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DESCRIPTION

Field of the Disclosure

[0001] This disclosure relates to methods for treating a tumor in a subject comprising administering to the subject an anti-Programmed Death-1 (PD-1) antibody and an anti-CD30 antibody. In some embodiments, the tumor is derived from a lymphoma. In certain embodiments, the tumor is derived from a Hodgkin lymphoma, a non-Hodgkin lymphoma, or a combination thereof.

Background of the Disclosure

[0002] Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens potentially recognizable by the immune system (Sjoblom et al., (2006) Science 314:268-74). The adaptive immune system, comprised of T and B lymphocytes, has powerful anti-cancer potential, with a broad capacity and exquisite specificity to respond to diverse tumor antigens. Further, the immune system demonstrates considerable plasticity and a memory component. The successful harnessing of all these attributes of the adaptive immune system would make immunotherapy unique among all cancer treatment modalities.

[0003] Until recently, cancer immunotherapy had focused substantial effort on approaches that enhance anti-tumor immune responses by adoptive-transfer of activated effector cells, immunization against relevant antigens, or providing non-specific immune-stimulatory agents such as cytokines. In the past decade, however, intensive efforts to develop specific immune checkpoint pathway inhibitors have begun to provide new immunotherapeutic approaches for treating cancer, including the development of an antibody, ipilimumab (YERVOY®), that binds to and inhibits CTLA-4 for the treatment of patients with advanced melanoma (Hodi et al., 2010 N Engl J Med 363:711-23) and the development of antibodies, such as nivolumab and pembrolizumab (formerly lambrolizumab; USAN Council Statement, 2013), that bind specifically to the Programmed Death-1 (PD-1) receptor and block the inhibitory PD-1/PD-1 ligand pathway (Topalian et al., N Engl J Med 366:2443-54 (2012a); Topalian et al., Curr Opin Immunol 24:207-12 (2012b); Topalian et al., J Clin Oncol 32(10):1020-30 (2014); Hamid et al., N Engl J Med 369:134-144 (2013); Hamid and Carvajal, Expert Opin Biol Ther 13(6):847-61 (2013); and McDermott and Atkins, Cancer Med 2(5):662-73 (2013)). Clinical trials are described using anti-PD-1 antibodies such as nivolumab and pembrolizumab for treating relapsed or refractory Hodgkin's Lymphoma (Ansell et al., N Engl J Med 372(4):311-319 (2015); Maly et al., Eur J 97(3):219-227 (2016)).

[0004] Targeted therapy of multiple non-redundant molecular pathways regulating immune responses can enhance antitumor immunotherapy. However, not all combinations have acceptable safety and/or efficacy. There remains a need for combination therapies with an

acceptable safety profile and high efficacy that enhance antitumor immune responses compared to monotherapy and other immunotherapy combinations.

SUMMARY OF THE DISCLOSURE

[0005] In general, the present disclosure relates to a method of treating a subject afflicted with a tumor derived from a non-Hodgkin lymphoma comprising administering to the subject: (a) an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity ("anti-PD-1 antibody"); and (b) an antibody or an antigen-binding portion thereof that specifically binds to CD30 ("anti-CD30 antibody"). In some embodiments, the non-Hodgkin lymphoma is relapsed or refractory non-Hodgkin lymphoma. In certain embodiments, the non-Hodgkin lymphoma is selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), and any combination thereof.

[0006] The present disclosure further relates to a method of treating a subject afflicted with a tumor derived from a Hodgkin lymphoma comprising administering to the subject: (a) an anti-PD-1 antibody; and (b) an anti-CD30 antibody. In some embodiments, the Hodgkin lymphoma is classical Hodgkin lymphoma (cHL).

[0007] The claimed invention relates to nivolumab for use in a method of treating a relapsed or refractory Hodgkin lymphoma in a subject in need thereof, wherein the subject is administered a combination of:

1. (a) a dosage of 3 mg/kg of nivolumab; and
2. (b) a dosage of 1.8 mg/kg of brentuximab vedotin;

wherein (i) the dosage of brentuximab vedotin is administered to the subject on day 1 of a first 21-day cycle; (ii) the dosage of nivolumab is administered to the subject on day 8 of the first 21-day cycle; and (iii) a combination of 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab is administered on day 1 of each of a second 21-day cycle, a third 21-day cycle, and a fourth 21-day cycle, wherein the second 21-day cycle, the third 21-day cycle, and the fourth 21-day cycle follow in succession after the first 21-day cycle.

[0008] In some embodiments, the tumor comprises one or more cells that express CD30. In certain embodiments, at least 1% of the tumor cells express CD30.

[0009] In some embodiments, the tumor comprises one or more cells that express PD-L1, PD-L2, or both.

[0010] In some embodiments, the subject received at least one prior chemotherapy treatment. In certain embodiments, the subject was not responsive to a prior chemotherapy treatment.

[0011] In some embodiments, the method further comprises administering a stem cell transplant to the patient after administering the anti-PD-1 antibody and the anti-CD30 antibody.

[0012] The present disclosure is in general further directed to a kit for treating a subject afflicted with a cancer, the kit comprising: (a) a dosage ranging from about 4 mg to about 500 mg of an anti-PD-1 antibody; (b) a dosage ranging from about 0.1 mg to about 500 mg of an anti-CD30 antibody; and (c) instructions for using the anti-PD-1 antibody and the anti-CD30 antibody in the method.

[0013] The present disclosure is in general further directed to a kit for treating a subject afflicted with a lymphoma, the kit comprising: (a) a dosage ranging from about 4 mg to about 500 mg of an anti-PD-1 antibody; (b) a dosage ranging from about 0.1 mg to about 500 mg of brentuximab vedotin; and (c) instructions for using the anti-PD-1 antibody and the brentuximab vedotin in the method.

[0014] The claimed invention relates to a kit for use in a method of treating relapsed or refractory Hodgkin lymphoma in a subject in need thereof, wherein the subject is administered a combination of:

1. (a) a dosage of 3 mg/kg of nivolumab; and
2. (b) a dosage of 1.8 mg/kg of brentuximab vedotin;

wherein (i) the dosage of brentuximab vedotin is administered to the subject on day 1 of a first 21-day cycle; (ii) the dosage of nivolumab is administered to the subject on day 8 of the first 21-day cycle; and (iii) a combination of 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab is administered on day 1 of each of a second 21-day cycle, a third 21-day cycle, and a fourth 21-day cycle, wherein the second 21-day cycle, the third 21-day cycle, and the fourth 21-day cycle follow in succession after the first 21-day cycle, the kit comprising:

1. (a) a dosage of nivolumab; and
2. (b) a dosage of brentuximab vedotin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

FIG. 1 shows a schematic drawing of the PD-1 pathway and the mode of action of nivolumab. MHC = major histocompatibility complex; NFKB = nuclear factor kappa B; PI3K = phosphoinositide-3 kinase; Shp2 = Src homology 2 domain-containing tyrosine phosphatase.

