to twelve of the antigen binding domains of the IgM or IgM-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof are DR5-specific and agonistic; and (b) an effective amount of a cancer therapy, wherein the cancer therapy comprises radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, second mitochondria-derived activator of caspases (SMAC) mimetic, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof.

[0010] Provided herein is a method for inhibiting, delaying, or reducing malignant cell growth in a subject with cancer in need of treatment, comprising administering an effective amount of a pentameric or hexameric IgM or IgM-like antibody or a dimeric IgA or IgA-like antibody, or a multimerized antigen-binding fragment, variant, or derivative thereof that specifically and agonistically binds to DR5, where three to twelve of the antigen binding domains of the IgM or IgM-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof or three or four of the antigen binding domains of the IgA or IgA-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof are DR5-specific and agonistic, where the pentameric or hexameric IgM or IgM-like antibody or the dimeric IgA or IgA-like antibody, or the multimerized antigen-binding fragment, variant, or derivative thereof is administered with an effective amount of a cancer therapy, where the cancer therapy comprises a second mitochondria-derived activator of caspases (SMAC) mimetic, radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof.

[0010a] In one aspect, there is provided herein use of a pentameric or hexameric IgM or IgM-like antibody or a dimeric IgA or IgA-like antibody, or a multimerized antigen-binding fragment, variant, or derivative thereof that specifically and agonistically binds to DR5 in the manufacture of a medicament for inhibiting, delaying, or reducing malignant cell growth in a cancer in combination with a cancer therapy, wherein three to twelve of the antigen binding domains of the IgM or IgM-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof or three or four of the antigen binding domains of the IgA or IgA-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof are DR5-specific and agonistic, and wherein the cancer

therapy comprises a second mitochondria-derived activator of caspases (SMAC) mimetic, radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof.

[0011] Provided herein is a method for inhibiting, delaying, or reducing malignant cell growth in a subject with cancer in need of treatment, comprising administering an effective amount of a cancer therapy, where the cancer therapy comprises a second mitochondria-derived activator of caspases (SMAC) mimetic, radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof, where the cancer therapy is administered with a pentameric or hexameric IgM or IgM-like antibody or a dimeric IgA or IgA-like antibody, or a multimerized antigen-binding

agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof.

[0014] Provided herein is a method for inducing apoptosis in a cancer cell in in a subject with cancer in need of treatment, comprising administering an effective amount of a cancer therapy, where the cancer therapy comprises a second mitochondria-derived activator of caspases (SMAC) mimetic, radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof, where the cancer therapy is administered with a pentameric or hexameric IgM or IgM-like antibody or a dimeric IgA or IgA-like antibody, or a multimerized antigen-binding fragment, variant, or derivative thereof that specifically and agonistically binds to DR5, where three to twelve of the antigen binding domains of the IgM or IgM-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof or three or four of the antigen binding domains of the IgA or IgA-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof are DR5-specific and agonistic.

[0015] In some examples, the cancer therapy comprises a folic acid analog. In some examples, the folic acid analog comprises leucovorin.

[0016] In some examples, the cancer therapy comprises a platinum-based agent. In some examples, the platinum-based agent comprises oxaliplatin, carboplatin, or a combination thereof. In some examples, the platinum-based agent comprises oxaliplatin. In some examples, the platinum-based agent comprises carboplatin.

[0017] In some examples, the cancer therapy comprises a taxane. In some examples, the taxane comprises paclitaxel. In some examples, the paclitaxel comprises solvent-based paclitaxel, nab-paclitaxel, or a combination thereof. In some examples, the paclitaxel comprises solvent-based paclitaxel. In some examples, the paclitaxel comprises nab-paclitaxel.

[0018] In some examples, the cancer therapy comprises a topoisomerase II inhibitor. In some examples, the topoisomerase II inhibitor comprises an anthracycline. In some examples, the anthracycline comprises doxorubicin. In some examples, the topoisomerase II inhibitor comprises etoposide.

