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(54) Title: COMBINATION THERAPY WITH NOTCH AND PD-1 OR PD-L1 INHIBITORS

(57) Abstract: The present invention provides medicaments for use in treating and methods of treating T- cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma in a patient comprising combination therapy with 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxoethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and a PD-1 or a PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.



COMBINATION THERAPY WITH NOTCH AND PD-1 OR PD-L1 INHIBITORS

The present invention relates to cancer therapy with 4,4,4-trifluoro-N-[(1S)-2-
[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-
5 methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate
thereof (Compound A) and a Programmed Death Receptor 1 (PD-1) inhibitor, or a
Programmed Death Receptor Ligand 1 (PD-L1) inhibitor and to methods of using
combinations to treat cancer.

4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-
10 d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically
acceptable salt or hydrate thereof, is a Notch pathway signaling inhibitor compound. Notch
signaling plays an important role during development and tissue homeostasis. Dysregulation
of Notch signaling due to mutation, amplification, or overexpression of ligands and/or
receptors, is implicated in a number of malignancies. Inhibition of Notch signaling is a
15 potential target for the development of cancer therapeutics. Compound A and methods of
making and using this compound, including for the treatment of T-cell acute lymphoblastic
leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous
leukemia, erythroleukemia, breast cancer, ovarian cancer, melanoma, lung cancer, pancreatic
cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate
20 cancer, liver cancer, squamous cell carcinoma (oral), skin cancer and medulloblastoma are
disclosed in WO 2013/016081, and for treating leiomyosarcoma in PCT/US2016/026119.
Compound A is being investigated in a phase 1 clinical trial and expansion cohorts having a
defined molecular pathway alteration, or a tissue based malignant tumor, and in combination
with other specifically identified anticancer agents against specified tumor types showing
25 mutations, amplification, or gene expression alterations related to Notch pathway signaling,
and in a clinical trial in patients with T-cell acute lymphoblastic leukemia or T-cell
lymphoblastic lymphoma (T-ALL/T-LBL).

Tumor cells escape detection and elimination by the immune system through various
mechanisms. Endogenously, immune checkpoint pathways are used in maintenance of self-

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tolerance and control of T cell activation. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway contributes to inhibition of active T-cell immune surveillance of tumors. Inhibition of PD-1 or PD-L1, has been shown to restore immune mediated destruction of tumors. Clinical research has found that targeting PD-1 or PD-L1 with antagonist antibodies releases the PD-1 pathway mediated inhibition of the immune response, including the anti-tumor response.

Notch pathway signaling is reported to be a regulator of PD-1 expression by activated CD8⁺ T cells, Mathieu et al, *Immunology and Cell Biology*, 2013, 91: 82-88. Despite existing treatment options for patients with cancer, there continues to be a need for new and different therapies affording one or both of enhanced efficacy and lower toxicity. Current immunotherapies have shown a benefit in a subset of cancer types and only in a subset of patients. Novel therapies or combination strategies are needed to improve the overall response against specific cancers or to facilitate extension of these treatments into cancers that may currently be less responsive to either agent alone.

It is believed the present invention provides beneficial therapeutic effects from the combined activity of Compound A and anti-PD-1 or PD-L1 monoclonal antibody inhibitor activity against T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumors, soft tissue sarcoma, and adenoid cystic carcinoma as compared to the therapeutic effects provided by either agent alone.

One aspect of the present invention provides a method of treating T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia,

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acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma in a patient comprising administering to a patient in need of treatment an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

A further aspect of the present invention provides a method of treating colorectal cancer in a patient, comprising administering to the patient in need of treatment an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

Another aspect of the present invention provides a method of treating T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma in a patient, comprising administering to a patient in need of treatment, simultaneously, separately, or sequentially, an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-

hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

5 Another aspect of the present invention provides a method of treating colorectal cancer in a patient, comprising administering to a patient in need of treatment, simultaneously, separately, or sequentially, an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an
10 effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

A further aspect of the present invention provides a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof;
15 and a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab; for simultaneous, separate, or sequential use in the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma,
20 lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma.

25 Another aspect of the present invention provides a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof; and a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab,

durvalumab, and avelumab; for simultaneous, separate, or sequential use in the treatment of colorectal cancer.

A further aspect of the present invention provides: use of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament; and

use of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab for the manufacture of a medicament;

for the simultaneous, separate, or sequential treatment of T-cell acute lymphoblastic

leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma.

A further aspect of the present invention provides: use of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament; and

use of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab for the manufacture of a medicament;

for the simultaneous, separate, or sequential treatment of colorectal cancer.

Another aspect of the present invention is a commercial package comprising a separate composition of each of the therapeutic agents together with instructions for simultaneous, separate or sequential administration for use in treating T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple

negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic
5 cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma.

A still further aspect of the present invention is a commercial package comprising a separate composition of each of the therapeutic agents together with instructions for simultaneous, separate or sequential administration for use in treating colorectal cancer.