FIG. 2 shows a schematic drawing of the mechanism of action of brentuximab vedotin and secondary effects.

FIG. 3 shows the study design and treatment schedule for a Phase I/II clinical trial of brentuximab vedotin (BV) in combination with nivolumab.

FIG. 4 shows the treatment schedule for a Phase I/II clinical trial of brentuximab vedotin (BV) in combination with nivolumab.

FIGs. 5A and 5B show the tumor response of patients treated with brentuximab vedotin (BV) in combination with nivolumab. CR means complete response; PR means partial response; SD means no metabolic response; and PD means progressive disease.

FIGs. 6A-6D show priming of the immune system of patients treated with brentuximab vedotin (BV) in combination with nivolumab. Serum TARC levels were significantly lower compared to baseline following single agent BV administration and following BV and nivolumab dosing (FIG. 6A). T-cell chemokine IP10 levels were significantly higher after C1D1 BV and following C1D8 nivolumab dosing (FIG. 6B). Pro-inflammatory cytokine IL-18 levels were significantly higher after C1D1 BV dosing and remained stable with BV and nivolumab dosing (FIG. 6C). Pro-inflammatory cytokines such as IFN γ were significantly higher after BV and nivolumab dosing (C1D15) compared to baseline (FIG. 6D).

FIGs. 7A-7C show peripheral blood immunophenotyping. T helper subsets, such as Tregs, (FIG. 7A), activated CD4⁺ T cells (FIG. 7B), and proliferating CD4⁺ T cells (FIG. 7C), which were reduced after single agent BV dosing, expanded after BV and nivolumab combination dosing.

FIG. 8 shows adverse events associated with BV and nivolumab dosing.

FIG. 9 shows infusion-related reactions (IRRs) associated with BV and nivolumab dosing.

FIG. 10 shows the study design and treatment schedule for a Phase III clinical trial of brentuximab vedotin (BV) in combination with nivolumab.

FIG. 11 shows BV-killed A20 mouse lymphoma immunization confers anti-tumor protection.

FIGs. 12A and 12B show T cell transfer from mice immunized with BV-killed cells provides protective immunity.

FIG. 13 shows improved tumor clearance and survival associated with BV and nivolumab combination therapy.

FIGs. 14A-14D show immune cell infiltration into autologous tumors following BV and nivolumab combination therapy. CD8⁺ T cell and NK cell counts relative to tumor mass (FIG. 14A) and total cell count (FIG. 14B) were increased after BV and nivolumab combination dosing. CD8⁺ T cells and LCL tumor cells expressed increased levels of PD-1 (FIG. 14C) and PD-L1 (FIG. 14D). TIL = tumor infiltrating lymphocyte; PBMC = peripheral blood mononuclear cell.

FIGs. 15A-15B show BV enhances immune-mediated tumor clearance alone and in combination with nivolumab. Relative tumor volume decreased over time following treatment

(FIG. 15A), and mean tumor volume substantially decreased after treatment with BV and nivolumab in combination (FIG. 15B). BV = brentuximab vedotin; Nivo = nivolumab; PBMC = peripheral blood mononuclear cell; hlgG-MMAE = control.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0016] Disclosed herein are various aspects, embodiments and examples that may be either claimed or not claimed. Aspects, embodiments, and examples that are not claimed are presented herein to provide context to and understanding of the subject matter that is claimed.

[0017] The claimed invention relates to nivolumab for use in a method of treating a relapsed or refractory Hodgkin lymphoma in a subject in need thereof, wherein the subject is administered a combination of:

1. (a) a dosage of 3 mg/kg of nivolumab; and
2. (b) a dosage of 1.8 mg/kg of brentuximab vedotin;

wherein (i) the dosage of brentuximab vedotin is administered to the subject on day 1 of a first 21-day cycle; (ii) the dosage of nivolumab is administered to the subject on day 8 of the first 21-day cycle; and (iii) a combination of 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab is administered on day 1 of each of a second 21-day cycle, a third 21-day cycle, and a fourth 21-day cycle, wherein the second 21-day cycle, the third 21-day cycle, and the fourth 21-day cycle follow in succession after the first 21-day cycle.

[0018] Additionally, the present disclosure relates to methods for treating a tumor in a subject comprising administering to the subject an anti-Programmed Death-1 (PD-1) antibody and an anti-CD30 antibody in general. In some embodiments of the disclosure, the tumor is derived from a lymphoma. In certain embodiments of the disclosure, the tumor is derived from a Hodgkin lymphoma, a non-Hodgkin lymphoma, or a combination thereof.

Terms

[0019] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0020] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A"

(alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0021] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0023] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, dosing interval of once about every six weeks or once about every twelve weeks means that the first dose is administered on a particular day of the first week (e.g., Monday) and then the next dose is administered on the same day of the sixth or twelfth weeks (i.e., Monday), respectively.

[0024] As described herein, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[0025] Various aspects of the disclosure are described in further detail in the following subsections.

Methods of the Disclosure

[0026] The claimed invention is directed to nivolumab for use in a method of treating a relapsed or refractory Hodgkin lymphoma in a subject in need thereof as defined in the claims.

[0027] Additionally, the present disclosure goes beyond the claimed invention in that it is directed to a method for treating a tumor or a subject afflicted with a tumor comprising administering to the subject a therapeutically effective amount of an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity ("anti-PD-1 antibody") or an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death Ligand1 (PD-L1) receptor and inhibits PD-L1 activity ("anti-PD-L1 antibody") and a therapeutically effective amount of an antibody or an

antigen-binding portion thereof that binds specifically to CD30 ("anti-CD30 antibody").

[0028] In some embodiments of the disclosure, the tumor is derived from a Hodgkin lymphoma (HL), a non-Hodgkin lymphoma (NHL), or a combination thereof. In certain embodiments, the subject has received one, two, three, four, five or more prior cancer treatments. In other embodiments, the subject is treatment-naïve. In some embodiments, the subject has progressed on other cancer treatments. In some embodiments, the tumor has reoccurred. In some embodiments, the tumor is metastatic. In other embodiments, the tumor is not metastatic.

[0029] In certain embodiments, the tumor is derived from an HL (e.g., a tumor comprising an HL). In certain embodiments, the HL is a classical HL (cHL; e.g., a nodular sclerosing HL, a mixed cellularity HL, a lymphocyte rich HL, or a lymphocyte depleted HL). In other embodiments, the HL is a nodular lymphocyte predominant type HL. According to the invention, the tumor is relapsed or refractory Hodgkin lymphoma.