[0019] In some examples, the cancer therapy comprises a SMAC mimetic. In some examples, the SMAC mimetic comprises birinapant, GDC-0152, HGS-1029/AEG40826, Debio1143, APG-1387, ASTX660, or a combination thereof. In some examples, the SMAC mimetic comprises a bivalent SMAC mimetic. In some examples, the SMAC mimetic comprises birinapant. In some examples, the SMAC mimetic comprises APG-1387. In some examples, the SMAC mimetic comprises GDC-0152. In some examples, the SMAC mimetic comprises HGS-1029/AEG40826. In some examples, the SMAC mimetic comprises Debio1143. In some examples, the SMAC mimetic comprises ASTX660. In some examples, the SMAC mimetic comprises a monovalent SMAC mimetic.

[0020] In some examples, the cancer therapy comprises a vinca alkaloid. In some examples, the vinca alkaloid comprises vincristine.

[0021] In some examples, the cancer therapy comprises a BTK inhibitor. In some examples, the BTK inhibitor comprises ibrutinib.

[0022] In some examples, the cancer therapy comprises a PI3Kδ inhibitor. In some examples, the PI3Kδ inhibitor comprises idelalisib.

[0023] In some examples, the cancer therapy comprises a Mcl-1 inhibitor. In some examples, the Mcl-1 inhibitor comprises MIK665.

[0024] In some examples, the cancer therapy comprises an anti-VEGF antibody. In some examples, the anti-VEGF antibody is bevacizumab.

[0025] In some examples, the cancer therapy comprises radiation.

[0026] In some examples, the method further comprises administering an effective amount of an additional cancer therapy. In some examples, the additional cancer therapy comprises a topoisomerase I inhibitor, a nucleoside analog, a platinum-based agent, or any combination thereof. In some examples, the additional cancer therapy comprises a topoisomerase I inhibitor. In some examples, the topoisomerase I inhibitor comprises irinotecan, topotecan, or a combination thereof. In some examples, the topoisomerase I inhibitor comprises irinotecan. In some examples, the additional cancer therapy comprises a nucleoside analog. In some examples, the nucleoside analog comprises fluorouracil (5-FU), gemcitabine, or any combination thereof. In some examples, the nucleoside analog comprises fluorouracil (5-FU). In some examples, the nucleoside analog comprises gemcitabine.

[0027] In some examples, the cancer is a hematologic cancer or a solid tumor. In some examples, the cancer is a hematologic cancer. In some examples, the hematologic cancer is leukemia, lymphoma, myeloma, any metastases thereof, or any combination thereof. In some examples, the hematologic cancer is acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, any metastases thereof, or any combination thereof. In some examples, the hematologic cancer is acute myeloid leukemia (AML). In some examples, the cancer therapy comprises doxorubicin.

[0028] In some examples, the cancer is a solid tumor. In some examples, the cancer is bladder cancer, colorectal cancer, sarcoma, gastric cancer, lung cancer, pancreatic cancer, melanoma, ovarian cancer, head and neck cancer, or breast cancer.

[0029] In some examples, the cancer is sarcoma. In some examples, the sarcoma is fibrosarcoma, chondrosarcoma, or osteosarcoma. In some examples, the sarcoma is fibrosarcoma. In some examples, the cancer therapy comprises doxorubicin.

[0030] In some examples, the cancer is colorectal cancer. In some examples, the cancer therapy comprises oxaliplatin. In some examples, the additional therapy comprises 5-FU. In some examples, the cancer therapy comprises leucovorin. In some examples, the additional therapy comprises oxaliplatin or irinotecan.

[0031] In some examples, the cancer is gastric cancer. In some examples, the cancer therapy comprises carboplatin. In some examples, the cancer therapy comprises oxaliplatin. In some examples, the cancer therapy comprises paclitaxel.

[0032] In some examples, the cancer is lung cancer. In some examples, the lung cancer is non-small cell lung cancer (NSCLC). In some examples, the cancer therapy comprises carboplatin. In some examples, the cancer therapy comprises paclitaxel.