10 The compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, (Compound A) has the CAS registry number 142138-81-4. Alternatively, the compound may be named: N-[(1S)-2-[[[(7S)-6,7-dihydro-5-(2-hydroxyethyl)-6-oxo-5H-pyrido[3,2-a][3]benzazepin-7-yl]amino]-1-methyl-2-oxoethyl]-4,4,4-trifluorobutanamide. Other names may be used to unambiguously identify
15 Compound A.

The terms, as used herein, "PD-1 inhibitor" and PD-L1 inhibitor" mean a fully human, or humanized IgG, , optionally optimized, monoclonal antibody.

PD-1 inhibitors include nivolumab and pembrolizumab. Nivolumab, (Opdivo®) is
20 also known as iMDX- 1106, MDX-1106-04, ONO-4538, or BMS-936558 and has a CAS Registry Number: of 946414-94-4. Nivolumab is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO2006/121168. Pembrolizumab, (Keytruda®) (formerly lambrolizumab), also known as Merck 3745, MK-
25 3475 or SCH-900475, is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab is disclosed in Hamid, O. et al., *New England Journal of Medicine*, 2013, 369(2): 134-44; WO2009/114335; and US 8,354,509. Other anti- PD-1 antibodies are disclosed in US 8,609,089; US 2010028330; and/or US 20120114649.

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PD-L1 inhibitors include YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, and MDX-1105. YW243.55.S70 is an anti-PD-L1 antibody described in WO2010/077634 and US20100203056. MDPL3280A (also known as RG7446, RO5541267, atezolizumab, Tecentriq™) is a fully humanized Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MPDL3280A and other human monoclonal antibodies to PD-L1 are disclosed in US 7,943,743 and US 20120039906. MEDI-4736 (also known as durvalumab) is an Fc optimized IgG1 monoclonal antibody to PD-L1 and is described in WO2011/066389. MSB-0010718C (also known as avelumab) is a fully human IgG1 monoclonal antibody to PD-L1 and is described in WO2013/079174. MDX-1105, also known as BMS-936559, is a fully human IgG4 monoclonal anti-PD-L1 antibody described in WO2007/005874.

As used herein, the term "patient" refers to a mammal, preferably a human.

"Therapeutically effective amount" or "effective amount" means the dosage of Compound A, or pharmaceutically acceptable salt or hydrate thereof, or pharmaceutical composition containing Compound A, or pharmaceutically acceptable salt or hydrate thereof, and the dosage of a PD-1 or PD-L1 inhibitor, or pharmaceutical composition containing a PD-1 or PD-L1 inhibitor necessary to inhibit tumor cell growth and eliminate or slow or arrest the progression of the cancer in a patient. Dosages of Compound A, or a pharmaceutically acceptable salt or hydrate thereof, are in the range of 2.5 mg/patient to 75 mg/patient once per day every other day over a five day period followed by two days without dosing (T.I.W.). Dosages of a PD-1 or PD-L1 inhibitor, unless otherwise specified on the label, are in the range of 1-3 mg/kg intravenous infusion over 30 to 60 minutes once every 14-21 days. Preferred dosages of Compound A, or a pharmaceutically acceptable salt or hydrate thereof, are in the range of 10 mg to 50 mg T.I.W. The exact dosage required to treat a patient and the length of treatment time will be determined by a physician in view of the stage and severity of the disease as well as the specific needs and response of the individual patient. The dosing administration may be adjusted to provide a more optimal therapeutic benefit to a patient and to manage or ameliorate any drug related toxicities. Alternative dosing schedules such as once per day (QD), twice per day (B.I.D.), three times a day

(T.I.D.); dosing once per day every other day (Q2D); or every third day (Q3D) may be appropriate for Compound A. Dosing administration for PD-1 or PD-L1 inhibitors may be adjusted, including withholding a dose or permanently discontinuing further dosing to manage or ameliorate drug related toxicities.

5 A combination therapy of the present invention is carried out by administering to a T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non
10 small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic
 cholangiocarcinoma, desmoid tumor, soft ntissue sarcoma, and adenoid cystic carcinoma preferably a soft tissue sarcoma patient requiring treatment, an effective amount of
 Compound A, or a pharmaceutically acceptable salt or hydrate thereof, once per day every
15 other day over five days and two days without dosing each week (7-days) over a 28 day cycle and a PD-1 or PD-L1 inhibitor at 1-3 mg/kg over 30-60 minutes once every 14 -21
 days.

 The terms "treatment," "treat," and "treating," are meant to include the full spectrum of intervention for the cancer from which the patient is suffering, such as administration of
20 Compound A and A PD-1 or PD-L1 inhibitor to alleviate, slow, stop, or reverse one or more of the symptoms and to delay, stop, or reverse progression of the cancer even if the cancer is not actually eliminated.