[0030] In other (non-claimed) embodiments of the disclosure, the tumor is derived from a NHL. In some embodiments, the tumor comprises an NHL. In certain embodiments, the NHL is a relapsed or refractor NHL. In some embodiments, the NHL is a B-cell lymphoma, e.g., a diffuse large B-cell lymphoma (DLBCL), a follicular lymphoma (FL), a Burkitt lymphoma, an immunoblastic large cell lymphoma, a precursor B-lymphoblastic lymphoma, a mantle cell lymphoma, or any combination thereof. In some embodiments, the NHL is a T-cell lymphoma, e.g., a cutaneous T-cell lymphoma (CTCL), a peripheral T-cell lymphoma (PTCL), a mycosis fungoides, an anaplastic large cell lymphoma, a precursor T-lymphoblastic lymphoma, or any combination thereof. In certain embodiments, the NHL is selected from a DLBCL, a PTCL, a CTCL, and any combination thereof.

[0031] In other embodiments, the present methods comprise administering an effective amount of an anti-PD-1 antibody and an effective amount of an anti-CD30 antibody. An effective amount of an anti-PD-1 antibody and/or an anti-CD30 antibody can be a flat dose or a weight based dose.

[0032] In some embodiments, the disclosure includes a method of treating a cancer or a subject afflicted with cancer comprising administering an anti-PD-1 antagonist in combination with an anti-CD30 antibody to treat cancer. An "anti-PD-1 antagonist" as referred herein includes any molecule that inhibits interaction between PD-1 (receptor) and PD-L1 (ligand) such that the signal pathway of PD-1/PD-L1 is blocked. In other embodiments, an anti-PD-1 antagonist is a PD-1-Fc fusion protein. In certain embodiments, an anti-PD-1 antagonist includes an anti-PD-1 fusion protein, an antisense molecule, a small molecule, a ribozyme, or a nanobody that inhibits or prevents interaction between PD-1 and PD-L1. According to the claimed invention, the anti-PD-1 antagonist is nivolumab.

[0033] In certain embodiments, the therapy of the present disclosure (e.g., administration of an anti-PD-1 antibody the anti-CD30 antibody) effectively increases the duration of survival of the

subject. For example, the duration of survival of the subject is increased by at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 1 year or more when compared to another subject treated with only either another therapy or, only one of the two members of the combination therapy alone (e.g., an anti-PD-1 antibody alone) or an alternative combination therapy. In other embodiments, the combination therapy of an anti-PD-1 antibody and an anti-CD30 antibody increases the duration of survival of the subject at a level similar to the duration of survival of the subject using a combination therapy of an anti-PD-L1 antibody and brentuximab vedotin (anti-CD30 antibody). In still other embodiments, the combination therapy of an anti-PD-1 antibody (e.g., nivolumab or pembrolizumab) and an anti-CD30 antibody (e.g., brentuximab vedotin) increases the duration of survival of the subject at a level higher than (about one month higher than, about two months higher than, about three months higher than, about four months higher than, about five months higher than, about six months higher than, about seven months higher than, about eight months higher than, about nine months higher than, about ten months higher than, about eleven months higher than, or about one year higher than the duration of survival of the subject using a combination therapy of an anti-PD-L1 antibody (e.g., MPDL3280A or atezolizumab) and brentuximab vedotin (anti-CD30 antibody).

[0034] In certain embodiments, the therapy of the present disclosure effectively increases the duration of progression-free survival of the subject. For example, the progression free survival of the subject is increased by at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 1 year when compared to another subject treated with only either another therapy or only one of the two members of the combination therapy alone (e.g., an anti-PD-1 antibody alone) or an alternative combination therapy.

[0035] In certain embodiments, the therapy of the present disclosure effectively increases the response rate in a group of subjects. For example, the response rate in a group of subjects is increased by at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 99% or at least about 100% when compared to another group of subjects treated with only either another therapy or, only one of the two members of the combination therapy alone (e.g., an anti-PD-1 antibody alone) or an alternative combination therapy.

[0036] In certain embodiments, the methods of the present disclosure lower a serum thymus and activation-regulated chemokine (TARC) level in the subject after the administration of the anti-PD-1 antibody and the anti-CD30 antibody in combination, compared to the serum TARC level at the baseline (no administration or before the administration) or after the administration

of the anti-PD-1 antibody or the anti-CD30 antibody alone (monotherapy). In some embodiments, the serum TARC level is lowered after the administration at least one fold, at least 1.5 fold, at least two fold, at least three fold, at least four fold, at least five fold, at least six fold, at least seven fold, at least eight fold, at least nine fold, at least ten fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 14 fold, at least 15 fold, at least 16 fold, at least 17 fold, at least 18 fold, at least 19 fold, or at least 20 fold compared to the serum TARC level at the baseline (no administration or before the administration) or after the monotherapy. In other embodiments, the methods of the present disclosure increase the level of a pro-inflammatory cytokine, e.g., Interleukin-18 (IL-18) and/or Interferon- γ , in the subject after the administration of the anti-PD-1 antibody and the anti-CD30 antibody in combination, compared to the level of the pro-inflammatory cytokine at the baseline (no administration or before the administration) or after the administration of the anti-PD-1 antibody or the anti-CD30 antibody alone (monotherapy). The level of the pro-inflammatory cytokine can be increased at least 1 fold, at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 14 fold, at least 15 fold, at least 16 fold, at least 17 fold, at least 18 fold, at least 19 fold, or at least 20 fold after the administration of the combination therapy. In yet other embodiments, the methods of the present disclosure increase the level of a T cell chemokine, e.g., IP10, in the subject after the administration of the anti-PD-1 antibody and the anti-CD30 antibody in combination, compared to the level of the T cell chemokine at the baseline (no administration or before the administration) or after the administration of the anti-PD-1 antibody or the anti-CD30 antibody alone (monotherapy). In some embodiments, the level of the T cell chemokine is increased at least 1 fold, at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 14 fold, at least 15 fold, at least 16 fold, at least 17 fold, at least 18 fold, at least 19 fold, or at least 20 fold after the administration of the combination therapy.

[0037] In other embodiments of the disclosure, the present method provides a method of reducing the serum level of TARC in a subject afflicted with a tumor derived from a Hodgkin lymphoma (HL), a non-Hodgkin lymphoma (NHL), or a combination thereof comprising administering to the subject a therapeutically effective amount of an anti-PD-1 antibody and an anti-CD30 antibody. In some embodiments, the serum TARC level is lowered after the administration at least one fold, at least 1.5 fold, at least two fold, at least three fold, at least four fold, at least five fold, at least six fold, at least seven fold, at least eight fold, at least nine fold, at least ten fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 14 fold, at least 15 fold, at least 16 fold, at least 17 fold, at least 18 fold, at least 19 fold, or at least 20 fold compared to the serum TARC level at the baseline (no administration or before the administration) or after the monotherapy.

[0038] In some embodiments of the disclosure, the present method provides a method of increasing the level of a pro-inflammatory cytokine (e.g., IL-18 and/or IFN γ) and/or a T cell chemokine (e.g., IP10) in a subject afflicted with a tumor derived from a Hodgkin lymphoma (HL), a non-Hodgkin lymphoma (NHL), or a combination thereof comprising administering to

the subject a therapeutically effective amount of an anti-PD-1 antibody and an anti-CD30 antibody. In some embodiments, the level of the pro-inflammatory cytokine and/or T cell chemokine is increased at least 1 fold, at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 14 fold, at least 15 fold, at least 16 fold, at least 17 fold, at least 18 fold, at least 19 fold, or at least 20 fold after the administration of the combination therapy.