[0033] In some examples, the cancer is pancreatic cancer. In some examples, the cancer therapy comprises paclitaxel. In some examples, the additional therapy comprises gemcitabine.

[0034] In some examples, the cancer is head and neck cancer. In some examples, the head and neck cancer is head and neck sarcoma. In some examples, the cancer is breast cancer. In some examples, the breast cancer is triple negative breast cancer (TNBC). In some examples, the cancer therapy comprises a SMAC mimetic.

[0035] In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 82 and SEQ ID NO: 83; SEQ ID NO: 84 and SEQ ID NO: 85; SEQ ID NO: 86 and SEQ ID NO: 87; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or the ScFv sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73 or the six CDRs with one or two amino acid substitutions in one or more of the CDRs.

[0036] In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise

the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; or SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

[0037] In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6, respectively. In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

[0038] In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise an antibody VH and a VL, wherein the VH and VL comprise amino acid sequences at least 90% identical to SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52;

SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 82 and SEQ ID NO: 83; SEQ ID NO: 84 and SEQ ID NO: 85; SEQ ID NO: 86 and SEQ ID NO: 87; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or wherein the VH and VL are contained in an ScFv with an amino acid sequence at least 90% identical to SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73, respectively.

[0039] In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise an antibody VH and a VL, wherein the VH and VL comprise amino acid sequences at least 90% identical to SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; or SEQ ID NO: 7 and SEQ ID NO: 8, respectively. In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise an antibody VH and a VL, wherein the VH and VL comprise amino acid sequences at least 90% identical to SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6, respectively. In some examples, the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise an antibody VH and a VL, wherein the VH and VL comprise amino acid sequences at least 90% identical to SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

[0040] In some examples, the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is a dimeric IgA or IgA-like antibody comprising two bivalent IgA binding units or multimerizing fragments thereof and a J-chain or fragment or variant thereof, wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing fragments thereof each associated with an antigen-binding domain. In some examples, the IgA or IgA-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof further comprises a secretory component, or fragment or variant thereof. In some examples, the IgA heavy chain constant regions or multimerizing fragments thereof each comprise a Cα3-tp domain. In some examples, the IgA heavy chain constant regions or multimerizing fragments thereof each comprise a Cα1 domain and/or a Cα2 domain. In some examples, the IgA heavy chain constant

region is a human IgA constant region. In some examples, each binding unit comprises two IgA heavy chains each comprising a VH situated amino terminal to the IgA constant region or multimerizing fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

[0041] In some examples, the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is a pentameric or a hexameric IgM antibody comprising five or six bivalent IgM binding units, respectively, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing fragments thereof each associated with an antigen-binding domain. In some examples, the IgM heavy chain constant regions or multimerizing fragments thereof each comprise a Cμ4-tp domain. In some examples, the IgM heavy chain constant regions or multimerizing fragments thereof each comprise a Cμ1 domain, a Cμ2 domain, and/or a Cμ3 domain. In some examples, the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is pentameric, and further comprises a J-chain, or functional fragment thereof, or variant thereof. In some examples, the IgM heavy chain constant region is a human IgM constant region. In some examples, each binding unit comprises two IgM heavy chains each comprising a VH situated amino terminal to the IgM constant region or multimerizing fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

[0042] In some examples, the J-chain or functional fragment or variant thereof is a variant J-chain comprising one or more single amino acid substitutions, deletions, or insertions relative to a wild-type J-chain that can affect serum half-life of the multimeric binding molecule; and wherein the multimeric binding molecule exhibits an increased serum half-life upon administration to an animal relative to a reference multimeric binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions, and is administered in the same way to the same animal species.

[0043] In some examples, the J-chain or functional fragment thereof comprises an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the wild-type human J-chain (SEQ ID NO: 97). In some examples, the amino acid corresponding to Y102 of SEQ ID NO: 97 is substituted with alanine (A), serine (S), or arginine (R). In some examples, the amino acid corresponding to Y102 of SEQ ID

NO: 97 is substituted with alanine (A). In some examples, the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 98.