 Compound A or a pharmaceutically acceptable salt or hydrate thereof, is preferably formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and
25 administered by a variety of routes. Preferably, such compositions are for oral administration. A PD-1 or PD-L1 inhibitor is preferably formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and administered by a parenteral route, preferably intravenous infusion. Preferably, such compositions may be a lyophilized

powder or a liquid composition. Reconstitution or dilution to ready for administration dosages are according to label or by routine skill in the art. Such pharmaceutical compositions and processes for preparing them are well known in the art. *See, for example*, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, 5th edition, Rowe et al., Eds.,
5 Pharmaceutical Press (2006); and REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Troy, *et al.*, Eds., 21st edition, Lippincott Williams & Wilkins (2006).

Compound A is capable of reaction with a number of inorganic and organic counterions to form pharmaceutically acceptable salts. Such pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. *See, for*
10 *example*, P. Stahl, *et al.*, HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

The efficacy of the combination treatment of the invention can be measured by various endpoints commonly used in evaluating cancer treatments, including but not
15 limited to, tumor regression, tumor weight or size shrinkage, time to progression, overall survival, progression free survival, overall response rate, duration of response, inhibition of metastatic spread without tumor regression, and PET/CT imaging.

The terms "combination," "therapeutic combination" and "pharmaceutical combination" refer to a non-fixed dose combination, optionally packaged together with
20 instructions for combined administration where the individual therapeutic agents, Compound A, or a pharmaceutically acceptable salt or hydrate thereof, and a PD-1 or PD-L1 inhibitor may be administered independently at the same time or separately within time intervals that allow the therapeutic agents to exert a cooperative effect.

The term "simultaneous" administration means the administration of each of
25 Compound A and a PD-1 or PD-L1 inhibitor to a patient in a single action such as where each of Compound A and a PD-1 or PD-L1 inhibitor are administered independently at substantially the same time or separately within time intervals that allow Compounds A and a PD-1 or PD-L1 inhibitor to show a cooperative therapeutic effect.

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The term “separate” administration means the administration of each of Compound A and a PD-1 or PD-L1 inhibitor to a patient from non-fixed dose dosage forms simultaneously, substantially concurrently, or sequentially in any order. There may, or may not, be a specified time interval for administration of each Compound A and a PD-1 or PD-L1 inhibitor.

The term “sequential” administration means the administration of each of Compound A and a PD-1 or PD-L1 inhibitor to a patient from non-fixed (separate) dosage forms in separate actions. The two administration actions may, or may not, be linked by a specified time interval. For example, administering Compound A T.I.W. and administering a PD-1 or PD-L1 inhibitor over a specified time such as once every 14 to 21 days..

The phrase “in combination with” includes the simultaneous, separate, and sequential administration of each of Compound A and a PD-1 or PD-L1 inhibitor to a cancer patient in need of treatment, particularly a colorectal cancer patient.

The term “co-administration” or “combined administration” encompasses the administration of the therapeutic agents to a single patient, and include treatment regimens in which the agents may be administered by different routes of administration or at different times.

The beneficial action of two therapeutic agents producing an effect in a single patient which is greater than the simple additive effects of each agent administered alone may be calculated, for example, using suitable methods known in the art such as the Sigmoid-Emax equation (Holford and Scheiner, *Clin. Pharmacokinet.*, 1981, 6: 429-453), the equation of Loewe additivity (Loewe and Muischenk, *Arch. Exp. Pathol. Pharmacol.*, 1926, 114: 313-326), the median-effect equation (Chou and Talalay, *Adv. Enzyme Regul.*, 1984, 22: 27-55), and the Bliss Independence method, or known equivalents. Each equation may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of a drug combination as additive, within a biologically relevant range of additive, less than additive, or greater than additive.

The oncogenic role of Notch was first reported in human T-cell leukemia involving a translocation of the Notch1 intracellular domain to the T-cell receptor- β promoter region, resulting in the over expression of Notch1 intracellular domain (Grabher et al. Nature Review Cancer, 2006(6):347-359; Weng et al. Science, 2004(306):269-271). Over expression of

5 Notch1 intracellular domain in hematopoietic progenitor cells of mice caused the mice to exhibit T-cell acute lymphoblastic leukemia similar to humans. In addition to T-cell acute lymphoblastic leukemia, there is increasing evidence that Notch signals are oncogenic in other cancers through multiple mechanisms including receptor amplification and over expression of ligands and/or receptors including acute lymphoblastic leukemia, chronic

10 lymphoblastic leukemia (Rosati et al, Blood, 2009(113): 856-865), acute myelogenous leukemia (Sliwa et al. Int J Clin Exp Pathol, 2014(7(3)): 882-889), chronic myelogenous leukemia (Nakahara et al. Blood, 2010(115(14)): 2872-2881), and erythroleukemia (Robert-Moreno et al, Leukemia, 2007(21): 1496-1503). Aberrant constitutive Notch signaling due to mutation or over expression of ligands and/or receptors is also implicated in a number of

