDKSISTAYLQ LSSLKASDTAMYYCVRGGIGTLAYFAYWGQGTLVTVSS	**SEQ ID NO:273** DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSYGNTYL YWFQQRPGQSPRLLIYRVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQGTHVPYTFGGGTKVEIK
70	**SEQ ID NO:274** QVQLVQSGAEVKKPGASVKVSCKASGYTFRGYGISWVRQAP GQGLEWMGWISAYGGETNYAQKLQGRVTMTTDTSTSTAYME LRSLRSDDTAVYYCAREAGSSWYDFDLWGRGTLVTVSS	**SEQ ID NO:275** DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQ KPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQGASFPITFGGGTKVEIK

c. SIRPα-Fc Fusion Protein

[0052] In various embodiments, the agent that inhibits binding between CD47 and SIRPα CD47 is a SIRPα-Fc fusion protein or a "high affinity SIRPα reagent", which includes SIRPα-derived polypeptides and analogs thereof. High affinity SIRPα reagents are described in international application WO2013109752A1, which is hereby specifically incorporated by reference. High affinity SIRPα reagents are variants of the native SIRPα protein. In some embodiments, a high affinity SIRPα reagent is soluble, where the polypeptide lacks the SIRPα transmembrane domain and comprises at least one amino acid change relative to the wild-type SIRPα sequence, and wherein the amino acid change increases the affinity of the SIRPα polypeptide binding to CD47, for example by decreasing the off-rate by at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, at least 500-fold, or more.

[0053] A high affinity SIRPα reagent comprises the portion of SIRPα that is sufficient to bind CD47 at a recognizable affinity, *e.g.*, high affinity, which normally lies between the signal sequence and the transmembrane domain, or a fragment thereof that retains the binding activity. The high affinity SIRPα reagent will usually comprise at least the d1 domain of SIRPα with modified amino acid residues to increase affinity. In some embodiments, a SIRPα variant is a fusion protein, *e.g.*, fused in frame with a second polypeptide. In some embodiments, the second polypeptide is capable of increasing the size of the fusion protein, *e.g.*, so that the fusion protein will not be cleared from the circulation rapidly. In some embodiments, the second polypeptide is part or whole of an immunoglobulin Fc region. The Fc region aids in phagocytosis by providing an "eat me" signal, which enhances the block of the "don't eat me" signal provided by the high affinity SIRPα reagent. In other embodiments, the second polypeptide is any suitable polypeptide that is substantially similar to Fc, *e.g.*, providing increased size, multimerization domains, and/or additional binding or interaction with Ig molecules. The amino acid changes that provide for increased affinity are localized in the d1 domain, and thus high affinity SIRPα reagents comprise a d1 domain of human SIRPα, with at least one amino acid change relative to the wild-type sequence within the d1 domain. Such a high affinity SIRPα reagent optionally comprises additional amino acid sequences, for example antibody Fc sequences; portions of the wild-type human SIRPα protein other than the d1 domain, including without limitation residues 150 to 374 of the native protein or fragments thereof, usually fragments contiguous with the d1 domain; and the like. High affinity SIRPα reagents may be monomeric or multimeric, *i.e.*, dimer, trimer, tetramer, *etc.*

[0054] Illustrative SIRPα-Fc fusion proteins of use include ALX-148 (*a.k.a.*, evorpacept, described in WO2013109752), timdarpacept, TTI-621 or maplirpacept (TTI-622) (described in WO2014094122), SIRPa-F8, JY002-M2G1(N297A), JMT601 (CPO107), SS002M91, SIRPalpha-lgG4-Fc-Fc, and hCD172a(SIRPa)-Fc-LIGHT.

3. Focally Delivered Ionizing Radiation Therapy

[0055] The methods entail administering focally-delivered (*e.g.*, directly to or aimed at the *in situ* location of a solid tumor) radiotherapy (RT) in a subject in need thereof. Numerous techniques for focally delivering RT are known and can be applied in the present methods. Illustrative methodologies for focally delivering RT that can be use include without limitation microbeam radiation therapy (MRT), external beam radiation therapy (EBRT), internal radiotherapy (brachytherapy), volumetric modulated arc therapy (VMAT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic ablative radiation therapy (SABR), stereotactic body radiation (SBRT), selective internal radiation therapy (SIRT), preoperative RT, intra-operative radiation therapy (IORT), postoperative RT (PORT), pulsed low-dose rate radiation therapy, and combinations thereof. *See, e.g.*, Song, *et al., Radiation Oncology* (2020) 15:192; Paly, *et al., Am J Clin Oncol* (2020) 43(10):748-751; Ibáñez, *et al., Med Phys.* (2021) 48(12):8089-8106; Donzelli, *et al., Phys Med Biol* (2018) 63(4):045013; and Bartzsch, *et al*, (2020) *Phys. Med. Biol.* 65 02TR01). The technique(s) of RT applied will depend on many factors, including *e.g.*, the type, size and location of tumor, the health of the patient and the professional judgment of the treating physician.

[0056] For example, in some embodiments, the subject has a soft tissue sarcoma, and a RT, *e.g.*, selected from neoadjuvant external beam RT (EBRT), preoperative RT, postoperative RT (PORT), intra-operative RT (IORT) and brachytherapy, is administered, *e.g.*, at a cumulative dose in the range of 8 to 80 Gray (Gy) (Devisetty, *et al., Int. J. Radiation Oncology Biol. Phys.* (2011) 80(3):779–786; Roeder and Krempien, *Radiation Oncology* (2017) 12:20; and Lam, *et al., Curr. Treat. Options in Oncol.* (2021) 22:75).

[0057] In some embodiments, the subject has prostate cancer, and a RT, *e.g.*, selected from EBRT, image-guided RT (IGRT) and brachytherapy, is administered, *e.g.*, at a cumulative dose in the range of 3500 centiGray (cGy) to 145 Gy (Morgan, *et al., Practical Radiation Oncology* (2018) 8, 354-360; Li, *et al., Acta Oncologica*, 60:10, 1291-1295; and Kubo *et al., J Med Case Reports* (2021) 15:296).

[0058] In some embodiments, the subject has pancreatic cancer and a RT, *e.g.*, selected from stereotactic body radiation (SBRT), is administered, *e.g.*, using cone beam CT image (CBCT) guidance, *e.g.*, at a cumulative dose in the range of 100 to 200 Gy (Reyngold, *et al., Radiation Oncology* (2019) 14:95).

[0059] In some embodiments, the subject has small cell lung cancer (SCLC), and a RT, *e.g.*, selected from intensity-modulated RT (IMRT), consolidative thoracic RT and stereotactic ablative RT (SABR), is administered at a cumulative dose in the range of 30 Gy to 70 Gy, *e.g.*, at fractioned doses in the range of 2 to 3 Gy, *e.g.*, 45 or 66 Gy, *e.g.*, 45 Gy in 15 fractions; 45 Gy in 30 twice-daily fractions (accelerated fractionation) or 66 Gy in 33 daily fractions (standard fractionation) (Gensheimer, *et al.*, *Curr. Treat. Options in Oncol.* (2017) 18: 21; Welsh, *et al.*, *J Thorac Oncol.* (2020) 15(12):1919-1927, RAPTOR trial (NCT04402788)).

[0060] In some embodiments, the subject has non-small cell lung cancer (NSCLC), and a RT selected from, *e.g.*, stereotactic body radiation (SBRT), intensity-modulated RT (IMRT), consolidative thoracic RT and stereotactic ablative RT (SABR), is administered at a cumulative dose in the range of 24 Gy to 70 Gy, *e.g.*, at fractioned doses in the range of 2 to 10 Gy, *e.g.*, 24, 30, 45 or 50 Gy, *e.g.*, 24, 30 or 45 Gy in 3 fractions; 50 Gy in 4 or 5 fractions; 45 Gy in 15 fractions (Willemijn, *et al.*, *Lancet Respir Med* (2021) 9(5):467-475; PEMBRO-RT trial (NCT02492568); MDACC trial (NCT02444741); Bestvina, *et al.*, *J Thorac Oncol* (2022) 17(1):130-140; Schoenfeld, *et al.*, *Lancet Oncol* (2022) 23(2):279-291 (NCT02888743)).

[0061] In some embodiments, the subject has a head and neck cancer, and a RT, *e.g.*, selected from intensity-modulated RT (IMRT), external beam radiation therapy (EBRT), stereotactic body radiotherapy (SBRT), postoperative RT (PORT), brachytherapy, proton therapy and reirradiation, is administered at a cumulative dose in the range of 35 Gy to 82 Gy, *e.g.*, at fractioned doses in the range of 7 to 35 Gy, *e.g.*, 7, 9, 10, 12, 15, 16, 17, 25 or 35 Gy, (Alterio, *et al.*, *Semin Oncol* (2019) 46(3):233-245; Caudell, *et al.*, *Lancet Oncol* (2017) 18(5):e266-e273; Kim, *et al.*, *Curr Treat Options Oncol* (2018) 19(6):28; Swain, *et al.*, *Oral Oncol* (2021) 116:105265; Ortholan, *et al.*, *Cancer Radiother* (2018) 22(6-7):640-643; NCT02775812, NCT02952586, NCT02764593 and NCT02684253).

[0062] In some embodiments, the subject has colorectal cancer (CRC), *e.g.*, rectal cancer, adenomatous polyps, liver metastases of CRC, brain metastases of CRC, oligometastatic CRC and a RT, *e.g.*, selected from preoperative RT, selective internal RT (SIRT) and stereotactic body radiotherapy (SBRT), is administered at a cumulative dose in the range of 1.5 to 115 Gy, *e.g.*, in 3 x 20 Gy or 3 x 15 Gy fractionated doses, *e.g.*, as standard fractionated

chemoradiation (5000-5400 cGy in 180-200 cGy per fraction) or short-course RT (2500 cGy in 500 cGy per fraction) (Wo, *et al.*, *Pract Radiat Oncol* (2021) 11(1):13-25; Au, *et al.*, *Dig Dis Sci* (2018) 63(9):2451-2455; Flamarique, *et al.*, *Clin Transl Oncol* (2020) 22(12):2350-2356; and Townsend, *et al.*, *Cochrane Database Syst Rev* (2009) 2009(4):CD007045; Paix, *et al.*, *Cancer Radiother* (2017) 21(3):199-204; and Dell'Acqua, *et al.*, *Clin Exp Metastasis* (2019) 36(4):331-342).

[0063] In some embodiments, the subject has a brain cancer, *e.g.*, a glioblastoma, and a RT, *e.g.*, selected from postoperative radiation therapy (RT), MRI-guided RT, abbreviated course RT, pulsed RT and reirradiation, is administered at a cumulative dose in the range of 5 to 60 Gy, *e.g.*, at fractioned doses in the range of 2 to 3 Gy, *e.g.*, 60 Gy in 30 fractions; 40 Gy in 15 fractions (Barani, *et al.*, *Cancer Treat Res* (2015) 163:49-73; Vanhove, *et al.*, *Br J Radiol* (2019) 92(1095):20180713; Roa, *et al.*, *J Clin Oncol* (2004) 22(9):1583-8; Almahariq, *et al.*, *Neuro Oncol.* (2021) 23(3):447-456; Lu, *et al.*, *J Neurooncol.* (2019) 143(2):177-185; Sulman, *et al.*, *J Clin Oncol.* (2017) 35(3):361-369; Minniti, *et al.*, *Radiat Oncol.* (2021) 16(1):36).

[0064] In various embodiments, the RT dose is fractionated (180 to 200 cGy per fraction), moderately hypofractionated (240-340 cGy per fraction) or ultrahypofractionated (500 cGy or more per fraction). In various embodiments, the RT dose is conventionally fractionated (CFRT, 74–78 Gy in 1.8–2.0 Gy per Fraction), moderately hypofractionated (HFRT, 60 Gy in 3 Gy per fraction) or ultra-hypofractionated (UHRT, 36.3–37.5 Gy in 7.3–7.5 Gy per fraction).

4. Additional Combination Agents

[0065] Additional agents, such as small molecules, antibodies, adoptive cellular therapies and chimeric antigen receptor T cells (CAR-T), checkpoint inhibitors, and vaccines, that are appropriate for treating hematological malignancies can be administered in combination with the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein. Additional immunotherapeutic agents for hematological malignancies are described in Dong, *et al, J Life Sci* (Westlake Village). 2019 June; 1(1): 46–52; and Cuesta-Mateos, *et al, Front. Immunol.* 8:1936. doi: 10.3389/fimmu.2017.01936, each of which are hereby incorporated by reference in their entireties for all purposes.

[0066] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more additional therapeutic agents, *e.g.*, an inhibitory

immune checkpoint blocker or inhibitor, a stimulatory immune checkpoint stimulator, agonist or activator, a chemotherapeutic agent, an anti-cancer agent, a radiotherapeutic agent, an anti-neoplastic agent, an anti-proliferation agent, an anti-angiogenic agent, an anti-inflammatory agent, an immunotherapeutic agent, a therapeutic antigen-binding molecule (mono- and multi-specific antibodies and fragments thereof in any format (*e.g.*, including without limitation DARTs®, Duobodies®, BiTEs®, BiKEs, TriKEs, XmAbs®, TandAbs®, scFvs, Fabs, Fab derivatives), bi-specific antibodies, non-immunoglobulin antibody mimetics (*e.g.*, including without limitation adnectins, affibody molecules, affilins, affimers, affitins, alphabodies, anticalins, peptide aptamers, armadillo repeat proteins (ARMs), atrimers, avimers, designed ankyrin repeat proteins (DARPins®), fynomers, knottins, Kunitz domain peptides, monobodies, and nanoCLAMPs), antibody-drug conjugates (ADC), antibody-peptide conjugate), an oncolytic virus, a gene modifier or editor, a cell comprising a chimeric antigen receptor (CAR), *e.g.*, including a T cell immunotherapeutic agent, an NK-cell immunotherapeutic agent, or a macrophage immunotherapeutic agent, a cell comprising an engineered T-cell receptor (TCR-T), or any combination thereof.

[0067] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more additional therapeutic agents including, without limitation, an inhibitor, agonist, antagonist, ligand, modulator, stimulator, blocker, activator or suppressor of a target (*e.g.*, polypeptide or polynucleotide) including without limitation: Abelson murine leukemia viral oncogene homolog 1 gene (ABL, such as ABL1), Acetyl-CoA carboxylase (such as ACC1/2), activated CDC kinase (ACK, such as ACK1), Adenosine deaminase, adenosine receptor (such as A2BR, A2aR, A3aR), Adenylate cyclase, ADP ribosyl cyclase-1, adrenocorticotropic hormone receptor (ACTH), Aerolysin, AKT1 gene, Alk-5 protein kinase, Alkaline phosphatase, Alpha 1 adrenoceptor, Alpha 2 adrenoceptor, Alpha-ketoglutarate dehydrogenase (KGDH), Aminopeptidase N, AMP activated protein kinase, anaplastic lymphoma kinase (ALK, such as ALK1), Androgen receptor, Angiopoietin (such as ligand-1, ligand-2), Angiotensinogen (AGT) gene, murine thymoma viral oncogene homolog 1 (AKT) protein kinase (such as AKT1, AKT2, AKT3), apolipoprotein A-I (APOA1) gene, Apoptosis inducing factor, apoptosis protein (such as 1, 2), apoptosis signal-regulating kinase (ASK, such as ASK1), Arginase (I), Arginine deiminase, Aromatase, Asteroid homolog 1 (ASTE1) gene, ataxia telangiectasia and Rad 3 related (ATR) serine/threonine protein kinase, Aurora protein kinase (such as 1, 2), Axl tyrosine kinase receptor, 4-1BB ligand (CD137L), Baculoviral IAP repeat containing 5 (BIRC5) gene, Basigin, B-cell lymphoma 2 (BCL2) gene, Bcl2 binding

component 3, Bcl2 protein, BCL2L11 gene, BCR (breakpoint cluster region) protein and gene, Beta adrenoceptor, Beta-catenin, B-lymphocyte antigen CD19, B-lymphocyte antigen CD20, B-lymphocyte cell adhesion molecule, B-lymphocyte stimulator ligand, Bone morphogenetic protein-10 ligand, Bone morphogenetic protein-9 ligand modulator, Brachyury protein, Bradykinin receptor, B-Raf proto-oncogene (BRAF), Brc-Abl tyrosine kinase, Bromodomain and external domain (BET) bromodomain containing protein (such as BRD2, BRD3, BRD4), Bruton's tyrosine kinase (BTK), Calmodulin, calmodulin-dependent protein kinase (CaMK, such as CAMKII), Cancer testis antigen 2, Cancer testis antigen NY-ESO-1, cancer/testis antigen 1B (CTAG1) gene, Cannabinoid receptor (such as CB1, CB2), Carbonic anhydrase, casein kinase (CK, such as CKI, CKII), Caspase (such as caspase-3, caspase-7, Caspase-9), caspase 8 apoptosis-related cysteine peptidase CASP8-FADD-like regulator, Caspase recruitment domain protein-15, Cathepsin G, CCR5 gene, CDK-activating kinase (CAK), Checkpoint kinase (such as CHK1, CHK2), chemokine (C-C motif) receptor (such as CCR2, CCR4, CCR5, CCR8), chemokine (C-X-C motif) receptor (such as CXCR1, CXCR2, CXCR3 and CXCR4), Chemokine CC21 ligand, Cholecystokinin CCK2 receptor, Chorionic gonadotropin, c-Kit (tyrosine-protein kinase Kit or CD117), CISH (Cytokine-inducible SH2-containing protein), Claudin (such as 6, 18), cluster of differentiation (CD) such as CD4, CD27, CD29, CD30, CD33, CD37, CD40, CD40 ligand receptor, CD40 ligand, CD40LG gene, CD44, CD45, CD47, CD49b, CD51, CD52, CD55, CD58, CD66e (CEACAM6), CD70 gene, CD74, CD79, CD79b, CD79B gene, CD80, CD95, CD99, CD117, CD122, CDw123, CD134, CDw137, CD158a, CD158b1, CD158b2, CD223, CD276 antigen; clusterin (CLU) gene, Clusterin, c-Met (hepatocyte growth factor receptor (HGFR)), Complement C3, Connective tissue growth factor, COP9 signalosome subunit 5, CSF-1 (colony-stimulating factor 1 receptor), CSF2 gene, CTLA-4 (cytotoxic T-lymphocyte protein 4) receptor, C-type lectin domain protein 9A (CLEC9A), Cyclin D1, Cyclin G1, cyclin-dependent kinases (CDK, such as CDK1, CDK12, CDK1B, CDK2-9), cyclooxygenase (such as COX1, COX2), CYP2B1 gene, Cysteine palmitoyltransferase porcupine, Cytochrome P450 11B2, Cytochrome P450 17, cytochrome P450 17A1, Cytochrome P450 2D6, cytochrome P450 3A4, Cytochrome P450 reductase, cytokine signalling-1, cytokine signalling-3, Cytoplasmic isocitrate dehydrogenase, Cytosine deaminase, cytosine DNA methyltransferase, cytotoxic T-lymphocyte protein-4, DDR2 gene, DEAD-box helicase 6 (DDX6), Death receptor 5 (DR5, TRAILR2), Death receptor 4 (DR4, TRAILR1), Delta-like protein ligand (such as 3, 4), Deoxyribonuclease, Deubiquitinating enzymes (DUBs), Dickkopf-1 ligand, dihydrofolate reductase (DHFR), Dihydropyrimidine dehydrogenase, Dipeptidyl peptidase IV, discoidin domain receptor (DDR, such as DDR1),

Diacylglycerol kinase zeta (DGKZ), DNA binding protein (such as HU-beta), DNA dependent protein kinase, DNA gyrase, DNA methyltransferase, DNA polymerase (such as alpha), DNA primase, dUTP pyrophosphatase, L-dopachrome tautomerase, E3 ubiquitin-protein ligase (such as RNF128, CBL-B), echinoderm microtubule like protein 4, EGFR tyrosine kinase receptor, Elastase, Elongation factor 1 alpha 2, Elongation factor 2, Endoglin, Endonuclease, endoplasmic reticulum aminopeptidase (ERAP, such as ERAP 1, ERAP2), Endoplasmin, Endosialin, Endostatin, endothelin (such as ET-A, ET-B), Enhancer of zeste homolog 2 (EZH2), Ephrin (EPH) tyrosine kinase (such as Epha3, Ephb4), Ephrin B2 ligand, epidermal growth factor, epidermal growth factor receptors (EGFR), epidermal growth factor receptor (EGFR) gene, Epigen, Epithelial cell adhesion molecule (EpCAM), Erb-b2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2) tyrosine kinase receptor, Erb-b3 tyrosine kinase receptor, Erb-b4 tyrosine kinase receptor, E-selectin, Estradiol 17 beta dehydrogenase, Estrogen receptor (such as alpha, beta), Estrogen related receptor, Eukaryotic translation initiation factor 5A (EIF5A) gene, Exportin 1, Extracellular signal related kinase (such as 1, 2), Extracellular signal-regulated kinases (ERK), Hypoxia-inducible factor prolyl hydroxylase (HIF-PH or EGLN), Factor (such as Xa, VIIa), farnesoid x receptor (FXR), Fas ligand, Fatty acid synthase (FASN), Ferritin, FGF-2 ligand, FGF-5 ligand, fibroblast growth factor (FGF, such as FGF1, FGF2, FGF4), Fibronectin, focal adhesion kinase (FAK, such as FAK2), folate hydrolase prostate-specific membrane antigen 1 (FOLH1), Folate receptor (such as alpha), Folate, Folate transporter 1, FYN tyrosine kinase, paired basic amino acid cleaving enzyme (FURIN), Beta-glucuronidase, Galactosyltransferase, Galectin-3, Ganglioside GD2, Glucocorticoid, glucocorticoid-induced TNFR-related protein GITR receptor, Glutamate carboxypeptidase II, glutaminase, Glutathione S-transferase P, glycogen synthase kinase (GSK, such as 3-beta), Glypican 3 (GPC3), gonadotropin-releasing hormone (GNRH), Granulocyte macrophage colony stimulating factor (GM-CSF) receptor, Granulocyte-colony stimulating factor (GCSF) ligand, growth factor receptor-bound protein 2 (GRB2), Grp78 (78 kDa glucose-regulated protein) calcium binding protein, molecular chaperone groEL2 gene, Heme oxygenase 1 (HO1), Heme oxygenase 2 (HO2), Heat shock protein (such as 27, 70, 90 alpha, beta), Heat shock protein gene, Heat stable enterotoxin receptor, Hedgehog protein, Heparanase, Hepatocyte growth factor, HERV-H LTR associating protein 2, Hexose kinase, Histamine H2 receptor, Histone methyltransferase (DOT1L), histone deacetylase (HDAC, such as 1, 2, 3, 6, 10, 11), Histone H1, Histone H3, HLA class I antigen (A-2 alpha), HLA class II antigen, HLA class I antigen alpha G (HLA-G), Non-classical HLA, Homeobox protein NANOG, HSPB1 gene, Human leukocyte antigen (HLA), Human papillomavirus (such as E6, E7) protein, Hyaluronic acid,

Hyaluronidase, Hypoxia inducible factor-1 alpha (HIF1α), Imprinted Maternally Expressed Transcript (H19) gene, mitogen-activated protein kinase 1 (MAP4K1), tyrosine-protein kinase HCK, I-Kappa-B kinase (IKK, such as IKKbe), IL-1 alpha, IL-1 beta, IL-12, IL-12 gene, IL-15, IL-17, IL-2 gene, IL-2 receptor alpha subunit, IL-2, IL-3 receptor, IL-4, IL-6, IL-7, IL-8, immunoglobulin (such as G, G1, G2, K, M), Immunoglobulin Fc receptor, Immunoglobulin gamma Fc receptor (such as I, III, IIIA), indoleamine 2,3-dioxygenase (IDO, such as IDO1 and IDO2), indoleamine pyrrole 2,3-dioxygenase 1 inhibitor, insulin receptor, Insulin-like growth factor (such as 1, 2), Integrin alpha-4/beta-1, integrin alpha-4/beta-7, Integrin alpha-5/beta-1, Integrin alpha-V/beta-3, Integrin alpha-V/beta-5, Integrin alpha-V/beta-6, Intercellular adhesion molecule 1 (ICAM-1), interferon (such as alpha, alpha 2, beta, gamma), Interferon inducible protein absent in melanoma 2 (AIM2), interferon type I receptor, Interleukin 1 ligand, Interleukin 13 receptor alpha 2, interleukin 2 ligand, interleukin-1 receptor-associated kinase 4 (IRAK4), Interleukin-2, Interleukin-29 ligand, Interleukin 35 (IL-35), isocitrate dehydrogenase (such as IDH1, IDH2), Janus kinase (JAK, such as JAK1, JAK2), Jun N terminal kinase, kallikrein-related peptidase 3 (KLK3) gene, Killer cell Ig like receptor, Kinase insert domain receptor (KDR), Kinesin-like protein KIF11, Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, Kisspeptin (KiSS-1) receptor, KIT gene, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) tyrosine kinase, lactoferrin, Lanosterol-14 demethylase, LDL receptor related protein-1, Leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2), Leukocyte immunoglobulin-like receptor subfamily B member 2 (ILT4), Leukotriene A4 hydrolase, Listeriolysin, L-Selectin, Luteinizing hormone receptor, Lyase, lymphocyte activation gene 3 protein (LAG-3), Lymphocyte antigen 75, Lymphocyte function antigen-3 receptor, lymphocyte-specific protein tyrosine kinase (LCK), Lymphotactin, Lyn (Lck/Yes novel) tyrosine kinase, lysine demethylases (such as KDM1, KDM2, KDM4, KDM5, KDM6, A/B/C/D), Lysophosphatidate-1 receptor, lysosomal-associated membrane protein family (LAMP) gene, Lysyl oxidase homolog 2, lysyl oxidase protein (LOX), 5-Lipoxygenase (5-LOX), Hematopoietic Progenitor Kinase 1 (HPK1), Hepatocyte growth factor receptor (MET) gene, macrophage colony-stimulating factor (MCSF) ligand, Macrophage migration inhibitory fact, MAGEC1 gene, MAGEC2 gene, Major vault protein, MAPK-activated protein kinase (such as MK2), Mas-related G-protein coupled receptor, matrix metalloprotease (MMP, such as MMP2, MMP9), Mcl-1 differentiation protein, Mdm2 p53-binding protein, Mdm4 protein, Melan-A (MART-1) melanoma antigen, Melanocyte protein Pmel 17, melanocyte stimulating hormone ligand, melanoma antigen family A3 (MAGEA3) gene, Melanoma associated antigen (such as 1, 2, 3, 6), Membrane copper amine oxidase, Mesothelin, MET tyrosine kinase,

Metabotropic glutamate receptor 1, Metalloreductase STEAP1 (six transmembrane epithelial antigen of the prostate 1), Metastin, methionine aminopeptidase-2, Methyltransferase, Mitochondrial 3 ketoacyl CoA thiolase, mitogen-activate protein kinase (MAPK), mitogen-activated protein kinase (MEK, such as MEK1, MEK2), mTOR (mechanistic target of rapamycin (serine/threonine kinase), mTOR complex (such as 1,2), mucin (such as 1, 5A, 16), mut T homolog (MTH, such as MTH1), Myc proto-oncogene protein, myeloid cell leukemia 1 (MCL1) gene, myristoylated alanine-rich protein kinase C substrate (MARCKS) protein, NAD ADP ribosyltransferase, natriuretic peptide receptor C, Neural cell adhesion molecule 1, Neurokinin 1 (NK1) receptor, Neurokinin receptor, Neuropilin 2, NF kappa B activating protein, NIMA-related kinase 9 (NEK9), Nitric oxide synthase, NK cell receptor, NK3 receptor, NKG2 A B activating NK receptor, NLRP3 (NACHT LRR PYD domain protein 3) modulators, Noradrenaline transporter, Notch (such as Notch-2 receptor, Notch-3 receptor, Notch-4 receptor), Nuclear erythroid 2-related factor 2, Nuclear Factor (NF) kappa B, Nucleolin, Nucleophosmin, nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), 2 oxoglutarate dehydrogenase, 2,5-oligoadenylate synthetase, O-methylguanine DNA methyltransferase, Opioid receptor (such as delta), Ornithine decarboxylase, Orotate phosphoribosyltransferase, orphan nuclear hormone receptor NR4A1, Osteocalcin, Osteoclast differentiation factor, Osteopontin, OX-40 (tumor necrosis factor receptor superfamily member 4 TNFRSF4, or CD134) receptor, P3 protein, p38 kinase, p38 MAP kinase, p53 tumor suppressor protein, Parathyroid hormone ligand, peroxisome proliferator-activated receptors (PPAR, such as alpha, delta, gamma), P-Glycoprotein (such as 1), phosphatase and tensin homolog (PTEN), phosphatidylinositol 3-kinase (PI3K), phosphoinositide-3 kinase (PI3K such as alpha, delta, gamma), phosphorylase kinase (PK), PKN3 gene, placenta growth factor, platelet-derived growth factor (PDGF, such as alpha, beta), Platelet-derived growth factor (PDGF, such as alpha, beta), Pleiotropic drug resistance transporter, Plexin B1, PLK1 gene, polo-like kinase (PLK), Polo-like kinase 1, Poly (ADP- ribose) polymerase (PARP, such as PARP1, PARP2 and PARP3, PARP7, and mono-PARPs), Preferentially expressed antigen in melanoma (PRAME) gene, Prenyl-binding protein (PrPB), Probable transcription factor PML, Progesterone receptor, Programmed cell death 1 (PD-1), Programmed cell death ligand 1 inhibitor (PD-L1), Prosaposin (PSAP) gene, Prostanoid receptor (EP4), Prostaglandin E2 synthase, prostate specific antigen, Prostatic acid phosphatase, proteasome, Protein E7, Protein farnesyltransferase, protein kinase (PK, such as A, B, C), protein tyrosine kinase, Protein tyrosine phosphatase beta, Proto-oncogene serine/threonine-protein kinase (PIM, such as PIM-1, PIM-2, PIM-3), P-Selectin, Purine nucleoside phosphorylase, purinergic receptor P2X ligand gated ion channel 7 (P2X7),

Pyruvate dehydrogenase (PDH), Pyruvate dehydrogenase kinase, Pyruvate kinase (PYK), 5-Alpha-reductase, Raf protein kinase (such as 1, B), RAF1 gene, Ras gene, Ras GTPase, RET gene, Ret tyrosine kinase receptor, retinoblastoma associated protein, retinoic acid receptor (such as gamma), Retinoid X receptor, Rheb (Ras homolog enriched in brain) GTPase, Rho (Ras homolog) associated protein kinase 2, ribonuclease, Ribonucleotide reductase (such as M2 subunit), Ribosomal protein S6 kinase, RNA polymerase (such as I, II), Ron (Recepteur d'Origine Nantais) tyrosine kinase, ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase) gene, Ros1 tyrosine kinase, Runt-related transcription factor 3, Gamma-secretase, S100 calcium binding protein A9, Sarco endoplasmic calcium ATPase, Second mitochondria-derived activator of caspases (SMAC) protein, Secreted frizzled related protein-2, Secreted phospholipase A2, Semaphorin-4D, Serine protease, serine/threonine kinase (STK), serine/threonine-protein kinase (TBK, such as TBK1), signal transduction and transcription (STAT, such as STAT-1, STAT-3, STAT-5), Signaling lymphocytic activation molecule (SLAM) family member 7, six-transmembrane epithelial antigen of the prostate (STEAP) gene, SL cytokine ligand, smoothened (SMO) receptor, Sodium iodide cotransporter, Sodium phosphate cotransporter 2B, Somatostatin receptor (such as 1, 2, 3, 4, 5), Sonic hedgehog protein, Son of sevenless (SOS), Specific protein 1 (Sp1) transcription factor, Sphingomyelin synthase, Sphingosine kinase (such as 1, 2), Sphingosine-1-phosphate receptor-1, spleen tyrosine kinase (SYK), SRC gene, Src tyrosine kinase, Stabilin-1 (STAB1), STAT3 gene, Steroid sulfatase, Stimulator of interferon genes (STING) receptor, stimulator of interferon genes protein, Stromal cell-derived factor 1 ligand, SUMO (small ubiquitin-like modifier), Superoxide dismutase, Suppressor of cytokine signaling modulators (SOCS), Survivin protein, Synapsin 3, Syndecan-1, Synuclein alpha, T cell surface glycoprotein CD28, tank-binding kinase (TBK), TATA box-binding protein-associated factor RNA polymerase I subunit B (TAF1B) gene, T-cell CD3 glycoprotein zeta chain, T-cell differentiation antigen CD6, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), T-cell surface glycoprotein CD8, Tec protein tyrosine kinase, Tek tyrosine kinase receptor, telomerase, Telomerase reverse transcriptase (TERT) gene, Tenascin, Three prime repair exonuclease 1 (TREX1), Three prime repair exonuclease 2 (TREX2), Thrombopoietin receptor, Thymidine kinase, Thymidine phosphorylase, Thymidylate synthase, Thymosin (such as alpha 1), Thyroid hormone receptor, Thyroid stimulating hormone receptor, Tissue factor, TNF related apoptosis inducing ligand, TNFR1 associated death domain protein, TNF-related apoptosis-inducing ligand (TRAIL) receptor, TNFSF11 gene, TNFSF9 gene, Toll-like receptor (TLR such as 1-13), topoisomerase (such as I, II, III), Transcription factor, Transferase, transferrin (TF), transforming growth factor alpha (TGFα), transforming growth factor beta (TGFB) and

isoforms thereof, TGF beta 2 ligand, Transforming growth factor TGF-β receptor kinase, Transglutaminase, Translocation associated protein, Transmembrane glycoprotein NMB, Trop-2 calcium signal transducer, trophoblast glycoprotein (TPBG) gene, Trophoblast glycoprotein, Tropomyosin receptor kinase (Trk) receptor (such as TrkA, TrkB, TrkC), tryptophan 2,3-dioxygenase (TDO), Tryptophan 5-hydroxylase, Tubulin, Tumor necrosis factor (TNF, such as alpha, beta), Tumor necrosis factor 13C receptor, tumor progression locus 2 (TPL2), Tumor protein 53 (TP53) gene, Tumor suppressor candidate 2 (TUSC2) gene, Tumor specific neoantigens, Tyrosinase, Tyrosine hydroxylase, tyrosine kinase (TK), Tyrosine kinase receptor, Tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE) receptor, Tyrosine protein kinase ABL1 inhibitor, Ubiquitin, Ubiquitin carboxyl hydrolase isozyme L5, Ubiquitin thioesterase-14, Ubiquitin-conjugating enzyme E2I (UBE2I, UBC9), Ubiquitin-specific-processing protease 7 (USP7), Urease, Urokinase plasminogen activator, Uteroglobin, Vanilloid VR1, Vascular cell adhesion protein 1, vascular endothelial growth factor receptor (VEGFR), V-domain Ig suppressor of T-cell activation (VISTA), VEGF-1 receptor, VEGF-2 receptor, VEGF-3 receptor, VEGF-A, VEGF-B, Vimentin, Vitamin D3 receptor, Proto-oncogene tyrosine-protein kinase, Mer (Mer tyrosine kinase receptor modulators), YAP (Yes-associated protein modulators)es, Wee-1 protein kinase, Werner Syndrome RecQ Like Helicase (WRN), Wilms' tumor antigen 1, Wilms' tumor protein, WW domain containing transcription regulator protein 1 (TAZ), X-linked inhibitor of apoptosis protein, Zinc finger protein transcription factor or any combination thereof.