[0039] In certain embodiments, the present methods (e.g., combination therapy of an anti-PD-1 antibody and an anti-CD30 antibody) also activate and/or proliferate T cells, e.g., CD4⁺ T cells, e.g., Follicular helper CD4 T cells (T_{fh}), T helper cells (Th1 and/or Th2), T helper 17 (T_H17) cells, and/or regulatory T cells (Tregs), or CD8⁺ T cells, compared to the administration of the anti-CD30 antibody alone or the baseline (no administration or before the administration). In some embodiments, the present methods increase the number of T cells, e.g., CD4⁺ T cells, regulatory T cells (Tregs) compared to the administration of the anti-CD30 antibody alone or the baseline (no administration or before the administration).

[0040] In some embodiments, the anti-PD-1 and anti-CD30 antibodies are formulated for intravenous administration. In certain embodiments, the anti-PD-1 and anti-CD30 antibodies are administered sequentially. In certain embodiments, the anti-PD-1 and anti-CD30 antibodies are administered within 30 minutes of each other. In one embodiment, the anti-PD-1 antibody or antigen-binding portion thereof is administered before the anti-CD30 antibody or antigen-binding portion thereof. In another embodiment, the anti CD30 antibody or antigen-binding portion thereof is administered before the anti-PD-1 antibody or antigen-binding portion thereof. In another embodiment, the anti-PD-1 antibody or antigen-binding portion thereof and the anti-CD30 antibody or antigen-binding portion thereof are administered concurrently in separate compositions. In a further embodiment, the anti-PD-1 antibody or antigen-binding portion thereof and the anti-CD30 antibody or antigen-binding portion thereof are admixed as a single composition for concurrent administration.

[0041] In some embodiments, the anti-PD-1 antibody and anti-CD30 antibody are administered in a fixed dose.

Anti-PD-1 and Anti-PD-L1 antibodies

[0042] The combination therapy of the present disclosure can utilize an anti-PD-1 antibody or an antigen-binding fragment thereof. PD-1 is a key immune checkpoint receptor expressed by activated T and B cells and mediates immunosuppression. PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA. Two cell surface glycoprotein ligands for PD-1 have been identified, Programmed Death Ligand-1 (PD-L1) and Programmed Death Ligand-2 (PD-L2), that are expressed on antigen-presenting cells as well as many human cancers and have been shown to down regulate T cell activation and cytokine

secretion upon binding to PD-1. Inhibition of the PD-1/PD-L1 interaction mediates potent antitumor activity in preclinical models.

[0043] Human monoclonal antibodies that bind specifically to PD-1 with high affinity have been disclosed in U.S. Patent No. 8,008,449. Other anti-PD-1 mABs have been described in, for example, U.S. Patent Nos. 6,808,710, 7,488,802, 8,168,757 and 8,354,509, and PCT Publication No. WO 2012/145493. Each of the anti-PD-1 human monoclonal antibodies disclosed in U.S. Patent No. 8,008,449 has been demonstrated to exhibit one or more of the following characteristics: (a) binds to human PD-1 with a K_D of 1×10^{-7} M or less, as determined by surface plasmon resonance using a Biacore biosensor system; (b) does not substantially bind to human CD28, CTLA-4 or ICOS; (c) increases T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay; (d) increases interferon- γ production in an MLR assay; (e) increases IL-2 secretion in an MLR assay; (f) binds to human PD-1 and cynomolgus monkey PD-1; (g) inhibits the binding of PD-L1 and/or PD-L2 to PD-1; (h) stimulates antigen-specific memory responses; (i) stimulates antibody responses; and/or (j) inhibits tumor cell growth *in vivo*. Anti-PD-1 antibodies usable in the present disclosure include monoclonal antibodies that bind specifically to human PD-1 and exhibit at least one, at least two, at least three, at least four, or at least five of the preceding characteristics.

[0044] In one embodiment and according to the claimed invention, the anti-PD-1 antibody is nivolumab. Nivolumab (also known as "OPDIVO®"; formerly designated 5C4, BMS-936558, MDX-1106, or ONO-4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the down-regulation of antitumor T-cell functions (U.S. Patent No. 8,008,449; Wang et al., 2014 Cancer Immunol Res. 2(9):846-56). Nivolumab has shown activity in a variety of advanced solid tumors including renal cell carcinoma (renal adenocarcinoma, or hypernephroma), melanoma, and non-small cell lung cancer (NSCLC) (Topalian et al., 2012a; Topalian et al., 2014; Drake et al., 2013; WO 2013/173223). In other embodiments of the disclosure, the anti-PD-1 antibody or fragment thereof cross-competes with nivolumab. In some embodiments of the disclosure, the anti-PD-1 antibody binds to the same epitope as nivolumab. In certain embodiments of the disclosure, the anti-PD-1 antibody has the same CDRs as nivolumab.

[0045] In another embodiment of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with pembrolizumab. In some embodiments, the anti-PD-1 antibody binds to the same epitope as pembrolizumab. In certain embodiments, the anti-PD-1 antibody has the same CDRs as pembrolizumab. In another embodiment, the anti-PD-1 antibody is pembrolizumab. Pembrolizumab (also known as "KEYTRUDA®", lambrolizumab, and MK-3475) is a humanized monoclonal IgG4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1). Pembrolizumab is described, for example, in U.S. Patent No. 8,900,587; see also <http://www.cancer.gov/drugdictionary?cdrid=695789> (last accessed: December 14, 2014). Pembrolizumab has been approved by the FDA for the treatment of relapsed or refractory

melanoma and advanced NSCLC.

[0046] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with MEDI0680. In some embodiments, the anti-PD-1 antibody binds to the same epitope as MEDI0680. In certain embodiments, the anti-PD-1 antibody has the same CDRs as MEDI0680. In other embodiments, the anti-PD-1 antibody is MEDI0680 (formerly AMP-514), which is a monoclonal antibody against the PD-1 receptor. MEDI0680 is described, for example, in U.S. Pat. No. 8,609,089B2 or in <http://www.cancer.gov/drugdictionary?cdrid=756047> (last accessed December 14, 2014).

[0047] In certain embodiments of the disclosure, an immune checkpoint inhibitor is AMP-224, which is a B7-DC Fc fusion protein. AMP-224 is discussed in U.S. Publ. No. 2013/0017199 or in <http://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=700595> (last accessed July 8, 2015).

[0048] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with BGB-A317. In some embodiments, the anti-PD-1 antibody binds to the same epitope as BGB-A317. In certain embodiments, the anti-PD-1 antibody has the same CDRs as BGB-A317. In certain embodiments, the anti-PD-1 antibody is BGB-A317, which is a humanized monoclonal antibody. BGB-A317 is described in U.S. Publ. No. 2015/0079109.