15 solid tumor malignancies including triple negative breast cancer (Stoeck et al, Cancer Discovery, 2014(4): 1154-1167), breast cancer, ovarian cancer (Park et al. Cancer Research, 2006(66):6312-6318), melanoma (Gast et al. Genes, Chromosomes & Cancer, 2010(49):733-745), lung cancer, non small cell lung cancer (Westhoff et al. PNAS, 2009(106):22293-22298), pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical

20 cancer, prostate cancer, liver cancer, squamous cell carcinoma (oral), skin cancer and medulloblastoma (Rangathan et al., Nature Review Cancer, 2011(11):338-351 and Supplementary information S1 (table)). Aberrant constitutive Notch signaling due to mutation or over expression of ligands and/or receptors is also implicated in angiosarcoma (Ravi et al, J Clin Oncol, 2007, (25(18S, June 20 Supplement)): Abstract 10030),

25 rhabdomyosarcoma (Belyea et al, Clin Cancer Res, 2011(17(23)): 7324-7336; Roma et al, Clin Cancer Res, 2011(17(3)): 505-513), liposarcoma (J Clin Oncol, 2009, (27(15S, Supplement)): Abstract 10526), malignant fibrous histiocytoma (Wang et al, Cancer Res, 2012, (72): 1013-1022), hepatocellular carcinoma (Villanueva et al, Gastroenterology, 2012, (143): 1660-1669), intrahepatic and extrahepatic cholangiocarcinoma (Wu et al, Int J Exp

Pathol, 2014, (7(6)): 3272-3279; Sekiya et al, J Clin Invest, 2012, (122(11)): 3914-3918; Yoon et al, World J Gastroenterol, 2011, (17(35)): 4023-4030), and adenoid cystic carcinoma (Bell et al, Annals of Diagnostic Pathology, 2014, (18): 10-13; Stoeck et al, Cancer Discov, 2014, (4): 1154-1167).

5 The nature of cancer is multifactorial. Under appropriate circumstances, therapeutic agents with different mechanisms of action may be combined. However, only considering a combination of therapeutic agents having different modes of action does not necessarily lead to combinations with advantageous effects. Specific therapeutic agents affording demonstrated beneficial effects (therapeutic effect such as enhanced efficacy and/or lower
10 toxicity) compared with monotherapy of only one of the therapeutic agents is preferred.

 The combination of the present invention is believed suitable for the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non
15 small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft ntissue sarcoma, and adenoid cystic carcinoma, and particularly suitable for the treatment of soft tissue sarcoma patients, who have failed
20 standard therapy. This includes patients having cancer showing resistance to monotherapy or showing resistance to combinations different from those of the present invention.

 The terms “Complete Response” (CR), “Partial Response” (PR), “Progressive Disease” (PD), “Stable Disease” (SD), “Objective Response” (OR) are used consistent with definitions according to RECIST v1.1, Eisenhauer et al., *European Journal of*
25 *Cancer*, 2009, 45, 228-247.

 The term “time to disease progression” (TTP) refers to the time, generally measured in weeks or months, from the time of initial treatment, until the cancer progresses (see RECIST v1.1 definition for progressive disease) which is at

least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. Such progression is evaluated by a skilled clinician.

The term “extending TTP” refers to increasing the time to disease progression in a treated patient relative to i) an untreated patient, or ii) a patient treated with less than both of Compound A and a PD-1 or PD-L1 inhibitor.

The term “survival” refers to the patient remaining alive, and includes overall survival as well as progression free survival.

The term, “overall survival” refers to the patient remaining alive for a defined period of time, such as 1 year, 5 years, etc. from the time of diagnosis or treatment.

The term, “progression free survival” refers to the patient remaining alive, without the cancer progressing.

As used herein, the term “extending survival” is meant increasing overall or progression free survival in a treated patient relative to i) an untreated patient, ii) a patient treated with less than both of Compound A and a PD-1 or PD-L1 inhibitor, or iii) a control treatment protocol. Survival is monitored for a defined period of time, such as one month, six months, 1 year, 5 years, or 10 years, etc., following the initiation of treatment or following the initial diagnosis of cancer.

The term “primary tumor” or “primary lesion” is meant the original cancer and not a metastatic tumor or lesion located in another tissue, organ, or location in the patient’s body.

In one embodiment, the dose of Compound A is escalated until the Maximum Tolerated Dosage is reached, and a PD-1 or PD-L1 inhibitor of the present invention is administered with a fixed dose. Alternatively, Compound A may be administered in a fixed dose and the dose of a PD-1 or PD-L1 inhibitor may be escalated. Each patient may receive doses of Compound A and/or a PD-1 or PD-L1 inhibitor either daily or intermittently. The

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efficacy of the treatment may be determined in such studies, e.g., after 12, 18 or 24 weeks by evaluation of symptom scores every 6 weeks.

Compound A may be prepared by the procedures described in WO 2013/016081.