[0044] In some examples, the J-chain or functional fragment thereof comprises an amino acid substitution at the amino acid position corresponding to amino acid N49, amino acid S51, or both N49 and S51 of the human J-chain (SEQ ID NO: 97), wherein a single amino acid substitution corresponding to position S51 of SEQ ID NO: 97 is not a threonine (T) substitution. In some examples, the position corresponding to N49 of SEQ ID NO: 97 is substituted with alanine (A), glycine (G), threonine (T), serine (S) or aspartic acid (D). In some examples, the position corresponding to N49 of SEQ ID NO: 97 is substituted with alanine (A). In some examples, the position corresponding to S51 of SEQ ID NO: 97 is substituted with alanine (A) or glycine (G). In some examples, the position corresponding to S51 of SEQ ID NO: 97 is substituted with alanine (A).

[0045] In some examples, the J-chain or functional fragment or variant thereof further comprises a heterologous polypeptide, wherein the heterologous polypeptide is directly or indirectly fused to the J-chain or functional fragment or variant thereof. In some examples, the heterologous polypeptide is fused to the J-chain or functional fragment thereof via a peptide linker. In some examples, the peptide linker comprises at least 5 amino acids, but no more than 25 amino acids. In some examples, the peptide linker consists of GGGGS (SEQ ID NO: 99), GGGGSGGGGS (SEQ ID NO: 100), GGGGSGGGGSGGGGS (SEQ ID NO: 101), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 102), or GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 103). In some examples, the heterologous polypeptide is fused to the N-terminus of the J-chain or functional fragment or variant thereof, the C-terminus of the J-chain or functional fragment or variant thereof, or to both the N-terminus and C-terminus of the J-chain or functional fragment or variant thereof.

[0046] In some examples, the heterologous polypeptide can influence the absorption, distribution, metabolism and/or excretion (ADME) of the multimeric binding molecule. In some examples, the heterologous polypeptide comprises an antigen binding domain. In some examples, the antigen binding domain of the heterologous polypeptide is an antibody or antigen-binding fragment thereof. In some examples, the antigen-binding fragment comprises an Fab fragment, an Fab' fragment, an F(ab')2 fragment, an Fd fragment, an Fv fragment, a single-chain Fv (scFv) fragment, a disulfide-linked Fv (sdFv)

fragment, or any combination thereof. In some examples, the antigen-binding fragment is a scFv fragment.

[0047] In some examples, administration of the combination therapy results in enhanced therapeutic efficacy relative to administration of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof or the cancer therapy alone. In some examples, the enhanced therapeutic efficacy comprises a reduced tumor growth rate, tumor regression, or increased survival. In some examples, the subject is human.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0048] FIGS. 1A-1D show 3D surface plots of synergy scores from a continuum of dose combinations of Mab A and doxorubicin applied to MOLM13 (FIG. 1A), MV411 (FIG. 1B), HT1080 (FIG. 1C), or primary human hepatocytes (FIG. 1D) cells *in vitro*, with valleys reflecting antagonism and hills representing synergy.

[0049] FIGS. 2A-2I show 3D surface plots of synergy scores from a continuum of dose combinations of Mab A and paclitaxel applied to NCIH460 (FIG. 2A), NCIH2228 (FIG. 2B), NCIN87 (FIG. 2C), PANC1 (FIG. 2D), primary human hepatocytes (FIG. 2E), SNU5 (FIG. 2F), NUCG4 (FIG. 2G), ASPC1 (FIG. 2H), or BXPC3 (FIG2I) cells *in vitro*, with valleys reflecting antagonism and hills representing synergy.

[0050] FIGS. 3A-3E show 3D surface plots of synergy scores from a continuum of dose combinations of Mab A and carboplatin applied to NCIH460 (FIG. 3A), NCIH2228 (FIG. 3B), NCIN87 (FIG. 3C), NUGC4 (FIG. 3D), or SNU5 (FIG. 3E) cells *in vitro*, with valleys reflecting antagonism and hills representing synergy.