[0049] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with INCSHR1210 (SHR-1210). In some embodiments, the anti-PD-1 antibody binds to the same epitope as INCSHR1210 (SHR-1210). In certain embodiments, the anti-PD-1 antibody has the same CDRs as INCSHR1210 (SHR-1210). In certain embodiments, the anti-PD-1 antibody is INCSHR1210 (SHR-1210), which is a human monoclonal antibody. INCSHR1210 (SHR-1210) is described in WO2015/085847.

[0050] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with REGN-2810. In some embodiments, the anti-PD-1 antibody binds to the same epitope as REGN-2810. In certain embodiments, the anti-PD-1 antibody has the same CDRs as REGN-2810. In certain embodiments, the anti-PD-1 antibody is REGN-2810, which is a human monoclonal antibody. REGN-2810 is described in WO2015/112800.

[0051] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with PDR001. In some embodiments, the anti-PD-1 antibody binds to the same epitope as PDR001. In certain embodiments, the anti-PD-1 antibody has the same CDRs as PDR001. In certain embodiments, the anti-PD-1 antibody is PDR001, which is a humanized monoclonal antibody. PDR001 is described in WO2015/112900.

[0052] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with TSR-042 (ANB011). In some embodiments, the anti-PD-1

antibody binds to the same epitope as TSR-042 (ANB011). In certain embodiments, the anti-PD-1 antibody has the same CDRs as TSR-042 (ANB011). In certain embodiments, the anti-PD-1 antibody is TSR-042 (ANB011), which is a humanized monoclonal antibody. TSR-042 (ANB011) is described in WO2014/179664.

[0053] In other embodiments of the disclosure, the anti-PD-1 antibody (or antigen-binding portion thereof) cross-competes with STI-1110. In some embodiments, the anti-PD-1 antibody binds to the same epitope as STI-1110. In certain embodiments, the anti-PD-1 antibody has the same CDRs as STI-1110. In certain embodiments, the anti-PD-1 antibody is STI-1110, which is a human monoclonal antibody. STI-1110 is described in WO2014/194302.

[0054] Anti-PD-1 antibodies usable in the disclosed methods also include isolated antibodies that bind specifically to human PD-1 and cross-compete for binding to human PD-1 with nivolumab (see, e.g., U.S. Patent No. 8,008,449; WO 2013/173223). The ability of antibodies to cross-compete for binding to an antigen indicates that these antibodies bind to the same epitope region of the antigen and sterically hinder the binding of other cross-competing antibodies to that particular epitope region. These cross-competing antibodies are expected to have functional properties very similar to those of nivolumab by virtue of their binding to the same epitope region of PD-1. Cross-competing antibodies can be readily identified based on their ability to cross-compete with nivolumab in standard PD-1 binding assays such as Biacore analysis, ELISA assays or flow cytometry (see, e.g., WO 2013/173223).

[0055] In certain embodiments of the disclosure, the antibodies that cross-compete for binding to human PD-1 with, or bind to the same epitope region of human PD-1 as nivolumab are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies can be chimeric antibodies, or can be humanized or human antibodies. Such chimeric, humanized or human monoclonal antibodies can be prepared and isolated by methods well known in the art.

[0056] Anti-PD-1 antibodies usable in the methods of the disclosed disclosure also include antigen-binding portions of the above antibodies. It has been amply demonstrated that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L , V_H , C_L , and C_{H1} domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, or any combination thereof.

[0057] In certain embodiments of the disclosure, the anti-PD-1 antibody or antigen-binding portion thereof comprises a heavy chain constant region which is of a human IgG1 or IgG4 isotype. In certain other embodiments, the sequence of the IgG4 heavy chain constant region of the anti-PD-1 antibody or antigen-binding portion thereof contains an S228P mutation which replaces a serine residue in the hinge region with the proline residue normally found at the

corresponding position in IgG1 isotype antibodies. This mutation, which is present in nivolumab, prevents Fab arm exchange with endogenous IgG4 antibodies, while retaining the low affinity for activating Fc receptors associated with wild-type IgG4 antibodies (Wang *et al.*, 2014). In yet other embodiments, the antibody comprises a light chain constant region which is a human kappa or lambda constant region. In other embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is a monoclonal antibody or an antigen-binding portion thereof. In certain embodiments of any of the therapeutic methods described herein comprising administration of an anti-PD-1 antibody, the anti-PD-1 antibody is nivolumab. In other embodiments, the anti-PD-1 antibody is pembrolizumab. In other embodiments, the anti-PD-1 antibody is chosen from the human antibodies 17D8, 2D3, 4H1, 4A11, 7D3, and 5F4 described in U.S. Patent No. 8,008,449. In still other embodiments, the anti-PD-1 antibody is MEDI0680 (formerly AMP-514), AMP-224, or BGB-A317.

[0058] In other embodiments of the disclosure, the anti-PD-1 antibody or antigen-binding portion thereof is a chimeric, humanized or human monoclonal antibody or a portion thereof. In certain embodiments for treating a human subject, the antibody is a humanized antibody. In other embodiments for treating a human subject, the antibody is a human antibody. Antibodies of an IgG1, IgG2, IgG3, or IgG4 isotype can be used.

[0059] In certain embodiments of the disclosure, an anti-PD-1 antibody used in the methods can be replaced with another PD-1 or anti-PD-L1 antagonist. For example, because an anti-PD-L1 antibody prevents interaction between PD-1 and PD-L1, thereby exerting similar effects to the signaling pathway of PD-1, an anti-PD-L1 antibody can replace the use of an anti-PD-1 antibody in the methods disclosed herein. Therefore, in one embodiment, the present disclosure is directed to a method for treating a subject afflicted with a tumor comprising administering to the subject a therapeutically effective amount an anti-PD-L1 antibody and an anti-CD30 antibody.

[0060] In certain embodiments of the disclosure, the anti-PD-L1 antibody is BMS-936559 (formerly 12A4 or MDX-1105) (see, e.g., U.S. Patent No. 7,943,743; WO 2013/173223).

[0061] In other embodiments of the disclosure, the anti-PD-L1 antibody is MPDL3280A (also known as RG7446 and atezolizumab) (see, e.g., Herbst *et al.* (2013) *J Clin Oncol* 31 (suppl): 3000. Abstract.; U.S. Patent No. 8,217,149).

[0062] In other embodiments of the disclosure, the anti-PD-L1 antibody is MEDI4736 (also called Durvalumab; Khleif (2013) In: *Proceedings from the European Cancer Congress 2013*; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract 802, See US Patent No. 8,779,108 or US 2014/0356353, filed May 6, 2014).

[0063] In further embodiments of the disclosure, the anti-PD-L1 antibody is MSB0010718C (also called Avelumab; See US 2014/0341917).

[0064] In other embodiments of the disclosure, the anti-PD-L1 antibody is CX-072 (also called

CytomX; See WO2016/149201).