5 A PD-1 or PD-L1 inhibitor may be prepared by the procedures described in US 8,008,449 and WO2006/121168; Hamid, O. et al., *New England Journal of Medicine*, 2013, 369 (2): 134-44; WO2009/114335, and US 8,354,509; US 8,609,089, US 2010028330, and/or US 20120114649; WO2010/077634; US2010203056; US 7,943,743; US 20120039906; WO2011/066389; WO2013/079174; and WO2007/005874; or by procedures
10 well known and routinely used by one skilled in the art.

The following Examples illustrate the activity of each of Compound A alone, a PD-1 inhibitor alone, or a PD-L1 inhibitor alone, and the combination of Compound A and a PD-1 or PD-L1 inhibitor.

15

Biological Example 1

In-vivo study:

20 For in-vivo studies 1×10^6 CT26 cells (ATCC® CRL2639™) a colorectal cancer cell line, in 0.2 mL Hank's Balanced Salt Solution (HBSS) is implanted by subcutaneous injection in the hind leg of 6-8 weeks of age BALB/C female mice (Harlan Laboratories). Mice are fed *ad libitum* on normal chow. Treatment is initiated on day 6 of tumor implantation with oral administration (gavage) of Compound A in 1% Sodium
25 carboxymethyl cellulose (Na-CMC) in 0.25% Tween® 80, or intraperitoneal injection of mouse anti PD-L1 antibody (10F.9G2, BioXcell Catalogue #: BE0101) in phosphate buffered saline (PBS) or intraperitoneal injection of mouse anti PD-1 (CD279) antibody (Clone: RMP1-14, BioXCell#: BP0146-R) in PBS or their respective vehicle in 0.2 mL volume. Compound A is administered at 8 mg/kg on a Monday, Wednesday and Friday

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schedule for 2 weeks and 10F.9G2 and RMP1-14 are administered at 250 µg/dose/animal on Monday and Thursday schedule for 2 weeks.

Tumor growth and body weight are monitored over time to evaluate efficacy and signs of toxicity. Bidimensional measurements of tumors are performed twice a week and tumor
5 volumes are calculated based on the following formula: (Tumor Volume) = $[(L) \times (W^2) \times (\pi/6)]$ where L is mid-axis length and W is mid-axis width. Tumor volume data are transformed to a log scale to equalize variance across time and treatment groups. The log volume data are analyzed with a two-way repeated measures analysis of variance by time and treatment using the MIXED™ procedures in SAS™ software (version 8.2). The correlation
10 model for the repeated measures is spatial power. Least squares means from the repeated measures analysis, anti-logged to the tumor volume scale, are shown in Table 1. P-values for comparing each pair of groups on study day 20 are shown in Table 2. Test Groups are:

- 1: 1% CMC/0.25% Tween® 80/0.05% Antifoam, Monday-Wednesday-Friday x2, PO / PBS
Monday-Thursday x2, IP
- 15 2: Compound A , 8 mg/kg, Monday-Wednesday-Friday x2, PO
- 3: Compound B (PD-L1), 250 µg/dose, Monday-Thursday x2, IP
- 4: Compound C (PD-1), 250 µg/dose, Monday-Thursday x2, IP
- 5: Compound A, 8 mg/kg, Monday-Wednesday-Friday x2, PO / Compound B (PD-L1), 250 µg/dose, Monday-Thursday x2, IP
- 20 6: Compound A, 8 mg/kg, Monday-Wednesday-Friday x2, PO / Compound C (PD-1), 250 µg/dose, Monday-Thursday x2, IP

Tumor growth and body weight are monitored over time to evaluate efficacy and signs of toxicity. Bidimensional measurements of tumors are performed twice a week and tumor volumes are calculated based on the following formula: (Tumor Volume) = $[(L) \times$
25 $(W^2) \times (\pi/6)]$ where L is mid-axis length and W is mid-axis width. Tumor volume data are

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transformed to a log scale to equalize variance across time and treatment groups. The log volume data are analyzed with a two-way repeated measures analysis of variance by time and treatment using the MIXED™ procedures in SAS™ software (version 8.2). The correlation model for the repeated measures is spatial power. Treated groups are compared to the control group at each time point. The MIXED™ procedure is also used separately for each treatment group to calculate adjusted means and standard errors at each time point. Both analyses account for the autocorrelation within each animal and the loss of data that occurs when animals with large tumors are removed from the study early. The adjusted means and standard errors are plotted for each treatment group versus time. Antitumor activity is expressed as a tumor volume percentage for treatment versus control (% T/C) and is calculated by comparing tumor volume in the treatment group with vehicle treatment group. Percentage T/C and statistical significance value (p value) for the treatment groups is measured essentially as described above and summarized in Table 2.

Table 1. Tumor volume (mm³): Geometric Mean

Group	Study Days				
	8	10	14	17	20
1	52.92	99.25	486.99	1045.42	1643.20

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Vehicle					
2					
Compound A	47.96	88.80	376.50	751.13	1227.40
3					
Compound B	49.82	96.48	378.49	790.67	1313.36
4					
Compound C	45.30	87.73	241.50	491.72	622.56
5					
Compound A+B	42.79	88.58	221.73	321.19	472.83
6					
Compound A+C	47.88	102.62	245.30	501.45	569.20

Table 2.