[0068] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is combined with one or more additional therapeutic agents that may be categorized by their mechanism of action into, for example, the following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs floxuridine, capecitabine, cytarabine, CPX-351 (liposomal cytarabine, daunorubicin), and TAS-118; Alpha 1 adrenoceptor/Alpha 2 adrenoceptor antagonists, such as phenoxybenzamine hydrochloride (injectable, pheochromocytoma); Androgen receptor antagonists, such as nilutamide; anti-cadherin antibodies, such as HKT-288; anti-leucine-rich repeat containing 15 (LRRC15) antibodies, such as ABBV-085. ARGX-110; angiotensin receptor blockers, nitric oxide donors; antisense oligonucleotides, such as AEG35156, IONIS-KRAS-2.5Rx, EZN-3042, RX-0201, IONIS-AR-2.5Rx, BP-100 (prexigebersen), IONIS-STAT3-2.5Rx; anti-angiopoietin (ANG)-2 antibodies, such as MEDI3617, and LY3127804; anti-ANG-1/ANG-2 antibodies, such as AMG-780; anti-CSF1R antibodies, such as emactuzumab, LY3022855, AMG-820, FPA-008 (cabiralizumab); anti-

endoglin antibodies, such as TRC105 (carotuximab); anti-ERBB antibodies, such as CDX-3379, HLX-02, seribantumab; anti-HER2 antibodies, such as HERCEPTIN® (trastuzumab), trastuzumab biosimimar, margetuximab, MEDI4276, BAT-8001, Pertuzumab (Perjeta), RG6264, ZW25 (a bispecific HER2-directed antibody targeting the extracellular domains 2 and 4; Cancer Discov. 2019 Jan;9(1):8; PMID: 30504239); anti-HLA-DR antibodies, such as IMMU-114; anti-IL-3 antibodies, such as JNJ-56022473; anti-TNF receptor superfamily member 18 (TNFRSF18, GITR; NCBI Gene ID: 8784) antibodies, such as MK-4166, MEDI1873, FPA-154, INCAGN-1876, TRX-518, BMS-986156, MK-1248, GWN-323; and those described, *e.g.*, in Intl. Patent Publ. Nos. WO 2017/096179, WO 2017/096276, WO 2017/096189; and WO 2018/089628; anti-EphA3 antibodies, such as KB-004; anti-CD37 antibodies, such as otlertuzumab (TRU-016); anti-FGFR-3 antibodies, such as LY3076226, B-701; anti-FGFR-2 antibodies, such as GAL-F2; anti-C5 antibodies, such as ALXN-1210; anti-EpCAM antibodies, such as VB4-845; anti-CEA antibodies, such as RG-7813; anti-Carcinoembryonic-antigen-related-cell-adhesion-molecule-6 (CEACAM6, CD66C) antibodies, such as BAY-1834942, NEO-201 (CEACAM 5/6); anti-GD2 antibodies, such as APN-301; anti-interleukin-17 (IL-17) antibodies, such as CJM-112; anti-interleukin-1 beta antibodies, such as canakinumab (ACZ885), VPM087; anti-carbonic anhydrase 9 (CA9, CAIX) antibodies, such as TX-250; anti-Mucin 1 (MUC1) antibodies, such as gatipotuzumab, Mab-AR-20.5; anti-KMA antibodies, such as MDX-1097; anti-CD55 antibodies, such as PAT-SC1; anti-c-Met antibodies, such as ABBV-399; anti-PSMA antibodies, such as ATL-101; anti-CD100 antibodies, such as VX-15; anti-EPHA3 antibodies, such as fibatuzumab; anti-APRIL antibodies, such as BION-1301; anti-fibroblast activation protein (FAP)/IL-2R antibodies, such as RG7461; anti-fibroblast activation protein (FAP)/TRAIL-R2 antibodies, such as RG7386; anti-fucosyl-GM1 antibodies, such as BMS-986012; anti-IL-8 (Interleukin-8) antibodies, such as HuMax-Inflam; anti-myostatin inhibitors, such as landogrozumab; anti-delta-like protein ligand 3 (DDL3) antibodies, such as rovalpituzumab tesirine; anti-DLL4 (delta like ligand 4) antibodies, such as demcizumab; anti-clusterin antibodies, such as AB-16B5; anti-Ephrin-A4 (EFNA4) antibodies, such as PF-06647263; anti-mesothelin antibodies, such as BMS-986148, Anti-MSLN-MMAE; anti-sodium phosphate cotransporter 2B (NaP2B) antibodies, such as lifastuzumab; anti-TGFβ antibodies, such as SAR439459; anti-transforming growth factor-beta (TGF-beta) antibodies, such as ABBV-151, LY3022859, NIS793, XOMA 089; purine analogs, folate antagonists (such as pralatrexate), cladribine, pentostatin, fludarabine and related inhibitors; antiproliferative/antimitotic agents including natural products, such as vinca alkaloids (vinblastine, vincristine) and microtubule disruptors such as taxane (paclitaxel, docetaxel),

vinblastin, nocodazole, epothilones, vinorelbine (NAVELBINE®), and epipodophyllotoxins (etoposide, teniposide); DNA damaging agents, such as actinomycin, amsacrine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide (CYTOXAN®), dactinomycin, daunorubicin, doxorubicin, DEBDOX, epirubicin, iphosphamide, melphalan, merchlorethamine, mitomycin C, mitoxantrone, nitrosourea, procarbazine, taxol, Taxotere, teniposide, etoposide, and triethylenethiophosphoramide; DNA-hypomethylating agents, such as guadecitabine (SGI-110), oral decitabine and cedazuridine (ASTX727); antibiotics such as dactinomycin, daunorubicin, doxorubicin, idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin); enzymes such as L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine; DNAi oligonucleotides targeting Bcl-2, such as PNT2258; agents that activate or reactivate latent human immunodeficiency virus (HIV), such as panobinostat and romidepsin; asparaginase stimulators, such as crisantaspase (Erwinase®) and GRASPA (ERY-001, ERY-ASP), calaspargase pegol, pegaspargase; pan-Trk, ROS1 and ALK inhibitors, such as entrectinib, TPX-0005; anaplastic lymphoma kinase (ALK) inhibitors, such as alectinib, ceritinib, alecensa (RG7853), ALUNBRIG® (brigatinib); antiproliferative/antimitotic alkylating agents, such as nitrogen mustard cyclophosphamide and analogs (*e.g.*, melphalan, chlorambucil, hexamethylmelamine, thiotepa), alkyl nitrosoureas (*e.g.*, carmustine) and analogs, streptozocin, and triazenes (*e.g.*, dacarbazine); antiproliferative/antimitotic antimetabolites, such as folic acid analogs (methotrexate); platinum coordination complexes (*e.g.*, cisplatin, oxiloplatinim, and carboplatin), procarbazine, hydroxyurea, mitotane, and aminoglutethimide; hormones, hormone analogs (*e.g.*, estrogen, tamoxifen, goserelin, bicalutamide, and nilutamide), and aromatase inhibitors (*e.g.*, letrozole and anastrozole); antiplatelet agents; anticoagulants such as heparin, synthetic heparin salts, and other inhibitors of thrombin; fibrinolytic agents such as tissue plasminogen activator, streptokinase, urokinase, aspirin, dipyridamole, ticlopidine, and clopidogrel; antimigratory agents; antisecretory agents (*e.g.*, breveldin); immunosuppressives, such as tacrolimus, sirolimus, azathioprine, and mycophenolate; growth factor inhibitors, and vascular endothelial growth factor inhibitors; fibroblast growth factor inhibitors, such as FPA14; AMP activated protein kinase stimulators, such as metformin hydrochloride; ADP ribosyl cyclase-1 inhibitors, such as daratumumab (DARZALEX®); Caspase recruitment domain protein-15 stimulators, such as mifamurtide (liposomal); CCR5 chemokine antagonists, such as MK-7690 (vicriviroc); CDC7 protein kinase inhibitors, such as TAK-931; Cholesterol side-chain cleavage enzyme inhibitors, such as ODM-209; Dihydropyrimidine dehydrogenase/Orotate phosphoribosyltransferase inhibitors, such as Cefesone (tegafur +

gimeracil + oteracil potassium); DNA polymerase/Ribonucleotide reductase inhibitors, such as clofarabine; DNA interference oligonucleotides, such as PNT2258, AZD-9150; Estrogen receptor modulators, such as bazedoxifene; Estrogen receptor agonists/Progesterone receptor antagonists, such as TRI-CYCLEN LO (norethindrone + ethinyl estradiol); HLA class I antigen A-2 alpha modulators, such as FH-MCVA2TCR; HLA class I antigen A-2 alpha/MART-1 melanoma antigen modulators, such as MART-1 F5 TCR engineered PBMC; Human Granulocyte Colony Stimulating Factors, such as PF-06881894; GNRH receptor agonists, such as leuprorelin acetate, leuprorelin acetate sustained release depot (ATRIGEL), triptorelin pamoate, goserelin acetate; GNRH receptor antagonists, such as elagolix, relugolix, degarelix; Endoplasmin modulators, such as anlotinib; H+ K+ ATPase inhibitors, such as omeprazole, esomeprazole; ICAM-1/CD55 modulators, such as cavatak (V-937); IL-15/IL-12 modulators, such as SAR441000; Interleukin 23A inhibitors, such as guselkumab; Lysine specific histone demethylase 1 inhibitors, such as CC-90011; IL-12 Mrna, such as MEDI1191; RIG-I modulators, such as RGT-100; NOD2 modulators, such as SB-9200, and IR-103; Progesterone receptor agonists, such as levonorgestrel; Protein cereblon modulators, such as CC-92480, CC-90009; Protein cereblon modulators/DNA binding protein Ikaros inhibitors/Zinc finger binding protein Aiolos inhibitors, such as iberdomide; Retinoid X receptor modulators, such as alitretinoin, bexarotene (oral formulation); RIP-1 kinase inhibitors, such as GSK-3145095; selective oestrogen receptor degraders, such as AZD9833; SUMO inhibitors, such as TAK-981; Thrombopoietin receptor agonists, such as eltrombopag; Thyroid hormone receptor agonists, such as levothyroxine sodium; TNF agonists, such as tasonermin; Tyrosine phosphatase substrate 1 inhibitors, such as CC-95251; HER2 inhibitors, such as neratinib, tucatinib (ONT-380); EGFR/ErbB2/Ephb4 inhibitors, such as tesevatinib; EGFR/HER2 inhibitors, such as TAK-788; EGFR family tyrosine kinase receptor inhibitors, such as DZD-9008; EGFR/ErbB-2 inhibitors, such as varlitinib; mutant selective EGFR inhibitors, such as PF-06747775, EGF816 (nazartinib), ASP8273, ACEA-0010, BI-1482694; epha2 inhibitors, such as MM-310; polycomb protein (EED) inhibitors, such as MAK683; DHFR inhibitor/Folate transporter 1 modulator/Folate receptor antagonist, such as pralatrexate; DHFR/GAR transformylase/Thymidylate synthase/Transferase inhibitors, such as pemetrexed disodium; p38 MAP kinase inhibitors, such as ralimetinib; PRMT inhibitors, such as MS203, PF-06939999, GSK3368715, GSK3326595; Sphingosine kinase 2 (SK2) inhibitors, such as opaganib; Nuclear erythroid 2-related factor 2 stimulators, such as omaveloxolone (RTA-408); Tropomyosin receptor kinase (TRK) inhibitors, such as LOXO-195, ONO-7579; Mucin 1 inhibitors, such as GO-203-2C; MARCKS protein inhibitors, such as BIO-11006; Folate antagonists, such as

arfolitixorin; Galectin-3 inhibitors, such as GR-MD-02; Phosphorylated P68 inhibitors, such as RX-5902; CD95/TNF modulators, such as ofranergene obadenovec; pan-PIM kinase inhibitors, such as INCB-053914; IL-12 gene stimulators, such as EGEN-001, tavokinogene telseplasmid; Heat shock protein HSP90 inhibitors, such as TAS-116, PEN-866; VEGF/HGF antagonists, such as MP-0250; VEGF ligand inhibitors, such as bevacizumab biosimilar; VEGF receptor antagonists/VEGF ligand inhibitors, such as ramucirumab; VEGF-1/VEGF-2/VEGF-3 receptor antagonists; such as fruquintinib; VEGF-1/VEGF-2 receptor modulators, such as HLA-A2402/HLA-A0201 restricted epitope peptide vaccine; Placenta growth factor ligand inhibitor/VEGF-A ligand inhibitor, such as aflibercept; SYK tyrosine kinase/JAK tyrosine kinase inhibitors, such as ASN-002; Trk tyrosine kinase receptor inhibitors, such as larotrectinib sulfate; JAK3/JAK1/TBK1 kinase inhibitors, such as CS-12912; IL-24 antagonist, such as AD-IL24; NLRP3 (NACHT LRR PYD domain protein 3) modulators, such as BMS-986299; RIG-I agonists, such as RGT-100; Aerolysin stimulators, such as topsalysin; P-Glycoprotein 1 inhibitors, such as HM-30181A; CSF-1 antagonists, such as ARRY-382, BLZ-945; CCR8 inhibitors, such as JTX-1811, I-309, SB-649701, HG-1013, RAP-310; anti-Mesothelin antibodies, such as SEL-403; Thymidine kinase stimulators, such as aglatimagene besadenovec; Polo-like kinase 1 inhibitors, such as PCM-075, onvansertib; NAE inhibitors, such as pevonedistat (MLN-4924); Trop-2 inhibitors, such as sacituzumab govitecan (TRODELVY®), TAS-4464; Pleiotropic pathway modulators, such as avadomide (CC-122); Amyloid protein binding protein-1 inhibitors/Ubiquitin ligase modulators; FoxM1 inhibitors, such as thiostrepton; UBA1 inhibitors, such as TAK-243; Src tyrosine kinase inhibitors, such as VAL-201; VDAC/HK inhibitors, such as VDA-1102; Elf4a inhibitors, such as rohinitib, eFT226; TP53 gene stimulators, such as ad-p53; Retinoic acid receptor agonists, such as tretinoin; Retinoic acid receptor alpha (RARα) inhibitors, such as SY-1425; SIRT3 inhibitors, such as YC8-02; Stromal cell-derived factor 1 ligand inhibitors, such as olaptesed pegol (NOX-A12); IL-4 receptor modulators, such as MDNA-55; Arginase-I stimulators, such as pegzilarginase; Topoisomerase I inhibitors, such as irinotecan hydrochloride, Onivyde; Topoisomerase I inhibitor/hypoxia inducible factor-1 alpha inhibitors, such as PEG-SN38 (firtecan pegol); Hypoxia inducible factor-1 alpha inhibitors, such as PT-2977, PT-2385; CD122 (IL-2 receptor) agonists, such as proleukin (aldesleukin, IL-2); pegylated IL-2 (*e.g.*, NKTR-214); modified variants of IL-2 (*e.g.*, THOR-707); TLR7/TLR8 agonist, such as NKTR-262; TLR7 agonists, such as DS-0509, GS-9620, LHC-165, TMX-101 (imiquimod); p53 tumor suppressor protein stimulators such as kevetrin; Mdm4/Mdm2 p53-binding protein inhibitors, such as ALRN-6924; kinesin spindle protein (KSP) inhibitors, such as filanesib (ARRY-520); CD80-Fc fusion protein inhibitors, such

as FPT-155; Menin and mixed lineage leukemia (MLL) inhibitors such as KO-539; Liver x receptor agonists, such as RGX-104; IL-10 agonists, such as Pegilodecakin (AM-0010); VEGFR/PDGFR inhibitors, such as vorolanib; IRAK4 inhibitors, such as CA-4948; anti-TLR-2 antibodies, such as OPN-305; Calmodulin modulators, such as CBP-501.

[0069] Glucocorticoid receptor antagonists, such as relacorilant (CORT-125134); Second mitochondria-derived activator of caspases (SMAC) protein inhibitors, such as BI-891065; Lactoferrin modulators, such as LTX-315; KIT proto-oncogene, receptor tyrosine kinase (KIT) inhibitors, such as PLX-9486; platelet derived growth factor receptor alpha (PDGFRA)/KIT proto-oncogene, receptor tyrosine kinase (KIT) mutant-specific antagonists/inhibitors such as BLU-285, DCC-2618; Exportin 1 inhibitors, such as eltanexor; CHST15 gene inhibitors, such as STNM-01; Somatostatin receptor antagonist, such as OPS-201; CEBPA gene stimulators, such as MTL-501; DKK3 gene modulators, such as MTG-201; Chemokine (CXCR1/CXCR2) inhibitors, such as SX-682; p70s6k inhibitors, such as MSC2363318A; methionine aminopeptidase 2 (MetAP2) inhibitors, such as M8891, APL-1202; arginine N-methyltransferase 5 inhibitors, such as GSK-3326595; CD71 modulators, such as CX-2029 (ABBV-2029); ATM (ataxia telangiectasia) inhibitors, such as AZD0156, AZD1390; CHK1 inhibitors, such as GDC-0575, LY2606368 (prexasertib), SRA737, RG7741 (CHK1/2); CXCR4 antagonists, such as BL-8040, LY2510924, burixafor (TG-0054), X4P-002, X4P-001-IO, Plerixafor; EXH2 inhibitors, such as GSK2816126; KDM1 inhibitors, such as ORY-1001, IMG-7289, INCB-59872, GSK-2879552; CXCR2 antagonists, such as AZD-5069; DNA dependent protein kinase inhibitors, such as MSC2490484A (nedisertib), VX-984, AsiDNA (DT-01); protein kinase C (PKC) inhibitors, such as LXS-196, sotrastaurin; selective estrogen receptor downregulators (SERD), such as fulvestrant (Faslodex®), RG6046, RG6047, RG6171, elacestrant (RAD-1901), SAR439859 and AZD9496; selective estrogen receptor covalent antagonists (SERCAs), such as H3B-6545; selective androgen receptor modulator (SARM), such as GTX-024, darolutamide; transforming growth factor-beta (TGF-beta) kinase antagonists, such as galunisertib, LY3200882; TGF-beta inhibitors described in WO 2019/103203; TGF beta receptor 1 inhibitors, such as PF-06952229; bispecific antibodies, such as ABT-165 (DLL4/VEGF), MM-141 (IGF-1/ErbB3), MM-111 (Erb2/Erb3), JNJ-64052781 (CD19/CD3), PRS-343 (CD-137/HER2), AFM26 (BCMA/CD16A), JNJ-61186372 (EGFR/cMET), AMG-211 (CEA/CD3), RG7802 (CEA/CD3), ERY-974 (CD3/GPC3) vancizumab (angiopoietins/VEGF), PF-06671008 (Cadherins/CD3), AFM-13 (CD16/CD30), APVO436 (CD123/CD3), flotetuzumab (CD123/CD3), REGN-1979 (CD20/CD3), MCLA-117 (CD3/CLEC12A), MCLA-128 (HER2/HER3), JNJ-0819, JNJ-7564 (CD3/heme), AMG-757 (DLL3-CD3), MGD-013 (PD-

1/LAG-3), FS-118 (LAG-3/PD-L1) MGD-019 (PD-1/CTLA-4), KN-046 (PD-1/CTLA-4), MEDI-5752 (CTLA-4/PD-1), RO-7121661 (PD-1/TIM-3), XmAb-20717 (PD-1/CTLA-4), AK-104 (CTLA-4/PD-1), AMG-420 (BCMA/CD3), BI-836880 (VEFG/ANG2), JNJ-63709178 (CD123/CD3), MGD-007 (CD3/gpA33), MGD-009 (CD3/B7H3), AGEN1223, IMCgp100 (CD3/gp100), AGEN-1423, ATOR-1015 (CTLA-4/OX40), LY-3415244 (TIM-3/PDL1), INHIBRX-105 (4-1BB/PDL1), faricimab (VEGF-A/ANG-2), FAP-4-IBBL (4-1BB/FAP), XmAb-13676 (CD3/CD20), TAK-252 (PD-1/OX40L), TG-1801 (CD19/CD47), XmAb-18087 (SSTR2/CD3), catumaxomab (CD3/EpCAM), SAR-156597 (IL4/IL13), EMB-01 (EGFR/cMET), REGN-4018 (MUC16/CD3), REGN-1979 (CD20/CD3), RG-7828 (CD20/CD3), CC-93269 (CD3/BCMA), REGN-5458 (CD3/BCMA), navicixizumab (DLL4/VEGF), GRB-1302 (CD3/Erbb2), vanucizumab (VEGF-A/ANG-2), GRB-1342 (CD38/CD3), GEM-333 (CD3/CD33), IMM-0306 (CD47/CD20), RG6076, MEDI5752 (PD-1/CTLA-4), LY3164530 (MET/EGFR); Alpha-ketoglutarate dehydrogenase (KGDH) inhibitors, such as CPI-613; XPO1 inhibitors, such as selinexor (KPT-330); Isocitrate dehydrogenase 2 (IDH2) inhibitors, such as enasidenib (AG-221); IDH1 inhibitors such as AG-120, and AG-881 (IDH1 and IDH2), IDH-305, BAY-1436032; IDH1 gene inhibitors, such as ivosidenib; interleukin-3 receptor (IL-3R) modulators, such as SL-401; Arginine deiminase stimulators, such as pegargiminase (ADI-PEG-20); claudin-18 inhibitors, such as claudiximab; β-catenin inhibitors, such as CWP-291; chemokine receptor 2 (CCR) inhibitors, such as PF-04136309, CCX-872, BMS-813160 (CCR2/CCR5); thymidylate synthase inhibitors, such as ONX-0801; ALK/ROS1 inhibitors, such as lorlatinib; tankyrase inhibitors, such as G007-LK; triggering receptor expressed on myeloid cells 1 (TREM1; NCBI Gene ID: 54210), such as PY159; triggering receptor expressed on myeloid cells 2 (TREM2; NCBI Gene ID: 54209), such as PY314; Mdm2 p53-binding protein inhibitors, such as CMG-097, HDM-201; c-PIM inhibitors, such as PIM447; sphingosine kinase-2 (SK2) inhibitors, such as Yeliva® (ABC294640); DNA polymerase inhibitors, such as sapacitabine; Cell cycle/Microtubule inhibitors, such as eribulin mesylate; c-MET inhibitors, such as AMG-337, savolitinib, tivantinib (ARQ-197), capmatinib, and tepotinib, ABT-700, AG213, AMG-208, JNJ-38877618 (OMO-1), merestinib, HQP-8361; c-Met/VEGFR inhibitors, such as BMS-817378, TAS-115; c-Met/RON inhibitors, such as BMS-777607; BCR/ABL inhibitors, such as rebastinib, asciminib, ponatinib (ICLUSIG®); MNK1/MNK2 inhibitors, such as eFT-508; Cytochrome P450 11B2/Cytochrome P450 17/AKT protein kinase inhibitors, such as LAE-201; Cytochrome P450 3A4 stimulators, such as mitotane; lysine-specific demethylase-1 (LSD1) inhibitors, such as CC-90011; CSF1R/KIT and FLT3 inhibitors, such as pexidartinib (PLX3397); Flt3 tyrosine kinase/Kit tyrosine kinase

inhibitor and PDGF receptor antagonists, such as quizartinib dihydrochloride; kinase inhibitors, such as vandetanib; E selectin antagonists, such as GMI-1271; differentiation inducers, such as tretinoin; epidermal growth factor receptor (EGFR) inhibitors, such as osimertinib (AZD-9291), cetuximab; topoisomerase inhibitors, such as Adriamycin, doxorubicin, daunorubicin, dactinomycin, DaunoXome, Caelyx, eniposide, epirubicin, etoposide, idarubicin, irinotecan, mitoxantrone, pixantrone, sobuzoxane, topotecan, irinotecan, MM-398 (liposomal irinotecan), vosaroxin and GPX-150, aldoxorubicin, AR-67, mavelertinib, AST-2818, avitinib (ACEA-0010), irofulven (MGI-114); corticosteroids, such as cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone; growth factor signal transduction kinase inhibitors; nucleoside analogs, such as DFP-10917; Axl inhibitors, such as BGB-324 (bemcentinib), SLC-0211; Axl/Flt3 inhibitors, such as gilteritinib; Inhibitors of bromodomain and extraterminal motif (BET) proteins, including ABBV-744, BRD2 (NCBI Gene ID: 6046), BRD3 (NCBI Gene ID: 8019), BRD4 (NCBI Gene ID: 23476), and bromodomain testis-specific protein (BRDT; NCBI Gene ID: 676), such as INCB-054329, INCB057643, TEN-010, AZD-5153, ABT-767, BMS-986158, CC-90010, GSK525762 (molibresib), NHWD-870, ODM-207, GSK-2820151, GSK-1210151A, ZBC246, ZBC260, ZEN3694, FT-1101, RG-6146, CC-90010, CC-95775, mivebresib, BI-894999, PLX-2853, PLX-51107, CPI-0610, GS-5829; PARP inhibitors, such as pamiparib, fuzuloparib, talazoparib tosylate, niraparib tosylate monohydrate, rucaparib camsylate, olaparib, veliparib, ABT-767, BGB-290, bendamustine hydrochloride; PARP/Tankyrase inhibitors such as 2X-121 (e-7499); IMP-4297, SC-10914, IDX-1197, HWH-340, CK-102, simmiparib; Proteasome inhibitors, such as ixazomib (NINLARO®), carfilzomib (Kyprolis®), marizomib, bortezomib; Glutaminase inhibitors, such as CB-839 (telaglenastat), bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES); mitochondrial complex I inhibitors, such as metformin, phenformin; vaccines, such as peptide vaccine TG-01 (RAS), GALE-301, GALE-302, nelipepimut-s, SurVaxM, DSP-7888, TPIV-200, PVX-410, VXL-100, DPX-E7, ISA-101, 6MHP, OSE-2101, galinpepimut-S, SVN53-67/M57-KLH, IMU-131, peptide subunit vaccine (acute lymphoblastic leukemia, University Children's Hospital Tuebingen); bacterial vector vaccines such as CRS-207/GVAX, axalimogene filolisbac (ADXS11-001); adenovirus vector vaccines such as nadofaragene firadenovec; autologous Gp96 vaccine; dendritic cells vaccines, such as CVactm, stapuldencel-T, eltrapuldencel-T, rocapuldencel-T (AGS-003), DCVAC, SL-701, BSK01TM, ADXS31-142, autologous dendritic cell vaccine (metastatic malignant melanoma, intradermal/intravenous, Universitatsklinikum Erlangen); oncolytic vaccines such as, talimogene laherparepvec, pexastimogene devacirepvec, GL-ONC1, MG1-MA3, parvovirus H-1, ProstAtak, enadenotucirev, MG1MA3, ASN-002 (TG-

1042); therapeutic vaccines, such as CVAC-301, CMP-001, CreaVax-BC, PF-06753512, VBI-1901, TG-4010, ProscaVax™; tumor cell vaccines, such as Vigil® (IND-14205), Oncoquest-L vaccine; live attenuated, recombinant, serotype 1 poliovirus vaccine, such as PVS-RIPO; Adagloxad simolenin; MEDI-0457; DPV-001 a tumor-derived, autophagosome enriched cancer vaccine; RNA vaccines such as, CV-9209, LV-305; DNA vaccines, such as MEDI-0457, MVI-816, INO-5401; modified vaccinia virus Ankara vaccine expressing p53, such as MVA-p53; DPX-Survivac; BriaVax™; GI-6301; GI-6207; GI-4000; IO-103; Neoantigen peptide vaccines, such as AGEN-2017, GEN-010, NeoVax, RG-6180, GEN-009, PGV-001 (TLR-3 agonist), GRANITE-001, NEO-PV-01; Peptide vaccines that target heat shock proteins, such as PhosphoSynVax™; Vitespen (HSPPC-96-C), NANT Colorectal Cancer Vaccine containing aldoxorubicin, autologous tumor cell vaccine + systemic CpG-B + IFN-alpha (cancer), IO-120 + IO-103 (PD-L1/PD-L2 vaccines), HB-201, HB-202, HB-301, TheraT®-based vaccines; TLR-3 agonist/interferon inducers, such as Poly-ICLC (NSC-301463); STAT-3 inhibitors, such as napabucasin (BBI-608); ATPase p97 inhibitors, such as CB-5083; smoothened (SMO) receptor inhibitors, such as Odomzo® (sonidegib, formerly LDE-225), LEQ506, vismodegib (GDC-0449), BMS-833923, glasdegib (PF-04449913), LY2940680, and itraconazole; interferon alpha ligand modulators, such as interferon alpha-2b, interferon alpha-2a biosimilar (Biogenomics), ropeginterferon alfa-2b (AOP-2014, P-1101, PEG IFN alpha-2b), Multiferon (Alfanative, Viragen), interferon alpha 1b, Roferon-A (Canferon, Ro-25-3036), interferon alfa-2a follow-on biologic (Biosidus)(Inmutag, Inter 2A), interferon alfa-2b follow-on biologic (Biosidus - Bioferon, Citopheron, Ganapar, Beijing Kawin Technology – Kaferon), Alfaferone, pegylated interferon alpha-1b, peginterferon alfa-2b follow-on biologic (Amega), recombinant human interferon alpha-1b, recombinant human interferon alpha-2a, recombinant human interferon alpha-2b, veltuzumab-IFN alpha 2b conjugate, Dynavax (SD-101), and interferon alfa-n1 (Humoferon, SM-10500, Sumiferon); interferon gamma ligand modulators, such as interferon gamma (OH-6000, Ogamma 100); telomerase modulators, such as, tertomotide (GV-1001, HR-2802, Riavax) and imetelstat (GRN-163, JNJ-63935937); DNA methyltransferases inhibitors, such as temozolomide (CCRG-81045), decitabine, oral decitabine and cedazuridine (ASTX727), guadecitabine (S-110, SGI-110), KRX-0402, RX-3117, RRx-001, and azacytidine (CC-486); DNA gyrase inhibitors, such as pixantrone and sobuzoxane; DNA gyrase inhibitors/Topoisimerase II inhibitors, such as amrubicin; Bcl-2 family protein inhibitors, such as ABT-263, venetoclax (ABT-199), obatoclax mesylate, pelcitoclax, ABT-737, RG7601, and AT-101; Bcl-2/Bcl-XL inhibitors, such as navitoclax (ABT-263; RG-7433); Notch inhibitors, such as LY3039478 (crenigacestat), tarextumab (anti-Notch2/3), BMS-906024; hyaluronidase

stimulators, such as PEGPH-20; Erbb2 tyrosine kinase receptor inhibitors/Hyaluronidase stimulators, such as Herceptin Hylecta; Wnt pathway inhibitors, such as SM-04755, PRI-724, WNT-974; gamma-secretase inhibitors, such as PF-03084014, MK-0752, RO-4929097; Grb-2 (growth factor receptor bound protein-2) inhibitors, such as BP1001; TRAIL pathway-inducing compounds, such as ONC201, ABBV-621; TRAIL modulators, such as SCB-313; Focal adhesion kinase inhibitors, such as VS-4718, defactinib, GSK2256098; hedgehog inhibitors, such as saridegib, sonidegib (LDE225), glasdegib; Aurora kinase inhibitors, such as alisertib (MLN-8237), and AZD-2811, AMG-900, barasertib, ENMD-2076; HSPB1 modulators (heat shock protein 27, HSP27), such as brivudine, apatorsen; ATR inhibitors, such as BAY-937, AZD6738, AZD6783, VX-803, VX-970 (berzosertib) and VX-970; Hsp90 inhibitors, such as AUY922, onalespib (AT13387), SNX-2112, SNX5422; murine double minute (mdm2) oncogene inhibitors, such as DS-3032b, RG7775, AMG-232, HDM201, and idasanutlin (RG7388); CD137 agonists, such as urelumab, utomilumab (PF-05082566), AGEN2373, ADG-106, BT-7480, QL1806; STING agonists, such as ADU-S100 (MIW-815), SB-11285, MK-1454, SR-8291, AdVCA0848, GSK-532, SYN-STING, MSA-1, SR-8291, GSK3745417; FGFR inhibitors, such as FGF-401, INCB-054828, BAY-1163877, AZD4547, JNJ-42756493, LY2874455, Debio-1347; fatty acid synthase (FASN) inhibitors, such as TVB-2640; CD44 binders, such as A6; protein phosphatease 2A (PP2A) inhibitors, such as LB-100; CYP17 inhibitors, such as seviteronel (VT-464), ASN-001, ODM-204, CFG920, abiraterone acetate; RXR agonists, such as IRX4204; hedgehog/smoothened (hh/Smo) antagonists, such as taladegib, patidegib, vismodegib; complement C3 modulators, such as Imprime PGG; IL-15 agonists, such as ALT-803, NKTR-255, interleukin-15/Fc fusion protein, AM-0015, NIZ-985, and hetIL-15; EZH2 (enhancer of zeste homolog 2) inhibitors, such as tazemetostat, CPI-1205, GSK-2816126, PF-06821497; oncolytic viruses, such as pelareorep, CG-0070, MV-NIS therapy, HSV-1716, DS-1647, VCN-01, ONCOS-102, TBI-1401, tasadenoturev (DNX-2401), vocimagene amiretrorepvec, RP-1, CVA21, Celyvir, LOAd-703, OBP-301, IMLYGIC®; DOT1L (histone methyltransferase) inhibitors, such as pinometostat (EPZ-5676); toxins such as Cholera toxin, ricin, Pseudomonas exotoxin, Bordetella pertussis adenylate cyclase toxin, diphtheria toxin, and caspase activators; DNA plasmids, such as BC-819; PLK inhibitors of PLK 1, 2, and 3, such as volasertib (PLK1); WEE1 inhibitors, such as AZD-1775 (adavosertib); Rho kinase (ROCK) inhibitors, such as AT13148, KD025; Inhibition of Apoptosis Protein (IAP) inhibitors, such as ASTX660, debio-1143, birinapant, APG-1387, LCL-161; RNA polymerase inhibitors, such has lurbinectedin (PM-1183), CX-5461; Tubulin inhibitors, such as PM-184, BAL-101553 (lisavanbulin), and OXI-4503, fluorapacin (AC-0001), plinabulin, vinflunine;

Toll-like receptor 4 (TLR-4) agonists, such as G100, GSK1795091, and PEPA-10; Elongation factor 1 alpha 2 inhibitors, such as plitidepsin; Elongation factor 2 inhibitors/Interleukin-2 ligands/NAD ADP ribosyltransferase stimulators, such as denileukin diftitox; CD95 inhibitors, such as APG-101, APO-010, asunercept; WT1 inhibitors, such as DSP-7888; splicing factor 3B subunit1 (SF3B1) inhibitors, such as H3B-8800; retinoid Z receptor gamma (RORγ) agonists, such as LYC-55716; and microbiome modulators, such as SER-401, EDP-1503, MRx-0518.

