[0025] As described in detail below, the present invention relates to novel antibodies, including in particular dual affinity retargeting reagents ("DART™s") that comprise modulators of B7-H3 T-cell activation, that are capable of influencing T-cell activation as well as novel antibodies that bind to B7-H3 receptors of cancer cells and facilitate or mediate the death of such cells. The present invention is directed to such compositions and to their uses in diagnostics and in the treatment of diseases such as cancer.

Summary:

[0026] The present disclosure relates to antibodies and their fragments that are immunoreactive to the mammalian, and more particularly, the human B7-H3 receptor and to uses thereof, particularly in the treatment of cancer and inflammation. The disclosure thus particularly concerns humanized B7-H3-reactive antibodies and their immunoreactive fragments that are capable of mediating, and more preferably enhancing the activation of the immune system against cancer cells that are associated with a variety of human cancers.

[0026a] In one aspect, there is provided a diabody comprising: (A) a polypeptide chain I that comprises an immunoglobulin VL epitope binding domain specific for binding B7-H3 and a VH epitope binding domain specific for binding a molecule other than B7-H3; and (B) a polypeptide chain II that comprises an immunoglobulin VH epitope binding domain specific for binding B7-H3 and a VL epitope binding domain specific for binding said molecule other than B7-H3; wherein said polypeptide chains I and II are associated together so as to form functional epitope-binding domains capable of binding to B7-H3 and said molecule other than B7-H3, and wherein:

(1) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 21), CDR_2 (SEQ ID NO: 23) and CDR_3 (SEQ ID NO: 25), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 29), CDR_2 (SEQ ID NO: 31) and CDR_3 (SEQ ID NO: 33); or

(2) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 5), CDR_2 (SEQ ID NO: 7) and CDR_3 (SEQ ID NO: 9), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 13), CDR_2 (SEQ ID NO: 15) and CDR_3 (SEQ ID NO: 17); or

(3) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 37), CDR_2 (SEQ ID NO: 39) and CDR_3 (SEQ ID NO: 41), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 45), CDR_2 (SEQ ID NO: 47) and CDR_3 (SEQ ID NO: 49).

[0027] In detail, the disclosure concerns an isolated antibody or an immunoreactive fragment thereof, wherein the isolated antibody or the fragment comprises a variable domain that specifically binds an extracellular domain of B7-H3, wherein the antibody competes for binding to the B7-H3 with any of antibodies: BRCA69D, BRCA84D, or PRCA157.

[0028] The disclosure further concerns the above-described isolated antibody or immunoreactive fragment thereof, wherein the antibody or the fragment comprises a variable domain that comprises:

(A) CDR_1 (**SEQ ID NO: 21**), CDR_2 (**SEQ ID NO: 23**) and CDR_3 (**SEQ ID NO: 25**) of the light chain of BRCA69D and CDR_1 (**SEQ ID NO: 29**), CDR_2 (**SEQ ID NO: 31**) and CDR_3 (**SEQ ID NO: 33**) of the heavy chain of BRCA69D;

(B) CDR_1 (**SEQ ID NO: 5**), CDR_2 (**SEQ ID NO: 7**) and CDR_3 (**SEQ ID NO: 9**) of the light chain of BRCA84D and CDR_1 (**SEQ ID NO: 13**), CDR_2 (**SEQ ID NO: 15**) and CDR_3 (**SEQ ID NO: 17**) of the heavy chain of BRCA84D; or

(C) CDR_1 (**SEQ ID NO: 37**), CDR_2 (**SEQ ID NO: 39**) and CDR_3 (**SEQ ID NO: 41**) of the light chain of PRCA157 and CDR_1 (**SEQ ID NO: 45**), CDR_2 (**SEQ ID NO: 47**) and CDR_3 (**SEQ ID NO: 49**) of the heavy chain of PRCA157.

[0040] The disclosure further concerns a dual affinity retargeting reagent (DART™), the reagent comprising:

(A) a polypeptide chain I that comprises an immunoglobulin VL epitope binding domain specific for binding B7-H3 and a VH epitope binding domain specific for binding a molecule other than B7-H3; and

(B) a polypeptide chain II that comprises an immunoglobulin VH epitope binding domain specific for binding B7-H3 and a VL epitope binding domain specific for binding the molecule other than B7-H3;

wherein the polypeptide chains I and II are associated together so as to form functional epitope binding domains capable of binding to B7-H3 and the molecule other than B7-H3.