Tumor volume all pairs comparison p value

Group	2 Compound A	3 Compound B	4 Compound C	5 Compound A+B	6 Compound A+C
1 Vehicle	0.26	0.362	<0.001	<0.001	<0.001
2 Compound A		0.828	0.009	<0.001	0.001

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3					
Compound B			0.005	<0.001	<0.001
4					
Compound C				0.036	0.455
5					
Compound A+B					0.17

Table 2 shows the combination of Compound A and PD-L1 (Group 5), in this test, demonstrated statistically significant tumor growth inhibition results over each of Compound A (Group 2) and PD-L1 alone (Group 3). The combination of Compound A and PD-1 (Group 6) demonstrated statistically significant growth inhibition results over Compound A (Group 2) alone, but not over PD-1 (Group 4) alone.

Combination analysis

Using the repeated measures analysis previously described, a contrast statement is used to test for an interaction effect on study day 20, using the two specific treatments (Compound A and PD-L1) that were combined. This test is statistically significant with $p = 0.008$, demonstrating better than additive, or synergistic activity, since the estimated mean tumor volume in the combination group (298 mm^3) is less than the expected additive tumor volume per the Bliss Independence method ($1134 \times 1069 / 1448 = 837 \text{ mm}^3$).

Using the repeated measures analysis previously described, a contrast statement is used to test for an interaction effect on study day 20, using the two specific treatments (Compound A and PD-1) that were combined. This test is not statistically significant with $p = 0.769$, demonstrating an additive effect, since the estimated mean tumor volume in the

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combination group (431 mm^3) is close to the expected additive tumor volume per the Bliss Independence method ($526 \times 1069 / 1448 = 389 \text{ mm}^3$).

Mechanism analysis

5 For mechanism analysis CT-26 tumors are excised on day 20, 1h following the last dose of Compound A. A small piece of approximately 30 mg is cut and stored in RNALater for gene expression analysis. The remainder of the tumor is processed for the flow-cytometry analysis.

10 *Flow-cytometry*

Tumors are weighed and then homogenized in 5 ml 4°C complete media (CM; RPMI-1640/10% fetal bovine serum (FBS)) through 100 μm strainers to produce single-cell suspensions. Cells are centrifuged for 5 minutes at $466 \times g$, 4°C ; the pellets are resuspended in fresh CM (0.5 – 3 ml, depending on pellet volume), and cells are counted using a Vi-Cell
15 XR (Beckman Coulter). An equal number of total cells per tumor (10×10^6) are transferred to 96-well V-bottom microplates (Fisher Scientific). Cells are centrifuged ($700 \times g$, 3 min., 4°C) and resuspended in 100 μl 1 $\mu\text{g/ml}$ Fc block in CM (anti-CD16/32 (clone 2.4G2); Tonbo Biosciences) for 30 minutes on ice. Cells are centrifuged ($700 \times g$, 3 minutes, 4°C) and resuspended in 100 μl of one of several fluochrome-conjugated surface marker antibody
20 cocktails [anti-CD3 (clone 145-2C11), -Ly-6G (clone 1A8), -CD11c (clone HL3), -CD45 (clone 30-F11) (BD Biosciences), anti-CD8 (clone 53-6.7) (Biolegend), -CD11b (clone M1/70), -CD3 (clone 145-2C11), -F4/80 (clone BM8), -CD4 (clone RM4-5), (eBioscience)] containing a fixable viability dye (eBioscience) and incubated for 30 minutes on ice covered from light. Cells are twice washed with 200 μl CM and centrifuged ($700 \times g$, 3 min., 4°C).
25 Following the second wash, cells are fixed, permeabilized, and intracellularly stained for Ki67 (clone SolA15) (eBioscience) using the Foxp3/Transcription Factor Staining Buffer Set

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(eBioscience), following the manufacturer's instructions with noted modifications. Briefly, cells are fixed in 100 μ l/well for 30 min., followed by 100 μ l/well permeabilization buffer with or without intracellular stain (depending on the staining panel used) for 30 min. Cells are twice washed with 200 μ l 1X permeabilization buffer and centrifuged (700 x g, 3 min., 4°C), followed by resuspension in PBS with 2% FBS. 1 x 10⁶ events, excluding debris, are captured for each sample using a 10-channel LSR II cytometer (BD Biosciences) and analyzed using FlowJo V.10.0.8 software. Data is represented as percent of tumor cells, with noted exceptions where represented as percent of parent population. Post-hoc t-test following ANOVA is used for statistical analysis between vehicle and treatment groups. The results are summarized in the Table 3.

Table 3.