[0070] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more additional therapeutic agents comprising an inhibitor or antagonist of: myeloid cell leukemia sequence 1 (MCL1) apoptosis regulator (NCBI Gene ID: 4170); mitogen-activated protein kinase 1 (MAP4K1) (also called Hematopoietic Progenitor Kinase 1 (HPK1), NCBI Gene ID: 11184); diacylglycerol kinase alpha (DGKA, DAGK, DAGK1 or DGK-alpha; NCBI Gene ID: 1606); 5'-nucleotidase ecto (NT5E or CD73; NCBI Gene ID: 4907); ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1 or CD39; NCBI Gene ID: 593); transforming growth factor beta 1 (TGFB1 or TGFβ; NCBI Gene ID: 7040); heme oxygenase 1 (HMOX1, HO-1 or HO1; NCBI Gene ID: 3162); heme oxygenase 2 (HMOX2, HO-2 or HO2; NCBI Gene ID: 3163); vascular endothelial growth factor A (VEGFA or VEGF; NCBI Gene ID: 7422); erb-b2 receptor tyrosine kinase 2 (ERBB2, HER2, HER2/neu or CD340; NCBI Gene ID: 2064), epidermal growth factor receptor (EGFR, ERBB, ERBB1 or HER1; NCBI Gene ID: 1956); ALK receptor tyrosine kinase (ALK, CD246; NCBI Gene ID: 238); poly(ADP-ribose) polymerase 1 (PARP1; NCBI Gene ID: 142); poly(ADP-ribose) polymerase 2 (PARP2; NCBI Gene ID: 10038); TCDD inducible poly(ADP-ribose) polymerase (TIPARP, PARP7; NCBI Gene ID: 25976); cyclin dependent kinase 4 (CDK4; NCBI Gene ID: 1019); cyclin dependent kinase 6 (CDK6; NCBI Gene ID: 1021); TNF receptor superfamily member 14 (TNFRSF14, HVEM, CD270; NCBI Gene ID: 8764); T cell immunoreceptor with Ig and ITIM domains (TIGIT; NCBI Gene ID: 201633); X-linked inhibitor of apoptosis (XIAP, BIRC4, IAP-3; NCBI Gene ID: 331); baculoviral IAP repeat containing 2 (BIRC2, cIAP1; NCBI Gene ID: 329); baculoviral IAP repeat containing 3 (BIRC3, cIAP2; NCBI Gene ID: 330); baculoviral IAP repeat containing 5 (BIRC5, surviving; NCBI Gene ID: 332); C-C motif chemokine receptor 2 (CCR2, CD192; NCBI Gene ID: 729230); C-C motif chemokine receptor 5 (CCR5, CD195; NCBI Gene ID: 1234); C-C motif chemokine receptor 8 (CCR8, CDw198; NCBI Gene ID: 1237); C-X-C motif chemokine receptor 2 (CXCR2, CD182; NCBI Gene ID: 3579); C-X-C motif chemokine receptor 3 (CXCR3, CD182, CD183; NCBI Gene ID: 2833); C-X-C motif chemokine receptor 4 (CXCR4, CD184; NCBI Gene ID: 7852); arginase (ARG1

(NCBI Gene ID: 383), ARG2 (NCBI Gene ID: 384)), carbonic anhydrase (CA1 (NCBI Gene ID: 759), CA2 (NCBI Gene ID: 760), CA3 (NCBI Gene ID: 761), CA4 (NCBI Gene ID: 762), CA5A (NCBI Gene ID: 763), CA5B (NCBI Gene ID: 11238), CA6 (NCBI Gene ID: 765), CA7 (NCBI Gene ID: 766), CA8 (NCBI Gene ID: 767), CA9 (NCBI Gene ID: 768), CA10 (NCBI Gene ID: 56934), CA11 (NCBI Gene ID: 770), CA12 (NCBI Gene ID: 771), CA13 (NCBI Gene ID: 377677), CA14 (NCBI Gene ID: 23632)), prostaglandin-endoperoxide synthase 1 (PTGS1, COX-1; NCBI Gene ID: 5742), prostaglandin-endoperoxide synthase 2 (PTGS2, COX-2; NCBI Gene ID: 5743), secreted phospholipase A2, prostaglandin E synthase (PTGES, PGES; Gene ID: 9536), arachidonate 5-lipoxygenase (ALOX5, 5-LOX; NCBI Gene ID: 240) and/or soluble epoxide hydrolase 2 (EPHX2, SEH; NCBI Gene ID: 2053); a secreted phospholipase A2 (*e.g.*, PLA2G1B (NCBI Gene ID: 5319); PLA2G7 (NCBI Gene ID: 7941), PLA2G3 (NCBI Gene ID: 50487), PLA2G2A (NCBI Gene ID: 5320); PLA2G4A (NCBI Gene ID: 5321); PLA2G12A (NCBI Gene ID: 81579); PLA2G12B (NCBI Gene ID: 84647); PLA2G10 (NCBI Gene ID: 8399); PLA2G5 (NCBI Gene ID: 5322); PLA2G2D (NCBI Gene ID: 26279); PLA2G15 (NCBI Gene ID: 23659)); indoleamine 2,3-dioxygenase 1 (IDO1; NCBI Gene ID: 3620); indoleamine 2,3-dioxygenase 2 (IDO2; NCBI Gene ID: 169355); hypoxia inducible factor 1 subunit alpha (HIF1A; NCBI Gene ID: 3091); angiopoietin 1 (ANGPT1; NCBI Gene ID: 284); Endothelial TEK tyrosine kinase (TIE-2, TEK, CD202B; NCBI Gene ID: 7010); Janus kinase 1 (JAK1; NCBI Gene ID: 3716); catenin beta 1 (CTNNB1; NCBI Gene ID: 1499); histone deacetylase 9 (HDAC9; NCBI Gene ID: 9734), and/or 5'-3' exoribonuclease 1 (XRN1; NCBI Gene ID: 54464).

[0071] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an agonist of fms related receptor tyrosine kinase 3 (FLT3); FLK2; STK1; CD135; FLK-2; NCBI Gene ID: 2322). Examples of FLT3 agonists include, but are not limited to, CDX-301 and GS-3583. GS-3583 is described, *e.g.*, in WO 2020/263830, hereby incorporated herein by reference in its entirety for all purposes.

[0072] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD19 agent or antibody. Examples of anti-CD19 agents or antibodies that can be co-administered include without limitation: blinatumomab, tafasitamab, XmAb5574 (Xencor), AFM-11, inebilizumab, loncastuximab, MEDI 551 (Cellective Therapeutics); and MDX-1342 (Medarex).

[0073] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD20 agent or antibody. Examples of anti-CD20 agents or antibodies that can be co-administered include without limitation: IGN-002, PF-05280586; Rituximab (Rituxan/Biogen Idec), Ofatumumab (Arzerra/Genmab), Obinutuzumab (Gazyva/Roche Glycart Biotech), Alemtuzumab, Veltuzumab, Veltuzumab, Ocrelizumab (Ocrevus/Biogen Idec; Genentech), Ocaratuzumab and Ublituximab, and LFB-R603 (LFB Biotech.; rEVO Biologics).

[0074] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD22 agent or antibody. Examples of anti-CD22 agents or antibodies that can be co-administered include without limitation: Epratuzumab, AMG-412, IMMU-103 (Immunomedics).

[0075] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD30 agent or antibody. Examples of anti-CD30 agents or antibodies that can be co-administered include without limitation: Brentuximab vedotin (Seattle Genetics).

[0076] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD33 agent or antibody. Examples of anti-CD33 agents or antibodies that can be co-administered include without limitation: gemtuzumab, lintuzumab, vadastuximab, CIK-CAR.CD33; CD33CART, AMG-330 (CD33/CD3), AMG-673 (CD33/CD3), and GEM-333 (CD3/CD33), and IMGN-779.

[0077] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD37 agent or antibody. Examples of anti- CD37 agents or antibodies that can be co-administered include without limitation: BI836826 (Boehringer Ingelheim), Otlertuzumab, and TRU-016 (Trubion Pharmaceuticals).

[0078] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD38 agent or antibody. Examples of anti-CD38

agents or antibodies that can be co-administered include without limitation: CD38, such as T-007, UCART-38; Darzalex (Genmab), Daratumumab, JNJ-54767414 (Darzalex/Genmab), Isatuximab, SAR650984 (ImmunoGen), MOR202, MOR03087 (MorphoSys), TAK-079; and anti-CD38-attenukine, such as TAK573.

[0079] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD52 agent or antibody. Examples of anti-CD52 agents or antibodies that can be co-administered include without limitation: anti-CD52 antibodies, such as Alemtuzumab (Campath/University of Cambridge).

[0080] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD98 (4F2, FRP-1) agent or antibody. Examples of anti-CD98 agents or antibodies that can be co-administered include without limitation: IGN523 (Igenica).

[0081] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD157 (BST-1) agent or antibody. Examples of anti-CD157 agents or antibodies that can be co-administered include without limitation: OBT357, MEN1112 (Menarini; Oxford BioTherapeutics).

[0082] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti- DKK-1 agent or antibody. Examples of anti-DKK-1 agents or antibodies that can be co-administered include without limitation: BHQ880 (MorphoSys; Novartis), and DKN-01, LY-2812176 (Eli Lilly).

[0083] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-GRP78 (BiP) agent or antibody. Examples of anti-GRP78 agents or antibodies that can be co-administered include without limitation: PAT-SM6 (OncoMab GmbH).

[0084] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-NOTCH1 agent or antibody. Examples of anti-

NOTCH1 agents or antibodies that can be co-administered include without limitation: Brontictuzumab, OMP-52M51 (OncoMed Pharmaceuticals).

[0085] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-ROR1 agent or antibody. Examples of anti- ROR1 agents or antibodies that can be co-administered include without limitation: Mapatumumab, TRM1, and HGS-1012 (Cambridge Antibody Technology).

[0086] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-SLAMF7 (CS1, CD319) agent or antibody. Examples of anti-SLAMF7 agents or antibodies that can be co-administered include without limitation: Elotuzumab, HuLuc63, BMS-901608 (Empliciti/PDL BioPharma), Mogamulizumab (KW-0761).

[0087] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-TNFRSF10A (DR4; APO2; CD261; TRAILR1; TRAILR-1) agent or antibody. Examples of anti- TNFRSF10A agents or antibodies that can be co-administered include without limitation: Mapatumumab, TRM1, and HGS-1012 (Cambridge Antibody Technology).

[0088] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-Transferrin Receptor (TFRC; CD71) agent or antibody. Examples of anti-Transferrin Receptor agents or antibodies that can be co-administered include without limitation: E2.3/A27.15 (University of Arizona).

[0089] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-EPHA3 agent or antibody. Examples of anti-EPHA3 agents or antibodies that can be co-administered include without limitation: Ifabotuzumab, KB004 (Ludwig Institute for Cancer Research).

[0090] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CCR4 agent or antibody. Examples of anti- CCR4

agents or antibodies that can be co-administered include without limitation: Mogamulizumab, KW-0761 (Poteligeo/Kyowa Hakko Kirin Co.).

[0091] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CXCR4 agent or antibody. Examples of anti-CXCR4 agents or antibodies that can be co-administered include without limitation: Ulocuplumab, BMS-936564, MDX-1338 (Medarex), and PF-06747143 (Pfizer).

[0092] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-BAFF agent or antibody. Examples of anti-BAFF agents or antibodies that can be co-administered include without limitation: Tabalumab, LY2127399 (Eli Lilly).

[0093] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-BAFF Receptor (BAFF-R) agent or antibody. Examples of anti-BAFF-R agents or antibodies that can be co-administered include without limitation: VAY736 (MorphoSys; Novartis).

[0094] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-RANKL agent or antibody. Examples of anti-RANKL agents or antibodies that can be co-administered include without limitation: Denosumab, AMG-162 (Prolia; Ranmark; Xgeva/Amgen).

[0095] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-IL-6 agent or antibody. Examples of anti-IL-6 agents or antibodies that can be co-administered include without limitation: Siltuximab, CNTO-328 (Sylvant/Centocor).

[0096] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-IL-6 Receptor (IL-6R) agent or antibody. Examples of anti-IL-6R agents or antibodies that can be co-administered include without limitation:

Tocilizumab, R-1569 (Actemra/Chugai Pharmaceutical; Osaka University), or AS-101 (CB-06-02, IVX-Q-101).

[0097] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-IL3RA (CD123) agent or antibody. Examples of anti-IL3RA (CD123) agents or antibodies that can be co-administered include without limitation: tagraxofusp, talacotuzumab (JNJ-56022473; CSL362 (CSL)), pivekimab sunirine (IMGN632), MB-102 (Mustang Bio), CSL360 (CSL); vibecotamab (XmAb14045; Xencor); KHK2823 (Kyowa Hakko Kirin Co.); MGD-024 (CD123/CD3; Macrogenics), APVO436 (CD123/CD3); flotetuzumab (CD123/CD3); JNJ-63709178 (CD123/CD3); and XmAb-14045 (CD123/CD3) (Xencor).

[0098] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-IL2RA (CD25) agent or antibody. Examples of anti-IL2RA agents or antibodies that can be co-administered include without limitation: Basiliximab, SDZ-CHI-621 (Simulect/Novartis), and Daclizumab.

[0099] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-IGF-1R (CD221) agent or antibody. Examples of anti-IGF-1R agents or antibodies that can be co-administered include without limitation: Ganitumab, AMG-479 (Amgen); Ganitumab, AMG-479 (Amgen), Dalotuzumab, MK-0646 (Pierre Fabre), and AVE1642 (ImmunoGen).

[0100] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-GM-CSF (CSF2) agent or antibody. Examples of anti-GM-CSF agents or antibodies that can be co-administered include without limitation: Lenzilumab (*a.k.a.*, KB003; KaloBios Pharmaceuticals).

[0101] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-HGF agent or antibody. Examples of anti-HGF agents or antibodies that can be co-administered include without limitation: Ficlatuzumab, AV-299 (AVEO Pharmaceuticals).

[0102] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD44 agent or antibody. Examples of anti- CD44 agents or antibodies that can be co-administered include without limitation: RG7356, RO5429083 (Chugai Biopharmaceuticals; Roche).

[0103] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-VLA-4 (CD49d) agent or antibody. Examples of anti-VLA-4 agents or antibodies that can be co-administered include without limitation: Natalizumab, BG-0002-E (Tysabri/Elan Corporation).

[0104] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-ICAM-1 (CD54) agent or antibody. Examples of anti-ICAM-1 agents or antibodies that can be co-administered include without limitation: BI-505 (BioInvent International).

[0105] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-VEGF-A agent or antibody. Examples of anti-VEGF-A agents or antibodies that can be co-administered include without limitation: Bevacizumab (Avastin/Genentech; Hackensack University Medical Center).

[0106] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-Endosialin (CD248, TEM1) agent or antibody. Examples of antiEndosialin agents or antibodies that can be co-administered include without limitation: Ontecizumab, MORAB-004 (Ludwig Institute for Cancer Research; Morphotek).

[0107] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-CD79 agent or antibody. Examples of anti-CD79 agents or antibodies that can be co-administered include without limitation: polatuzumab, DCDS4501A, RG7596 (Genentech).

[0108] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described

herein, is further combined with an anti- Isocitrate dehydrogenase (IDH) agent or antibody. Examples of anti-IDH agents or antibodies that can be co-administered include without limitation: IDH1 inhibitor ivosidenib (Tibsovo; Agios) and the IDH2 inhibitor enasidenib (Idhifa; Celgene/Agios).

[0109] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an antibody that targets tumor associated calcium signal transducer 2 (TACSTD2) (NCBI Gene ID: 4070; EGP-1, EGP1, GA733-1, GA7331, GP50, M1S1, TROP2), such as sacituzumab, *e.g.*, sacituzumab govitecan (TRODELVY™).

[0110] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-major histocompatibility complex, class I, G (HLA-G; NCBI Gene ID: 3135) antibody, such as TTX-080.

[0111] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-leukocyte immunoglobulin like receptor B2 (LILRB2, *a.k.a.*, CD85D, ILT4; NCBI Gene ID: 10288) antibody, such as JTX-8064 or MK-4830.

TNF Receptor Superfamily (TNFRSF) Member Agonists or Activators

[0112] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an agonist of one or more TNF receptor superfamily (TNFRSF) members, *e.g.*, an agonist of one or more of TNFRSF1A (NCBI Gene ID: 7132), TNFRSF1B (NCBI Gene ID: 7133), TNFRSF4 (OX40, CD134; NCBI Gene ID: 7293), TNFRSF5 (CD40; NCBI Gene ID: 958), TNFRSF6 (FAS, NCBI Gene ID: 355), TNFRSF7 (CD27, NCBI Gene ID: 939), TNFRSF8 (CD30, NCBI Gene ID: 943), TNFRSF9 (4-1BB, CD137, NCBI Gene ID: 3604), TNFRSF10A (CD261, DR4, TRAILR1, NCBI Gene ID: 8797), TNFRSF10B (CD262, DR5, TRAILR2, NCBI Gene ID: 8795), TNFRSF10C (CD263, TRAILR3, NCBI Gene ID: 8794), TNFRSF10D (CD264, TRAILR4, NCBI Gene ID: 8793), TNFRSF11A (CD265, RANK, NCBI Gene ID: 8792), TNFRSF11B (NCBI Gene ID: 4982), TNFRSF12A (CD266, NCBI Gene ID: 51330), TNFRSF13B (CD267, NCBI Gene ID: 23495), TNFRSF13C (CD268, NCBI Gene ID: 115650), TNFRSF16 (NGFR, CD271, NCBI Gene ID: 4804), TNFRSF17 (BCMA, CD269, NCBI Gene ID: 608), TNFRSF18 (GITR, CD357, NCBI Gene ID: 8784), TNFRSF19

(NCBI Gene ID: 55504), TNFRSF21 (CD358, DR6, NCBI Gene ID: 27242), and TNFRSF25 (DR3, NCBI Gene ID: 8718).

[0113] Examples anti-TNFRSF4 (OX40) antibodies that can be co-administered include without limitation, MEDI6469, MEDI6383, MEDI0562 (tavolixizumab), MOXR0916, PF-04518600, RG-7888, GSK-3174998, INCAGN1949, BMS-986178, GBR-8383, ABBV-368, and those described in WO2016179517, WO2017096179, WO2017096182, WO2017096281, and WO2018089628, each of which is hereby incorporated by reference in its entirety.

[0114] Examples anti-TNF receptor superfamily member 10b (TNFRSF10B, DR5, TRAILR2) antibodies that can be co-administered include without limitation, such as DS-8273, CTB-006, INBRX-109, and GEN-1029.

[0115] Examples of anti-TNFRSF5 (CD40) antibodies that can be co-administered include without limitation selicrelumab (RO7009789), mitazalimab (*a.k.a.*, vanalimab, ADC-1013, JNJ-64457107), RG7876, SEA-CD40, APX-005M and ABBV-428, ABBV-927, and JNJ-64457107.

[0116] Examples of anti-TNFRSF7 (CD27) that can be co-administered include without limitation varlilumab (CDX-1127).

[0117] Examples of anti-TNFRSF9 (4-1BB, CD137) antibodies that can be co-administered include without limitation urelumab, utomilumab (PF-05082566), AGEN2373, and ADG-106, BT-7480, and QL1806.

[0118] Examples of anti-TNFRSF17 (BCMA) that can be co-administered include without limitation GSK-2857916.

[0119] Examples of anti-TNFRSF18 (GITR) antibodies that can be co-administered include without limitation, MEDI1873, FPA-154, INCAGN-1876, TRX-518, BMS-986156, MK-1248, GWN-323, and those described in WO2017096179, WO2017096276, WO2017096189, and WO2018089628. In some embodiments, an antibody, or fragment thereof, co-targeting TNFRSF4 (OX40) and TNFRSF18 (GITR) is co-administered. Such antibodies are described, *e.g.*, in WO2017096179 and WO2018089628, each of which is hereby incorporated by reference in its entirety.

[0120] Example anti-TRAILR1, anti-TRAILR2, anti-TRAILR3, anti-TRAILR4 antibodies that can be co-administered include without limitation ABBV-621.

[0121] Examples of Bi-specific antibodies targeting TNFRSF family members that can be co-administered include without limitation PRS-343 (CD-137/HER2), AFM26 (BCMA/CD16A), AFM-13 (CD16/CD30), REGN-1979 (CD20/CD3), AMG-420 (BCMA/CD3), INHIBRX-105 (4-1BB/PDL1), FAP-4-IBBL (4-1BB/FAP), XmAb-13676 (CD3/CD20), RG-7828 (CD20/CD3), CC-93269 (CD3/BCMA), REGN-5458 (CD3/BCMA), and IMM-0306 (CD47/CD20), and AMG-424 (CD38.CD3).

[0122] Examples of inhibitors of PVR related immunoglobulin domain containing (PVRIG, CD112R) that can be co-administered include without limitation: COM-701.

[0123] Examples of inhibitors of T cell immunoreceptor with Ig and ITIM domains (TIGIT; NCBI Gene ID: 201633) that can be co-administered include without limitation: BMS-986207, RG-6058, AGEN-1307, and COM-902, etigilimab, tiragolumab (*a.k.a.*, MTIG-7192A; RG-6058; RO 7092284), AGEN1777, IBI-939, AB154, MG1131 and EOS884448 (EOS-448).

[0124] Examples of inhibitors of hepatitis A virus cellular receptor 2 (HAVCR2, TIMD3, TIM-3) that can be co-administered include without limitation: cobolimab (TSR-022), LY-3321367, sabatolimab (MBG-453), INCAGN-2390, RO-7121661 (PD-1/TIM-3), LY-3415244 (TIM-3/PDL1), and RG7769 (PD-1/TIM-3).

[0125] Examples of inhibitors of lymphocyte activating 3 (LAG-3, CD223) that can be co-administered include without limitation: relatlimab (ONO-4482), LAG-525, MK-4280, REGN-3767, INCAGN2385, TSR-033, MGD-013 (PD-1/LAG-3), and FS-118 (LAG-3/PD-L1).

[0126] Examples of anti-killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1; KIR; NCBI Gene ID: 3811) monoclonal antibodies, such as lirilumab (IPH-2102), and IPH-4102.

[0127] Examples of anti-NKG2a antibodies that can be co-administered include without limitation: monalizumab.

[0128] Examples of anti-V-set immunoregulatory receptor (VSIR, B7H5, VISTA) antibodies that can be co-administered include without limitation: HMBD-002, and CA-170 (PD-L1/VISTA).

[0129] Examples of anti-CD70 antibodies that can be co-administered include without limitation: AMG-172.

[0130] Examples of anti-ICOS antibodies that can be co-administered include without limitation: JTX-2011, GSK3359609.

[0131] Examples of ICOS agonists that can be co-administered include without limitation: ICOS-L.COMP (Gariepy, *et al.* 106th Annu Meet Am Assoc Immunologists (AAI) (May 9-13, San Diego) 2019, Abst 71.5).

Immune checkpoint inhibitors

[0132] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more immune checkpoint inhibitors. In some embodiments, the one or more immune checkpoint inhibitors is a proteinaceous (*e.g.*, antibody or fragment thereof, or antibody mimetic) inhibitor of PD-L1 (CD274), PD-1 (PDCD1) or CTLA4. In some embodiments, the one or more immune checkpoint inhibitors comprises a small organic molecule inhibitor of PD-L1 (CD274), PD-1 (PDCD1) or CTLA4.

[0133] Examples of inhibitors of CTLA4 that can be co-administered include without limitation ipilimumab, tremelimumab, BMS-986218, AGEN1181, AGEN1884, BMS-986249, MK-1308, REGN-4659, ADU-1604, CS-1002, BCD-145, APL-509, JS-007, BA-3071, ONC-392, AGEN-2041, JHL-1155, KN-044, CG-0161, ATOR-1144, PBI-5D3H5, BPI-002, HBM-4003, as well as multi-specific inhibitors FPT-155 (CTLA4/PD-L1/CD28), PF-06936308 (PD-1/CTLA4), MGD-019 (PD-1/CTLA4), KN-046 (PD-1/CTLA4), MEDI-5752 (CTLA4/PD-1), XmAb-20717 (PD-1/CTLA4), and AK-104 (CTLA4/PD-1).

[0134] Examples of inhibitors/antibodies of PD-L1 (CD274) or PD-1 (PDCD1) that can be co-administered include without limitation zimberelimab, pembrolizumab (KEYTRUDA®, MK-3477), nivolumab (OPDIVO®, BMS-936558, MDX-1106), cemiplimab, pidilizumab, spartalizumab (PDR-001), atezolizumab (RG-7446; TECENTRIQ, MPDL3280A), durvalumab (MEDI-4736), avelumab (MSB0010718C), tislelizumab (BGB-A317), toripalimab (JS-001), genolimzumab (CBT-501), camrelizumab (SHR-1210), dostarlimab (TSR-042), sintilimab (IBI-308), tislelizumab (BGB-A317), cemiplimab (REGN-2810), lambrolizumab (CAS Reg. No. 1374853-91-4), AMG-404, AMP-224, MEDI0680 (AMP-514), BMS-936559, CK-301, PF-06801591, GEN-1046 (PD-L1/4-1BB), GLS-010 (WBP-3055), AK-103 (HX-008), AK-105, CS-1003, HLX-10, MGA-012, BI-754091, AGEN-2034, JNJ-63723283, LZM-009, BCD-100, LY-3300054, SHR-1201, Sym-021, ABBV-181, PD1-PIK, BAT-1306, CX-072, CBT-502, MSB-2311, JTX-4014, BGB-A333, SHR-1316, CS-1001 (WBP-3155, KN-035, HLX-20, KL-A167, STI-A1014, STI-A1015 (IMC-001), BCD-135, FAZ-053, TQB-2450, MDX1105-01, GS-4224, GS-4416, INCB086550, MAX10181, as well as multi-specific inhibitors FPT-155 (CTLA4/PD-L1/CD28), PF-06936308 (PD-1/CTLA4), MGD-013 (PD-1/LAG-3), RO-7247669

(PD-1/LAG-3), FS-118 (LAG-3/PD-L1) MGD-019 (PD-1/CTLA4), KN-046 (PD-1/CTLA4), MEDI-5752 (CTLA4/PD-1), RO-7121661 (PD-1/TIM-3), XmAb-20717 (PD-1/CTLA4), AK-104 (CTLA4/PD-1), M7824 (PD-L1/TGFβ-EC domain), CA-170 (PD-L1/VISTA), CDX-527 (CD27/PD-L1), LY-3415244 (TIM-3/PDL1), RG7769 (PD-1/TIM-3) and INBRX-105 (4-1BB/PDL1), GNS-1480 (PD-L1/EGFR), SCH-900475, PF-06801591, AGEN-2034, AK-105, PD1-PIK, BAT-1306, BMS-936559, CK-301, MEDI-0680, PDR001 + Tafinlar ® + Mekinist ®, and those described, *e.g.*, in Intl. Patent Publ. Nos. WO2018195321, WO2020014643, WO2019160882, and WO2018195321.

[0135] In various embodiments, an anti-CD47 agent as described herein, is combined with an inhibitor of MCL1 apoptosis regulator, BCL2 family member (MCL1, TM; EAT; MCL1L; MCL1S; Mcl-1; BCL2L3; MCL1-ES; bcl2-L-3; mcl1/EAT; NCBI Gene ID: 4170). Examples of MCL1 inhibitors include AMG-176, AMG-397, S-64315, and AZD-5991, 483-LM, A-1210477, UMI-77, JKY-5-037, and those described in WO2018183418, WO2016033486, and WO2017147410.

Toll-Like Receptor (TLR) Agonists

[0136] In various embodiments, an anti-CD47 agent or an anti-SIRPα agent as described herein, is combined with an agonist of a toll-like receptor (TLR), *e.g.*, an agonist of TLR1 (NCBI Gene ID: 7096), TLR2 (NCBI Gene ID: 7097), TLR3 (NCBI Gene ID: 7098), TLR4 (NCBI Gene ID: 7099), TLR5 (NCBI Gene ID: 7100), TLR6 (NCBI Gene ID: 10333), TLR7 (NCBI Gene ID: 51284), TLR8 (NCBI Gene ID: 51311), TLR9 (NCBI Gene ID: 54106), and/or TLR10 (NCBI Gene ID: 81793). Example TLR7 agonists that can be co-administered include without limitation DS-0509, GS-9620, LHC-165, TMX-101 (imiquimod), GSK-2245035, resiquimod, DSR-6434, DSP-3025, IMO-4200, MCT-465, MEDI-9197, 3M-051, SB-9922, 3M-052, Limtop, TMX-30X, TMX-202, RG-7863, RG-7795, and the compounds disclosed in US20100143301 (Gilead Sciences), US20110098248 (Gilead Sciences), and US20090047249 (Gilead Sciences), US20140045849 (Janssen), US20140073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), US20140350031 (Janssen), WO2014/023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), and US20130251673 (Novira Therapeutics). An TLR7/TLR8 agonist that can be co-administered is NKTR-262. Example TLR8 agonists that

can be co-administered include without limitation E-6887, IMO-4200, IMO-8400, IMO-9200, MCT-465, MEDI-9197, motolimod, resiquimod, GS-9688, VTX-1463, VTX-763, 3M-051, 3M-052, and the compounds disclosed in US20140045849 (Janssen), US20140073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), US20140350031 (Janssen), WO2014/023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), and US20130251673 (Novira Therapeutics). Example TLR9 agonists that can be co-administered include without limitation AST-008, CMP-001, IMO-2055, IMO-2125, litenimod, MGN-1601, BB-001, BB-006, IMO-3100, IMO-8400, IR-103, IMO-9200, agatolimod, DIMS-9054, DV-1079, DV-1179, AZD-1419, leftolimod (MGN-1703), CYT-003, CYT-003-QbG10 and PUL-042. Examples of TLR3 agonist include rintatolimod, poly-ICLC, RIBOXXON®, Apoxxim, RIBOXXIM®, IPH-33, MCT-465, MCT-475, and ND-1.1.

[0137] Examples of TLR8 inhibitors include, but are not limited to, E-6887, IMO-8400, IMO-9200 and VTX-763.

[0138] Examples of TLR8 agonists include, but are not limited to, MCT-465, motolimod, GS-9688, and VTX-1463.

[0139] Examples of TLR9 agonists include but are not limited to, AST-008, IMO-2055, IMO-2125, lefitolimod, litenimod, MGN-1601, and PUL-042.

[0140] Examples of TLR7/TLR8 agonists include without limitation NKTR-262, IMO-4200, MEDI-9197 (telratolimod) and resiquimod.

[0141] Examples of TLR agonists include without limitation: lefitolimod, tilsotolimod, rintatolimod, DSP-0509, AL-034, G-100, cobitolimod, AST-008, motolimod, GSK-1795091, GSK-2245035, VTX-1463, GS-9688, LHC-165, BDB-001, RG-7854, telratolimod.

[0142] In some embodiments, the therapeutic agent is a stimulator of interferon genes (STING) In some embodiments, the STING receptor agonist or activator is selected from ADU-S100 (MIW-815), SB-11285, MK-1454, SR-8291, AdVCA0848, GSK-532, SYN-STING, MSA-1, SR-8291, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), cyclic-GAMP (cGAMP), and cyclic-di-AMP.

TCR Signaling Modulators

[0143] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more agonist or antagonist of T-Cell Receptor (TCR) signaling modulators. Activation of T cells through the TCR and is essential for thymocyte development and effector T cell function. TCR activation promotes signaling cascades that ultimately determine cell fate through regulating cytokine production, cell survival, proliferation, and differentiation. Examples of TCR signaling modulators include without limitation CD2 (cluster of differentiation 2, LFA-2, T11, LFA-3 receptor), CD3 (cluster of differentiation 3), CD4 (cluster of differentiation 4), CD8 (cluster of differentiation 8), CD28 (cluster of differentiation 28), CD45 (PTPRC, B220, GP180), LAT (Linker for activation of T cells, LAT1), Lck, LFA-1 (ITGB2, CD18, LAD, LCAMB), Src, Zap-70, SLP-76, DGKalpha, CBL-b, CISH, HPK1. Examples of agonist of cluster of differentiation 3 (CD3) that can be co-administered include without limitation MGD015.

[0144] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more blockers or inhibitors of inhibitory immune checkpoint proteins or receptors and/or with one or more stimulators, activators or agonists of one or more stimulatory immune checkpoint proteins or receptors. Blockade or inhibition of inhibitory immune checkpoints can positively regulate T-cell or NK cell activation and prevent immune escape of cancer cells within the tumor microenvironment. Activation or stimulation of stimulatory immune check points can augment the effect of immune checkpoint inhibitors in cancer therapeutics. In various embodiments, the immune checkpoint proteins or receptors regulate T cell responses (*e.g.*, reviewed in Xu, et al., J Exp Clin Cancer Res. (2018) 37:110). In various embodiments, the immune checkpoint proteins or receptors regulate NK cell responses (*e.g.*, reviewed in Davis, et al., Semin Immunol. (2017) 31:64–75 and Chiossone, et al., Nat Rev Immunol. (2018) 18(11):671-688).