[0041] The disclosure further concerns the above-described dual affinity retargeting reagent (DART™), wherein the molecule other than B7-H3 that may be bound by the DART™ is a hapten, and particularly wherein the hapten is fluorescein isothiocyanate.

[0042] The disclosure further concerns the above-described dual affinity retargeting reagent (DART™), wherein the molecule other than B7-H3 that may be bound by the DART™ is a T-Cell Receptor or the NKG2D receptor.

[0043] The disclosure further concerns the above-described dual affinity retargeting reagent (DART™), wherein the molecule other than B7-H3 that may be bound by the DART™ is a tumor-associated antigen, and particularly, wherein the tumor-associated antigen is selected from the group consisting of A33; ADAM-9; ALCAM; BAGE; beta-catenin; CA125; Carboxypeptidase M; CD103; CD19; CD20; CD22; CD23; CD25; CD27; CD28; CD36; CD40/CD154; CD45; CD46; CD5; CD56; CD79a/CD79b; CDK4; CEA; CTLA4; Cytokeratin 8; EGF-R; EphA2; ErbB1; ErbB3; ErbB4; GAGE-1; GAGE-2; GD2/GD3/GM2; gp100; HER-2/neu; human papillomavirus-E6; human papillomavirus-E7; Integrin Alpha-V-Beta-6; JAM-3; KID3; KID31; KSA (17-1A); LUCA-2; MAGE-1; MAGE-3; MART; MUC-1; MUM-1; N-acetylglucosaminyltransferase; Oncostatin M; p15; PIPA; PSA; PSMA; ROR1; sTn; TNF-ß receptor; TNF-α receptor; TNF-γ receptor; Transferrin Receptor; and VEGF receptor.

[0043a] In one aspect, there is provided a nucleic acid molecule that encodes a polypeptide chain of the diabody as defined herein.

[0044] The disclosure further concerns a nucleic acid molecule that encodes a polypeptide chain of any of the above-described dual affinity retargeting reagents (DART™s).

[0044a] In one aspect, there is provided a pharmaceutical composition comprising (i) a therapeutically effective amount of the diabody as defined herein and (ii) a pharmaceutically acceptable carrier**..**

[0045] The disclosure further concerns a pharmaceutical composition comprising (i) a therapeutically effective amount of any of the above-described isolated antibodies or immunoreactive fragments or dual affinity retargeting reagents (DART™s) and (ii) a pharmaceutically acceptable carrier.

[0046] The disclosure further concerns the above-described pharmaceutical composition, wherein the antibody is a humanized antibody that comprises:

(A) a variable domain that comprises CDR_1 (**SEQ ID NO: 5**), CDR_2 (**SEQ ID NO: 7**) and CDR_3 (**SEQ ID NO: 9**) of the light chain of BRCA84D and CDR_1 (**SEQ ID NO: 13**), CDR_2 (**SEQ ID NO: 15**) and CDR_3 (**SEQ ID NO: 17**) of the heavy chain of BRCA84D; and

(B) an Fc region modification that comprises the substitutions: L235V, F243L, R292P, Y300L, and P396L.

[0047] The disclosure further concerns the above-described pharmaceutical composition, wherein the antibody is a humanized antibody that comprises:

(A) a variable light chain having the amino acid sequence of hBRCA84D-2 VL (**SEQ ID NO: 89**);

(B) a variable heavy chain having the amino acid sequence of hBRCA84D-2 VH (**SEQ ID NO: 99**); and

(C) an Fc-region having the substitutions: L235V, F243L, R292P, Y300L, and P396L.

[0048] The disclosure further concerns any of the above-described pharmaceutical compositions, which further comprises one or more additional anti-cancer agents, and particularly wherein the additional anti-cancer agent is a chemotherapeutic agent, a radiation therapeutic agent, a hormonal therapeutic agent, or an immunotherapeutic agent.

[0048a] In one aspect, there is provided the use of the diabody as defined herein, or the pharmaceutical composition as defined herein, in an *ex vivo* method for the diagnosis of cancer, wherein said diabody is detectably labeled

[0049] The disclosure further concerns the use of any of the above-described antibodies or immunoreactive fragments or dual affinity retargeting reagents (DART™s) in the diagnosis of cancer, wherein the isolated antibody, immunoreactive fragment, or DART™ is detectably labeled.