[0051] FIGS. 4A-4H show 3D surface plots of synergy scores from a continuum of dose combinations of Mab A and doxorubicin applied to NUGC4 (FIG. 4A), NCIN87 (FIG. 4B), SNU5 (FIG. 4C), NCIH508 (FIG. 4D), HCT15 (FIG. 4E), HT55 (FIG. 4F), NCI-H2228 (FIG. 4G), or primary human hepatocytes (FIG. 4H) cells *in vitro*, with valleys reflecting antagonism and hills representing synergy.

[0052] FIGS. 5A, 5C, 5E, 5G, and 5I show tumor volume over time for mice treated with Mab A and/or radiation (FIG. 5A), oxaliplatin (FIG. 5C), paclitaxel (FIG. 5E), irinotecan (FIG. 5G), or ABT-199 (FIG. 5I). FIGS. 5B, 5D, 5F, 5H, and 5J show survival over time for mice treated with Mab A and/or radiation (FIG. 5B), oxaliplatin (FIG. 5D), paclitaxel (FIG. 5F), irinotecan (FIG. 5H), or ABT-199 (FIG. 5J).

WHAT IS CLAIMED IS:

1. Use of a pentameric or hexameric IgM or IgM-like antibody or a dimeric IgA or IgA-like antibody, or a multimerized antigen-binding fragment, variant, or derivative thereof that specifically and agonistically binds to DR5 in the manufacture of a medicament for inhibiting, delaying, or reducing malignant cell growth in a cancer in combination with a cancer therapy, wherein three to twelve of the antigen binding domains of the IgM or IgM-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof or three or four of the antigen binding domains of the IgA or IgA-like antibody or multimerized antigen-binding fragment, variant, or derivative thereof are DR5-specific and agonistic,

and wherein the cancer therapy comprises a second mitochondria-derived activator of caspases (SMAC) mimetic, radiation, a folic acid analog, a platinum-based agent, a taxane, a topoisomerase II inhibitor, a vinca alkaloid, a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, a myeloid cell leukemia-1 (Mcl-1) inhibitor, an anti-VEGF antibody, or any combination thereof.

2. The use of claim 1, wherein the cancer therapy comprises a SMAC mimetic, and wherein the SMAC mimetic comprises a bivalent SMAC mimetic.

3. The use of claim 2, wherein the SMAC mimetic comprises birinapant.

4. The use of claim 1, wherein the cancer therapy comprises leucovorin, oxaliplatin, carboplatin, paclitaxel, an anthracycline, etoposide, vincristine, ibrutinib, idelalisib, MIK665, bevacizumab, birinapant, GDC-0152, HGS-1029/AEG40826, Debio1143, APG-1387, ASTX660, or any combination thereof.

5. The use of claim 1, wherein the combination further comprises an additional cancer therapy.

6. The use of claim 5, wherein the additional cancer therapy comprises a topoisomerase I inhibitor, a nucleoside analog, a platinum-based agent, or any combination thereof.

7. The use of claim 6, wherein the additional cancer therapy comprises irinotecan, topotecan, fluorouracil (5-FU), gemcitabine, or any combination thereof.

8. The use of claim 1, wherein the cancer is a hematologic cancer.

9. The use of claim 8, wherein the hematologic cancer is leukemia, lymphoma, myeloma, any metastases thereof, or any combination thereof.

10. The use of claim 8, wherein the hematologic cancer is acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, any metastases thereof, or any combination thereof.

11. The use of claim 1, wherein the cancer is a solid tumor.

12. The use of claim 11, wherein the cancer is bladder cancer, colorectal cancer, sarcoma, gastric cancer, lung cancer, pancreatic cancer, head and neck cancer, melanoma, ovarian cancer, or breast cancer.

13. The use of claim 12, wherein the cancer is fibrosarcoma, chondrosarcoma, osteosarcoma, non-small cell lung cancer (NSCLC), head and neck sarcoma, or triple negative breast cancer (TNBC).