[0145] Examples of immune checkpoint proteins or receptors include without limitation CD27, CD70; CD40, CD40LG; CD47, CD48 (SLAMF2), transmembrane and immunoglobulin domain containing 2 (TMIGD2, CD28H), CD84 (LY9B, SLAMF5), CD96, CD160, MS4A1 (CD20), CD244 (SLAMF4); CD276 (B7H3); V-set domain containing T cell activation inhibitor 1 (VTCN1, B7H4); V-set immunoregulatory receptor (VSIR, B7H5, VISTA); immunoglobulin superfamily member 11 (IGSF11, VSIG3); natural killer cell cytotoxicity receptor 3 ligand 1

(NCR3LG1, B7H6); HERV-H LTR-associating 2 (HHLA2, B7H7); inducible T cell co-stimulator (ICOS, CD278); inducible T cell costimulator ligand (ICOSLG, B7H2); TNF receptor superfamily member 4 (TNFRSF4, OX40); TNF superfamily member 4 (TNFSF4, OX40L); TNFRSF8 (CD30), TNFSF8 (CD30L); TNFRSF10A (CD261, DR4, TRAILR1), TNFRSF9 (CD137), TNFSF9 (CD137L); TNFRSF10B (CD262, DR5, TRAILR2), TNFRSF10 (TRAIL); TNFRSF14 (HVEM, CD270), TNFSF14 (HVEML); CD272 (B and T lymphocyte associated (BTLA)); TNFRSF17 (BCMA, CD269), TNFSF13B (BAFF); TNFRSF18 (GITR), TNFSF18 (GITRL); MHC class I polypeptide-related sequence A (MICA); MHC class I polypeptide-related sequence B (MICB); CD274 (PDL1, PD-L1); programmed cell death 1 (PDCD1, PD-1, PD-1); cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152); CD80 (B7-1), CD28; nectin cell adhesion molecule 2 (NECTIN2, CD112); CD226 (DNAM-1); Poliovirus receptor (PVR) cell adhesion molecule (PVR, CD155); T cell immunoreceptor with Ig and ITIM domains (TIGIT); T cell immunoglobulin and mucin domain containing 4 (TIMD4; TIM4); hepatitis A virus cellular receptor 2 (HAVCR2, TIMD3, TIM-3); galectin 9 (LGALS9); lymphocyte activating 3 (LAG-3, CD223); signaling lymphocytic activation molecule family member 1 (SLAMF1, SLAM, CD150); lymphocyte antigen 9 (LY9, CD229, SLAMF3); SLAM family member 6 (SLAMF6, CD352); SLAM family member 7 (SLAMF7, CD319); UL16 binding protein 1 (ULBP1); UL16 binding protein 2 (ULBP2); UL16 binding protein 3 (ULBP3); retinoic acid early transcript 1E (RAET1E; ULBP4); retinoic acid early transcript 1G (RAET1G; ULBP5); retinoic acid early transcript 1L (RAET1L; ULBP6); lymphocyte activating 3 (CD223); killer cell immunoglobulin like receptor (KIR); killer cell lectin like receptor C1 (KLRC1, NKG2A, CD159A); killer cell lectin like receptor K1 (KLRK1, NKG2D, CD314); killer cell lectin like receptor C2 (KLRC2, CD159c, NKG2C); killer cell lectin like receptor C3 (KLRC3, NKG2E); killer cell lectin like receptor C4 (KLRC4, NKG2F); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (KIR2DL3); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1); killer cell lectin like receptor D1 (KLRD1).

[0146] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more blockers or inhibitors of one or more T-cell inhibitory immune checkpoint proteins or receptors. Illustrative T-cell inhibitory immune checkpoint proteins or receptors include without limitation CD274 (PDL1, PD-L1); programmed

cell death 1 ligand 2 (PDCD1LG2, PD-L2, CD273); programmed cell death 1 (PDCD1, PD1, PD-1); cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152); CD276 (B7H3); V-set domain containing T cell activation inhibitor 1 (VTCN1, B7H4); V-set immunoregulatory receptor (VSIR, B7H5, VISTA); immunoglobulin superfamily member 11 (IGSF11, VSIG3); TNFRSF14 (HVEM, CD270), TNFSF14 (HVEML); CD272 (B and T lymphocyte associated (BTLA)); PVR related immunoglobulin domain containing (PVRIG, CD112R); T cell immunoreceptor with Ig and ITIM domains (TIGIT); lymphocyte activating 3 (LAG-3, CD223); hepatitis A virus cellular receptor 2 (HAVCR2, TIMD3, TIM-3); galectin 9 (LGALS9); killer cell immunoglobulin like receptor (KIR); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (KIR2DL3); and killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1).

[0147] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more agonist or activators of one or more T-cell stimulatory immune checkpoint proteins or receptors. Illustrative T-cell stimulatory immune checkpoint proteins or receptors include without limitation CD27, CD70; CD40, CD40LG; inducible T cell costimulator (ICOS, CD278); inducible T cell costimulator ligand (ICOSLG, B7H2); TNF receptor superfamily member 4 (TNFRSF4, OX40); TNF superfamily member 4 (TNFSF4, OX40L); TNFRSF9 (CD137), TNFSF9 (CD137L); TNFRSF18 (GITR), TNFSF18 (GITRL); CD80 (B7-1), CD28; nectin cell adhesion molecule 2 (NECTIN2, CD112); CD226 (DNAM-1); CD244 (2B4, SLAMF4), Poliovirus receptor (PVR) cell adhesion molecule (PVR, CD155). See, *e.g.*, Xu, et al., J Exp Clin Cancer Res. (2018) 37:110.

[0148] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more blockers or inhibitors of one or more NK-cell inhibitory immune checkpoint proteins or receptors. Illustrative NK-cell inhibitory immune checkpoint proteins or receptors include without limitation killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR, CD158E1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3

(KIR2DL3); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1); killer cell lectin like receptor C1 (KLRC1, NKG2A, CD159A); and killer cell lectin like receptor D1 (KLRD1, CD94).

[0149] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more agonist or activators of one or more NK-cell stimulatory immune checkpoint proteins or receptors. Illustrative NK-cell stimulatory immune checkpoint proteins or receptors include without limitation CD16, CD226 (DNAM-1); CD244 (2B4, SLAMF4); killer cell lectin like receptor K1 (KLRK1, NKG2D, CD314); SLAM family member 7 (SLAMF7). See, *e.g.*, Davis, et al., Semin Immunol. (2017) 31:64–75; Fang, et al., Semin Immunol. (2017) 31:37-54; and Chiossone, et al., Nat Rev Immunol. (2018) 18(11):671-688.

Adenosine Generation and Signaling

[0150] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an agonist or antagonist of A1R, A2AR, A2BR, A3R, CD73, CD39, CD26; *e.g.*, Adenosine A3 receptor (A3R) agonists, such as namodenoson (CF102); A2aR/A2bR antagonists, such as AB928; anti-CD73 antibodies, such as MEDI-9447 (oleclumab), CPX-006, IPH-53, BMS-986179, NZV-930, CPI-006; CD73 inhibitors, such as AB-680, PSB-12379, PSB-12441, PSB-12425, CB-708, and those described in Int Patent Publication No. WO19173692; CD39/CD73 inhibitors, such as PBF-1662; anti-CD39 antibodies, such as TTX-030; adenosine A2A receptor antagonists, such as CPI-444, AZD-4635, preladenant, PBF-509; and adenosine deaminase inhibitors, such as pentostatin, cladribine.

Bi-Specific T-Cell Engagers

[0151] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with a bi-specific T-cell engager (*e.g.*, not having an Fc) or an anti-CD3 bi-specific antibody (*e.g.*, having an Fc). Illustrative anti-CD3 bi-specific antibodies or BiTEs that can be co-administered include AMG-160 (PSMA/CD3), AMG-212 (PSMA/CD3), AMG-330 (CD33/CD3), AMG-420 (BCMA/CD3), AMG-427 (FLT3/CD3), AMG-562 (CD19/CD3), AMG-596 (EGFRvIII/CD3), AMG-701 (BCMA/CD3), AMG-757 (DLL3/CD3), JNJ-64052781 (CD19/CD3), AMG-211 (CEA/CD3), BLINCYTO® (CD19/CD3), RG7802

(CEA/CD3), ERY-974 (CD3/GPC3), huGD2-BsAb (CD3/GD2), PF-06671008 (Cadherins/CD3), APVO436 (CD123/CD3), ERY974, flotetuzumab (CD123/CD3), GEM333 (CD3/CD33), GEMoab (CD3/PSCA), REGN-1979 (CD20/CD3), REGN-5678 (PSMA/CD28), MCLA-117 (CD3/CLEC12A), JNJ-0819, JNJ-7564 (CD3/heme), JNJ-63709178 (CD123/CD3), MGD-007 (CD3/gpA33), MGD-009 (CD3/B7H3), IMCgp100 (CD3/gp100), XmAb-14045 (CD123/CD3), XmAb-13676 (CD3/CD20), XmAb-18087 (SSTR2/CD3), catumaxomab (CD3/EpCAM), REGN-4018 (MUC16/CD3), RG6026, RG6076, RG6194, RG-7828 (CD20/CD3), CC-93269 (CD3/BCMA), REGN-5458 (CD3/BCMA), GRB-1302 (CD3/Erbb2), GRB-1342 (CD38/CD3), PF-06863135 (BCMA/CD3), SAR440234 (CD3/CDw123). As appropriate, the anti-CD3 binding bi-specific molecules may or may not have an Fc. Illustrative bi-specific T-cell engagers that can be co-administered target CD3 and a tumor-associated antigen as described herein, including, *e.g.*, CD19 (*e.g.*, blinatumomab); CD33 (*e.g.*, AMG330); CEA (*e.g.*, MEDI-565); receptor tyrosine kinase-like orphan receptor 1 (ROR1) (Gohil, et al., Oncoimmunology. (2017) May 17;6(7):e1326437); PD-L1 (Horn, et al., Oncotarget. 2017 Aug 3;8(35):57964-57980); and EGFRvIII (Yang, et al., Cancer Lett. 2017 Sep 10;403:224-230).

Bi-and Tri-Specific Natural Killer (NK)-Cell Engagers

[0152] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with a bi-specific NK-cell engager (BiKE) or a tri-specific NK-cell engager (TriKE) (*e.g.*, not having an Fc) or bi-specific antibody (*e.g.*, having an Fc) against an NK cell activating receptor, *e.g.*, CD16A, C-type lectin receptors (CD94/NKG2C, NKG2D, NKG2E/H and NKG2F), natural cytotoxicity receptors (NKp30, NKp44 and NKp46), killer cell C-type lectin-like receptor (NKp65, NKp80), Fc receptor FcγR (which mediates antibody-dependent cell cytotoxicity), SLAM family receptors (*e.g.*, 2B4, SLAM6 and SLAM7), killer cell immunoglobulin-like receptors (KIR) (KIR-2DS and KIR-3DS), DNAM-1 and CD137 (41BB). Illustrative anti-CD16 bi-specific antibodies, BiKEs or TriKEs that can be co-administered include AFM26 (BCMA/CD16A) and AFM-13 (CD16/CD30). As appropriate, the anti-CD16 binding bi-specific molecules may or may not have an Fc. Illustrative bi-specific NK-cell engagers that can be co-administered target CD16 and one or more tumor-associated antigens as described herein, including, *e.g.*, CD19, CD20, CD22, CD30, CD33, CD123, EGFR, EpCAM, ganglioside GD2, HER2/neu, HLA Class II and FOLR1. BiKEs and TriKEs are described, *e.g.*, in Felices, et al., Methods Mol Biol. (2016) 1441:333–346; Fang, et al., Semin Immunol. (2017) 31:37-54.

Hematopoietic Progenitor Kinase 1 (HPK1) Inhibitors

[0153] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1, HPK1; NCBI Gene ID: 11184). Examples of Hematopoietic Progenitor Kinase 1 (HPK1) inhibitors include without limitation, those described in WO-2018183956, WO-2018183964, WO-2018167147, WO-2018183964, WO-2016205942, WO-2018049214, WO-2018049200, WO-2018049191, WO-2018102366, WO-2018049152, WO2020092528, WO2020092621 and WO-2016090300.

Apoptosis Signal-Regulating Kinase (ASK) Inhibitors

[0154] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of an ASK inhibitor, *e.g.*, mitogen-activated protein kinase kinase kinase 5 (MAP3K5; ASK1, MAPKKK5, MEKK5; NCBI Gene ID: 4217). Examples of ASK1 inhibitors include without limitation, those described in WO 2011/008709 (Gilead Sciences) and WO 2013/112741 (Gilead Sciences).

Bruton Tyrosine Kinase (BTK) Inhibitors

[0155] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of Bruton tyrosine kinase (BTK, AGMX1, AT, ATK, BPK, IGHD3, IMD1, PSCTK1, XLA; NCBI Gene ID: 695). Examples of BTK inhibitors include without limitation, (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one, acalabrutinib (ACP-196), BGB-3111, CB988, HM71224, ibrutinib (Imbruvica), M-2951 (evobrutinib), M7583, tirabrutinib (ONO-4059), PRN-1008, spebrutinib (CC-292), TAK-020, vecabrutinib, ARQ-531, SHR-1459, DTRMWXHS-12, TAS-5315, Calquence + AZD6738, Calquence + danvatirsen.

Cyclin-dependent Kinase (CDK) Inhibitors

[0156] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of cyclin dependent kinase 1 (CDK1, CDC2; CDC28A; P34CDC2; NCBI Gene ID: 983); cyclin dependent kinase 2 (CDK2, CDKN2; p33(CDK2); NCBI Gene ID: 1017); cyclin dependent kinase 3 (CDK3; NCBI Gene ID: 1018);

cyclin dependent kinase 4 (CDK4, CMM3; PSK-J3; NCBI Gene ID: 1019); cyclin dependent kinase 6 (CDK6, MCPH12; PLSTIRE; NCBI Gene ID: 1021); cyclin dependent kinase 7 (CDK7, CAK; CAK1; HCAK; MO15; STK1; CDKN7; p39MO15; NCBI Gene ID: 1022); cyclin dependent kinase 9 (CDK9, TAK; C-2k; CTK1; CDC2L4; PITALRE; NCBI Gene ID: 1025). Inhibitors of CDK 1, 2, 3, 4, 6, 7 and/or 9, include without limitation abemaciclib, alvocidib (HMR-1275, flavopiridol), AT-7519, dinaciclib, ibrance, FLX-925, LEE001, palbociclib, ribociclib, rigosertib, selinexor, UCN-01, SY1365, CT-7001, SY-1365, G1T38, milciclib, trilaciclib, PF-06873600, AZD4573, and TG-02.

Discoidin Domain Receptor (DDR) Inhibitors.

[0157] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of discoidin domain receptor tyrosine kinase 1 (DDR1, CAK, CD167, DDR, EDDR1, HGK2, MCK10, NEP, NTRK4, PTK3, PTK3A, RTK6, TRKE; NCBI Gene ID: 780); and/or discoidin domain receptor tyrosine kinase 2 (DDR2, MIG20a, NTRKR3, TKT, TYRO10, WRCN; NCBI Gene ID: 4921). Examples of DDR inhibitors include without limitation, dasatinib and those disclosed in WO2014/047624 (Gilead Sciences), US 2009-0142345 (Takeda Pharmaceutical), US 2011-0287011 (Oncomed Pharmaceuticals), WO 2013/027802 (Chugai Pharmaceutical), and WO2013/034933 (Imperial Innovations).

Histone Deacetylase (HDAC) Inhibitors

[0158] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of a histone deacetylase, *e.g.*, histone deacetylase 9 (HDAC9, HD7, HD7b, HD9, HDAC, HDAC7, HDAC7B, HDAC9B, HDAC9FL, HDRP, MITR; Gene ID: 9734). Examples of HDAC inhibitors include without limitation, abexinostat, ACY-241, AR-42, BEBT-908, belinostat, CKD-581, CS-055 (HBI-8000), CUDC-907 (fimepinostat), entinostat, givinostat, mocetinostat, panobinostat, pracinostat, quisinostat (JNJ-26481585), resminostat, ricolinostat, SHP-141, valproic acid (VAL-001), vorinostat, tinostamustine, remetinostat, entinostat, romidepsin, tucidinostat.

Indoleamine-pyrrole-2,3-dioxygenase (IDO1) inhibitors

[0159] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described

herein, is further combined with an inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1; NCBI Gene ID: 3620). Examples of IDO1 inhibitors include without limitation, BLV-0801, epacadostat, F-001287, GBV-1012, GBV-1028, GDC-0919, indoximod, NKTR-218, NLG-919-based vaccine, PF-06840003, pyranonaphthoquinone derivatives (SN-35837), resminostat, SBLK-200802, BMS-986205, and shIDO-ST, EOS-200271, KHK-2455, LY-3381916.

Janus Kinase (JAK) Inhibitors

[0160] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of Janus kinase 1 (JAK1, JAK1A, JAK1B, JTK3; NCBI Gene ID: 3716); Janus kinase 2 (JAK2, JTK10, THCYT3; NCBI Gene ID: 3717); and/or Janus kinase 3 (JAK3, JAK-3, JAK3_HUMAN, JAKL, L-JAK, LJAK; NCBI Gene ID: 3718). Examples of JAK inhibitors include without limitation, AT9283, AZD1480, baricitinib, BMS-911543, fedratinib, filgotinib (GLPG0634), gandotinib (LY2784544), INCB039110 (itacitinib), lestaurtinib, momelotinib (CYT0387), NS-018, pacritinib (SB1518), peficitinib (ASP015K), ruxolitinib, tofacitinib (formerly tasocitinib), INCB052793, and XL019.

Matrix Metalloprotease (MMP) Inhibitors

[0161] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of a matrix metallopeptidase (MMP), *e.g.*, an inhibitor of MMP1 (NCBI Gene ID: 4312), MMP2 (NCBI Gene ID: 4313), MMP3 (NCBI Gene ID: 4314), MMP7 (NCBI Gene ID: 4316), MMP8 (NCBI Gene ID: 4317), MMP9 (NCBI Gene ID: 4318); MMP10 (NCBI Gene ID: 4319); MMP11 (NCBI Gene ID: 4320); MMP12 (NCBI Gene ID: 4321), MMP13 (NCBI Gene ID: 4322), MMP14 (NCBI Gene ID: 4323), MMP15 (NCBI Gene ID: 4324), MMP16 (NCBI Gene ID: 4325), MMP17 (NCBI Gene ID: 4326), MMP19 (NCBI Gene ID: 4327), MMP20 (NCBI Gene ID: 9313), MMP21 (NCBI Gene ID: 118856), MMP24 (NCBI Gene ID: 10893), MMP25 (NCBI Gene ID: 64386), MMP26 (NCBI Gene ID: 56547), MMP27 (NCBI Gene ID: 64066) and/or MMP28 (NCBI Gene ID: 79148). Examples of MMP9 inhibitors include without limitation, marimastat (BB-2516), cipemastat (Ro 32-3555), GS-5745 (andecaliximab) and those described in WO 2012/027721 (Gilead Biologics).

RAS and RAS Pathway Inhibitors

[0162] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of KRAS proto-oncogene, GTPase (KRAS; *a.k.a.*, NS; NS3; CFC2; RALD; K-Ras; KRAS1; KRAS2; RASK2; KI-RAS; C-K-RAS; K-RAS2A; K-RAS2B; K-RAS4A; K-RAS4B; c-Ki-ras2; NCBI Gene ID: 3845); NRAS proto-oncogene, GTPase (NRAS; *a.k.a.*, NS6; CMNS; NCMS; ALPS4; N-ras; NRAS1; NCBI Gene ID: 4893); HRas proto-oncogene, GTPase (HRAS; *a.k.a.*, CTLO; KRAS; HAMSV; HRAS1; KRAS2; RASH1; RASK2; Ki-Ras; p21ras; C-H-RAS; c-K-ras; H-RASIDX; c-Ki-ras; C-BAS/HAS; C-HA-RAS1; NCBI Gene ID: 3265). The Ras inhibitors can inhibit Ras at either the polynucleotide (*e.g.*, transcriptional inhibitor) or polypeptide (*e.g.*, GTPase enzyme inhibitor) level. In some embodiments, the inhibitors target one or more proteins in the Ras pathway, *e.g.*, inhibit one or more of EGFR, Ras, Raf (A-Raf, B-Raf, C-Raf), MEK (MEK1, MEK2), ERK, PI3K, AKT and mTOR.

[0163] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of KRAS. Examples of KRAS inhibitors include AMG-510, COTI-219, MRTX-1257, ARS-3248, ARS-853, WDB-178, BI-3406, BI-1701963, ARS-1620 (G12C), SML-8-73-1 (G12C), Compound 3144 (G12D), Kobe0065/2602 (Ras GTP), RT11, MRTX-849 (G12C) and K-Ras(G12D)-selective inhibitory peptides, including KRpep-2 (Ac-RRCPLYISYDPVCRR-NH2) (SEQ ID NO: 256) and KRpep-2d (Ac-RRRRCPLYISYDPVCRRRR-NH2) (SEQ ID NO: 257).

[0164] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of KRAS mRNA. Illustrative KRAS mRNA inhibitors include anti-KRAS U1 adaptor, AZD-4785, siG12D-LODER™, and siG12D exosomes.

[0165] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of MEK. Illustrative MEK inhibitors that can be co-administered include binimetinib, cobimetinib, PD-0325901, pimasertib, RG-7304, selumetinib, trametinib, and selumetinib.

[0166] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of AKT. Illustrative AKT inhibitors that can be co-administered include RG7440, MK-2206, ipatasertib, afuresertib, AZD5363, and ARQ-092, capivasertib, triciribine, ABTL-0812 (PI3K/Akt/mTOR).

[0167] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of Raf. Illustrative Raf inhibitors that can be co-administered BGB-283 (Raf/EGFR), HM-95573, LXH-254, LY-3009120, RG7304, TAK-580, dabrafenib, vemurafenib, encorafenib (LGX818), PLX8394. RAF-265 (Raf/VEGFR), ASN-003 (Raf/PI3K).

[0168] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of ERK. Illustrative ERK inhibitors that can be co-administered include LTT-462, LY-3214996, MK-8353, ravoxertinib, GDC-0994, and ulixertinib.

[0169] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of PI3K. Illustrative PI3K inhibitors that can be co-administered include idelalisib (Zydelig®), alpelisib, buparlisib, pictilisib, eganelisib (IPI-549). Illustrative PI3K/mTOR inhibitors that can be co-administered include dactolisib, omipalisib, voxtalisib, gedatolisib, GSK2141795, RG6114.

[0170] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of mTOR. Illustrative mTOR inhibitors that can be co-administered include as sapanisertib, vistusertib (AZD2014), ME-344, sirolimus (oral nano-amorphous formulation, cancer), TYME-88 (mTOR/cytochrome P450 3A4).

[0171] In certain embodiments, Ras-driven cancers (*e.g.*, NSCLC) having CDKN2A mutations can be inhibited by co-administration of the MEK inhibitor selumetinib and the CDK4/6 inhibitor palbociclib. See, *e.g.*, Zhou, et al., Cancer Lett. 2017 Nov 1;408:130-137. Also, K-RAS and mutant N-RAS can be reduced by the irreversible ERBB1/2/4 inhibitor neratinib. See, *e.g.*, Booth, et al., Cancer Biol Ther. 2018 Feb 1;19(2):132-137.

[0172] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of RAS. Examples of RAS inhibitors include NEO-100 and rigosertib.

[0173] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an antagonist of EGFR, such as AMG-595, necitumumab, ABBV-221, depatuxizumab mafodotin (ABT-414), tomuzotuximab, ABT-806, vectibix, modotuximab, RM-1929.

[0174] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of protein tyrosine phosphatase non-receptor type 11 (PTPN11; BPTP3, CFC, JMML, M*ETC*DS, NS1, PTP-1D, PTP2C, SH-PTP2, SH-PTP3, SHP2; NCBI Gene ID: 5781). Examples of SHP2 inhibitors include TNO155 (SHP-099), RMC-4550, JAB-3068, RMC-4630, SAR442720 and those described in WO2018172984 and WO2017211303.

[0175] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of mitogen-activated protein kinase 7 (MAP2K7, JNKK2, MAPKK7, MEK, MEK 7, MKK7, PRKMK7, SAPKK-4, SAPKK4; NCBI Gene ID: 5609). Examples of MEK inhibitors include antroquinonol, binimetinib, CK-127, cobimetinib (GDC-0973, XL-518), MT-144, selumetinib (AZD6244), sorafenib, trametinib (GSK1120212), uprosertib + trametinib, PD-0325901, pimasertib, LTT462, AS703988, CC-90003, refametinib, TAK-733, CI-1040, RG7421.

[0176] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, *e.g.*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA, CLAPO, CLOVE, CWS5, MCAP, MCM, MCMTC, PI3K, PI3K-alpha, p110-alpha; NCBI Gene ID: 5290); phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB, P110BETA, PI3K, PI3KBETA, PIK3C1; NCBI Gene ID: 5291); phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PIK3CG, PI3CG, PI3K, PI3Kgamma, PIK3, p110gamma, p120-PI3K; Gene ID: 5494); and/or

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD, APDS, IMD14, P110DELTA, PI3K, p110D, NCBI Gene ID: 5293). In some embodiments, the PI3K inhibitor is a pan-PI3K inhibitor. Examples of PI3K inhibitors include without limitation, ACP-319, AEZA-129, AMG-319, AS252424, AZD8186, BAY 1082439, BEZ235, bimiralisib (PQR309), buparlisib (BKM120), BYL719 (alpelisib), carboxyamidotriazole orotate (CTO), CH5132799, CLR-457, CLR-1401, copanlisib (BAY 80-6946), DS-7423, dactolisib, duvelisib (IPI-145), fimepinostat (CUDC-907), gedatolisib (PF-05212384), GDC-0032, GDC-0084 (RG7666), GDC-0077, pictilisib (GDC-0941), GDC-0980, GSK2636771, GSK2269577, GSK2141795, idelalisib (Zydelig®), INCB040093, INCB50465, IPI-443, IPI-549, KAR4141, LY294002, LY3023414, NERLYNX® (neratinib), nemiralisib (GSK2269557), omipalisib (GSK2126458, GSK458), OXY111A, panulisib (P7170, AK151761), PA799, perifosine (KRX-0401), Pilaralisib (SAR245408; XL147), puquitinib mesylate (XC-302), SAR260301, seletalisib (UCB-5857), serabelisib (INK-1117,MLN-1117,TAK-117), SF1126, sonolisib (PX-866), RG6114, RG7604, rigosertib sodium (ON-01910 sodium), RP5090, tenalisib (RP6530), RV-1729, SRX3177, taselisib, TG100115, umbralisib (TGR-1202), TGX221, voxtalisib (SAR245409), VS-5584, WX-037, X-339, X-414, XL499, XL756, wortmannin, ZSTK474, and the compounds described in WO 2005/113556 (ICOS), WO 2013/052699 (Gilead Calistoga), WO 2013/116562 (Gilead Calistoga), WO 2014/100765 (Gilead Calistoga), WO 2014/100767 (Gilead Calistoga), and WO 2014/201409 (Gilead Sciences).

Spleen Tyrosine Kinase (SYK) Inhibitors

[0177] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of spleen associated tyrosine kinase (SYK, p72-Syk, Gene ID: 6850). Examples of SYK inhibitors include without limitation, 6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine, BAY-61-3606, cerdulatinib (PRT-062607), entospletinib, fostamatinib (R788), HMPL-523, NVP-QAB 205 AA, R112, R343, tamatinib (R406), and those described in US 8450321 (Gilead Connecticut) and those described in U.S. 2015/0175616.

Tyrosine-kinase Inhibitors (TKIs)

[0178] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with a tyrosine kinase inhibitor (TKI). TKIs may target epidermal growth factor receptors (EGFRs) and receptors for fibroblast growth factor (FGF), platelet-

derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Examples of TKIs include without limitation, axitinib, afatinib, ARQ-087 (derazantinib), asp5878, AZD3759, AZD4547, bosutinib, brigatinib, cabozantinib, cediranib, crenolanib, crizotinib, dacomitinib, dasatinib, dovitinib, E-6201, erdafitinib, erlotinib, gefitinib, gilteritinib (ASP-2215), FP-1039, HM61713, icotinib, imatinib, KX2-391 (Src), lapatinib, lestaurtinib, lenvatinib, midostaurin, nintedanib, ODM-203, olmutinib, osimertinib (AZD-9291), pazopanib, ponatinib, poziotinib, quizartinib, radotinib, rociletinib, sulfatinib (HMPL-012), sunitinib, famitinib L-malate, (MAC-4), TH-4000, tivoanib, MEDI-575 (anti-PDGFR antibody) and TAK-659.

Chemotherapeutic agents (standard of care)

[0179] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with a chemotherapeutic agent or anti-neoplastic agent.

[0180] As used herein, the term "chemotherapeutic agent" or "chemotherapeutic" (or "chemotherapy" in the case of treatment with a chemotherapeutic agent) is meant to encompass any non-proteinaceous (*e.g.*, non-peptidic) chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include but not limited to: alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan, and piposulfan; aziridines such as benzodepa, carboquone, meturedepa, and uredepa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, and trimemylolomelamine; acetogenins, *e.g.*, bullatacin and bullatacinone; a camptothecin, including synthetic analog topotecan; bryostatin, callystatin; CC-1065, including its adozelesin, carzelesin, and bizelesin synthetic analogs; cryptophycins, particularly cryptophycin 1 and cryptophycin 8;dolastatin; duocarmycin, including the synthetic analogs KW-2189 and CBI-TMI; eleutherobin; 5-azacytidine; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, glufosfamide, evofosfamide, bendamustine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitrosoureas such as carmustine, chlorozotocin, foremustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammaII and calicheamicin phiI1), dynemicin including dynemicin A, bisphosphonates such as clodronate, an esperamicin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores, aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin,

carrninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as demopterin, methotrexate, pteropterin, and trimetrexate; purine analogs such as cladribine, pentostatin, fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals such as aminoglutethimide, mitotane, and trilostane; folic acid replinishers such as frolinic acid; radiotherapeutic agents such as Radium-223, 177-Lu-PSMA-617; trichothecenes, especially T-2 toxin, verracurin A, roridin A, and anguidine; taxoids such as paclitaxel (TAXOL®), albumin-bound or nab-paclitaxel (ABRAXANE®), docetaxel (TAXOTERE®), cabazitaxel, BIND-014, tesetaxel; platinum analogs such as cisplatin and carboplatin, NC-6004 nanoplatin; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; hestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformthine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; leucovorin; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; phenamet; pirarubicin; losoxantrone; fluoropyrimidine; folinic acid; podophyllinic acid; 2-ethylhydrazide; procarbazine; polysaccharide-K (PSK); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; trabectedin, triaziquone; 2,2',2"-trichlorotriemylamine; urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; chlorambucil; gemcitabine (GEMZAR®); 6-thioguanine; mercaptopurine; methotrexate; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitroxantrone; vancristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeoloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DFMO); retinoids such as retinoic acid; capecitabine; NUC-1031; FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin); FOLFIRI (folinic acid, 5-fluorouracil, irinotecan); FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, irinotecan), FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin), and pharmaceutically acceptable salts, acids, or derivatives of any of the above. Such agents can be conjugated onto

an antibody or any targeting agent described herein to create an antibody-drug conjugate (ADC) or targeted drug conjugate.

[0181] Also included in the definition of "chemotherapeutic agent" are anti-hormonal agents such as anti-estrogens and selective estrogen receptor modulators (SERMs), inhibitors of the enzyme aromatase, anti-androgens, and pharmaceutically acceptable salts, acids or derivatives of any of the above that act to regulate or inhibit hormone action on tumors. Examples of anti-estrogens and SERMs include, for example, tamoxifen (including NOLVADEXTM), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON®). Inhibitors of the enzyme aromatase regulate estrogen production in the adrenal glands. Examples include 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGACE®), exemestane, formestane, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), and anastrozole (ARIMIDEX®). Examples of anti-androgens include apalutamide, abiraterone, enzalutamide, flutamide, galeterone, nilutamide, bicalutamide, leuprolide, goserelin, ODM-201, APC-100, ODM-204. An example progesterone receptor antagonist includes onapristone.

Anti-Angiogenic Agents

[0182] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-angiogenic agent. Anti-angiogenic agents that can be co-administered include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN®, ENDOSTATIN®, regorafenib, necuparanib, suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inbibitor-2, cartilage-derived inhibitor, paclitaxel (nab-paclitaxel), platelet factor 4, protamine sulphate (clupeine), sulphated chitin derivatives (prepared from queen crab shells), sulphated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism including proline analogs such as l-azetidine-2-carboxylic acid (LACA), cishydroxyproline, d,I-3,4-dehydroproline, thiaproline, α,α'-dipyridyl, beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3h)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chicken inhibitor of metalloproteinase-3 (ChIMP-3), chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin, fumagillin, gold sodium thiomalate, d-penicillamine, beta-1-anticollagenase-serum, alpha-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide, angiostatic steroid, carboxy aminoimidazole,

metalloproteinase inhibitors such as BB-94, inhibitors of S100A9 such as tasquinimod. Other anti-angiogenesis agents include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: beta-FGF, alpha-FGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF, and Ang-1/Ang-2.

Anti-fibrotic Agents

[0183] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-fibrotic agent. Anti-fibrotic agents that can be co-administered include, but are not limited to, the compounds such as beta-aminoproprionitrile (BAPN), as well as the compounds disclosed in US 4965288 relating to inhibitors of lysyl oxidase and their use in the treatment of diseases and conditions associated with the abnormal deposition of collagen and US 4997854 relating to compounds which inhibit LOX for the treatment of various pathological fibrotic states, which are herein incorporated by reference. Further exemplary inhibitors are described in US 4943593 relating to compounds such as 2-isobutyl-3-fluoro-, chloro-, or bromo-allylamine, US 5021456, US 5059714, US 5120764, US 5182297, US 5252608 relating to 2-(1-naphthyloxymemyl)-3-fluoroallylamine, and US 2004-0248871, which are herein incorporated by reference.

[0184] Exemplary anti-fibrotic agents also include the primary amines reacting with the carbonyl group of the active site of the lysyl oxidases, and more particularly those which produce, after binding with the carbonyl, a product stabilized by resonance, such as the following primary amines: emylenemamine, hydrazine, phenylhydrazine, and their derivatives; semicarbazide and urea derivatives; aminonitriles such as BAPN or 2-nitroethylamine; unsaturated or saturated haloamines such as 2-bromo-ethylamine, 2-chloroethylamine, 2-trifluoroethylamine, 3-bromopropylamine, and p-halobenzylamines; and selenohomocysteine lactone.