Population n	Vehicle		Compound A		Compound B PD-L1 (10F.9G2)		Compound C PD-1 (RMPI-14)		Compound A + PD-L1 (10F.9G2)		Compound A + PD-1 (RMP1-14)	
	Mean % ± SEM	p valu e	Mean % ± SEM	p valu e	Mean % ± SEM	p valu e	Mean % ± SEM	p valu e	Mean % ± SEM	p valu e	Mean % ± SEM	p valu e
CD4+/Ki67+ (% of CD4+)	5.7 ± 0.9	n.s.	7.6 ± 0.5	n.s.	8.8 ± 1.2	0.02 2	13.7 ± 2.0	<0.0 01	14.1 ± 1.2	<0.0 01	16.3 ± 1.4	<0.0 01
CD8+/Ki67+ (% of CD8+)	21.8 ± 3.6	n.s.	23.1 ± 2.0	n.s.	24.1 ± 1.9	n.s.	32.1 ± 4.0	0.01 7	31.5 ± 1.2	0.00 5	34.4 ± 2.5	0.00 2
CD11b+ (% of Tumor)	1.8 ± 0.2	n.s.	2.9 ± 0.2	0.00 2	2.1 ± 0.2	n.s.	3.9 ± 0.3	<0.0 01	4.4 ± 0.5	<0.0 01	4.2 ± 0.6	<0.0 01
CD11b+F4/80+ (% of Tumor)	0.62 ± 0.11	n.s.	0.89 ± 0.15	-	0.67 ± 0.07	n.s.	1.87 ± 0.18	<0.0 01	1.75 ± 0.28	<0.0 01	1.77 ± 0.33	<0.0 01
CD11c+ (% of Tumor)	0.24 ± 0.04	n.s.	0.42 ± 0.06	0.03 5	0.27 ± 0.03	n.s.	0.31 ± 0.05	n.s.	0.46 ± 0.08	0.03 9	0.32 ± 0.07	n.s.

CD11b+L y- 6G+F4/80 - (% of Tumor)	0.61 ± 0.08	n.s.	1.12 ± 0.08	<0.0 01	0.76 ± 0.07	n.s.	0.99 ± 0.10	0.00 3	1.29 ± 0.16	<0.0 01	1.29 ± 0.19	<0.0 01
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The data in Table 3 shows elevated inflammatory response as demonstrated by intra-tumoral CD4+Ki67+ (activated CD4+ T-cells), CD8+Ki67+ (activated CD8+ T-cells), CD11b+ (myeloid cells), CD11b+F4/80+ (macrophages), CD11c+ (Dendritic cells), and CD11b+Ly-6G+F4/80- (Neutrophils).

5

Gene expression analysis

For RNA isolation from the tumor, approximately 30 mg tissue is cut. RNA is extracted by RNeasy Protocol (version Jan 2002) using RNeasy 96-well Column Plates (Qiagen, Valencia, CA; Cat# 74182) and QiaVac 96 vacuum manifold at 15 psi vacuum.

- 10 Briefly, tissues are homogenized in 800 μ L Buffer- RLT containing 1% β -mercaptoethanol in 2 mL Lysing Matrix-D® tubes (MP Biomedicals, Solon, OH; Cat# 6913-500, Lot# 6913-500-120156) in FP120 (ThermoFisher Scientific, Waltham, MA; Cat# 6001-120) or FastPrep-24 (MP Biomedicals; Cat#116003500) at speed 6.0 for two mixings each of 30 seconds. Tubes are centrifuged at 14,000 revolutions per minute (RPM) for 30 minutes.
- 15 Between 400- 600 μ L of supernatant is removed and mixed with equal volumes of 70% ethanol (Decon Labs, King of Prussia, PA; Cat#2401), and transferred onto 96-well RNeasy Plate. Any potential contaminating DNA is removed by additional DNase-I digestion (Qiagen, Cat# 79254) on the column as per supplier's protocol. Total RNA is extracted in two 40 μ L aliquots of DNase/RNase-free water. The total RNA concentration is estimated
- 20 using Nanodrop ND-1000 spectrophotometer by absorbance at 260nm (Thermo Scientific). Total RNA is stored at -80°C until needed for cDNA synthesis.

- The High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Framingham, MA; Cat# 4368813) is used to reverse transcribe 3 μ g total RNA in a final volume of 100 μ L in 96-Well PCR Plates (Molecular Bioproducts, San Diego, CA; Cat#
- 25 3419) using GeneAmp PCR System 9700 (Applied Biosystems) with following parameters:

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25°C for 10 minutes, 37°C for 2 hours, and 4°C for infinity. For long term storage, cDNA is stored at -30°C, and total RNA is stored at -80°C.