[0050] The disclosure further concerns the above-described use characterised in that the cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a dhordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a

multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious unveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0050a] In one aspect, there is provided the use of the diabody as defined herein, or the pharmaceutical composition as defined herein, in the preparation of a medicament for the treatment of cancer in a patient.

[0051] The disclosure further concerns the use of any of the above-described antibodies or immunoreactive fragments or dual affinity retargeting reagents (DART™s) in the preparation of a medicament for the treatment or the prevention of cancer in a patient. The disclosure further concerns such uses characterised in that the cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a dhordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious unveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0052] The disclosure further concerns the above described uses characterised in that the use further comprises administration of one or more additional cancer therapies selected from the group consisting of chemotherapy, immunotherapy, radiation therapy, hormonal therapy, and surgery.

What is Claimed Is:

Claim 1. A diabody comprising:

(A) a polypeptide chain I that comprises an immunoglobulin VL epitope binding domain specific for binding B7-H3 and a VH epitope binding domain specific for binding a molecule other than B7-H3; and

(B) a polypeptide chain II that comprises an immunoglobulin VH epitope binding domain specific for binding B7-H3 and a VL epitope binding domain specific for binding said molecule other than B7-H3;

wherein said polypeptide chains I and II are associated together so as to form functional epitope-binding domains capable of binding to B7-H3 and said molecule other than B7-H3, and wherein:

(1) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 21), CDR_2 (SEQ ID NO: 23) and CDR_3 (SEQ ID NO: 25), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 29), CDR_2 (SEQ ID NO: 31) and CDR_3 (SEQ ID NO: 33); or

(2) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 5), CDR_2 (SEQ ID NO: 7) and CDR_3 (SEQ ID NO: 9), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 13), CDR_2 (SEQ ID NO: 15) and CDR_3 (SEQ ID NO: 17); or

(3) said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 37), CDR_2 (SEQ ID NO: 39) and CDR_3 (SEQ ID NO: 41), and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 45), CDR_2 (SEQ ID NO: 47) and CDR_3 (SEQ ID NO: 49).

Claim 2. The diabody of claim 1, wherein said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 21), CDR_2 (SEQ ID NO: 23) and CDR_3 (SEQ ID NO: 25) and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 29), CDR_2 (SEQ ID NO: 31) and CDR_3 (SEQ ID NO: 33).

Claim 3. The diabody of claim 1, wherein said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 5), CDR_2 (SEQ ID NO: 7) and CDR_3 (SEQ ID NO: 9) and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 13), CDR_2 (SEQ ID NO: 15) and CDR_3 (SEQ ID NO: 17).

Claim 4. The diabody of claim 1, wherein said VL epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 37), CDR_2 (SEQ ID NO: 39) and CDR_3 (SEQ ID NO: 41) and said VH epitope binding domain specific for binding B7-H3 comprises the amino acid sequences of CDR_1 (SEQ ID NO: 45), CDR_2 (SEQ ID NO: 47) and CDR_3 (SEQ ID NO: 49).

Claim 5. The diabody of claim 1, which comprises:

(A) a light chain variable domain having the amino acid sequence of SEQ ID NO: 89; and

(B) a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 99.

Claim 6. The diabody of any one of claims 1-5, wherein said diabody comprises at least a portion of an Fc domain.

Claim 7. The diabody of any one of claims 1-6, wherein said diabody comprises a variant Fc domain comprising at least one amino acid modification(s) relative to a wild-type Fc domain, said amino acid modification(s) comprising amino acid modification(s) that alters the affinity or avidity of said variant Fc domain for binding to an FcγR such that said diabody exhibits enhanced effector function relative to said wild-type Fc domain.

Claim 8. The diabody of claim 7, wherein said Fc domain modification(s) comprises:

(A) at least one substitution selected from the group consisting of:

(1) F243L;

(2) D270E;

(3) R292P;

(4) S298N;

(5) Y300L;

(6) V305I;

(7) A330V; and

(8) P396L;

(B) at least one substitution of two amino acid residues, said substitutions being selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P; and

(3) R292P and V305I;

(C) at least one substitution of three amino acid residues, said substitutions being selected from the group consisting of:

(1) F243L, R292P and Y300L;

(2) F243L, R292P and V305I;

(3) F243L, R292P and P396L; and

(4) R292P, V305I and P396L;

(D) at least one substitution of four amino acid residues, said substitutions being selected from the group consisting of:

(1) F243L, R292P, Y300L and P396L; and

(2) F243L, R292P, V305I and P396L;

or

(E) a substitution of at least the five amino acid residues: F243L, R292P, Y300L, V305I and P396L;

wherein said numbering is according to the Kabat numbering scheme.