[0185] Other anti-fibrotic agents are copper chelating agents penetrating or not penetrating the cells. Exemplary compounds include indirect inhibitors which block the aldehyde derivatives originating from the oxidative deamination of the lysyl and hydroxylysyl residues by the lysyl oxidases. Examples include the thiolamines, particularly D-penicillamine, and its analogs such as 2-amino-5-mercapto-5-methylhexanoic acid, D-2-amino-3-methyl-3-((2-acetamidoethyl)dithio)butanoic acid, p-2-amino-3-methyl-3-((2-aminoethyl)dithio)butanoic acid, sodium-4-((p-1-dimethyl-2-amino-2-carboxyethyl)dithio)butane sulphurate, 2-

acetamidoethyl-2-acetamidoethanethiol sulphanate, and sodium-4-mercaptobutanesulphinate trihydrate.

Anti-Inflammatory Agents

[0186] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an anti-inflammatory agent. Example anti-inflammatory agents include without limitation inhibitors of one or more of arginase (ARG1 (NCBI Gene ID: 383), ARG2 (NCBI Gene ID: 384)), carbonic anhydrase (CA1 (NCBI Gene ID: 759), CA2 (NCBI Gene ID: 760), CA3 (NCBI Gene ID: 761), CA4 (NCBI Gene ID: 762), CA5A (NCBI Gene ID: 763), CA5B (NCBI Gene ID: 11238), CA6 (NCBI Gene ID: 765), CA7 (NCBI Gene ID: 766), CA8 (NCBI Gene ID: 767), CA9 (NCBI Gene ID: 768), CA10 (NCBI Gene ID: 56934), CA11 (NCBI Gene ID: 770), CA12 (NCBI Gene ID: 771), CA13 (NCBI Gene ID: 377677), CA14 (NCBI Gene ID: 23632)), prostaglandin-endoperoxide synthase 1 (PTGS1, COX-1; NCBI Gene ID: 5742), prostaglandin-endoperoxide synthase 2 (PTGS2, COX-2; NCBI Gene ID: 5743), secreted phospholipase A2, prostaglandin E synthase (PTGES, PGES; Gene ID: 9536), arachidonate 5-lipoxygenase (ALOX5, 5-LOX; NCBI Gene ID: 240), soluble epoxide hydrolase 2 (EPHX2, SEH; NCBI Gene ID: 2053) and/or mitogen-activated protein kinase kinase kinase 8 (MAP3K8, TPL2; NCBI Gene ID: 1326). In some embodiments, the inhibitor is a dual inhibitor, *e.g.*, a dual inhibitor of COX-2/COX-1, COX-2/SEH, COX-2/CA, COX-2/5-LOX.

[0187] Examples of inhibitors of prostaglandin-endoperoxide synthase 1 (PTGS1, COX-1; NCBI Gene ID: 5742) that can be co-administered include without limitation mofezolac, GLY-230, and TRK-700.

[0188] Examples of inhibitors of prostaglandin-endoperoxide synthase 2 (PTGS2, COX-2; NCBI Gene ID: 5743) that can be co-administered include without limitation diclofenac, meloxicam, parecoxib, etoricoxib, AP-101, celecoxib, AXS-06, diclofenac potassium, DRGT-46, AAT-076, meisuoshuli, lumiracoxib, meloxicam, valdecoxib, zaltoprofen, nimesulide, Anitrazafen, Apricoxib, Cimicoxib, Deracoxib, Flumizole, Firocoxib, Mavacoxib, NS-398, Pamicogrel, Parecoxib, Robenacoxib, Rofecoxib, Rutecarpine, Tilmacoxib, and Zaltoprofen. Examples of dual COX1/COX2 inhibitors that can be co-administered include without limitation, HP-5000, lornoxicam, ketorolac tromethamine, bromfenac sodium, ATB-346, HP-5000. Examples of dual COX-2/carbonic anhydrase (CA) inhibitors that can be co-administered include without limitation polmacoxib and imrecoxib.

[0189] Examples of inhibitors of secreted phospholipase A2, prostaglandin E synthase (PTGES, PGES; Gene ID: 9536) that can be co-administered include without limitation LY3023703, GRC 27864, and compounds described in WO2015158204, WO2013024898, WO2006063466, WO2007059610, WO2007124589, WO2010100249, WO2010034796, WO2010034797, WO2012022793, WO2012076673, WO2012076672, WO2010034798, WO2010034799, WO2012022792, WO2009103778, WO2011048004, WO2012087771, WO2012161965, WO2013118071, WO2013072825, WO2014167444, WO2009138376, WO2011023812, WO2012110860, WO2013153535, WO2009130242, WO2009146696, WO2013186692, WO2015059618, WO2016069376, WO2016069374, WO2009117985, WO2009064250, WO2009064251, WO2009082347, WO2009117987, and WO2008071173. Metformin has further been found to repress the COX2/PGE2/STAT3 axis, and can be co-administered. See, *e.g.*, Tong, et al., Cancer Lett. (2017) 389:23-32; and Liu, et al., Oncotarget. (2016) 7(19):28235-46.

[0190] Examples of inhibitors of carbonic anhydrase (*e.g.*, one or more of CA1 (NCBI Gene ID: 759), CA2 (NCBI Gene ID: 760), CA3 (NCBI Gene ID: 761), CA4 (NCBI Gene ID: 762), CA5A (NCBI Gene ID: 763), CA5B (NCBI Gene ID: 11238), CA6 (NCBI Gene ID: 765), CA7 (NCBI Gene ID: 766), CA8 (NCBI Gene ID: 767), CA9 (NCBI Gene ID: 768), CA10 (NCBI Gene ID: 56934), CA11 (NCBI Gene ID: 770), CA12 (NCBI Gene ID: 771), CA13 (NCBI Gene ID: 377677), CA14 (NCBI Gene ID: 23632)) that can be co-administered include without limitation acetazolamide, methazolamide, dorzolamide, zonisamide, brinzolamide and dichlorphenamide. A dual COX-2/CA1/CA2 inhibitor that can be co-administered includes CG100649.

[0191] Examples of inhibitors of arachidonate 5-lipoxygenase (ALOX5, 5-LOX; NCBI Gene ID: 240) that can be co-administered include without limitation meclofenamate sodium, zileuton.

[0192] Examples of inhibitors of soluble epoxide hydrolase 2 (EPHX2, SEH; NCBI Gene ID: 2053) that can be co-administered include without limitation compounds described in WO2015148954. Dual inhibitors of COX-2/SEH that can be co-administered include compounds described in WO2012082647. Dual inhibitors of SEH and fatty acid amide hydrolase (FAAH; NCBI Gene ID: 2166) that can be co-administered include compounds described in WO2017160861.

[0193] Examples of inhibitors of mitogen-activated protein kinase kinase kinase 8 (MAP3K8, tumor progression loci-2, TPL2; NCBI Gene ID: 1326) that can be co-administered

include without limitation GS-4875, GS-5290, BHM-078 and those described, *e.g.*, in WO2006124944, WO2006124692, WO2014064215, WO2018005435, Teli, et al., J Enzyme Inhib Med Chem. (2012) 27(4):558-70; Gangwall, et al., Curr Top Med Chem. (2013) 13(9):1015-35; Wu, et al., Bioorg Med Chem Lett. (2009) 19(13):3485-8; Kaila, et al., Bioorg Med Chem. (2007) 15(19):6425-42; and Hu, et al., Bioorg Med Chem Lett. (2011) 21(16):4758-61.

Tumor Oxygenation Agents

[0194] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an agent that promotes or increases tumor oxygenation or reoxygenation, or prevents or reduces tumor hypoxia. Illustrative agents that can be co-administered include, *e.g.*, Hypoxia inducible factor-1 alpha (HIF-1α) inhibitors, such as PT-2977, PT-2385; VEGF inhibitors, such as bevasizumab, IMC-3C5, GNR-011, tanibirumab, LYN-00101, ABT-165; and/or an oxygen carrier protein (*e.g.*, a heme nitric oxide and/or oxygen binding protein (HNOX)), such as OMX-302 and HNOX proteins described in WO 2007/137767, WO 2007/139791, WO 2014/107171, and WO 2016/149562.

Immunotherapeutic Agents

[0195] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an immunotherapeutic agent. Example immunotherapeutic agents that can be co-administered include without limitation abagovomab, ABP-980, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab biosimilar, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, CC49, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, dacetuzumab, dalotuzumab, daratumumab, detumomab, dinutuximab, drozitumab, duligotumab, dusigitumab, ecromeximab, emibetuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, figitumumab, flanvotumab, futuximab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab (YERVOY®, MDX-010, BMS-734016, and MDX-101), iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, moxetumomab pasudotox, naptumomab, narnatumab, necitumumab, nimotuzumab, nofetumomab, OBI-833, obinutuzumab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab,

oportuzumab, oregovomab, panitumumab, parsatuzumab, pasudotox, patritumab, pemtumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, ramucirumab (Cyramza®), rilotumumab, rituximab, robatumumab, samalizumab, satumomab, sibrotuzumab, siltuximab, solitomab, simtuzumab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, trastuzumab biosimilar, tucotuzumab, ubilituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, and 3F8. Rituximab can be used for treating indolent B-cell cancers, including marginal-zone lymphoma, WM, CLL and small lymphocytic lymphoma. A combination of Rituximab and chemotherapy agents is especially effective.

[0196] The exemplified therapeutic antibodies may be further labeled or combined with a radioisotope particle such as indium-111, yttrium-90 (90Y-clivatuzumab), or iodine-131.

[0197] In some embodiments, the immunotherapeutic agent is an antibody-drug conjugate (ADC). Illustrative ADCs that can be co-administered include without limitation drug-conjugated antibodies, fragments thereof, or antibody mimetics targeting the proteins or antigens listed above and herein (*e.g.*, in Table B). Example ADCs that can be co-administered include without limitation gemtuzumab, brentuximab, trastuzumab, inotuzumab, glembatumumab, anetumab, mirvetuximab, depatuxizumab, rovalpituzumab, vadastuximab, labetuzumab, lifastuzumab, indusatumab, polatzumab, pinatuzumab, coltuximab, indatuximab, milatuzumab, rovalpituzumab, ABBV-011, ABBV-2029, ABBV-321, ABBV-647, MLN0264 (anti-GCC, guanylyl cyclase C), T-DM1 (trastuzumab emtansine, Kadcycla); SYD985 (anti-HER2, Duocarmycin), milatuzumab-doxorubicin (hCD74-DOX), DCDT2980S, belantamab mafodotin (GSK2857916), polatuzumab vedotin (RG-7596), SGN-CD70A, SGN-CD19A, inotuzumab ozogamicin (CMC-544), lorvotuzumab mertansine, SAR3419, isactuzumab govitecan, enfortumab vedotin (ASG-22ME), ASG-15ME, DS-8201 ((trastuzumab deruxtecan), 225Ac-lintuzumab, U3-1402, 177Lu-tetraxetan-tetuloma, tisotumab vedotin, anetumab ravtansine, CX-2009, SAR-566658, W-0101, ABBV-085, gemtuzumab ozogamicin, ABT-414, glembatumumab vedotin (CDX-011), labetuzumab govitecan (IMMU-130), lifastuzumab vedotin, (RG-7599), milatuzumab-doxorubicin (IMMU-110), indatuximab ravtansine (BT-062), pinatuzumab vedotin (RG-7593), SGN-LIV1A, SGN-CD33A, SAR566658, MLN2704, SAR408701, rovalpituzumab tesirine, ABBV-399, AGS-16C3F, ASG-22ME, AGS67E, AMG 172, AMG 595, AGS-15E, BAY1129980, BAY1187982, BAY94-934 (anetumab ravtansine), GSK2857916, Humax-TF-ADC (tisotumab vedotin), IMGN289, IMGN529, IMGN853 (mirvetuximab soravtansine), LOP628, PCA062, MDX-1203, MEDI-547, PF-06263507, PF-

06647020, PF-06647263, PF-06664178, PF-06688992, PF-06804103, RG7450, RG7458, RG7598, SAR566658, SGN-CD33A, DS-1602 and DS-7300, DS-6157, DS-6000, TAK-164, MEDI2228, MEDI7247, AMG575. ADCs that can be co-administered are described, *e.g.*, in Lambert, et al., Adv Ther (2017) 34:1015–1035 and in de Goeij, Current Opinion in Immunology (2016) 40:14–23.

[0198] Illustrative therapeutic agents (*e.g.*, anticancer or antineoplastic agents) that can be conjugated to the drug-conjugated antibodies, fragments thereof, or antibody mimetics include without limitation monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), a calicheamicin, ansamitocin, maytansine or an analog thereof (*e.g.*, mertansine/emtansine (DM1), ravtansine/soravtansine (DM4)), an anthracyline (*e.g.*, doxorubicin, daunorubicin, epirubicin, idarubicin), pyrrolobenzodiazepine (PBD) DNA cross-linking agent SC-DR002 (D6.5), duocarmycin, a microtubule inhibitors (MTI) (*e.g.*, a taxane, a vinca alkaloid, an epothilone), a pyrrolobenzodiazepine (PBD) or dimer thereof, a duocarmycin (A, B1, B2, C1, C2, D, SA, CC-1065), and other anticancer or anti-neoplastic agents described herein.

Cancer Gene Therapy and Cell Therapy

[0199] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with a cancer gene therapy and cell therapy. Cancer gene therapies and cell therapies include the insertion of a normal gene into cancer cells to replace a mutated or altered gene; genetic modification to silence a mutated gene; genetic approaches to directly kill the cancer cells; including the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to cancer cells, or activate the patient's own immune system (T cells or Natural Killer cells) to kill cancer cells, or find and kill the cancer cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against cancer.

Cellular Therapies

[0200] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with one or more cellular therapies. Illustrative cellular therapies include without limitation co-administration of one or more of a population of immune cells. In some embodiments, the immune cells are natural killer (NK) cells, NK-T cells, T cells, gamma

delta T cells, B-cells, cytokine-induced killer (CIK) cells, macrophage (MAC) cells, tumor infiltrating lymphocytes (TILs) a granulocyte, an innate lymphoid cell, a megakaryocyte, a monocyte, a macrophage, a platelet, a thymocyte, a myeloid cell, and/or dendritic cells (DCs). In some embodiments, the cellular therapy entails a T cell therapy, *e.g.*, co-administering a population of alpha/beta TCR T cells, gamma/delta TCR T cells, regulatory T (Treg) cells and/or TRuC™ T cells. In some embodiments, the cellular therapy entails a NK cell therapy, *e.g.*, co-administering NK-92 cells or JK500 cells. As appropriate, a cellular therapy can entail the co-administration of cells that are autologous, syngeneic or allogeneic to the subject.

[0201] In some embodiments, the cellular therapy entails co-administering immune cells engineered to express chimeric antigen receptors (CARs) or T cell receptors (TCRs) TCRs. In particular embodiments, a population of immune cells is engineered to express a CAR, wherein the CAR comprises a tumor antigen-binding domain. In other embodiments, a population of immune cells is engineered to express T cell receptors (TCRs) engineered to target tumor derived peptides presented on the surface of tumor cells. In one embodiment, the immune cell engineered to express chimeric antigen receptors (CARs) or T cell receptors (TCRs) TCRs is a T cell. In another embodiment, the immune cell engineered to express chimeric antigen receptors (CARs) or T cell receptors (TCRs) TCRs is an NK cell.

[0202] With respect to the structure of a CAR, in some embodiments, the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain. In some embodiments, the intracellular domain comprises a primary signaling domain, a costimulatory domain, or both of a primary signaling domain and a costimulatory domain. In some embodiments, the primary signaling domain comprises a functional signaling domain of one or more proteins selected from CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCERIG), FcR beta (Fc Epsilon Rlb), CD79a, CD79b, Fcgamma RIIa, DAP10, and DAP12 4-1BB/CD137, activating NK cell receptors, an Immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CD11a, CD11b, CD11c, CD11d, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, ligand that

binds with CD83, LIGHT, LIGHT, LTBR, Ly9 (CD229), Ly108), lymphocyte function-associated antigen-1 (LFA-1; CD1-1a/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), Signaling Lymphocytic Activation Molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A, SLAMF7, SLP-76, TNF receptor proteins, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a fragment, truncation, or a combination thereof.

[0203] In some embodiments, the costimulatory domain comprises a functional domain of one or more proteins selected from CD27, CD28, 4-1BB(CD137), OX40, CD30, CD40, PD-1, ICOS, CD2, CD7, LIGHT, NKG2C, lymphocyte function-associated antigen-1 (LFA-1), MYD88, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRFI), CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, ITGAE, CD103, ITGAL, CD1A (NCBI Gene ID: 909), CD1B (NCBI Gene ID: 910), CD1C (NCBI Gene ID: 911), CD1D (NCBI Gene ID: 912), CD1E (NCBI Gene ID: 913), ITGAM, ITGAX, ITGB1, CD29, ITGB2 (CD18, LFA-1), ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, and NKG2D.

[0204] In some embodiments, the transmembrane domain comprises a transmembrane domain derived from a protein selected from the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD3 delta, CD3 gamma, CD45, CD4, CD5, CD7, CD8 alpha, CD8 beta, CD9, CD11a, CD11b, CD11c, CD11d, CD16, CD18, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, KIRDS2, OX40, CD2, CD27, ICOS (CD278), 4-1BB(CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD19, CD19a, IL2R beta, IL2R gamma, IL7R alpha, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD1A, CD1B, CD1C, CD1D, CD1E, ITGAE, CD103, ITGAL, ITGAM, ITGAX, ITGB1, ITGB2, ITGB7, CD29, ITGB2 (LFA-1, CD18), ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (TACTILE), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, and NKG2C activating NK cell receptors, an Immunoglobulin

protein, BTLA, CD247, CD276 (B7-H3), CD30, CD84, CDS, cytokine receptor, Fc gamma receptor, GADS, ICAM-1, Ig alpha (CD79a), integrins, LAT, a ligand that binds with CD83, LIGHT, MHC class 1 molecule, PAG/Cbp, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, or a fragment, truncation, or a combination thereof.

[0205] In some embodiments, the CAR comprises a hinge domain. A hinge domain may be derived from a protein selected from the CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8.alpha., CD8.beta., CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIRDL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, or Toll ligand receptor, IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM or fragment or combination thereof.

[0206] In some embodiments, the TCR or CAR antigen binding domain or the immunotherapeutic agent described herein (*e.g.*, monospecific or multi-specific antibody or antigen-binding fragment thereof or antibody mimetic) binds a tumor-associated antigen (TAA). In some embodiments, the tumor-associated antigen is selected from: CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECLI); CD33; epidermal growth factor receptor variant III (EGFRvlll); ganglioside G2 (GD2); ganglioside GD3 (αNeuSAc(2-

8)αNeuSAc(2-3)βDGaip(1-4)bDGIcp(1-1)Cer); ganglioside GM3 (αNeuSAc(2-3)βDGalp(1-4)βDGlcp(1-1)Cer); GM-CSF receptor; TNF receptor superfamily member 17 (TNFRSF17, BCMA); B-lymphocyte cell adhesion molecule; Tn antigen ((Tn Ag) or (GaINAcu-Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (RORI); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); HLA class I antigen A-2 alpha; HLA antigen; Lewis(Y)antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; delta like 3 (DLL3); Folate receptor alpha; Folate receptor beta, GDNF alpha 4 receptor, Receptor tyrosine-protein kinase, ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); APRIL receptor; ADP ribosyl cyclase-1; Ephb4 tyrosine kinase receptor, DCAMKL1 serine threonine kinase, Aspartate beta-hydroxylase, epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP);elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP);insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX);Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100);oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); ephrin type-A receptor 3 (EphA3), Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); transglutaminase 5 (TGS5); high molecular weight-melanomaassociatedantigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta;tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); six transmembrane epithelial antigen of the prostate I (STEAP1); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein-coupled receptor class C group 5, member D (GPRCSD); IL-15 receptor (IL-15); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycoceramide (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (ORS IE2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-la);

Melanoma associated antigen 1 (MAGE-A1); Melanoma associated antigen 3 (MAGE-A3); Melanoma associated antigen 4 (MAGE-A4); T cell receptor beta 2 chain C; ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MADCT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53, (p53); p53 mutant; prostein; survivin; telomerase; prostate carcinoma tumor antigen-1 (PCTA-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin-A1; Cyclin B1;v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1(CYP IBI); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES I); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); Peptidoglycan recognition protein, synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-I); renal ubiquitous 1 (RUI); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIRI); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-2 (GPC2); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1). In some embodiments, the target is an epitope of the tumor associated antigen presented in an MHC.

[0207] In some embodiments, the tumor antigen is selected from CD150, 5T4, ActRIIA, B7, TNF receptor superfamily member 17 (TNFRSF17, BCMA), CA-125, CCNA1, CD123, CD126, CD138, CD14, CD148, CD15, CD19, CD20, CD200, CD21, CD22, CD23, CD24, CD25, CD26, CD261, CD262, CD30, CD33, CD362, CD37, CD38, CD4, CD40, CD40L, CD44, CD46, CD5, CD52, CD53, CD54, CD56, CD66a-d, CD74, CD8, CD80, CD92, CE7, CS-

1, CSPG4, ED-B fibronectin, EGFR, EGFRvIII, EGP-2, EGP-4, EPHa2, ErbB2, ErbB3, ErbB4, FBP, HER1-HER2 in combination, HER2-HER3 in combination, HERV-K, HIV-1 envelope glycoprotein gp120, HIV-1 envelope glycoprotein gp41, HLA-DR, HLA class I antigen alpha G, HM1.24, K-Ras GTPase, HMW-MAA, Her2, Her2/neu, IGF-1R, IL-11Ralpha, IL-13R-alpha2, IL-2, IL-22R-alpha, IL-6, IL-6R, Ia, Ii, L1-CAM, L1-cell adhesion molecule, Lewis Y, Ll-CAM, MAGE A3, MAGE-A1, MART-1, MUC1, NKG2C ligands, NKG2D Ligands, NYESO-1, OEPHa2, PIGF, PSCA, PSMA, ROR1, T101, TAC, TAG72, TIM-3, TRAIL-R1, TRAIL-R1 (DR4), TRAIL-R2 (DR5), VEGF, VEGFR2, WT-I, a G-protein coupled receptor, alphafetoprotein (AFP), an angiogenesis factor, an exogenous cognate binding molecule (ExoCBM), oncogene product, anti-folate receptor, c-Met, carcinoembryonic antigen (CEA), cyclin (D 1), ephrinB2, epithelial tumor antigen, estrogen receptor, fetal acetylcholine e receptor, folate binding protein, gp100, hepatitis B surface antigen, Epstein-Barr nuclear antigen 1, Latent membrane protein 1, Secreted protein BARF1, P2X7 purinoceptor, Syndecan-1, kappa chain, kappa light chain, kdr, lambda chain, livin, melanoma-associated antigen, mesothelin, mouse double minute 2 homolog (MDM2), mucin 16 (MUC16), mutated p53, mutated ras, necrosis antigens, oncofetal antigen, ROR2, progesterone receptor, prostate specific antigen, tEGFR, tenascin, P2-Microgiobuiin, Fc Receptor-like 5 (FcRL5).

[0208] Examples of cell therapies include without limitation: AMG-119, Algenpantucel-L, ALOFISEL®, Sipuleucel-T, (BPX-501) rivogenlecleucel US9089520, WO2016100236, AU-105, ACTR-087, activated allogeneic natural killer cells CNDO-109-AANK, MG-4101, AU-101, BPX-601, FATE-NK100, LFU-835 hematopoietic stem cells, Imilecleucel-T, baltaleucel-T, PNK-007, UCARTCS1, ET-1504, ET-1501, ET-1502, ET-190, CD19-ARTEMIS, ProHema, FT-1050-treated bone marrow stem cell therapy, CD4CARNK-92 cells, SNK-01, NEXI-001, CryoStim, AlloStim, lentiviral transduced huCART-meso cells, CART-22 cells, EGFRt/19-28z/4-1BBL CAR T cells, autologous 4H11-28z/fIL-12/EFGRt T cell, CCR5-SBC-728-HSPC, CAR4-1BBZ, CH-296, dnTGFbRII-NY-ESOc259T, Ad-RTS-IL-12, IMA-101, IMA-201, CARMA-0508, TT-18, CMD-501, CMD-503, CMD-504, CMD-502,CMD-601,CMD-602, CSG-005, LAAP T-cell therapy, PD-1 knockout T cell therapy (esophageal cancer/NSCLC), anti-MUC1 CAR T-cell therapy (esophageal cancer/NSCLC), anti-MUC1 CAR T-cell therapy + PD-1 knockout T cell therapy (esophageal cancer/NSCLC), anti-KRAS G12D mTCR PBL, anti-CD123 CAR T-cell therapy, anti-mutated neoantigen TCR T-cell therapy, tumor lysate/MUC1/survivin PepTivator-loaded dendritic cell vaccine, autologous dendritic cell vaccine (metastatic malignant melanoma, intradermal/intravenous), anti-LeY-scFv-CD28-zeta CAR T-cells, PRGN-3005, iC9-GD2-CAR-IL-15 T-cells, HSC-100, ATL-DC-101, MIDRIX4-

LUNG, MIDRIXNEO, FCR-001, PLX stem cell therapy, MDR-101, GeniusVac-Mel4, ilixadencel, allogeneic mesenchymal stem cell therapy, romyelocel L, CYNK-001, ProTrans, ECT-100, MSCTRAIL, dilanubicel, FT-516, ASTVAC-2, E-CEL UVEC, CK-0801, allogenic alpha/beta CD3+ T cell and CD19+ B cell depleted stem cells (hematologic diseases, TBX-1400, HLCN-061, umbilical cord derived Hu-PHEC cells (hematological malignancies/aplastic anemia), AP-011, apceth-201, apceth-301, SENTI-101, stem cell therapy (pancreatic cancer), ICOVIR15-cBiTE, CD33HSC/CD33 CAR-T, PLX-Immune, SUBCUVAX, CRISPR allogeneic gamma-delta T-cell based gene therapy (cancer), ex vivo CRISPR allogeneic healthy donor NK-cell based gene therapy (cancer), ex-vivo allogeneic induced pluripotent stem cell-derived NK-cell based gene therapy (solid tumor), and anti-CD20 CAR T-cell therapy (non-Hodgkin's lymphoma).

Additional agents for targeting tumors

[0209] Additional agents for targeting tumors include without limitation: Alpha-fetoprotein modulators, such as ET-1402, and AFP-TCR; Anthrax toxin receptor 1 modulator, such as anti-TEM8 CAR T-cell therapy; TNF receptor superfamily member 17 (TNFRSF17, BCMA), such as bb-2121 (ide-cel), bb-21217, JCARH125, UCART-BCMA, ET-140, MCM-998, LCAR-B38M, CART-BCMA, SEA-BCMA, BB212, ET-140, P-BCMA-101, AUTO-2 (APRIL-CAR), JNJ-68284528; Anti-CLL-1 antibodies, (see, for example, PCT/US2017/025573); Anti-PD-L1-CAR tank cell therapy, such as KD-045; Anti-PD-L1 t-haNK, such as PD-L1 t-haNK; anti-CD45 antibodies, such as 131I-BC8 (lomab-B); anti-HER3 antibodies, such as LJM716, GSK2849330; APRIL receptor modulator, such as anti-BCMA CAR T-cell therapy, Descartes-011; ADP ribosyl cyclase-1/APRIL receptor modulator, such as dual anti-BCMA/anti-CD38 CAR T-cell therapy; CART-ddBCMA; B7 homolog 6, such as CAR-NKp30 and CAR-B7H6; B-lymphocyte antigen CD19, such as TBI-1501, CTL-119 huCART-19 T cells,l iso-cel, JCAR-015 US7446190, JCAR-014, JCAR-017, (WO2016196388, WO2016033570, WO2015157386), axicabtagene ciloleucel (KTE-C19, Yescarta®), KTE-X19, US7741465, US6319494, UCART-19, EBV-CTL, T tisagenlecleucel-T (CTL019), WO2012079000, WO2017049166, CD19CAR-CD28-CD3zeta-EGFRt-expressing T cells, CD19/4-1BBL armored CAR T cell therapy, C-CAR-011, CIK-CAR.CD19, CD19CAR-28-zeta T cells, PCAR-019, MatchCART, DSCAR-01, IM19 CAR-T, TC-110; anti-CD19 CAR T-cell therapy (B-cell acute lymphoblastic leukemia, Universiti Kebangsaan Malaysia); anti-CD19 CAR T-cell therapy (acute lymphoblastic leukemia/Non-Hodgkin's lymphoma, University Hospital Heidelberg), anti-CD19 CAR T-cell therapy (silenced IL-6 expression, cancer,

Shanghai Unicar-Therapy Bio-medicine Technology), MB-CART2019.1 (CD19/CD20), GC-197 (CD19/CD7), CLIC-1901, ET-019003, anti-CD19-STAR-T cells, AVA-001, BCMA-CD19 cCAR (CD19/APRIL), ICG-134, ICG-132 (CD19/CD20), CTA-101, WZTL-002, dual anti-CD19/anti-CD20 CAR T-cells (chronic lymphocytic leukemia/B-cell lymphomas), HY-001, ET-019002, YTB-323, GC-012 (CD19/APRIL), GC-022 (CD19/CD22), CD19CAR-CD28-CD3zeta-EGFRt-expressing Tn/mem; UCAR-011, ICTCAR-014, GC-007F, PTG-01, CC-97540; allogeneic anti-CD19 CART cells, such as GC-007G; APRIL receptor modulator; SLAM family member 7 modulator, BCMA-CS1 cCAR; autologous dendritic cell tumor antigen (ADCTA), such as ADCTA-SSI-G; B-lymphocyte antigen CD20, such as ACTR707 ATTCK-20, PBCAR-20A; allogenic T cells expressing CD20 CAR, such as LB-1905; B-lymphocyte antigen CD19/B-lymphocyte antigen 22, such as TC-310; B-lymphocyte antigen 22 cell adhesion, such as UCART-22, JCAR-018 WO2016090190; NY-ESO-1 modulators, such as GSK-3377794, TBI-1301, GSK3537142; Carbonic anhydrase, such as DC-Ad-GMCAIX; Caspase 9 suicide gene, such as CaspaCIDe DLI, BPX-501; CCR5, such as SB-728; CCR5 gene inhibitor/TAT gene/TRIM5 gene stimulator, such as lentivirus vector CCR5 shRNA/TRIM5alpha/TAR decoy-transduced autologous CD34-positive hematopoietic progenitor cells; CDw123, such as MB-102, IM-23, JEZ-567, UCART-123; CD4, such as ICG-122; CD5 modulators, such as CD5.28z CART cells; Anti-CD22, such as anti-CD22 CART; Anti-CD30, such as TT-11; Dual anti-CD33/anti-CLL1, such as LB-1910; CD40 ligand, such as BPX-201, MEDI5083; CD56, such as allogeneic CD56-positive CD3-negative natural killer cells (myeloid malignancies); CD19/CD7 modulator, such as GC-197; T-cell antigen CD7 modulator, such as anti-CD7 CAR T-cell therapy (CD7-positive hematological malignancies); CD123 modulator, such as UniCAR02-T-CD123; Anti-CD276, such as anti-CD276 CART; CEACAM protein 5 modulators, such as MG7-CART; Claudin 6, such as CSG-002; Claudin 18.2, such as LB-1904; Chlorotoxin, such as CLTX-CART; EBV targeted, such as CMD-003; MUC16EGFR, such as autologous 4H11-28z/fIL-12/EFGRt T cell; Endonuclease, such as PGN-514, PGN-201; Epstein-Barr virus specific T-lymphocytes, such as TT-10; Epstein-Barr nuclear antigen 1/Latent membrane protein 1/Secreted protein BARF1 modulator, such as TT-10X; Erbb2, such as CST-102, CIDeCAR; Ganglioside (GD2), such as 4SCAR-GD2; Gamma delta T cells, such as ICS-200; folate hydrolase 1 (FOLH1, Glutamate carboxypeptidase II, PSMA; NCBI Gene ID: 2346), such as CIK-CAR.PSMA, CART-PSMA-TGFβRDN, P-PSMA-101; Glypican-3(GPC3), such as TT-16, GLYCAR; Hemoglobin, such as PGN-236; Hepatocyte growth factor receptor, such as anti-cMet RNA CAR T; HLA class I antigen A-2 alpha modulator, such as FH-MCVA2TCR; HLA class I antigen A-2 alpha/Melanoma associated

antigen 4 modulator, such as ADP-A2M4CD8; HLA antigen modulator, such as FIT-001, NeoTCR-P1; Human papillomavirus E7 protein, such as KITE-439 (see, for example, PCT/US2015/033129); ICAM-1 modulator, such as AIC-100; Immunoglobulin gamma Fc receptor III, such as ACTR087; IL-12, such as DC-RTS-IL-12; IL-12 agonist/mucin 16, such as JCAR-020; IL-13 alpha 2, such as MB-101; IL-15 receptor agonist, such as PRGN-3006, ALT-803; interleukin-15/Fc fusion protein (*e.g.*, XmAb24306); recombinant interleukin-15 (*e.g.*, AM0015, NIZ-985); pegylated IL-15 (*e.g.*, NKTR-255); IL-2, such as CST-101; Interferon alpha ligand, such as autologous tumor cell vaccine + systemic CpG-B + IFN-alpha (cancer); K-Ras GTPase, such as anti-KRAS G12V mTCR cell therapy; Neural cell adhesion molecule L1 L1CAM (CD171), such as JCAR-023; Latent membrane protein 1/Latent membrane protein 2, such as Ad5f35-LMPd1-2-transduced autologous dendritic cells; MART-1 melanoma antigen modulator, such as MART-1 F5 TCR engineered PBMC; Melanoma associated antigen 10, such as MAGE-A10C796T MAGE-A10 TCR; Melanoma associated antigen 3/Melanoma associated antigen 6 (MAGE A3/A6) such as KITE-718 (see, for example, PCT/US2013/059608); Mesothelin, such as CSG-MESO, TC-210; Mucin 1 modulator, such as ICTCAR-052, Tn MUC-1 CAR-T, ICTCAR-053; Anti-MICA/MICB, such as CYAD-02; NKG2D, such as NKR-2; Ntrkr1 tyrosine kinase receptor, such as JCAR-024; PRAMET cell receptor, such as BPX-701; Prostate stem cell antigen modulator, such as MB-105; Roundabout homolog 1 modulator, such as ATCG-427; Peptidoglycan recognition protein modulator, such as Tag-7 gene modified autologous tumor cell vaccine; PSMA, such as PSMA-CAR T-cell therapy (lentiviral vector, castrate-resistant prostate cancer); SLAM family member 7 modulator, such as IC9-Luc90-CD828Z; TGF beta receptor modulator, such as DNR.NPC T-cells; T-lymphocyte, such as TT-12; T-lymphocyte stimulator, such as ATL-001; TSH receptor modulator, such as ICTCAR-051; Tumor infiltrating lymphocytes, such as LN-144, LN-145; and/or Wilms tumor protein, such as JTCR-016, WT1-CTL, ASP-7517.