[0065] In certain embodiments of the disclosure, the anti-PD-L1 antibodies cross-compete for binding to human PD-L1 with, or bind to the same epitope region of human PD-L1 as the above-references PD-L1 antibodies. In other embodiments, the anti-PD-L1 antibodies useful for the combination therapy with an anti-CD30 antibody are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies can be chimeric antibodies, or can be humanized or human antibodies. Such chimeric, humanized, or human monoclonal antibodies can be prepared and isolated by methods well known in the art.

Anti-CD30 antibodies

[0066] The combination therapy of the present disclosure also utilizes an anti-CD30 antibody or an antigen-binding fragment thereof. CD30 receptors are members of the tumor necrosis factor receptor superfamily involved in limiting the proliferative potential of autoreactive CD8 effector T cells. Antibodies targeting CD30 can potentially be either agonists or antagonists of these CD30 activities.

[0067] In some embodiments of the disclosure, the anti-CD30 antibody is cAC10. cAC10 is a chimeric IgG1 monoclonal antibody that specifically binds CD30. cAC10 induces growth arrest of CD30⁺ cell lines in vitro and has pronounced antitumor activity in severe combined immunodeficiency (SCID) mouse xenograft models of Hodgkin disease. See Francisco et al., Blood 102(4):1458-64 (2003).

[0068] In some embodiments of the disclosure, the anti-CD30 antibody is conjugated to a therapeutic agent, e.g., the anti-CD30 antibody comprises an anti-CD30 antibody-drug conjugate. In some embodiments, the therapeutic agent comprises an anti-neoplastic agent (e.g., an anti-mitotic agent). In certain embodiments, the therapeutic agent is selected from the group consisting of monomethyl auristatin E (MMAE), auristatin drug analogues, can tansinoids (maytansine; DMs), dolastatins, cryptophycin, duocarmycin, duocarmycin derivatives, esperamicin, calicheamicin, pyrrolobenzodiazepine (PBD), and any combination thereof. In one particular embodiment, the anti-CD30 antibody is conjugated to MMAE. The antibody can be conjugated to at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten molecules of the therapeutic agent. In one embodiment, the anti-CD30 antibody is conjugated to four molecules of the therapeutic agent, e.g., four molecules of MMAE.

[0069] In some embodiments of the disclosure, the anti-CD30 antibody-drug conjugate further comprises a linker between the therapeutic agent and the antibody. In some embodiments, the linker comprises one or more naturally occurring amino acids, one or more non-naturally occurring (e.g., synthetic) amino acids, a chemical linker, or any combination thereof. In certain embodiments, the linker is a cleavable linker, e.g., a protease cleavable linker. In certain

embodiments, the linker is specifically cleaved upon uptake by a target cell, *e.g.*, upon uptake by a cell expressing CD30. In some embodiments, cleavage of the linker activates a cytotoxic activity of the therapeutic agent.

[0070] In one embodiment of the disclosure, the anti-CD30 antibody comprises brentuximab vedotin. In one particular embodiment and according to the claimed invention, the anti-CD30 antibody is brentuximab vedotin. Brentuximab vedotin (BV; also known as "ADCETRIS[®]") is a CD30-directed antibody-drug conjugate (ADC) comprising a chimeric anti-CD30 antibody (cAC10), a therapeutic agent (MMAE), and a protease-cleavable linker between the cAC10 and the MMAE. BV comprises approximately four molecules of MMAE linked to each cAC10 antibody molecule. In one embodiment, the anti-CD30 antibody is ADCETRIS[®]. ADCETRIS[®] is approved by the FDA for treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.

[0071] In one embodiment of the disclosure, the anti-CD30 antibody is an anti-CD30 antibody or fragment thereof that binds to the same epitope as cAC10, *e.g.*, the same epitope as brentuximab vedotin. In certain embodiments, the anti-CD30 antibody is an antibody that has the same CDRs as cAC10, *e.g.*, the same CDRs as brentuximab vedotin. Antibodies that bind to the same epitope are expected to have functional properties very similar to those of cAC10 by virtue of their binding to the same epitope region of CD30. These antibodies can be readily identified based on their ability to, for example, cross-compete with cAC10 in standard CD30 binding assays such as Biacore analysis, ELISA assays, or flow cytometry.

[0072] In certain embodiments of the disclosure, the antibodies that cross-compete for binding to human CD30 with, or bind to the same epitope region of human CD30 as cAC10 are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies can be chimeric antibodies, or can be humanized or human antibodies. Such chimeric, humanized, or human monoclonal antibodies can be prepared and isolated by methods well known in the art. Anti-CD30 antibodies usable in the methods of the disclosed disclosure also include antigen-binding portions of the above antibodies.

[0073] In other embodiments of the disclosure, the anti-CD30 antibody or antigen-binding portion thereof is a chimeric, humanized, or human monoclonal antibody or a portion thereof. In certain embodiments for treating a human subject, the antibody is a humanized antibody. In other embodiments for treating a human subject, the antibody is a human antibody. Antibodies of an IgG1, IgG2, IgG3, or IgG4 isotype can be used.

Cancer and Standard-of-Care Therapies

[0074] In some embodiments, the methods disclosed herein are used in place of standard of care therapies. In certain embodiments, a standard of care therapy is used in combination with any method disclosed herein. Standard-of-care therapies for different types of cancer are well known by persons of skill in the art. For example, the National Comprehensive Cancer Network (NCCN), an alliance of 21 major cancer centers in the USA, publishes the NCCN Clinical Practice Guidelines in Oncology (NCCN GUIDELINES®) that provide detailed up-to-date information on the standard-of-care treatments for a wide variety of cancers (see NCCN GUIDELINES®, 2014, available at: www.nccn.org/professionals/physician_gls/f_guidelines.asp, last accessed May 14, 2014).

Lymphoma

[0075] The combination therapy of the present disclosure can be used to treat a tumor derived from a lymphoma. Lymphoma is a form of cancer that affects the immune system. The majority of lymphomas fall within two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). NHL is the most common form of lymphoma, accounting for about 90% of all cases of lymphoma, whereas HL accounts for only about 10% of all cases of lymphoma. Accordingly, in some embodiments, the lymphoma is an HL. In other embodiments, the lymphoma is an NHL. According to the invention, the lymphoma is relapsed or refractory Hodgkin lymphoma.