14. The use of claim 1, wherein the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise:

(a) six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ

ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 82 and SEQ ID NO: 83; SEQ ID NO: 84 and SEQ ID NO: 85; SEQ ID NO: 86 and SEQ ID NO: 87; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or the ScFv sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73, or the six CDRs with one or two amino acid substitutions in one or more of the CDRs; and/or

(b) amino acid sequences at least 90% identical to SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 82 and SEQ ID NO: 83; SEQ ID NO: 84 and SEQ ID NO: 85; SEQ ID NO: 86 and SEQ ID NO: 87; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or wherein the VH and VL are contained in an ScFv with an amino acid sequence at least 90% identical to SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73, respectively.

15. The use of claim 14, wherein the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding

fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise:

(a) six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; or SEQ ID NO: 7 and SEQ ID NO: 8, respectively; and/or

(b) amino acid sequences at least 90% identical to SEQ ID NO: 5 or SEQ ID NO: 90 and SEQ ID NO: 6; or SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

16. The use of claim 15, wherein the three or four antigen-binding domains or the three to twelve antigen-binding domains of the antibody or multimerized antigen-binding fragment, variant, or derivative thereof comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise:

(a) six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL amino acid sequences SEQ ID NO: 7 and SEQ ID NO: 8, respectively; and/or

(b) amino acid sequences at least 90% identical to SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

17. The use of any one of claims 1 to 16, wherein the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is a dimeric IgA or IgA-like antibody comprising two bivalent IgA binding units or multimerizing fragments thereof and a J-chain or fragment or variant thereof, wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing fragments thereof each associated with an antigen-binding domain, and wherein the IgA heavy chain constant regions or multimerizing fragments thereof each comprise a Cα3-tp domain.

18. The use of claim 17, wherein the IgA heavy chain constant regions or multimerizing fragments thereof each comprise a Cα1 domain and/or a Cα2 domain.

19. The use of claim 17, wherein the IgA heavy chain constant region is a human IgA constant region.

20. The use of claim 17, wherein each binding unit comprises two IgA heavy chains each comprising a VH situated amino terminal to the IgA constant region or multimerizing fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

21. The use of any one of claims 1 to 16, wherein the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is a pentameric or a hexameric IgM antibody comprising five or six bivalent IgM binding units, respectively, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing fragments thereof each associated with an antigen-binding domain, and wherein the IgM heavy chain constant regions or multimerizing fragments thereof each comprise a Cμ4-tp domain.

22. The use of claim 21, wherein the IgM heavy chain constant regions or multimerizing fragments thereof each comprise a Cμ1 domain, a Cμ2 domain, and/or a Cμ3 domain.

23. The use of claim 21, wherein the antibody or multimerized antigen-binding fragment, variant, or derivative thereof is pentameric, and further comprises a J-chain, or functional fragment thereof, or variant thereof.

24. The use of claim 21, wherein the IgM heavy chain constant region is a human IgM constant region.

25. The use of claim 21, wherein each binding unit comprises two IgM heavy chains each comprising a VH situated amino terminal to the IgM constant region or multimerizing fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

26. The use of claim 23, wherein the J-chain or functional fragment or variant thereof is a variant J-chain comprising one or more single amino acid substitutions, deletions, or insertions relative to a wild-type J-chain that can affect serum half-life of the multimeric binding molecule; and wherein the multimeric binding molecule exhibits an increased serum half-life upon administration to an animal relative to a reference multimeric binding molecule

that is identical except for the one or more single amino acid substitutions, deletions, or insertions, and is to be administered in the same way to the same animal species.

27. The use of claim 26, wherein the J-chain or functional fragment thereof comprises:

(a) an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the wild-type human J-chain (SEQ ID NO: 97),

(b) an alanine (a) substitution at the amino acid position corresponding to amino acid Y102 of the wild-type human J-chain (SEQ ID NO: 97), or

(c) the amino acid sequence SEQ ID NO: 98.

28. The use of claim 26, wherein the J-chain or functional fragment or variant thereof further comprises a heterologous polypeptide, wherein the heterologous polypeptide is directly or indirectly fused to the J-chain or functional fragment or variant thereof.