Claim 9. The diabody of claim 7, wherein said Fc domain modification(s) comprises substitutions of:

(A) F243L, R292P, and Y300L;

(B) L235V, F243L, R292P, Y300L, and P396L; or

(C) F243L, R292P, Y300L, V305I, and P396L;

wherein said numbering is according to the Kabat numbering scheme.

Claim 10. The diabody of any one of claims 1-9, wherein:

(A) said polypeptide chain I additionally comprises an E-coil domain and said polypeptide chain II additionally comprises a K-coil domain; or

(B) said polypeptide chain I additionally comprises a K-coil domain and said polypeptide chain II additionally comprises an E-coil domain.

Claim 11. The diabody of claim 10, wherein:

(A) said E-coil domain comprises the amino acid sequence of SEQ ID NO:63; or

(B) said K-coil domain comprises the amino acid sequence of SEQ ID NO:64.

Claim 12. The diabody of any one of claims 1-11, wherein said molecule other than B7-H3 is a hapten.

Claim 13. The diabody of claim 12, wherein said hapten is fluorescein isothiocyanate.

Claim 14. The diabody of any one of claims 1-11, wherein said molecule other than B7-H3 is a T-Cell Receptor, a T-Cell Co-Receptor, or the NKG2D receptor.

Claim 15. The diabody of any one of claims 1-11, wherein said molecule other than B7-H3 is a tumor-associated antigen.

Claim 16. The diabody of claim 15, wherein said tumor-associated antigen is selected from the group consisting of A33; ADAM-9; ALCAM; BAGE; beta-catenin; CA125; Carboxypeptidase M; CD103; CD19; CD20; CD22; CD23; CD25; CD27; CD28; CD36; CD40/CD154; CD45; CD46; CD5; CD56; CD79a/CD79b; CDK4; CEA; CTLA4; Cytokeratin 8; EGF-R; EphA2; ErbB1; ErbB3; ErbB4; GAGE-1; GAGE-2; GD2/GD3/GM2; gp100; HER-2/neu; human papillomavirus-E6; human papillomavirus-E7; Integrin Alpha-V-Beta-6; JAM-3; KID3; KID31; KSA (17-

1A); LUCA-2; MAGE-1; MAGE-3; MART; MUC-1; MUM-1; N-acetylglucosaminyltransferase; Oncostatin M; p15; PIPA; PSA; PSMA; ROR1; sTn; TNF-ß receptor; TNF-α receptor; TNF-γ receptor; Transferrin Receptor; and VEGF receptor.

Claim 17. A nucleic acid molecule that encodes a polypeptide chain of the diabody of any one of claims 1-16.

Claim 18. A pharmaceutical composition comprising (i) a therapeutically effective amount of the diabody of any one of claims 1-16 and (ii) a pharmaceutically acceptable carrier.

Claim 19. The pharmaceutical composition of claim 18, which further comprises an anti-cancer agent.

Claim 20. The pharmaceutical composition of claim 19, wherein said anti-cancer agent is a chemotherapeutic agent, a radiation therapeutic agent, a hormonal therapeutic agent, a toxin or an immunotherapeutic agent.

Claim 21. The pharmaceutical composition of claim 20, wherein said anti-cancer agent is a toxin selected from the group consisting of: a taxane, a maytansinoid, an auristatin, a calicheamicin, an anthracycline, a CC-1065 analog, docetaxel, a cathepsin, ricin, gelonin, *Pseudomonas* exotoxin, diphtheria toxin, RNase, and a toxic radioisotope.

Claim 22. Use of the diabody of any one of claims 1-16, or of the pharmaceutical composition of any one of claims 18-21, in an *ex vivo* method for the diagnosis of cancer, wherein said diabody is detectably labeled.

Claim 23. The use of claim 22, characterised in that said cancer is selected from the group consisting of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell

carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

Claim 24. Use of the diabody of any one of claims 1-16, or of the pharmaceutical composition of any one of claims 18-21, in the preparation of a medicament for the treatment of cancer in a patient.

Claim 25. The use of claim 24, characterised in that said cancer is selected from the group consisting of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a

multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.