[0076] NHL will account for an estimated 72,000 new cases (4.3% of all new cancer cases) and 20,000 deaths (3.4% of all cancer-related deaths) in the U.S. in 2017. Howlader N et al., SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission. Diffuse large B-cell lymphoma (DLBCL), the most common NHL subtype, has an incidence rate of 7.14 per 100,000 persons per year (P-Y), including up to 10% primary mediastinal B-cell lymphoma (PMBL). Dunleavy K et al., Blood 2015;125:33-39. Incidence rates of peripheral T-cell lymphoma (PTCL) and mycosis fungoides/Sézary syndrome (MF/SS) are 0.60 and 0.52 per 100,000 P-Y. Morton LM et al., Blood 2006; 107:265-276. Within the two main categories of lymphoma, HL and NHL, there are several specific subgroups of lymphomas. Hodgkin lymphomas can

include, but are not limited to, classical HL (cHL; e.g., nodular sclerosing HL, mixed cellularity HL, lymphocyte rich HL, and lymphocyte depleted HL) and nodular lymphocyte predominant type HL. Non-Hodgkin Lymphomas can include, but are not limited to, B-cell lymphomas (e.g., diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Burkitt lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma) and T cell lymphomas (e.g., a cutaneous T-cell lymphoma (CTCL), a peripheral T-cell lymphoma (PTCL), a mycosis fungoides, an anaplastic large cell lymphoma, and a precursor T-lymphoblastic lymphoma).

[0077] Treatment guidelines for relapsed/refractory (R/R) NHL recommend multi-agent chemotherapy (combined with targeted therapy for B-cell lymphomas), brentuximab vedotin (BV), autologous or allogeneic hematopoietic stem cell transplantation (HSCT), and/or

radiotherapy, with addition of topical therapies for MF/SS. National Comprehensive Cancer Network, Non-Hodgkin Lymphoma (version 3.2016). 5-year relative survival rates are 48%, 44%, and 86% in DLBCL, PTCL, and MF/SS, respectively. Han X et al., Cancer Causes Control 2008;19:841-858.

[0078] In certain aspects, the present disclosure is directed to a method of treating a subject afflicted with a tumor derived from a Hodgkin lymphoma (HL) comprising administering to the subject (a) an anti-PD-1 antibody, and (b) an anti-CD30 antibody. In some embodiments, the tumor comprises an HL. In one particular embodiment, the HL is classical HL (cHL).

[0079] In certain aspects, the present disclosure is directed to a method of treating a subject afflicted with a tumor derived from a non-Hodgkin lymphoma (NHL) comprising administering to the subject (a) an anti-PD-1 antibody, and (b) an anti-CD30 antibody. In some embodiments, the tumor comprises an NHL. In certain embodiments, the NHL is a relapsed or refractory NHL. In some embodiments, the NHL is a B-cell lymphoma, e.g., a diffuse large B-cell lymphoma (DLBCL), a follicular lymphoma (FL), a Burkitt lymphoma, an immunoblastic large cell lymphoma, a precursor B-lymphoblastic lymphoma, a mantle cell lymphoma, or any combination thereof. In some embodiments, the NHL is a T-cell lymphoma, e.g., a cutaneous T-cell lymphoma (CTCL), a peripheral T-cell lymphoma (PTCL), a mycosis fungoides, an anaplastic large cell lymphoma, a precursor T-lymphoblastic lymphoma, or any combination thereof. In particular embodiments, the NHL is selected from the group consisting of a DLBCL, a PTCL, a CTCL, and any combination thereof.

[0080] Various lymphomas are known to express CD30. For example, CD30 is expressed by Reed-Sternberg cells typical of HL, and CD30 expression has been observed in various forms of NHL, including, but not limited to, diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), and cutaneous T-cell lymphoma (CTCL). Accordingly, in some embodiments, the tumor comprises one or more cells that express CD30. In some embodiments, at least about 0.01%, at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% of the tumor cells express CD30. In one particular embodiment, at least about 1% of the tumor cells express CD30. In another embodiment, at least about 10% of the tumor cells express CD30. In another embodiment, at least about 20% of the tumor cells express CD30. In another embodiment, at least about 30% of the tumor cells express CD30. In another embodiment, at least about 40% of the tumor cells express CD30. In another embodiment, at least about 50% of the tumor cells express CD30.

[0081] The PD-L1 status of a tumor (e.g., a tumor derived from a NHL and/or a HL) in a subject can be measured prior to administering any composition or utilizing any method disclosed herein. PD-L1 expression can be determined by any methods known in the art.

[0082] In order to assess the PD-L1 expression, in one embodiment, a test tissue sample can be obtained from the patient who is in need of the therapy. In another embodiment, the assessment of PD-L1 expression can be achieved without obtaining a test tissue sample. In some embodiments, selecting a suitable patient includes (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells; and (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the surface of the cells based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is higher than a predetermined threshold level.

[0083] In any of the methods comprising the measurement of PD-L1 expression in a test tissue sample, however, it should be understood that the step comprising the provision of a test tissue sample obtained from a patient is an optional step. It should also be understood that in certain embodiments the "measuring" or "assessing" step to identify, or determine the number or proportion of, cells in the test tissue sample that express PD-L1 on the cell surface is performed by a transformative method of assaying for PD-L1 expression, for example by performing a reverse transcriptase-polymerase chain reaction (RT-PCR) assay or an IHC assay. In certain other embodiments, no transformative step is involved and PD-L1 expression is assessed by, for example, reviewing a report of test results from a laboratory. In certain embodiments, the steps of the methods up to, and including, assessing PD-L1 expression provides an intermediate result that may be provided to a physician or other healthcare provider for use in selecting a suitable candidate for the anti-PD-1 antibody or anti-PD-L1 antibody therapy. In certain embodiments, the steps that provide the intermediate result is performed by a medical practitioner or someone acting under the direction of a medical practitioner. In other embodiments, these steps are performed by an independent laboratory or by an independent person such as a laboratory technician.

[0084] In certain embodiments of any of the present methods, the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 RNA. In further embodiments, the presence of PD-L1 RNA is determined by RT-PCR, *in situ* hybridization or RNase protection. In other embodiments, the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide. In further embodiments, the presence of PD-L1 polypeptide is determined by immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), *in vivo* imaging, or flow cytometry. In some embodiments, PD-L1 expression is assayed by IHC. In other embodiments of all of these methods, cell surface expression of PD-L1 is assayed using, e.g., IHC or *in vivo* imaging. Chen et al., (2013) Clin Cancer Res 19(13): 3462-3473.

[0085] Imaging techniques have provided important tools in cancer research and treatment. Recent developments in molecular imaging systems, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), fluorescence reflectance imaging (FRI), fluorescence-mediated tomography (FMT), bioluminescence imaging (BLI), laser-scanning confocal microscopy (LSCM) and multiphoton microscopy (MPM), will likely

herald even greater use of these techniques in cancer research. Some of these molecular imaging systems allow clinicians to not only see where a tumor is located in the body, but also to visualize the expression and activity of specific molecules, cells, and biological processes that influence tumor behavior and/or responsiveness to therapeutic drugs (Condeelis and Weissleder, "In vivo imaging in cancer," Cold Spring Harb. Perspect. Biol. 2(12):a003848 (2010)). Antibody specificity, coupled with the sensitivity and resolution of PET, makes immunoPET imaging particularly attractive for monitoring and assaying expression of antigens in tissue samples (McCabe and Wu, "Positive progress in immunoPET-not just a coincidence," Cancer Biother. Radiopharm. 25(3):253-61 (2010); Olafsen et al., "ImmunoPET imaging of B-cell lymphoma using 124I-anti-CD20 scFv dimers (diabodies)," Protein Eng. Des. Sel. 23(4):243-9 (2010)). In certain embodiments of any of the present methods, PD-L1 expression is assayed by immunoPET imaging. In certain embodiments of any of the present methods, the proportion of cells in a test tissue sample that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide on the surface of cells in the test tissue sample. In certain embodiments, the test tissue sample is a FFPE tissue sample. In other embodiments, the presence of PD-L1 polypeptide is determined by IHC assay. In further embodiments, the IHC assay is performed using an automated process. In some embodiments, the IHC assay is performed using an anti-PD-L1 monoclonal antibody to bind to the PD-L1 polypeptide.