MCL1 apoptosis regulator, BCL2 family member (MCL1) Inhibitors

[0210] In various embodiments, an anti-CD47 agent or an anti-SIRPα agent as described herein, is combined with an inhibitor of MCL1 apoptosis regulator, BCL2 family member (MCL1, TM; EAT; MCL1L; MCL1S; Mcl-1; BCL2L3; MCL1-ES; bcl2-L-3; mcl1/EAT; NCBI Gene ID: 4170). Examples of MCL1 inhibitors include AMG-176, AMG-397, S-64315, and AZD-5991, 483-LM, A-1210477, UMI-77, JKY-5-037, and those described in WO2018183418, WO2016033486, WO2019222112 and WO2017147410.

Cytokine inducible SH2 containing protein (CISH) Inhibitors

[0211] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with an inhibitor of cytokine inducible SH2 containing protein (CISH; CIS; G18; SOCS; CIS-1; BACTS2; NCBI Gene ID: 1154). Examples of CISH inhibitors include those described in WO2017100861, WO2018075664 and WO2019213610.

Gene Editors

[0212] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab); and the focally delivered ionizing radiation therapy, as described herein, is further combined with gene editor. Illustrative gene editing system that can be co-administered include without limitation a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system (*e.g.*, an ARCUS), and a homing meganuclease system.

Other drugs with unspecified targets

[0213] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and the focally delivered ionizing radiation therapy, as described herein, is further combined with human immunoglobulin (10% liquid formulation), Cuvitru (human immunoglobulin (20% solution), levofolinate disodium, IMSA-101, BMS-986288, IMUNO BGC Moreau RJ, R-OKY-034F, GP-2250, AR-23, calcium levofolinate, porfimer sodium, RG6160, ABBV-155, CC-99282, polifeprosan 20 with carmustine, Veregen, gadoxetate disodium, gadobutrol, gadoterate meglumine, gadoteridol, 99mTc-sestamibi, pomalidomide, pacibanil, and/or valrubicin.

Exemplified Combination Therapies

[0214] In various embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and the focally delivered ionizing radiation therapy, as described herein, is further combined with standard of care regimens for treating solid cancers.

Breast Cancer Combination Therapy

[0215] Therapeutic agents used to treat breast cancer include albumin-bound paclitaxel, anastrozole, atezolizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, Ixabepilone, lapatinib, letrozole, methotrexate, mitoxantrone, paclitaxel, pegylated liposomal

doxorubicin, pertuzumab, tamoxifen, toremifene, trastuzumab, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat breast cancer (*e.g.*, HR+/-/HER2 +/-) include trastuzumab (HERCEPTIN®), pertuzumab (PERJETA®), docetaxel, carboplatin, palbociclib (IBRANCE®), letrozole, trastuzumab emtansine (KADCYLA®), fulvestrant (FASLODEX®), olaparib (LYNPARZA®), eribulin, tucatinib, capecitabine, lapatinib, everolimus (AFINITOR®), exemestane, eribulin mesylate (HALAVEN®), and combinations thereof. In some embodiments therapeutic agents used to treat breast cancer include trastuzumab + pertuzumab + docetaxel, trastuzumab + pertuzumab + docetaxel + carboplatin, palbociclib + letrozole, tucatinib + capecitabine, lapatinib + capecitabine, palbociclib + fulvestrant, or everolimus + exemestane. In some embodiments therapeutic agents used to treat breast cancer include trastuzumab deruxtecan (ENHERTU®), datopotamab deruxtecan (DS-1062), enfortumab vedotin (PADCEV®), balixafortide, elacestrant, or a combination thereof. In some embodiments therapeutic agents used to treat breast cancer include balixafortide + eribulin.

Triple Negative Breast Cancer (TNBC) Combination Therapy

[0216] Therapeutic agents used to treat TNBC include atezolizumab, cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, paclitaxel, and combinations thereof. In some embodiments therapeutic agents used to treat TNBC include olaparib (LYNPARZA®), atezolizumab (TECENTRIQ®), paclitaxel or nab-paclitaxel (ABRAXANE®), eribulin, bevacizumab (AVASTIN®), carboplatin, gemcitabine, eribulin mesylate (HALAVEN®), pembrolizumab (KEYTRUDA®), cisplatin, doxorubicin, epirubicin, or a combination thereof. In some embodiments therapeutic agents to treat TNBC include atezolizumab + paclitaxel, bevacizumab + paclitaxel, carboplatin + paclitaxel, carboplatin + gemcitabine, or paclitaxel + gemcitabine. In some embodiments therapeutic agents used to treat TNBC include eryaspase, capivasertib, alpelisib, rucaparib + nivolumab, atezolumab + paclitaxel + gemcitabine+ capecitabine + carboplatin, ipatasertib + paclitaxel, ladiratuzumab vedotin + pembrolimab, durvalumab + DS-8201a, trilaciclib + gemcitabine +carboplatin. In some embodiments therapeutic agents used to treat TNBC include trastuzumab deruxtecan (ENHERTU®), datopotamab deruxtecan (DS-1062), enfortumab vedotin (PADCEV®), balixafortide, adagloxad simolenin, nelipepimut-s (NEUVAX®), nivolumab (OPDIVO®), rucaparib, toripalimab (TUOYI®), camrelizumab, capivasertib, durvalumab (IMFINZI®), and combinations thereof. In some embodiments therapeutic agents use to treat TNBC include nivolumab + rucaparib, bevacizumab (AVASTIN®) + chemotherapy, toripalimab + paclitaxel, toripalimab + albumin-

bound paclitaxel, camrelizumab + chemotherapy, pembrolizumab + chemotherapy, balixafortide + eribulin, durvalumab + trastuzumab deruxtecan, durvalumab + paclitaxel, or capivasertib + paclitaxel.

Bladder Cancer Combination Therapy

[0217] Therapeutic agents used to treat bladder cancer include datopotamab deruxtecan (DS-1062), trastuzumab deruxtecan (ENHERTU®), erdafitinib, eganelisib, lenvatinib, bempegaldesleukin (NKTR-214), or a combination thereof. In some embodiments therapeutic agents used to treat bladder cancer include eganelisib + nivolumab, pembrolizumab (KEYTRUDA®) + enfortumab vedotin (PADCEV®), nivolumab + ipilimumab, duravalumab + tremelimumab, lenvatinib + pembrolizumab, enfortumab vedotin (PADCEV®) + pembrolizumab, and bempegaldesleukin + nivolumab.

Colorectal Cancer (CRC) Combination Therapy

[0218] Therapeutic agents used to treat CRC include bevacizumab, capecitabine, cetuximab, fluorouracil, irinotecan, leucovorin, oxaliplatin, panitumumab, ziv-aflibercept, and any combinations thereof. In some embodiments therapeutic agents used to treat CRC include bevacizumab (AVASTIN®), leucovorin, 5-FU, oxaliplatin (FOLFOX), pembrolizumab (KEYTRUDA®), FOLFIRI, regorafenib (STIVARGA®), aflibercept (ZALTRAP®), cetuximab (ERBITUX®), Lonsurf (ORCANTAS®), XELOX, FOLFOXIRI, or a combination thereof. In some embodiments therapeutic agents used to treat CRC include bevacizumab + leucovorin + 5-FU + oxaliplatin (FOLFOX), bevacizumab + FOLFIRI, bevacizumab + FOLFOX, aflibercept + FOLFIRI, cetuximab + FOLFIRI, bevacizumab + XELOX, and bevacizumab + FOLFOXIRI. In some embodiments therapeutic agents used to treat CRC include binimetinib + encorafenib + cetuximab, trametinib + dabrafenib + panitumumab, trastuzumab + pertuzumab, napabucasin + FOLFIRI + bevacizumab, nivolumab + ipilimumab.

Esophageal and Esophagogastric Junction Cancer Combination Therapy

[0219] Therapeutic agents used to treat esophageal and esophagogastric junction cancer include capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, fluoropyrimidine, fluorouracil, irinotecan, leucovorin, oxaliplatin, paclitaxel, ramucirumab, trastuzumab, and any combinations thereof. In some embodiments therapeutic agents used to treat gastroesophageal junction cancer (GEJ) include herceptin, cisplatin, 5-FU, ramicurimab, or paclitaxel. In some embodiments therapeutic agents used to treat GEJ cancer include ALX-148, AO-176, or IBI-188.

Gastric Cancer Combination Therapy

[0220] Therapeutic agents used to treat gastric cancer include capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, fluoropyrimidine, fluorouracil, Irinotecan, leucovorin, mitomycin, oxaliplatin, paclitaxel, ramucirumab, trastuzumab, and any combinations thereof.

Head and Neck Cancer Combination Therapy

[0221] Therapeutic agents used to treat head & neck cancer include afatinib, bleomycin, capecitabine, carboplatin, cetuximab, cisplatin, docetaxel, fluorouracil, gemcitabine, hydroxyurea, methotrexate, nivolumab, paclitaxel, pembrolizumab, vinorelbine, and any combinations thereof.

[0222] Therapeutic agents used to treat head and neck squamous cell carcinoma (HNSCC) include pembrolizumab, carboplatin, 5-FU, docetaxel, cetuximab (Erbitux®), cisplatin, nivolumab (OPDIVO®), and combinations thereof. In some embodiments therapeutic agents used to treat HNSCC include pembrolizumab + carboplatin + 5-FU, cetuximab + cisplatin + 5-FU, cetuximab + carboplatin + 5-FU, cisplatin + 5-FU, and carboplatin + 5-FU. In some embodiments therapeutic agents used to treat HNSCC include durvalumab, durvalumab + tremelimumab, nivolumab + ipilimumab, rovaluecel, pembrolizumab, pembrolizumab + epacadostat, GSK3359609 + pembrolizumab, lenvatinib + pembrolizumab, retifanlimab, retifanlimab + enobituzumab, ADU-S100 + pembrolizumab, epacadostat + nivolumab+ ipilimumab/lirilumab.

Non-Small Cell Lung Cancer Combination Therapy

[0223] Therapeutic agents used to treat non-small cell lung cancer (NSCLC) include afatinib, albumin-bound paclitaxel, alectinib, atezolizumab, bevacizumab, bevacizumab, cabozantinib, carboplatin, cisplatin, crizotinib, dabrafenib, docetaxel, erlotinib, etoposide, gemcitabine, nivolumab, paclitaxel, pembrolizumab, pemetrexed, ramucirumab, trametinib, trastuzumab, vandetanib, vemurafenib, vinblastine, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat NSCLC include alectinib (ALECENSA®), dabrafenib (TAFINLAR®), trametinib (MEKINIST®), osimertinib (TAGRISSO®), entrectinib (TARCEVA®), crizotinib (XALKORI®), pembrolizumab (KEYTRUDA®), carboplatin, pemetrexed (ALIMTA®), nab-paclitaxel (ABRAXANE®), ramucirumab (CYRAMZA®), docetaxel, bevacizumab (AVASTIN®), brigatinib, gemcitabine, cisplatin, afatinib (GILOTRIF®), nivolumab (OPDIVO®), gefitinib (IRESSA®), and combinations thereof. In some embodiments therapeutic agents used to treat NSCLC include

dabrafenib + trametinib, pembrolizumab + carboplatin + pemetrexed, pembrolizumab + carboplatin + nab-paclitaxel, ramucirumab + docetaxel, bevacizumab + carboplatin + pemetrexed, pembrolizumab + pemetrexed + carboplatin, cisplatin + pemetrexed, bevacizumab + carboplatin + nab-paclitaxel, cisplatin + gemcitabine, nivolumab + docetaxel, carboplatin + pemetrexed, carboplatin + nab-paclitaxel, or pemetrexed + cisplatin + carboplatin. In some embodiments therapeutic agents used to NSCLC include datopotamab deruxtecan (DS-1062), trastuzumab deruxtecan (ENHERTU®), enfortumab vedotin (PADCEV®), durvalumab, canakinumab, cemiplimab, nogapendekin alfa, avelumab, tiragolumab, domvanalimab, vibostolimab, ociperlimab, or a combination thereof. In some embodiments therapeutic agents used to treat NSCLC include datopotamab deruxtecan + pembrolizumab, datopotamab deruxtecan + durvalumab, durvalumab + tremelimumab, pembrolizumab + lenvatinib + pemetrexed, pembrolizumab + olaparib, nogapendekin alfa (N-803) + pembrolizumab, tiragolumab + atezolizumab, vibostolimab + pembrolizumab, or ociperlimab + tislelizumab.

Small Cell Lung Cancer Combination Therapy

[0224] Therapeutic agents used to treat small cell lung cancer (SCLC) include atezolizumab, bendamustime, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gemcitabine, ipillimumab, irinotecan, nivolumab, paclitaxel, temozolomide, topotecan, vincristine, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat SCLC include atezolizumab, carboplatin, cisplatin, etoposide, paclitaxel, topotecan, nivolumab, durvalumab, trilaciclib, or combinations thereof. In some embodiments therapeutic agents used to treat SCLC include atezolizumab + carboplatin + etoposide, atezolizumab + carboplatin, atezolizumab + etoposide, or carboplatin + paclitaxel.

Ovarian Cancer Combination Therapy

[0225] Therapeutic agents used to treat ovarian cancer include 5-flourouracil, albumin bound paclitaxel, altretamine, anastrozole, bevacizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, exemestane, gemcitabine, ifosfamide, irinotecan, letrozole, leuprolide acetate, liposomal doxorubicin, megestrol acetate, melphalan, olaparib, oxaliplatin, paclitaxel, pazopanib, pemetrexed, tamoxifen, topotecan, vinorelbine, and any combinations thereof.

Pancreatic Cancer Combination Therapies

[0226] Therapeutic agents used to treat pancreatic cancer include 5-FU, leucovorin, oxaliplatin, irinotecan, gemcitabine, nab-paclitaxel (ABRAXANE®), FOLFIRINOX, and

combinations thereof. In some embodiments therapeutic agents used to treat pancreatic cancer include 5-FU + leucovorin + oxaliplatin + irinotecan, 5-FU + nanoliposomal irinotecan, leucovorin + nanoliposomal irinotecan, and gemcitabine + nab-paclitaxel.

Prostate Cancer Combination Therapies

[0227] Therapeutic agents used to treat prostate cancer include enzalutamide (XTANDI®), leuprolide, trifluridine + tipiracil (LONSURF®), cabazitaxel, prednisone, abiraterone (ZYTIGA®), docetaxel, mitoxantrone, bicalutamide, LHRH, flutamide, ADT, sabizabulin (Veru-111), and combinations thereof. In some embodiments therapeutic agents used to treat prostate cancer include enzalutamide + leuprolide, trifluridine + tipiracil (LONSURF®), cabazitaxel + prednisone, abiraterone + prednisone, docetaxel + prednisone, mitoxantrone + prednisone, bicalutamide + LHRH, flutamide + LHRH, leuprolide + flutamide, and abiraterone + prednisone + ADT.

Additional Exemplified Combination Therapies

[0228] In some embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and the focally delivered ionizing radiation therapy, as described herein, are co-administered with one or more therapeutic agents selected from a PI3K inhibitor, a FLT3R agonist, a PD-1 antagonist, a PD-L1 antagonist, an MCL1 inhibitor, a CCR8 binding agent, an HPK1 antagonist, a DGKα inhibitor, a CISH inhibitor, a PARP-7 inhibitor, a Cbl-b inhibitor, a KRAS inhibitor (*e.g.*, a KRAS G12C or G12D inhibitor), a KRAS degrader, a beta-catenin degrader, a helios degrader, a CD73 inhibitor, an adenosine receptor antagonist, a TIGIT antagonist, a TREM1 binding agent, a TREM2 binding agent, a CD137 agonist, a GITR binding agent, an OX40 binding agent, and a CAR-T cell therapy.

[0229] In some embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and the focally delivered ionizing radiation therapy, as described herein, are co-administered with one or more therapeutic agents selected from a PI3Kδ inhibitor (*e.g.*, idealisib), a FLT3L-Fc fusion protein (*e.g.*, GS-3583), an anti-PD-1 antibody (pembrolizumab, nivolumab, zimberelimab), a small molecule PD-L1 inhibitor (*e.g.*, GS-4224), an anti-PD-L1 antibody (*e.g.*, atezolizumab, avelumab), a small molecule MCL1 inhibitor (*e.g.*, GS-9716), a small molecule HPK1 inhibitor (*e.g.*, GS-6451), a HPK1 degrader (PROTAC; *e.g.*, ARV-766), a small molecule DGKα inhibitor, a small molecule CD73 inhibitor (*e.g.*, quemliclustat (AB680)), an anti-CD73 antibody (*e.g.*, oleclumab), a dual A2a/A2b adenosine receptor antagonist (*e.g.*, etrumadenant (AB928)), an anti-TIGIT antibody (*e.g.*, tiragolumab, vibostolimab,

domvanalimab, AB308), an anti-TREM1 antibody (*e.g.*, PY159), an anti-TREM2 antibody (*e.g.*, PY314), a CD137 agonist (*e.g.*, AGEN-2373), a GITR/OX40 binding agent (*e.g.*, AGEN-1223) and a CAR-T cell therapy (*e.g.*, axicabtagene ciloleucel, brexucabtagene autoleucel, tisagenlecleucel).

[0230] In some embodiments, the agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and the focally delivered ionizing radiation therapy, as described herein, are co-administered with one or more therapeutic agents selected from idealisib, GS-3583, zimberelimab, GS-4224, GS-9716, GS-6451, quemliclustat (AB680), etrumadenant (AB928), domvanalimab, AB308, PY159, PY314, AGEN-1223, AGEN-2373, axicabtagene ciloleucel and brexucabtagene autoleucel.

5. Dosing and Scheduling

[0231] The methods described herein include administration of a therapeutically effective dose of compositions, *e.g.*, a therapeutically effective dose of an agent that inhibits binding between CD47 and SIRPα and a therapeutically effective dose of focally delivered RT.

[0232] Compositions are administered to a patient in an amount sufficient to substantially ablate targeted cells, as described above. An amount adequate to accomplish this is defined as a "therapeutically effective dose," which may provide for an improvement in overall survival rates. The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease (*e.g.*, a cancer as described herein). A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy. Single or multiple administrations of the compositions may be administered depending on the dosage and frequency as needed and tolerated by the patient. The particular dose used for a treatment will depend upon the medical condition and history of the mammal, as well as other factors such as age, weight, gender, administration route, efficiency, *etc.*

[0233] In some embodiments, combined therapeutic amounts of an agent that inhibits binding between CD47 and SIRPα; and focally delivered RT, as described herein, optionally, with one or more additional therapeutic agents, as described herein, can (i) reduce the number of diseased cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent, and preferably stop the diseased cell infiltration into peripheral organs; (iv) inhibit (*e.g.*, slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of a tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with cancer or myeloproliferative disease. In some embodiments, combined

therapeutic amounts of an agent that inhibits binding between CD47 and SIRPα; and focally delivered RT, as described herein, optionally, with one or more additional therapeutic agents, as described herein, can (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent, and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (*e.g.*, slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of a tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. In various embodiments, the amount is sufficient to ameliorate, palliate, lessen, and/or delay one or more of symptoms of cancer.

[0234] An "increased" or "enhanced" amount (*e.g.*, with respect to cancer cell proliferation or expansion, antitumor response, cancer cell metastasis) refers to an increase that is 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, or 50 or more times (*e.g.*, 100, 500, 1000 times) (including all integers and decimal points in between and above 1, *e.g.*, 2.1, 2.2, 2.3, 2.4, *etc.*) an amount or level described herein. It may also include an increase of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 150%, at least 200%, at least 500%, or at least 1000% of an amount or level described herein.

[0235] A "decreased" or "reduced" or "lesser" amount (*e.g.*, with respect to tumor size, cancer cell proliferation or growth) refers to a decrease that is about 1.1, 1.2, 1.3, 1.4, 1.5, 1.6 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, or 50 or more times (*e.g.*, 100, 500, 1000 times) (including all integers and decimal points in between and above 1, *e.g.*, 1.5, 1.6, 1.7, 1.8, *etc.*) an amount or level described herein. It may also include a decrease of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, at least 100%, at least 150%, at least 200%, at least 500%, or at least 1000% of an amount or level described herein. In various embodiments, tumor burden is determined using linear dimensional methods (*e.g.*, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer, *et al.*, *Eur J Cancer.* (2009) 45(2):228–47). In various embodiments, tumor burden is determined using volumetric analysis (*e.g.*, positron emission tomography (PET) / computed tomography (CT) scan). *See*, *e.g.*, Paydary, *et al.*, *Mol Imaging Biol.* (2019) 21(1):1-10; Li, *et al.*, *AJR Am J Roentgenol.* (2021) 217(6):1433-1443; and Kerner, *et al.*, EJNMMI Res. (2016) Dec;6(1):33.

[0236] An "anti-tumor effect" as used herein, refers to a biological effect that can present as a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell

proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or amelioration of various physiological symptoms associated with the tumor. An anti-tumor effect can also refer to the prevention of the occurrence or recurrence of a tumor, *e.g.*, a relapse after remission.

[0237] Effective doses of the combined agents for the treatment of cancer vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but nonhuman mammals may also be treated, *e.g.*, companion animals such as dogs, cats, horses, *etc.*, laboratory mammals such as non-human primates, rabbits, mice, rats, *etc.*, and the like. Treatment dosages can be titrated to optimize safety and efficacy.

[0238] A therapeutically effective dose of an anti-CD47 antibody can depend on the specific agent used, but is usually about 10 mg/kg body weight or more (*e.g.*, about 10 mg/kg or more, about 15 mg/kg or more, 20 mg/kg or more, about 25 mg/kg or more, about 30 mg/kg or more, about 35 mg/kg or more, about 40 mg/kg or more, about 45 mg/kg or more, about 50 mg/kg or more, or about 55 mg/kg or more, or about 60 mg/kg or more, or about 65 mg/kg or more, or about 70 mg/kg or more), or from about 10 mg/kg, from about 15 mg/kg to about 70 mg/kg (*e.g.*, from about 10 mg/kg to about 67.5 mg/kg, or from about 10 mg/kg, from about 15 mg/kg to about 60 mg/kg).

[0239] In some embodiments, the therapeutically effective dose of the anti-CD47 antibody is 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 67.5 mg/kg. In some embodiments, the therapeutically effective dose of the anti-CD47 antibody is 10 to 60 mg/kg. In some embodiments, the therapeutically effective dose of the anti-CD47 antibody is 10 to 67.5 mg/kg. In some embodiments, the anti-CD47 antibody is administered at a dose of at least 10-30, 20-30, 15-60, 30-60, 10, 15, 20, 30, 40, 45, 50, or 60 mg of antibody per kg of body weight.

[0240] A therapeutic dose of an anti-CD47 antibody can be a flat dose. For example, a flat dose can be given irrespective of a particular subject's weight. Alternatively, a flat dose can be given based on a particular subject's weight falling within a particular weight range, *e.g.*, a first range of less than or equal to 100 kg; or a second range of greater than 100 kg. A flat dose can be, *e.g.*, 1000-5000, 2000-4000, 2000-3500, 2400-3500, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, 4100, 4200, 4300, 4400, 4500, 4600, 4700, 4800, 4900, 5000 mg, or an interim number of mg thereof.

[0241] Methods can include a step of administering a primer agent to subject, followed by a step of administering a therapeutically effective dose of an anti-CD47 to the subject. In some embodiments, the step of administering a therapeutically effective dose is performed after at least about 3 days (*e.g.*, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, or at least about 10 days) after beginning the administration of a primer agent. This period of time is, for example, sufficient to provide for enhanced reticulocyte production by the individual. In some embodiments, the anti-CD47 agent is an isolated anti-CD47 antibody.

[0242] The administration of a therapeutically effective dose of an anti-CD47 can be achieved in a number of different ways. In some cases, two or more therapeutically effective doses are administered after a primer agent is administered. Suitable administration of a therapeutically effective dose can entail administration of a single dose, or can entail administration of doses daily, semi-weekly, weekly, once every two weeks, once a month, annually, *etc.* In some cases, a therapeutically effective dose is administered as two or more doses of escalating concentration (*i.e.*, increasing doses), where (i) all of the doses are therapeutic doses, or where (ii) a sub-therapeutic dose (or two or more sub-therapeutic doses) is initially given and therapeutic doses are achieved by said escalation. As one non-limiting example to illustrate escalating concentration (*i.e.*, increasing doses), a therapeutically effective dose can be administered weekly, beginning with a sub-therapeutic dose (*e.g.*, a dose of less than 10 mg/kg, *e.g.*, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg or 1 mg/kg), and each subsequent dose can be increased by a particular increment (*e.g.*, by 5 mg/kg, by 10 mg/kg, by 15 mg/kg), or by variable increments, until a therapeutic dose (*e.g.*, 15 mg/kg, 30 mg/kg, 45 mg/kg, 60 mg/kg) is reached, at which point administration may cease or may continue with one or more additional therapeutic doses (*e.g.*, continued therapeutic doses or escalated therapeutic doses, *e.g.*, doses of 15 mg/kg, 30 mg/kg, 45 mg/kg, 60 mg/kg). As another non-limiting example to illustrate escalating concentration (*i.e.*, increasing doses), a therapeutically effective dose can be administered weekly, beginning with one or more relatively lower therapeutic doses (*e.g.*, a dose of 10 mg/kg, 15 mg/kg or 30 mg/kg), and each subsequent dose can be increased by a particular increment (*e.g.*, by 10 mg/kg or 15 mg/kg), or by variable increments, until a relatively higher therapeutic dose (*e.g.*, 30 mg/kg, 45 mg/kg, 60 mg/kg, 100 mg/kg, *etc.*) is reached, at which point administration may cease or may continue (*e.g.*, one or more continued or escalated therapeutic doses, *e.g.*, doses of 30 mg/kg, 45 mg/kg, 60 mg/kg, 100 mg/kg, *etc.*). In various embodiments, relatively lower therapeutic doses are administered more often (*e.g.*, two or more doses of 15 mg/kg administered weekly (Q1W) or two or more doses of 30 mg/kg administered

every two weeks (Q2W)), and relatively higher therapeutic doses are administered less often (*e.g.*, two or more doses of 45 mg/kg administered every 3 weeks (Q3W) or two or more doses of 60 mg/kg administered monthly or every 4 weeks (Q4W)). In some embodiments, administration of a therapeutically effective dose can be a continuous infusion and the dose can altered (*e.g.*, escalated) over time.

[0243] The dose needed to achieve and/or maintain a particular serum level of the administered composition is proportional to the amount of time between doses and inversely proportional to the number of doses administered. Thus, as the frequency of dosing increases, the needed dose decreases. The optimization of dosing strategies will be readily understood and practiced by one of ordinary skill in the art. An exemplary treatment regime entails administration once every two weeks or once a month or once every 3 to 6 months. Therapeutic entities described herein are usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the therapeutic entity in the patient. Alternatively, therapeutic entities described herein can be administered as a sustained release formulation, in which case less frequent administration is used. Dosage and frequency vary depending on the half-life of the polypeptide in the patient. In some embodiments, the interval between each single dose is a week. In some embodiments, the interval between each single dose is two weeks. In some embodiments, the interval between each single dose is three weeks. In some embodiments, the interval between each single dose is four weeks. In some embodiments, the interval between each single dose of anti-CD47 antibody is a week. In some embodiments, the interval between each single dose of anti-CD47 antibody is two weeks. In some embodiments, the interval between each single dose of anti-CD47 antibody is three weeks. In some embodiments, the interval between each single dose of anti-CD47 antibody is four weeks. In some embodiments, the interval between each single dose of magrolimab is a week. In some embodiments, the interval between each single dose of magrolimab is two weeks. In some embodiments, the interval between each single dose of magrolimab is three weeks. In some embodiments, the interval between each single dose of magrolimab is four weeks.

[0244] A "maintenance dose" is a dose intended to be a therapeutically effective dose. For example, in experiments to determine the therapeutically effective dose, multiple different maintenance doses may be administered to different subjects. As such, some of the maintenance doses may be therapeutically effective doses and others may be sub-therapeutic doses.

[0245] In prophylactic applications, a relatively low dosage may be administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In other therapeutic applications, a relatively high dosage at relatively short intervals is sometimes used until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

[0246] The term "priming dose" or as used herein refers to a dose of an anti-CD47 antibody that primes a subject for administration of a therapeutically effective dose of anti-CD47 antibody such that the therapeutically effective dose does not result in a severe loss of RBCs (reduced hematocrit or reduced hemoglobin). The specific appropriate priming dose of an anti-CD47 antibody can vary depending on the nature of the agent used and on numerous subject-specific factors (*e.g.*, age, weight, etc.). Examples of suitable priming doses of an anti-CD47 antibody include from about 0.5 mg/kg to about 5 mg/kg, from about 0.5 mg/kg to about 4 mg/kg, from about 0.5 mg/kg to about 3 mg/kg, from about 1 mg/kg to about 5 mg/kg, from about 1 mg/kg to about 4 mg/kg, from about 1 mg/kg to about 3 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg. In some embodiments, the priming dose is preferably 1 mg/kg.

[0247] In some embodiments of the methods described herein, the anti-CD47 antibody is administered to the subject as a priming dose ranging from about 0.5 mg to about 10 mg, *e.g.*, from about 0.5 to about 5 mg/kg of antibody, optionally, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg of antibody. In some embodiments, the anti-CD47 antibody is administered to the subject as a therapeutic dose ranging from about 20 to about 67.5 mg/kg of antibody, optionally from 15 to 60 mg/kg of antibody, optionally from 30 to 60 mg/kg of antibody, optionally 15 mg/kg of antibody, 20 mg/kg of antibody, 30 mg/kg of antibody, 45 mg/kg of antibody, 60 mg/kg of antibody, or 67.5 mg/kg of antibody.

[0248] A priming dose of an anti-CD47 antibody can be a flat priming dose. For example, a flat priming dose can be given irrespective of a particular subject's weight. Alternatively, a flat priming dose can be given based on a particular subject's weight falling within a particular weight range, *e.g.*, a first range of less than or equal to 100 kg; or a second range of greater than 100 kg. A flat priming dose can be, *e.g.*, 10-200, 50-100, 80-800, 80-400, 80-200, 70-90, 75-85, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 240, 300, 320, 400, 500, 600, 700 or 800 mg, or an interim number of mg thereof.

[0249] In some embodiments, an effective priming dose of magrolimab is provided, where the effective priming dose for a human is around about 1 mg/kg, *e.g.*, from at least about 0.5 mg/kg up to not more than about 5 mg/kg; from at least about 0.75 mg/kg up to not more than about 1.25 mg/kg; from at least about 0.95 mg/kg up to not more than about 1.05 mg/kg; and may be around about 1 mg/kg.

[0250] In some embodiments, an initial dose of a CD47 or SIRPα binding agent is infused over a period of at least about 2 hours, at least about 2.5 hours, at least about 3 hours, at least about 3.5 hours, at least about 4 hours, at least about 4.5 hours, at least about 5 hours, at least about 6 hours or more. In some embodiments an initial dose is infused over a period of time from about 2.5 hours to about 6 hours; for example, from about 3 hours to about 4 hours. In some such embodiments, the dose of agent in the infusate is from about 0.05 mg/ml to about 0.5 mg/ml; for example, from about 0.1 mg/ml to about 0.25 mg/ml.

[0251] In other embodiments, an initial dose of a CD47 or SIRPα binding agent, *e.g.*, a priming dose, is administered by continuous fusion, *e.g.*, as an osmotic pump, delivery patch, *etc.*, where the dose is administered over a period of at least about 6 hours, at least about 12 hours, at least about 24 hours, at least about 2 days, at least about 3 days. Many such systems are known in the art. For example, DUROS technology, provides a bi-compartment system separated by a piston. One of the compartments consists of osmotic engine specifically formulated with an excess of solid NaCl, such that it remains present throughout the delivery period and results in a constant osmotic gradient. It also consists of a semi permeable membrane on one end through which water is drawn into the osmotic engine and establishes a large and constant osmotic gradient between the tissue water and the osmotic engine. Other compartment consists of a drug solution with an orifice from which the drug is released due to the osmotic gradient. This helps to provide site specific and systemic drug delivery when implanted in humans. The preferred site of implantation is subcutaneous placement in the inside of the upper arm.

[0252] Following administration of the priming agent, and allowing a period of time effective for an increase in reticulocyte production, a therapeutic dose of an anti-CD47 or anti-SIRPα agent is administered. The therapeutic dose can be administered in number of different ways. In some embodiments, two or more therapeutically effective doses are administered after a primer agent is administered, *e.g.*, in a weekly dosing schedule. In some embodiments a therapeutically effective dose of an anti-CD47 agent is administered as two or more doses of

escalating concentration, in others the doses are equivalent. There is reduced hemagglutination after the priming dose.

[0253] A therapeutically effective dose of an anti-SIRPα antibody can depend on the specific agent used, but is usually about 10 mg or more, *e.g.*, about 30 mg, 50 mg, 100 mg, 200 mg, 400 mg or 800 mg, or more. Multiple administrations of an anti-SIRPα antibody, *e.g.*, without Fc effector function, can be performed over an extended period of time, *e.g.*, over 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, at regular intervals, *e.g.*, every 2 weeks (Q2W), every 3 weeks (Q3W), every 4 weeks (Q4W).

[0254] In some embodiments, the magrolimab is first administered at a priming dose of 1 mg/kg, then administered at one or more therapeutic doses of 30 mg/kg, followed by administration of one or more therapeutic doses of 60 mg/kg. In some embodiments, the magrolimab is first administered at a priming dose of 1 mg/kg, then administered at one or more therapeutic doses of 20 mg/kg, followed by administration of one or more therapeutic doses of 45 mg/kg. In some embodiments, the magrolimab is first administered at a priming dose of 1 mg/kg, then administered at one or more therapeutic doses of 15 mg/kg, followed by administration of one or more therapeutic doses of 30 mg/kg.

[0255] In some embodiments, the agent that inhibits binding between CD47 and SIRPα; and the focally delivered ionizing radiation therapy are administered in a combined synergistic amount. A "combined synergistic amount" as used herein refers to the sum of a first amount (*e.g.*, an amount of an agent that inhibits binding between CD47 and SIRPα) and a second amount (*e.g.*, an amount of focally delivered ionizing radiation therapy) that results in a synergistic effect (*i.e.*, an effect greater than an additive effect). Therefore, the terms "synergy", "synergism", "synergistic", "combined synergistic amount", and "synergistic therapeutic effect" which are used herein interchangeably, refer to a measured effect of compounds administered in combination where the measured effect is greater than the sum of the individual effects of each of the compounds administered alone as a single agent.