For Taqman procedure, 100 µL of cDNA is diluted with 200 µL RNase/DNase-free water in 96-Well Clear Optical Reaction Plate (Applied Biosystems, Cat# 4306737) and transferred to 2 mL RNase/DNase-free tubes (Ambion, Cat# AM12475). Taqman reaction is carried out using 2x Universal Buffer (Applied Biosystems, Cat# 4318157) in a final volume of 20 µL in 384-Well Clear Optical Reaction Plate (Applied Biosystems, Cat# 4309849). Samples are dispensed with Tecan Automated Pipetting Workstation (Tecan US Inc., Durham, NC; Model: Freedom Evo-100 or Evo-150), and plates are read in ABI Prism 9700HT SDS plate reader with following protocol settings: 50°C for 2 minutes, 95°C for 10 minutes, and 40 cycles at 95°C for 15 seconds and 60°C for 1 minute. The absolute C_T values are normalized based on a standard curve-based method. All calculations are done in Microsoft Excel spreadsheet template, and % inhibition is calculated from control values. Statistical significance is analyzed on version 11 JMP Software (SAS, Cary, NC). The results are described in Table 4 as a fold change compared to vehicle control. Statistically significant values of ≥1.5-fold (1.5X) are shown. No significant change in the expression of genes examined in Compound A and PD-L1 alone treatment groups. The data demonstrates increased expression of genes associated with intra-tumoral inflammation and T-cell activation when Compound A is combined with PD-L1 or PD1 antibody. All Taqman primers and probes listed below were purchased from Applied Biosystems Inc. (ABI) and their catalogue number listed in the table as ABI# along with summary of the results.

Table 4.

Gene	PD-L1+Compound A	PD1	PD1+Compound A	ABI #
Ccl2		1.5x		Mm00441242_m1
Ccl3		2.4x		Mm00441259_g1

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Ccl4		2.4x		Mm00443111_m1
Ccl5	6.5x	4.1x	4.6x	Mm01302427_m1
Infy	4.6x	4.8x	4.4x	Mm01168134_m1
Il2	6.6x	3.5x	4.1x	Mm00434256_m1
Il4	5.9x	2.6x	4.1x	Mm00445259_m1
Il5	2.4x			Mm00439646_m1
Il10		2.0x		Mm01288386_m1
Il12b	2.9x	2.1x		Mm01288989_m1
Il13	11.2x	5.0x	8.0x	Mm00434204_m1
Tnfα	2.6x	2.2x		Mm00443260_g1
Gzmb	2.0x	2.3x	2.3x	Mm00442834_m1
Tgfbr1			1.2x	Mm00436964_m1
Tgfbr2	2.4x			Mm03024091_m1
Pd-l1	3.2x	2.7x	3.2x	Mm00452054_m1
Pd-l2	11.0x	7.1x	6.8x	Mm00451734_m1
Pd-1	2.9x	3.5x		Mm01285676_m1
Arg	2.1x			Mm00477592_m1
iNos	5.8x	4.7x	5.9x	Mm00440502_m1
Ido	4.6x	3.5x	4.9x	Mm00492590_m1
Icam	2.5x	2.0x	1.9x	Mm00516023_m1
Cd3e		3.2x		Mm01179194_m1
Cd4	3.1x	2.6x		Mm00442754_m1
Cd8b1	3.2x	3.3x		Mm00438116_m1
Cd20	8.9x			Mm00545909_m1
Cd45		1.7x		Mm01293577_m1
Cd68	1.6x		1.6x	Mm03047343_m1
Cd69	1.8x	1.7x		Mm01183378_m1
Cd86	2.0x	1.6x		Mm00444543_m1
Foxp3	2.8x	2.1x	2.4x	Mm00475162_m1
Icos	4.0x	2.7x	2.8x	Mm00497600_m1
Lag3	2.9x	2.7x		Mm00493071_m1
Tim3	2.3x	2.2x	2.1x	Mm00454540_m1
Tim4		2.8x	2.3x	Mm00724709_m1
Cd40l	4.3x	2.7x	2.8x	Mm00441911_m1
Cd200r1	2.1x	1.8x	1.7x	Mm00491164_m1
Tnfsf4(Ox40l)	1.8x		2.0x	Mm00437214_m1
Tnfsf18(Gitrl)	2.2x		1.9x	Mm00839222_m1
Tnfrsf4(Ox40)	2.2x	1.7x	1.6x	Mm00442039_m1
Tnfrsf18(Gitr)	2.5x	2.2x	2.0x	Mm00437136_m1

WE CLAIM:

1. A method of treating a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma in a patient, comprising administering to a patient in need of treatment an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

2. The method of Claim 1 wherein said cancer is colorectal cancer.

3. A method of treating a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma in a patient in need of such treatment, comprising administering simultaneously, separately, or sequentially, an effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, and an effective amount of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.

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4. The method of Claim 3 wherein said cancer is a colorectal cancer.

5. The compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof; and a PD-1 or PD-L1 inhibitor

5 selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab for simultaneous, separate, or sequential use in the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, or adenoid cystic carcinoma.

6. The use of Claim 5 wherein said cancer is colorectal cancer.

15 7. Use of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament; and use of a PD-1 or PD-L1 inhibitor selected from pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab for the independent manufacture of a medicament; for the simultaneous, separate, or sequential treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small-cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor soft tissue sarcoma, or adenoid cystic carcinoma.

8. The use of Claim 7 wherein said cancer is colorectal cancer.