[0256] Co-administration of an agent that inhibits binding between CD47 and SIRPα and a focally delivered ionizing radiation therapy can allow for lower doses of one or both therapeutic agents. In embodiments, a synergistic amount may be about 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% of the amount of the agent that inhibits binding between CD47 and SIRPα when used separately from the focally delivered ionizing radiation therapy. In embodiments, a synergistic amount may be about 50,

51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% of the amount of focally delivered ionizing radiation therapy when used separately from the agent that inhibits binding between CD47 and SIRPα.

[0257] Dosage and frequency may vary depending on the half-life of the therapeutic agent in the patient. It will be understood by one of skill in the art that such guidelines will be adjusted for the molecular weight of the active agent, *e.g.*, in the use of antibody fragments, in the use of antibody conjugates, in the use of SIRPα reagents, in the use of soluble CD47 peptides *etc*. The dosage may also be varied for localized administration, *e.g.*, intranasal, inhalation, *etc.*, or for systemic administration, *e.g.*, intramuscular (i.m.), intraperitoneal (i.p.), intravenous (i.v.), subcutaneous (s.c.), intratumoral, intracranial, as appropriate. In some embodiments, the agent that inhibits binding between CD47 and SIRPα; and the focally delivered ionizing radiation therapy are administered concurrently. In some embodiments, the agent that inhibits binding between CD47 and SIRPα; and the focally delivered ionizing radiation therapy are administered sequentially. For example, the agent that inhibits binding between CD47 and SIRPα, described herein, may be administered within seconds, minutes, hours or days of the administration of the focally delivered ionizing radiation therapy. In some embodiments, a unit dose of an agent that inhibits binding between CD47 and SIRPα is administered first, followed within seconds, minutes, hours or days by administration of a unit dose of focally delivered ionizing radiation therapy. Alternatively, a unit dose of focally delivered ionizing radiation therapy is administered first, followed by administration of a unit dose of an agent that inhibits binding between CD47 and SIRPα within seconds, minutes, hours or days. In other embodiments, a unit dose of an agent that inhibits binding between CD47 and SIRPα is administered first, followed, after a period of hours (*e.g.*, 1-12 hours, 1-24 hours, 1-36 hours, 1-48 hours, 1-60 hours, 1-72 hours), by administration of a unit dose of focally delivered ionizing radiation therapy. In yet other embodiments, a unit dose of focally delivered ionizing radiation therapy is administered first, followed, after a period of hours (*e.g.*, 1-12 hours, 1-24 hours, 1-36 hours, 1-48 hours, 1-60 hours, 1-72 hours), by administration of a unit dose of an agent that inhibits binding between CD47 and SIRPα.

6. Conditions Subject to Treatment

[0258] Provided are methods of treating, ameliorating, mitigating, or preventing or delaying the growth, proliferation, recurrence or metastasis of, a cancer in a subject comprising administering: (a) an agent that inhibits binding between CD47 and SIRPα; and (b) focally

delivered ionizing radiation therapy to the subject. In some embodiments, the subject is a human.

[0259] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For example, beneficial or desired clinical results may include one or more of the following: (i) decreasing one more symptoms resulting from the disease; (ii) diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease); (iii) preventing or delaying the spread (*e.g.*, metastasis) of the disease; (iv) preventing or delaying the occurrence or recurrence of the disease, delay or slowing the progression of the disease; (v) ameliorating the disease state, providing a remission (whether partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease; (vi) delaying the progression of the disease, increasing the quality of life, and/or (vii) prolonging survival. The beneficial or desired clinical results may be observed in more patients or subjects who have received the methods or treatments described herein. In some embodiments, the cancer has progressed following at least one prior anti-cancer therapy. In some embodiments, the cancer has progressed following at least one prior anti-cancer therapy selected from a taxane therapy (*e.g.*, paclitaxel, nab-paclitaxel (ABRAXANE®), docetaxel and cabazitaxel), an immune checkpoint inhibitor therapy (*e.g.,* anti-PD1 antibody therapy or an anti-PD-L1 antibody therapy), a platinum coordination complex therapy (*e.g.*, cisplatin, oxiloplatinim, and carboplatin) and enfortumab vedotin (PADCEV®) therapy. In some embodiments, the subject is treatment naïve, *i.e.*, combined administration of an agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and focally delivered ionizing radiation therapy is a first line cancer therapy.

[0260] "Prevention" or "preventing" means any treatment (*i.e.*, medication, drug, therapeutic) of a disease or condition (*i.e.*, cancer) that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0261] "Delaying" the development of a cancer means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease. The delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one of skill in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. A method that "delays" development of cancer is a method that reduces probability of disease development in a given time frame and/or reduces the extent of the disease in a given time frame, when compared to not using the method. Such

comparisons are typically based on clinical studies, using a statistically significant number of subjects. Disease development can be detectable using standard methods, such as routine physical exams, blood draw, mammography, imaging, or biopsy. Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence, and onset.

[0262] The term "ameliorating" refers to any therapeutically beneficial result in the treatment of a disease state, *e.g.*, a cancer disease state, including prophylaxis, lessening in the severity or progression, remission, or cure thereof.

[0263] Generally, the methods described herein are directed to treating, ameliorating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of, a solid cancer. Usually, the solid cancers are sensitive, or partially sensitive, to radiation therapy. Oftentimes, the solid cancer is an epithelial cancer or a soft tissue sarcoma. In some embodiments, cancers amenable to treatment by combined administration of an agent that inhibits binding between CD47 and SIRPα (*e.g.*, magrolimab) and focally delivered ionizing radiation therapy include without limitation colorectal cancer, lung cancer, prostate cancer, pancreatic cancer, breast cancer (*e.g.*, triple negative breast cancer), stomach cancer, urinary tract cancer, urothelial cancer, bladder cancer, renal cancer, ovarian cancer, uterine cancer and esophageal cancer.

[0264] In some embodiments, the subject has a solid tumor. In various embodiments, the solid tumor arises from a primary malignancy having increased CD47 cell surface expression the surface, *e.g.*, head and neck (HNSCC), melanoma, breast, lung, ovarian, pancreatic, colon, bladder, prostate, leiomyosarcoma, glioblastoma, medulloblastoma, oligodendroglioma, glioma, lymphoma, and multiple myeloma. In various embodiments, the cancer or tumor is malignant and/or metastatic. In various embodiments, the subject has a cancer selected from an epithelial tumor (*e.g.*, a carcinoma, a squamous cell carcinoma, a basal cell carcinoma, a squamous intraepithelial neoplasia), a glandular tumor (*e.g.*, an adenocarcinoma, an adenoma, an adenomyoma), a mesenchymal or soft tissue tumor (*e.g.*, a sarcoma, a rhabdomyosarcoma, a leiomyosarcoma, a liposarcoma, a fibrosarcoma, a dermatofibrosarcoma, a neurofibrosarcoma, a fibrous histiocytoma, an angiosarcoma, an angiomyxoma, a leiomyoma, a chondroma, a chondrosarcoma, an alveolar soft-part sarcoma, an epithelioid hemangioendothelioma, a Spitz tumor, a synovial sarcoma), and a lymphoma.

[0265] Further examples of tissues containing cancerous cells whose proliferation is reduced or inhibited by combined administration of an agent that inhibits binding between CD47

and SIRPα (*e.g.*, magrolimab) and focally delivered ionizing radiation therapy include without limitation breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, and stomach.

[0266] In various embodiments, the subject has a solid tumor in or arising from a tissue or organ selected from:

- breast (*e.g.*, triple-negative breast cancer (negative for erb-b2 receptor tyrosine kinase 2 (ERBB2- or HER2-) / negative for estrogen receptor (ER-) / negative for progesterone receptor (PR-)), HR+/HER2- breast cancer, and HER2+ breast cancer, invasive ductal carcinoma, including without limitation, acinic cell carcinoma, adenoid cystic carcinoma, apocrine carcinoma, cribriform carcinoma, glycogen-rich/clear cell, inflammatory carcinoma, lipid-rich carcinoma, medullary carcinoma, metaplastic carcinoma, micropapillary carcinoma, mucinous carcinoma, neuroendocrine carcinoma, oncocytic carcinoma, papillary carcinoma, sebaceous carcinoma, secretory breast carcinoma, tubular carcinoma; lobular carcinoma, including without limitation, pleomorphic carcinoma, signet ring cell carcinoma);
- lung (*e.g.*, small cell carcinoma (SCLC), non-small cell lung carcinoma (NSCLC), including squamous cell carcinoma (SCC), adenocarcinoma and large cell carcinoma, carcinoids (typical or atypical), carcinosarcomas, pulmonary blastomas, giant cell carcinomas, spindle cell carcinomas, pleuropulmonary blastoma);
- bone (*e.g.*, adamantinoma, aneurysmal bone cysts, angiosarcoma, chondroblastoma, chondroma, chondromyxoid fibroma, chondrosarcoma, chordoma, dedifferentiated chondrosarcoma, enchondroma, epithelioid hemangioendothelioma, fibrous dysplasia of the bone, giant cell tumour of bone, haemangiomas and related lesions, osteoblastoma, osteochondroma, osteosarcoma, osteoid osteoma, osteoma, periosteal chondroma, Desmoid tumor, Ewing sarcoma);
- lips and oral cavity (*e.g.*, odontogenic ameloblastoma, oral leukoplakia, oral squamous cell carcinoma, primary oral mucosal melanoma); salivary glands (*e.g.*, pleomorphic salivary gland adenoma, salivary gland adenoid cystic carcinoma, salivary gland mucoepidermoid carcinoma, salivary gland Warthin's tumors);
- esophagus (*e.g.*, Barrett's esophagus, dysplasia and adenocarcinoma);
- gastrointestinal tract, including stomach (*e.g.*, gastric adenocarcinoma, primary gastric lymphoma, gastrointestinal stromal tumors (GISTs), metastatic deposits, gastric carcinoids, gastric sarcomas, neuroendocrine carcinoma, gastric primary squamous cell carcinoma, gastric

adenoacanthomas), intestines and smooth muscle (*e.g.*, intravenous leiomyomatosis), colon (*e.g.*, colorectal adenocarcinoma), rectum, anus;

- pancreas (*e.g.*, serous neoplasms, including microcystic or macrocystic serous cystadenoma, solid serous cystadenoma, Von Hippel-Landau (VHL)-associated serous cystic neoplasm, serous cystadenocarcinoma; mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), intraductal oncocytic papillary neoplasms (IOPN), intraductal tubular neoplasms, cystic acinar neoplasms, including acinar cell cystadenoma, acinar cell cystadenocarcinoma, pancreatic adenocarcinoma, invasive pancreatic ductal adenocarcinomas, including tubular adenocarcinoma, adenosquamous carcinoma, colloid carcinoma, medullary carcinoma, hepatoid carcinoma, signet ring cell carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, acinar cell carcinoma, neuroendocrine neoplasms, neuroendocrine microadenoma, neuroendocrine tumors (NET), neuroendocrine carcinoma (NEC), including small cell or large cell NEC, insulinoma, gastrinoma, glucagonoma, serotonin-producing NET, somatostatinoma, VIPoma, solid-pseudopapillary neoplasms (SPN), pancreatoblastoma);
- gall bladder (*e.g.*, carcinoma of the gallbladder and extrahepatic bile ducts, intrahepatic cholangiocarcinoma);
- neuro-endocrine (*e.g.*, adrenal cortical carcinoma, carcinoid tumors, phaeochromocytoma, pituitary adenomas);
- thyroid (*e.g.*, anaplastic (undifferentiated) carcinoma, medullary carcinoma, oncocytic tumors, papillary carcinoma, adenocarcinoma);
- liver (*e.g.*, adenoma, combined hepatocellular and cholangiocarcinoma, fibrolamellar carcinoma, hepatoblastoma, hepatocellular carcinoma, mesenchymal, nested stromal epithelial tumor, undifferentiated carcinoma; hepatocellular carcinoma, intrahepatic cholangiocarcinoma, bile duct cystadenocarcinoma, epithelioid hemangioendothelioma, angiosarcoma, embryonal sarcoma, rhabdomyosarcoma, solitary fibrous tumor, teratoma, York sac tumor, carcinosarcoma, rhabdoid tumor);
- kidney (*e.g.*, ALK-rearranged renal cell carcinoma, chromophobe renal cell carcinoma, clear cell renal cell carcinoma, clear cell sarcoma, metanephric adenoma, metanephric adenofibroma, mucinous tubular and spindle cell carcinoma, nephroma, nephroblastoma (Wilms tumor), papillary adenoma, papillary renal cell carcinoma, renal oncocytoma, renal cell carcinoma, succinate dehydrogenase-deficient renal cell carcinoma, collecting duct carcinoma);
- peritoneum (*e.g.*, mesothelioma; primary peritoneal cancer);

- female sex organ tissues, including ovary (*e.g.*, choriocarcinoma, epithelial tumors, germ cell tumors, sex cord-stromal tumors), Fallopian tubes (*e.g.*, serous adenocarcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, clear cell adenocarcinoma, transitional cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma, müllerian tumors, adenosarcoma, leiomyosarcoma, teratoma, germ cell tumors, choriocarcinoma, trophoblastic tumors), uterus (*e.g.*, carcinoma of the cervix, endometrial polyps, endometrial hyperplasia, intraepithelial carcinoma (EIC), endometrial carcinoma (*e.g.*, endometrioid carcinoma, serous carcinoma, clear cell carcinoma, mucinous carcinoma, squamous cell carcinoma, transitional carcinoma, small cell carcinoma, undifferentiated carcinoma, mesenchymal neoplasia), leiomyoma (*e.g.*, endometrial stromal nodule, leiomyosarcoma, endometrial stromal sarcoma (ESS), mesenchymal tumors), mixed epithelial and mesenchymal tumors (*e.g.*, adenofibroma, carcinofibroma, adenosarcoma, carcinosarcoma (malignant mixed mesodermal sarcoma - MMMT)), endometrial stromal tumors, endometrial malignant mullerian mixed tumours, gestational trophoblastic tumors (partial hydatiform mole, complete hydatiform mole, invasive hydatiform mole, placental site tumour)), vulva, vagina;
- male sex organ tissues, including prostate, testis (*e.g.*, germ cell tumors, spermatocytic seminoma), penis;
- bladder (*e.g.*, squamous cell carcinoma, urothelial carcinoma, bladder urothelial carcinoma);
- brain, (*e.g.*, gliomas (*e.g.*, astrocytomas, including non-infiltrating, low-grade, anaplastic, glioblastomas; oligodendrogliomas, ependymomas), meningiomas, gangliogliomas); schwannomas (neurilemmomas), craniopharyngiomas, chordomas, Non-Hodgkin lymphomas (NHLs), indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, pituitary tumors;
- eye (*e.g.*, retinoma, retinoblastoma, ocular melanoma, posterior uveal melanoma, iris hamartoma);
- head and neck (*e.g.*, nasopharyngeal carcinoma, Endolymphatic Sac Tumor (ELST), epidermoid carcinoma, laryngeal cancers including squamous cell carcinoma (SCC) (*e.g.*, glottic carcinoma, supraglottic carcinoma, subglottic carcinoma, transglottic carcinoma), carcinoma in situ, verrucous, spindle cell and basaloid SCC, undifferentiated carcinoma, laryngeal adenocarcinoma, adenoid cystic carcinoma, neuroendocrine carcinomas, laryngeal sarcoma), head and neck paragangliomas (*e.g.*, carotid body, jugulotympanic, vagal);
- thymus (*e.g.*, thymoma);
- heart (*e.g.*, cardiac myxoma);
- lymph (*e.g.*, lymphomas, including Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, Epstein-Barr virus (EBV)-

associated lymphoproliferative diseases, including B cell lymphomas and T cell lymphomas (*e.g.*, Burkitt lymphoma; large B cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, indolent B-cell lymphoma, low grade B cell lymphoma, fibrin-associated diffuse large cell lymphoma; primary effusion lymphoma; plasmablastic lymphoma; extranodal NK/T cell lymphoma, nasal type; peripheral T cell lymphoma, cutaneous T cell lymphoma, angioimmunoblastic T cell lymphoma; follicular T cell lymphoma; systemic T cell lymphoma), lymphangioleiomyomatosis);

- central nervous system (CNS) (*e.g.*, gliomas including astrocytic tumors (*e.g.*, pilocytic astrocytoma, pilomyxoid astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, diffuse astrocytoma, fibrillary astrocytoma, gemistocytic astrocytoma, protoplasmic astrocytoma, anaplastic astrocytoma, glioblastoma (*e.g.*, giant cell glioblastoma, gliosarcoma, glioblastoma multiforme) and gliomatosis cerebri), oligodendroglial tumors (*e.g.*, oligodendroglioma, anaplastic oligodendroglioma), oligoastrocytic tumors (*e.g.*, oligoastrocytoma, anaplastic oligoastrocytoma), ependymal tumors (*e.g.*, subependymom, myxopapillary ependymoma, ependymomas (*e.g.*, cellular, papillary, clear cell, tanycytic), anaplastic ependymoma), optic nerve glioma, and non-gliomas (*e.g.*, choroid plexus tumors, neuronal and mixed neuronal-glial tumors, pineal region tumors, embryonal tumors, medulloblastoma, meningeal tumors, primary CNS lymphomas, germ cell tumors, Pituitary adenomas, cranial and paraspinal nerve tumors, stellar region tumors); neurofibroma, meningioma, peripheral nerve sheath tumors, peripheral neuroblastic tumours (including without limitation neuroblastoma, ganglioneuroblastoma, ganglioneuroma), trisomy 19 ependymoma);
- neuroendocrine tissues (*e.g.*, paraganglionic system including adrenal medulla (pheochromocytomas) and extra-adrenal paraganglia ((extra-adrenal) paragangliomas);
- skin (*e.g.*, clear cell hidradenoma, cutaneous benign fibrous histiocytomas, cylindroma, hidradenoma, melanoma (including cutaneous melanoma, mucosal melanoma), basal cell carcinoma, pilomatricoma, Spitz tumors); and
- soft tissues (*e.g.*, aggressive angiomyxoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, angiofibroma, angiomatoid fibrous histiocytoma, synovial sarcoma, biphasic synovial sarcoma, clear cell sarcoma, dermatofibrosarcoma protuberans, desmoid-type fibromatosis, small round cell tumor, desmoplastic small round cell tumor, elastofibroma, embryonal rhabdomyosarcoma, Ewing's tumors/primitive neurectodermal tumors (PNET), extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, paraspinal sarcoma, inflammatory myofibroblastic tumor, lipoblastoma, lipoma, chondroid lipoma, liposarcoma / malignant lipomatous tumors, liposarcoma, myxoid liposarcoma, fibromyxoid sarcoma,

lymphangioleiomyoma, malignant myoepithelioma, malignant melanoma of soft parts, myoepithelial carcinoma, myoepithelioma, myxoinflammatory fibroblastic sarcoma, undifferentiated sarcoma, pericytoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), soft tissue leiomyosarcoma, undifferentiated sarcoma, well-differentiated liposarcoma.

EXAMPLES

[0267] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Focal Radiotherapy Synergizes with CD47 Blockade to Induce Adaptive Immunity & Tumor Regression

[0268] This study determined if the therapeutic efficacy of CD47/SIRPα blockade could be enhanced by combining with radiotherapy in a subcutaneous murine tumor model.

[0269] Bilateral solid tumors were generated in the flanks of healthy C57BL6 mice by injecting MC38 colon carcinoma cells subcutaneously. Mice were randomized when tumor volumes were approximately 50-80 mm^3 and treated with 20 mg/kg mIgG1 isotype, or anti-CD47 mAb (MIAP410) by intraperitoneal injection (Figure 1A). The following day, the tumors were focally irradiated with a 2 Gray dose using a Phillip T 100 100KW machine. Antibody treatment was repeated daily (5x/week) for the course of the study, while radiotherapy was administered on day 1,2, and 3 post randomizations (Figure 1B). Tumor volumes were recorded by caliper measurements and reported relative to the study day.

[0270] While radiotherapy alone slowed the growth of the irradiated tumors, significant growth inhibition and regression was noted when CD47/SIRPα blockade was combined with focal radiotherapy (Figure 2A). Furthermore, low dose fractionated radiotherapy did not impede the growth of non-irradiated tumors that were present on an opposing flank of the mouse (Figure 2B; Figures 3A-3D).

[0271] To evaluate the contribution of adaptive immune cells such as cytotoxic lymphocytes, CD8+ T cells were depleted prior to the therapy using an anti-CD8 mAb. As shown in Figure 4, the therapeutic benefit of CD47/SIRPα blockade and focal radiotherapy is largely absent in mice that were depleted of CD8+ T cells. These findings are consistent with

the conclusion that the combination of focally delivered radiotherapy and CD47/SIRPα blockade can trigger an adaptive immune response that mediates tumor regression.

[0272] High-dose radiotherapy can induce apoptosis and immunogenic cell death. To evaluate the therapeutic benefit of combining high-dose radiotherapy with CD47/SIRPα blockade, bilateral MC38 tumors were generated as detailed in Figures 1A-1B and treated with a single dose of 10 Gray with or without anti-CD47 antibody. As expected, 10 Gray was significantly more effective as a single agent at inhibiting tumor growth compared to the fractioned 2 Gray treatment. In contrast to the low-dose regiment, abscopal responses were noted in mice treated with 10 Gray in combination with anti-CD47 mAb. The growth inhibition for the non-irradiated tumors was only observed in mice treated with the combination of high-dose radiotherapy and antiCD47 mAb, highlighting the therapeutic potential of this combination. The results are depicted in Figures 5A-5F.

[0273] To better characterize the anti-tumor immune response, immunophenotyping was performed on the draining lymph nodes and tumor-infiltrating immune cells. Single-cell suspensions were stained for various immune cell markers and analyzed by flow cytometry. A statistically significant increase in the frequency of CD3+/CD8+ T cells was observed in the tumor infiltrate of combo-treated mice. CD4+ or CD8+ T cells were also highly activated in mice treated with anti-CD47 antibody and RT as indicated by CD44 expression (Figure 6). The expression of MHC-II in draining lymph node DCs was also higher in response to treatment, suggesting these cells could be playing a role in the priming of cytotoxic T-cells. Tumor-infiltrating myeloid cells were also analyzed. Innate effector cells such as neutrophils and monocytes were more frequent in combo-treated mice. In addition, the expression of SIRPa on macrophages was significantly increased in response to treatment, suggesting that blockade of this axis by CD47 antibody could relieve inhibitory signals. Furthermore, the combination treatment was associated with an increase in M2-like macrophages, possibly reflecting a "satiated" phenotype post-phagocytosis, and is a rationale for including M1-polarizing therapeutics.

[0274] The abundance of various RNA transcripts from treated tumors was analyzed on the Nanostring nCounter® PanCancer IO360™ panel. The results from gene set enrichment analysis are shown in Table 1. The combination of RT and MIAP410 was associated with an increased signature for matrix remodeling and metastasis-associated genes, cytokine and chemokine signaling, and various other pathways. Significant changes were also observed in the

myeloid and macrophage compartments of combo-treated mice, mimicking the changes observed by flow cytometry (Tables 2 and 3).

Table 1

Displaying Directed Global Significance Scores from Tumor-Derived RNA

	RT vs. Iso	MIAP410 vs. Iso	Combo vs. Iso
Interferon Signaling	-1.091	-1.139	-1.047
Hedgehog Signaling	-1.201	-0.377	-0.3
Immune Cell Adhesion and Migration	-0.72	-0.935	-0.24
Antigen Presentation	0.734	-1.32	0.564
Lymphoid Compartment	1.297	-1.163	1.286
Cytotoxicity	0.523	-0.984	1.395
Costimulatory Signaling	1.364	-1.118	1.441
Hypoxia	0.636	-0.197	1.603
Apoptosis	-0.861	-1.037	1.638
JAK-STAT Signaling	1.26	-0.682	1.834
MAPK	0.864	-0.655	1.855
Angiogenesis	-0.8	0.694	2.031
Autophagy	0.895	0.907	2.297
DNA Damage Repair	1.626	-0.833	2.36
Matrix Remodeling and Metastasis	-0.817	1.096	2.602
Myeloid Compartment	2.323	-0.4	2.65
Cytokine and Chemokine Signaling	2.03	-0.898	2.655
Epigenetic Regulation	2.134	0.406	2.667
Metabolic Stress	1.622	0.049	2.833
Cell Proliferation	2.132	-0.729	2.95

RNA was isolated from subcutaneous MC38 tumors seven days post-treatment and hybridized on the Nanostring nCounter® PanCancer IO360™ panel for Gene Set Analysis. Directed global significance scores measure the extent to which a gene set's genes are up or down-regulated relative to the RNA expression profile of isotype-treated tumors.

TABLE 2 – MACROPHAGE SIGNATURE

Gene Name	1-1 (Iso)	1-4 (Iso)	1-5 (Iso)	1-2 (Iso)	1-3 (Iso)	4-4 (Combo)	4-3 (Combo)	4-5 (Combo)	4-1 (Combo)	4-2 (Combo)
Mmp12	-1.528	-2.101	-1.591	-1.039	-1.547	1.439	1.473	1.471	2.093	1.331
Cd36	-0.865	-0.202	-0.939	-1.179	-1.013	1.362	0.074	0.576	0.853	1.333
Ccl6	-0.515	-0.651	-1.370	-0.784	-1.315	1.244	0.341	0.754	0.767	1.529
Ccl9	-0.936	-0.770	-0.781	-0.777	-1.195	1.165	0.324	0.732	0.864	1.376
Ccl7	-0.310	-0.275	0.066	-0.953	-0.349	0.610	-0.210	-0.031	0.557	0.896
Cxcl2	-1.016	-0.749	0.095	-0.283	-0.264	0.147	-0.132	0.531	0.961	0711
Cxcl1	-0.864	-0.661	-0.026	-0.373	-0.476	0.571	0.331	0.176	0.620	0.702
Siglecf	0.457	-0.035	0.471	0.551	0.460	-0.527	-0.534	0.146	-0.163	-0.826
Tgfbr1	0.406	0.397	0.136	0.510	0.336	-0.216	-0.501	-0.078	-0.610	-0.381
Tlr2	0.651	0.503	0.398	0.680	0.475	-0.110	-0.771	-0.278	-0.763	-0.784
Cxcl16	0.747	0.797	0.718	-.687	0.449	-0.358	-0.780	-0.168	-0.914	-1.179
Cx3cr1	1.386	1.561	1.238	1.491	1.216	-0.963	-1.519	-0.551	-1.593	-2.266
H2-Ab1	1.936	1.477	0.588	1.303	0.957	-0.666	-0.857	-0.523	-1.975	-2.240
H2-Eb1	2.002	1.581	0.366	1.338	0.951	-0.652	-0.479	-0.496	-2.175	-2.434
Cd74	1.668	1.399	0.330	1.172	0.768	-0.306	-0.756	-0.333	-1.997	-1.945

TABLE 3 – MYELOID COMPARTMENT SIGNATURE										
Gene Name	**1-1 (Iso)**	**1-4 (Iso)**	**1-5 (Iso)**	**1-2 (Iso)**	**1-3 (Iso)**	**4-4 (Combo)**	**4-3 (Combo)**	**4-5 (Combo)**	**4-1 (Combo)**	**4-2 (Combo)**
Cxcl2	-1.016	-0.749	0.095	-0.283	-0.264	0.147	-0.132	0.531	0.961	0.711
Cxcl1	-0.864	-0.661	-0.026	-0.373	-0.476	0.571	0.331	0.176	0.620	0.702
Arg1	-0.908	-0.713	-0.640	0.443	-0.680	0.724	0.075	0.435	0.470	0.793
Ier3	-0.581	-0.674	-0.463	0.078	-0.286	0.461	0.178	0.233	0.593	0.461
Fosl1	-0.551	-0.205	-0.487	-0.539	-0.359	0.596	0.369	0.208	0.432	0.537
Il1rn	-0.919	-0.547	-0.777	-0.805	-0.803	0.910	0.735	0.636	0.830	0.738
Ptgs2	-0.801	-0.333	-0.544	-1.072	-0.360	0.823	0.611	0.214	0.627	0.837
S100a9	-1.423	-1.523	-1.534	-0.709	-0.908	1.175	0.336	1.010	1.916	1.658
Cxcl3	-0.725	-1.116	-0.421	-0.636	-0.924	0.402	0.127	0.187	1.587	1.519
Ccl9	-0.936	-0.770	-0.781	-0.777	-1.195	1.165	0.324	0.732	0.864	1.376
Ccl6	-0.515	-0.651	-1.370	-0.784	-1.315	1.244	0.341	0.754	0.767	1.529
Hck	0.782	1.082	.0625	0.313	0.644	-0.284	-1.200	-0.337	-1.051	-0.574
Tlr2	0.651	0.503	0.398	0.680	0.475	-0.110	-0.771	-0.278	-0.763	-0.784
Clec5a	0.616	0.481	0.470	0.244	0.399	-0.026	-0.541	-0.409	-0.584	-0.650

Tables 2 and 3 - RNA was isolated from subcutaneous MC38 tumors (7-days post-treatment) and analyzed on the Nanostring nCounter® PanCancer IO360™ panel. The directed significance statistic scores for genes representing the macrophage or myeloid compartment signatures are represented for mice treated with isotype or focal radiotherapy combined with anti-CD47 mAb. Increasing pathway scores corresponds to increasing expression.

[0275] Increases in S100A9 expression are consistent with the expansion of the neutrophil population observed in the immunophenotyping study. The genes differentially expressed in combo-treated mice relative to the radiotherapy alone are displayed in a volcano plot in Figure 8. The most noteworthy changes were proteases involved in matrix remodeling like MMP12 and MMP13, in addition to chemokines such as CCL6 or CCL9, which are known to attract neutrophils or DCs/macrophages, respectively. Of note was the dramatic reduction of MHC-II-related genes, which are consistent with the active migration of professional APCs into the draining lymph nodes, where they can prime a cytotoxic T-cell response.

[0276] It is understood that the examples and embodiments 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 and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

What is claimed is:

1. A method of treating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of a solid cancer in a mammalian subject in need thereof comprising co-administering to the subject an effective amount of:

a) radiation therapy (RT) focally-delivered to the solid cancer; and

b) an agent that inhibits binding between CD47 and SIRPα.

2. The method of claim 1, wherein the solid cancer is a non-irradiated tumor.

3. The method of any one of claims 1 to 2, wherein the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT.

4. The method of any one of claims 1 to 3, wherein the RT is focally-delivered via a technique selected from microbeam radiation therapy (MRT), external beam radiation therapy (EBRT), internal radiotherapy (brachytherapy), volumetric modulated arc therapy (VMAT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic ablative radiation therapy (SABR), low-dose stereotactic body radiation (SBRT), selective internal radiation therapy (SIRT), preoperative RT, intra-operative radiation therapy (IORT), postoperative RT (PORT), pulsed low-dose rate radiation therapy, pulsed low-dose rate radiation therapy, and combinations thereof.

5. The method of any one of claims 1 to 4, wherein the RT dose is a dose sufficient to induce abscopal effect (*i.e.*, reduction or elimination of non-irradiated tumors).

6. The method of any one of claims 1 to 5, wherein the RT dose is a maximum dose tolerated by the subject.

7. The method of any one of claims 1 to 6, wherein the RT dose is fractionated over multiple administrations.

8. The method of any one of claims 1 to 7, wherein the RT dose is hypofractionated or ultrahypofractionated.

9. The method of any one of claims 1 to 8, wherein administration of the RT and the agent that inhibits binding between CD47 and SIRPα are alternated over multiple administrations.

10. The method of any one of claims 1 to 9, wherein the RT and the agent that inhibits binding between CD47 and SIRPα are administered according to a regimen that entails first administering the agent that inhibits binding between CD47 and SIRPα.

11. The method of any one of claims 1 to 10, wherein the solid cancer is selected from an epithelial carcinoma, a squamous cell carcinoma, a sarcoma and a brain cancer.

12. The method of any one of claims 1 to 11, wherein the cancer is selected from lung cancer, colorectal cancer, head and neck cancer, glioblastoma, prostate cancer, pancreatic cancer, breast cancer, liver cancer, testicular cancer, nasopharyngeal cancer, stomach cancer, urinary tract cancer, urothelial cancer, bladder cancer, renal cancer, ovarian cancer, uterine cancer and esophageal cancer.

13. The method of any one of claims 1 to 12, wherein the cancer is (i) unresectable, locally advanced or (ii) metastatic.

14. The method of any one of claims 1 to 13, wherein the cancer has progressed after the subject has received a course of an immune checkpoint inhibitor.

15. The method of any one of claims 1 to 14, wherein the cancer has progressed after administration of the subject has received a course of a platinum coordination complex therapy.

16. The method of any one of claims 1 to 13, wherein the cancer is unresectable, locally advanced and the subject is treatment naïve.

17. The method of any one of claims 1 to 16, wherein the cancer is a lung cancer selected from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

18. The method of any one of claims 1 to 16, wherein the cancer is a colorectal cancer.

19. The method of any one of claims 1 to 18, wherein the treatment results in a reduction in overall tumor burden of at least 15%, at least 20%, at least 30%, or at least 40%, as determined using linear dimensional methods (*e.g.*, RECIST v1.1).

20. The method of any one of claims 1 to 19, comprising reducing in size or eliminating the metastases.

21. The method of any one of claims 1 to 20, wherein the cancer has cell surface expression of CD47.

22. The method of any one of claims 1 to 21, wherein the agent that inhibits binding between CD47 and SIRPα comprises an antibody that binds to CD47.

23. The method of claim 22, wherein the antibody that binds to CD47 is selected from magrolimab, lemzoparlimab, letaplimab, ligufalimab, gentulizumab, AO-176, simridarlimab (IBI-322), zeripatamig, ZL-1201, IMC-002, SRF-231, CC-90002 (*a.k.a.*, INBRX-103), NI-1701 (*a.k.a.*, TG-1801) and STI-6643.

24. The method of any one of claims 1 to 21, wherein the agent that inhibits binding between CD47 and SIRPα comprises an antibody that binds to SIRPα.

25. The method of claim 22, the antibody that binds to SIRPα is selected from anzurstobart (*a.k.a.*, BMS-986351; CC-95251), GS-0189 (*a.k.a.*, FSI-189), BI-765063 and APX-700.

26. The method of any one of claims 1 to 21, wherein the agent that inhibits binding between CD47 and SIRPα comprises a SIRPα-Fc fusion protein.

27. The method of claim 26, the SIRPα-Fc fusion protein is selected from evorpacept (ALX-148), timdarpacept, TTI-621, maplirpacept (TTI-622), JMT601 (CPO107) and SL-172154.

28. The method of any one of claims 1 to 27, wherein the agent that inhibits binding between CD47 and SIRPα is administered before the focally-delivered RT.

29. The method of any one of claims 1 to 28, wherein the subject is a human.

30. The method of any one of claims 1 to 29, wherein the method does not comprise further co-administering an immune checkpoint inhibitor.

31. The method of any one of claims 1 to 30, wherein an anti-PD-1 antibody is not co-administered.

32. A method of treating, mitigating, reducing, preventing or delaying the growth, proliferation, recurrence or metastasis of a solid cancer in a mammalian subject in need thereof comprising co-administering to the subject an effective amount of:

a) radiation therapy (RT) focally-delivered to the solid cancer; and

b) magrolimab.

33. The method of claim 32, wherein the solid cancer is a non-irradiated tumor.

34. The method of any one of claims 32 to 33, wherein the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT.

35. The method of any one of claims 32 to 34, wherein the RT is focally-delivered via a technique selected from microbeam radiation therapy (MRT), external beam radiation therapy (EBRT), internal radiotherapy (brachytherapy), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic ablative radiation therapy (SABR), low-dose stereotactic body radiation (SBRT), preoperative RT, intra-operative radiation therapy (IORT), postoperative RT (PORT), pulsed low-dose rate radiation therapy, and combinations thereof.

36. The method of any one of claims 32 to 35, wherein the RT dose is a dose sufficient to induce abscopal effect (*i.e.*, reduction or elimination of non-irradiated tumors).

37. The method of any one of claims 32 to 36, wherein the RT dose is a maximum dose tolerated by the subject.

38. The method of any one of claims 32 to 37, wherein the RT dose is fractionated over multiple administrations.

39. The method of any one of claims 32 to 38, wherein the RT dose is hypofractionated or ultrahypofractionated.

40. The method of any one of claims 32 to 39, wherein administration of the RT and the agent that inhibits binding between CD47 and SIRPα are alternated over multiple administrations.

41. The method of any one of claims 32 to 40, wherein the RT and the agent that inhibits binding between CD47 and SIRPα are administered according to a regimen that entails first administering the agent that inhibits binding between CD47 and SIRPα.

42. The method of any one of claims 32 to 41, wherein the solid cancer is selected from an epithelial carcinoma, a squamous cell carcinoma, a sarcoma and a brain cancer.

43. The method of any one of claims 32 to 42, wherein the cancer is selected from lung cancer, colorectal cancer, head and neck cancer, glioblastoma, prostate cancer, pancreatic cancer, breast cancer, liver cancer, testicular cancer, nasopharyngeal cancer, stomach cancer, urinary tract cancer, urothelial cancer, bladder cancer, renal cancer, ovarian cancer, uterine cancer and esophageal cancer.

44. The method of any one of claims 32 to 43, wherein the cancer is (i) unresectable, locally advanced or (ii) metastatic.

45. The method of any one of claims 32 to 44, wherein the cancer has progressed after the subject has received a course of an immune checkpoint inhibitor.

46. The method of any one of claims 32 to 45, wherein the cancer has progressed after administration of the subject has received a course of a platinum coordination complex therapy.

47. The method of any one of claims 32 to 44, wherein the cancer is unresectable, locally advanced and the subject is treatment naïve.

48. The method of any one of claims 32 to 47, wherein the cancer is a lung cancer selected from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

49. The method of any one of claims 32 to 48, wherein the cancer is a colorectal cancer.

50. The method of any one of claims 32 to 49, wherein the treatment results in a reduction in overall tumor burden of at least 15%, at least 20%, at least 30%, or at least 40%, as determined using linear dimensional methods (*e.g.*, RECIST v1.1).

51. The method of any one of claims 32 to 50, comprising reducing in size or eliminating the metastases.

52. The method of any one of claims 32 to 51, wherein the treatment results in abscopal effect of reduction or elimination of tumors not receiving focally delivered RT.

53. The method of any one of claims 32 to 52, wherein the cancer has cell surface expression of CD47.

54. The method of any one of claims 32 to 53, wherein the magrolimab and the focally-delivered RT are administered in a combined synergistic amount.

55. The method of any one of claims 32 to 54, wherein administration of the magrolimab and the focally-delivered RT provides a synergistic effect.

56. The method of claim 55, wherein the synergistic effect is increased cancer cell death and/or decreased cancer cell growth when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone.

57. The method of claim 55, wherein the synergistic effect is increased phagocytosis of cancer cells by macrophages when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone.

58. The method of claim 55, wherein the synergistic effect is increased or enhanced tumor burden reduction when comparing the effect of the combination versus either the magrolimab or the focally-delivered RT alone.

59. The method of any one of claims 32 to 58, wherein the magrolimab is administered before the focally-delivered RT.

60. The method of any one of claims 32 to 59, wherein the magrolimab is first administered at a priming dose of 0.5 mg/kg to 10 mg/kg and then administered at one or more therapeutic doses of at least 15 mg/kg, *e.g.*, at least 20 mg/kg, 30 mg/kg, 45 mg/kg, 60 mg/kg.

61. The method of any one of claims 32 to 60, wherein the magrolimab is first administered at a priming dose of 0.5 mg/kg to 5 mg/kg and then administered at one or more therapeutic doses of at least 20 mg/kg, *e.g.*, 30 mg/kg, 45 mg/kg, 60 mg/kg.

62. The method of any one of claims 32 to 61, wherein the magrolimab is first administered at a priming dose of 1 mg/kg and then administered at one or more therapeutic doses of at least 20 mg/kg, *e.g.*, 30 mg/kg, 45 mg/kg, 60 mg/kg.

63. The method of any one of claims 32 to 61, wherein the magrolimab is (1) administered at a priming dose of 1 mg/kg at week 1, (2) administered weekly (Q1W) at a dose of 30 mg/kg from week 2 to week 5, and (3) administered every 3 weeks (Q3W) at a dose of 60 mg/kg for week 6 and thereafter.

64. The method of any one of claims 32 to 61, wherein the magrolimab is (1) administered at a priming dose of 1 mg/kg at week 1, (2) administered weekly (Q1W) at a dose of 20 mg/kg from week 2 to week 5, and (3) administered every 3 weeks (Q3W) at a dose of 45 mg/kg for week 6 and thereafter.

65. The method of any one of claims 32 to 64, wherein the subject is a human.

66. The method of any one of claims 32 to 65, wherein the method does not comprise further co-administering an immune checkpoint inhibitor.

67. The method of any one of claims 32 to 66, wherein an anti-PD-1 antibody is not co-administered.

Fig. 1A

GROUP	TEST ARTICLE	FOCAL RT	mAb DOSE
1	migG1		20 mg/kg IP (QD 5x/WEEK)
2	RT+ migG1	2 Gy / QD x3	N/A
3	MIAP410		20 mg/kg IP (QD 5x/WEEK)
4	RT+ MIAP410	2 Gy / QD x3	20 mg/kg IP (QD 5x/WEEK)

Fig. 1B

Fig. 1A-1B

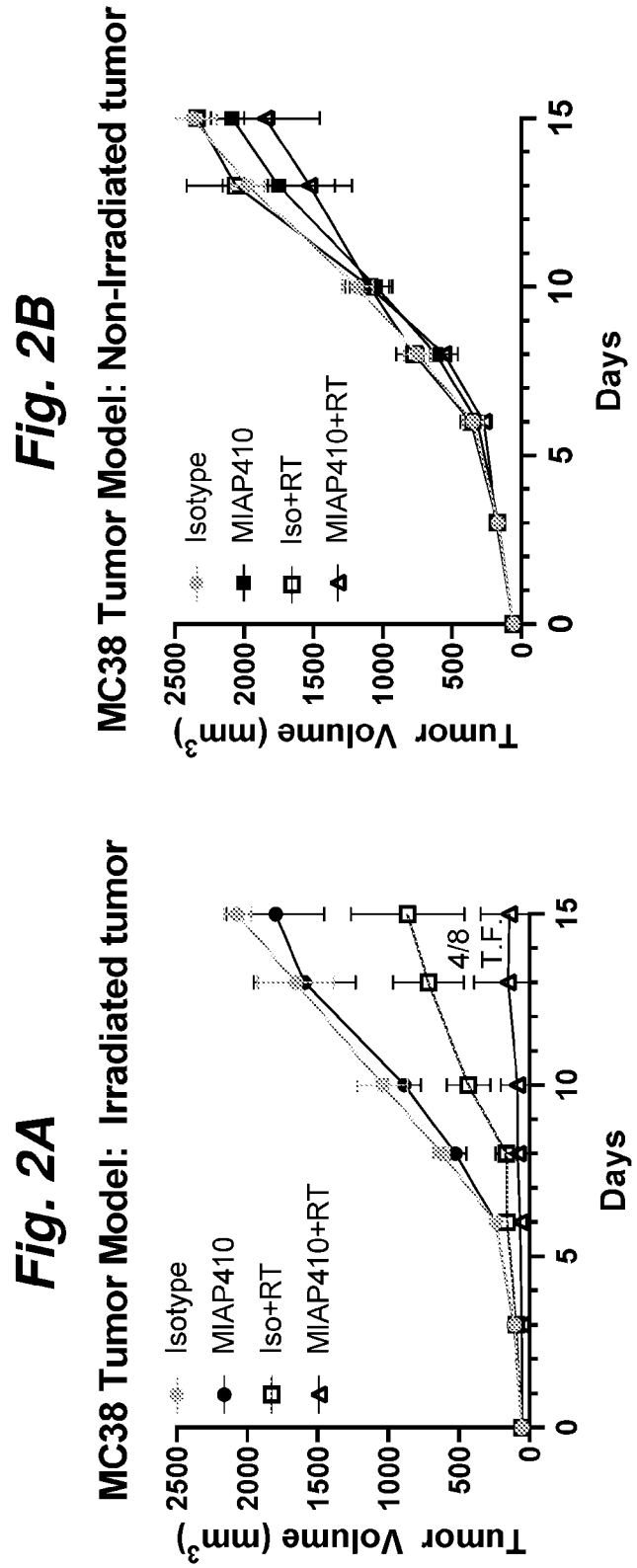

Fig. 2A

Fig. 2B

Fig. 2A-2B

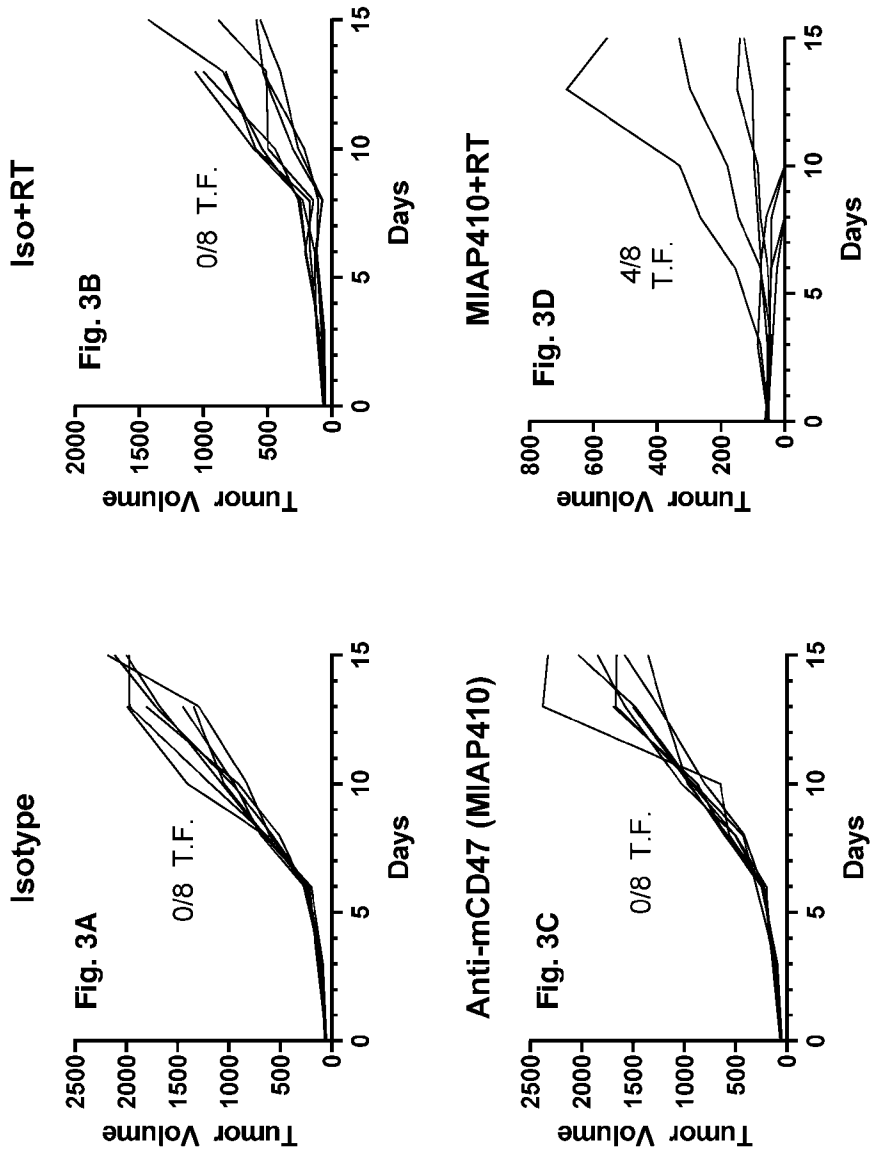
Isotype
Fig. 3A
0/8 T.F.
Tumor Volume
Days
Iso+RT
Fig. 3B
0/8 T.F.
Tumor Volume
Days
Anti-mCD47 (MIAP410)
Fig. 3C
0/8 T.F.
Tumor Volume
Days
MIAP410+RT
Fig. 3D
4/8
T.F.
Tumor Volume
Days

Fig. 3A-3D

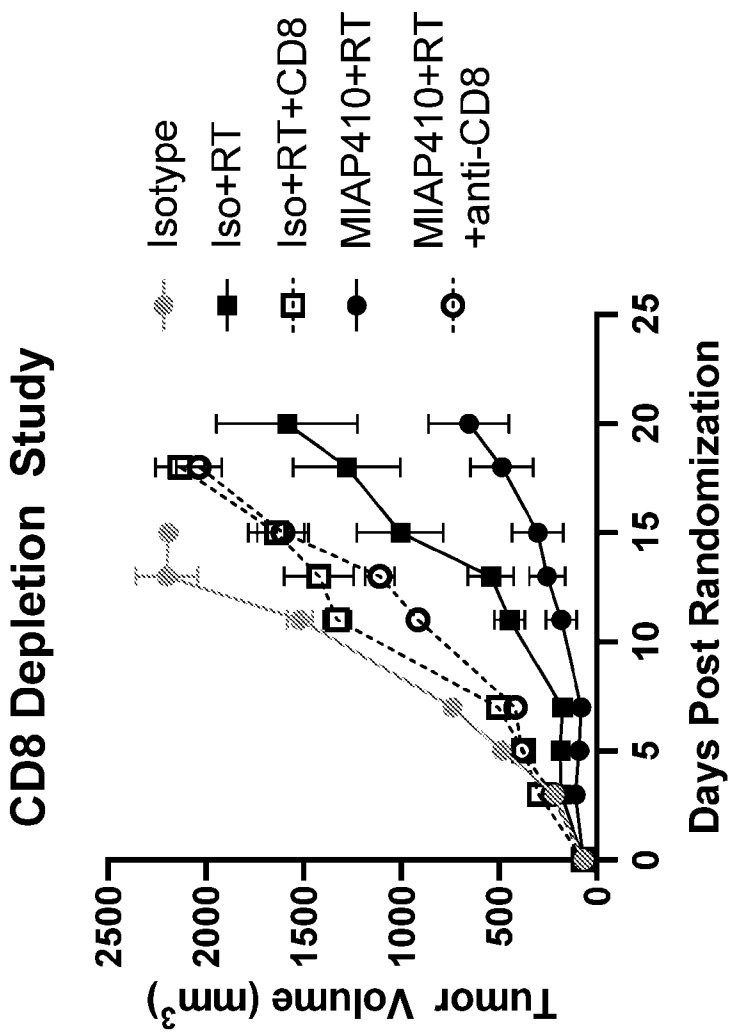
CD8 Depletion Study
Isotype
Iso+RT
Iso+RT+CD8
MIAP410+RT
MIAP410+RT
+anti-CD8
Tumor Volume (mm³)
2500
2000
1500
1000
500
0
0
5
10
15
20
25
Days Post Randomization

Fig. 4

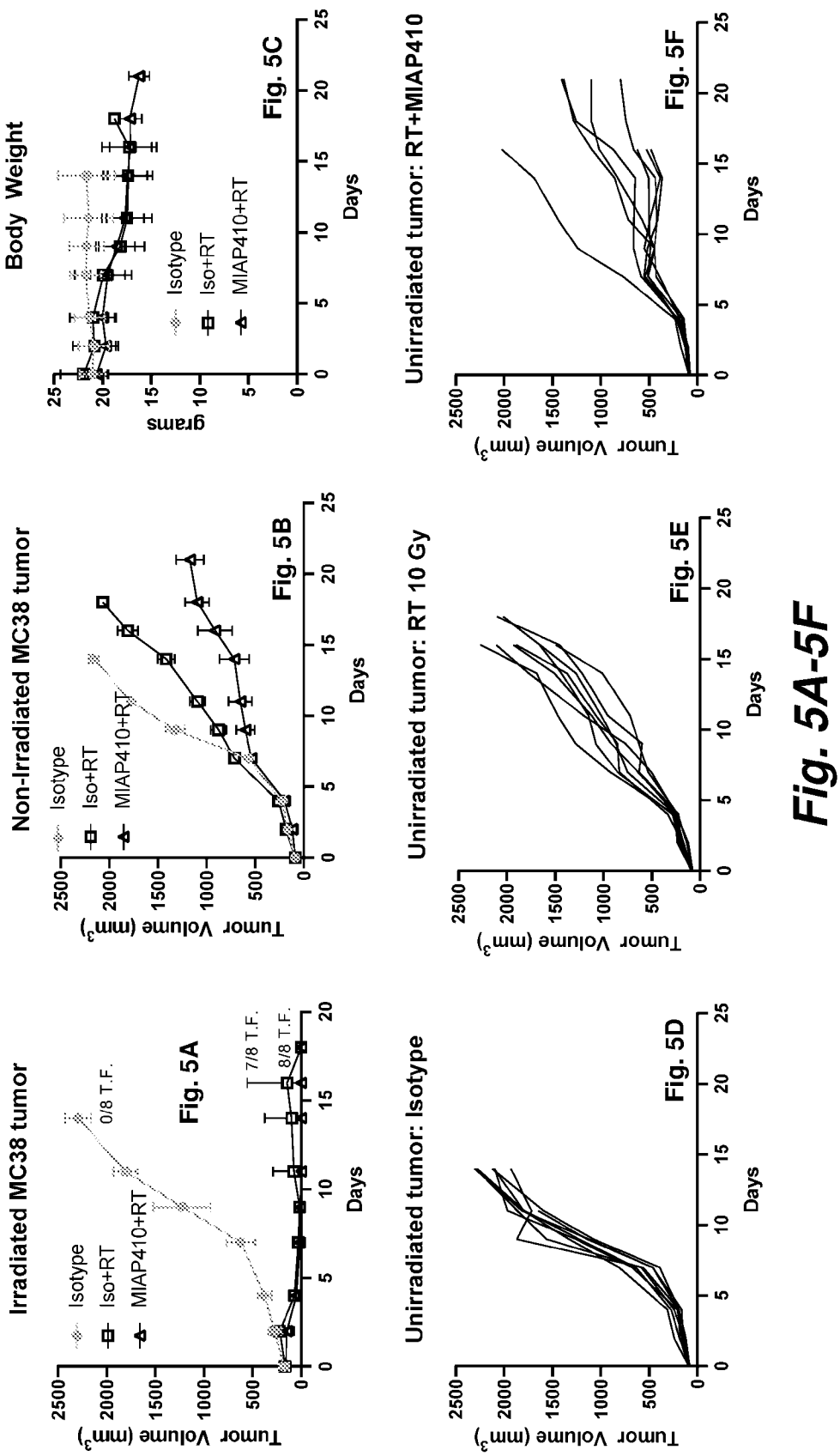
Irradiated MC38 tumor
Isotype
Iso+RT
MIAP410+RT
0/8 T.F.
7/8 T.F.
8/8 T.F.
Tumor Volume (mm3)
Days
Fig. 5A
Non-Irradiated MC38 tumor
Isotype
Iso+RT
MIAP410+RT
Tumor Volume (mm3)
Days
Fig. 5B
Body Weight
grams
Isotype
Iso+RT
MIAP410+RT
Days
Fig. 5C
Unirradiated tumor: Isotype
Tumor Volume (mm3)
Days
Fig. 5D
Unirradiated tumor: RT 10 Gy
Tumor Volume (mm3)
Days
Fig. 5E
Unirradiated tumor: RT+MIAP410
Tumor Volume (mm3)
Days
Fig. 5F

Fig. 5A-5F

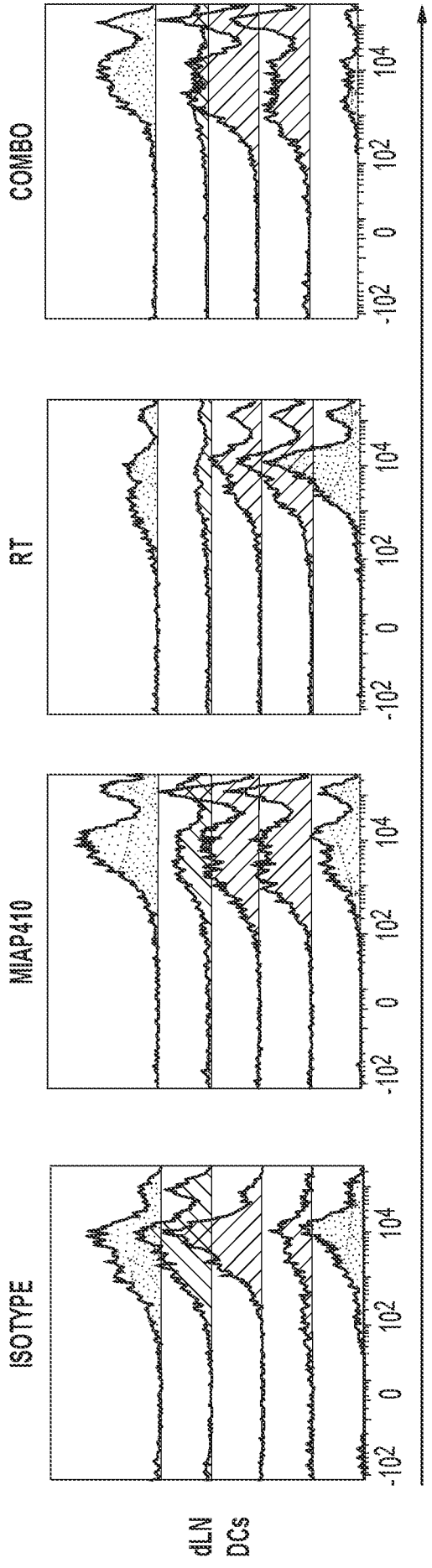

Fig. 6

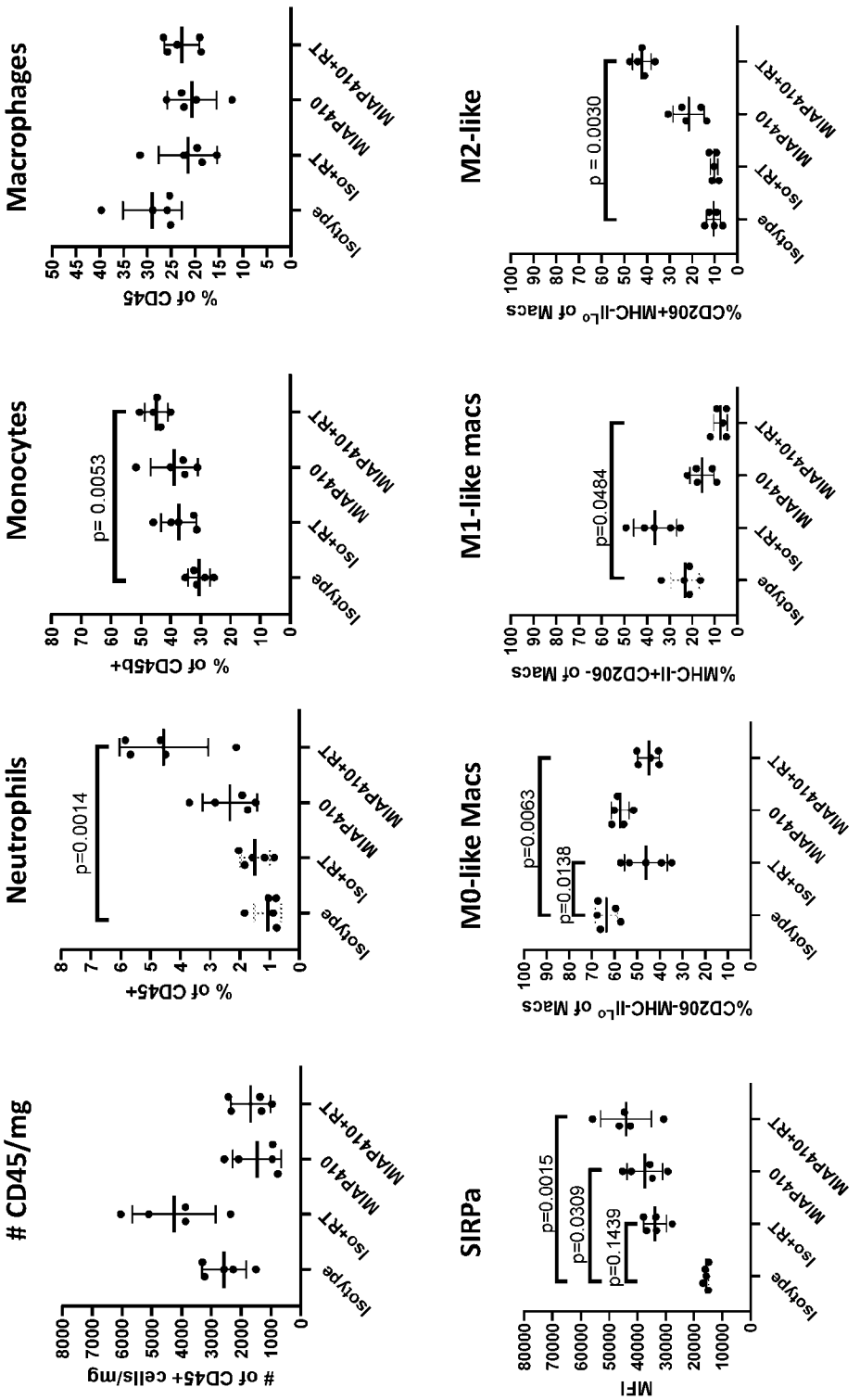
# CD45/mg
# of CD45+ cells/mg
p=0.0014
Neutrophils
% of CD45+
p= 0.0053
Monocytes
% of CD45b+
Macrophages
% of CD45
SIRPa
MFI
p=0.0015
p=0.0309
p=0.1439
M0-like Macs
%CD206-MHC-II^{Lo} of Macs
p=0.0063
p=0.0138
M1-like macs
%MHC-II+CD206- of Macs
p=0.0484
M2-like
%CD206+MHC-II^{Lo} of Macs
p = 0.0030
Isotype
Iso+RT
MIAP410
MIAP410+RT

Fig. 7

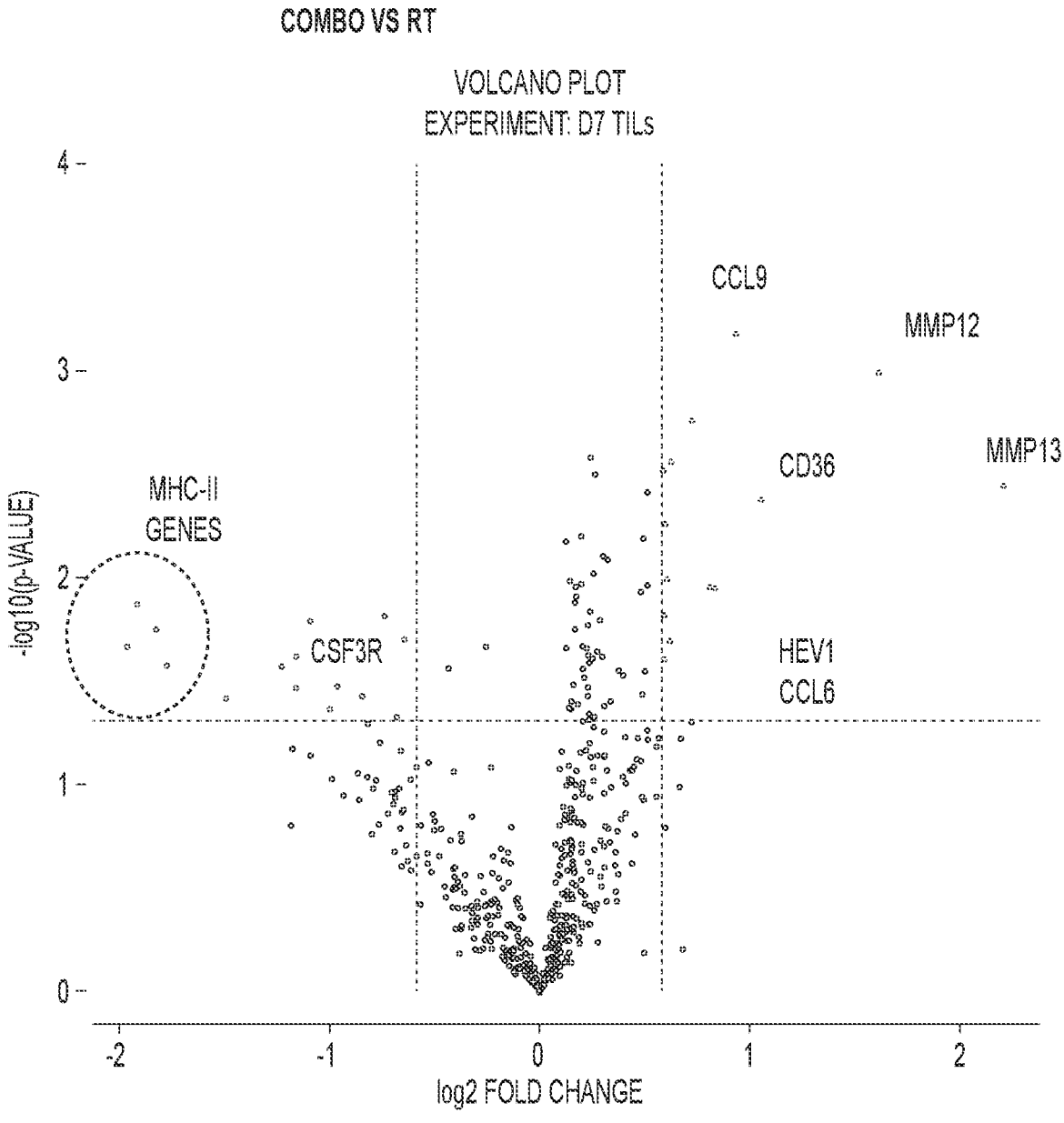
COMBO VS RT
VOLCANO PLOT
EXPERIMENT: D7 TILs
-log10(p-VALUE)
log2 FOLD CHANGE
MHC-II
GENES
CSF3R
CCL9
MMP12
MMP13
CD36
HEV1
CCL6
4
3
2
1
0
-2
-1
0
1
2

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/074560

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28
ADD.

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)
C07K A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/040341 A1 (UNIV LELAND STANFORD JUNIOR [US]) 24 February 2022 (2022-02-24) paragraphs [0005] - [0016], [0041] - [0051], [0069] - [0074], [0100] - [0109], [0133] - [0140]	1-67
A	US 2021/308195 A1 (DANINO TAL [US] ET AL) 7 October 2021 (2021-10-07) paragraphs [0026], [0143], [0144], [0086] - [0090], [0040], [0196] - [0199], [0140]	1-67
A	WO 2019/014391 A1 (SYNLOGIC OPERATING CO INC [US]) 17 January 2019 (2019-01-17) paragraphs [0087], [0171], [0223], [0370] - [0373], [0474]	1-67

-/--

[x] Further documents are listed in the continuation of Box C.

[x] 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

"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
5 December 2023	18/12/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Page, Michael

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/074560

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DIZMAN NAZLI ET AL: "Cancer Therapy Targeting CD47/SIRP[alpha]", CANCERS, 11 December 2021 (2021-12-11), pages 1-17, XP093034401, DOI: 10.3390/cancers13246229 paragraphs [6.Anti] - [CD47Antibodies]; table 1 paragraph [7.SIRPaTargetingAgents]	23,25,27
A	US 2022/211886 A1 (LUDWIG DALE L [US] ET AL) 7 July 2022 (2022-07-07) paragraphs [0004] - [0006], [0009], [0010], [0199] - [0215], [0219], [0246], [0261] - [0265], [0274], [0275]	23,25,27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/074560

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. [X] 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

Information on patent family members

International application No
PCT/US2023/074560

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022040341 A1	24-02-2022	NONE	
US 2021308195 A1	07-10-2021	EP 3823653 A1	26-05-2021
		US 2021308195 A1	07-10-2021
		WO 2020018989 A1	23-01-2020
WO 2019014391 A1	17-01-2019	AU 2018301668 A1	19-12-2019
		CA 3066109 A1	17-01-2019
		CN 111246865 A	05-06-2020
		EP 3651782 A1	20-05-2020
		IL 270892 A	30-01-2020
		JP 2020527025 A	03-09-2020
		KR 20200064980 A	08-06-2020
		SG 11201911031T A	30-01-2020
		US 2020149053 A1	14-05-2020
		WO 2019014391 A1	17-01-2019
US 2022211886 A1	07-07-2022	CA 3196402 A1	28-04-2022
		CN 116744976 A	12-09-2023
		EP 4232052 A1	30-08-2023
		JP 2023546679 A	07-11-2023
		US 2022211886 A1	07-07-2022
		WO 2022087416 A1	28-04-2022