[0086] In one embodiment of the present methods, an automated IHC method is used to assay the expression of PD-L1 on the surface of cells in FFPE tissue specimens. This disclosure provides methods for detecting the presence of human PD-L1 antigen in a test tissue sample, or quantifying the level of human PD-L1 antigen or the proportion of cells in the sample that express the antigen, which methods comprise contacting the test sample, and a negative control sample, with a monoclonal antibody that specifically binds to human PD-L1, under conditions that allow for formation of a complex between the antibody or portion thereof and human PD-L1. In certain embodiments, the test and control tissue samples are FFPE samples. The formation of a complex is then detected, wherein a difference in complex formation between the test sample and the negative control sample is indicative of the presence of human PD-L1 antigen in the sample. Various methods are used to quantify PD-L1 expression.

[0087] In a particular embodiment, the automated IHC method comprises: (a) deparaffinizing and rehydrating mounted tissue sections in an autostainer; (b) retrieving antigen using a decloaking chamber and pH 6 buffer, heated to 110°C for 10 min; (c) setting up reagents on an autostainer; and (d) running the autostainer to include steps of neutralizing endogenous peroxidase in the tissue specimen; blocking non-specific protein-binding sites on the slides; incubating the slides with primary antibody; incubating with a post primary blocking agent; incubating with NovoLink Polymer; adding a chromogen substrate and developing; and counterstaining with hematoxylin.

[0088] For assessing PD-L1 expression in tumor tissue samples, a pathologist examines the number of membrane PD-L1⁺ tumor cells in each field under a microscope and mentally

estimates the percentage of cells that are positive, then averages them to come to the final percentage. The different staining intensities are defined as 0/negative, 1+/weak, 2+/moderate, and 3+/strong. Typically, percentage values are first assigned to the 0 and 3+ buckets, and then the intermediate 1+ and 2+ intensities are considered. For highly heterogeneous tissues, the specimen is divided into zones, and each zone is scored separately and then combined into a single set of percentage values. The percentages of negative and positive cells for the different staining intensities are determined from each area and a median value is given to each zone. A final percentage value is given to the tissue for each staining intensity category: negative, 1+, 2+, and 3+. The sum of all staining intensities needs to be 100%. In one embodiment, the threshold number of cells that needs to be PD-L1 positive is at least about 100, at least about 125, at least about 150, at least about 175, or at least about 200 cells. In certain embodiments, the threshold number or cells that needs to be PD-L1 positive is at least about 100 cells.

[0089] Staining is also assessed in tumor-infiltrating inflammatory cells such as macrophages and lymphocytes. In most cases macrophages serve as an internal positive control since staining is observed in a large proportion of macrophages. While not required to stain with 3+ intensity, an absence of staining of macrophages should be taken into account to rule out any technical failure. Macrophages and lymphocytes are assessed for plasma membrane staining and only recorded for all samples as being positive or negative for each cell category. Staining is also characterized according to an outside/inside tumor immune cell designation. "Inside" means the immune cell is within the tumor tissue and/or on the boundaries of the tumor region without being physically intercalated among the tumor cells. "Outside" means that there is no physical association with the tumor, the immune cells being found in the periphery associated with connective or any associated adjacent tissue.

[0090] In certain embodiments of these scoring methods, the samples are scored by two pathologists operating independently, and the scores are subsequently consolidated. In certain other embodiments, the identification of positive and negative cells is scored using appropriate software.

[0091] A histoscore is used as a more quantitative measure of the IHC data. The histoscore is calculated as follows:

$$\text{Histoscore} = [(\% \text{ tumor} \times 1 (\text{low intensity})) + (\% \text{ tumor} \times 2 (\text{medium intensity})) + (\% \text{ tumor} \times 3 (\text{high intensity}))]$$

[0092] To determine the histoscore, the pathologist estimates the percentage of stained cells in each intensity category within a specimen. Because expression of most biomarkers is heterogeneous the histoscore is a truer representation of the overall expression. The final histoscore range is 0 (no expression) to 300 (maximum expression).

[0093] An alternative means of quantifying PD-L1 expression in a test tissue sample IHC is to determine the adjusted inflammation score (AIS) score defined as the density of inflammation

multiplied by the percent PD-L1 expression by tumor-infiltrating inflammatory cells (Taube et al., "Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape," Sci. Transl. Med. 4(127):127ra37 (2012)).

[0094] In one embodiment, the PD-L1 expression level of a tumor (e.g., a tumor derived from a NHL and/or a HL) is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%. In another embodiment, the PD-L1 status of a tumor is at least about 1%. In other embodiments, the PD-L1 status of a tumor is at least about 5%. In a certain embodiment, the PD-L1 status of a tumor is at least about 10%. In one embodiment, the PD-L1 status of the tumor is at least about 25%. In a particular embodiment, the PD-L1 status of the tumor is at least about 50%.

[0095] "PD-L1 positive" as used herein can be interchangeably used with "PD-L1 expression of at least about 1%". In one embodiment, the PD-L1 positive tumors can thus have at least about 1%, at least about 2%, at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% of the tumor cells expressing PD-L1 as measured by an automated IHC. In certain embodiments, "PD-L1 positive" means that there are at least 100 cells that express PD-L1 on the surface of the cells.

Pharmaceutical Compositions and Dosages

[0096] Therapeutic agents of the present disclosure can be constituted in a composition, e.g., a pharmaceutical composition containing an antibody and a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In some embodiments, the carrier for a composition containing an antibody is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal, or epidermal administration (e.g., by injection or infusion). A pharmaceutical composition of the disclosure can include one or more pharmaceutically acceptable salts, anti-oxidants, aqueous and non-aqueous carriers, and/or adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents.

[0097] The present invention relates to nivolumab for use in a method of treating a relapsed or refractory Hodgkin lymphoma in a subject in need thereof, wherein the subject is administered a combination of (a) a dosage of 3 mg/kg of nivolumab; and (b) a dosage of 1.8 mg/kg of

brentuximab vedotin; wherein (i) the dosage of brentuximab vedotin is administered to the subject on day 1 of a first 21-day cycle; (ii) the dosage of nivolumab is administered to the subject on day 8 of the first 21-day cycle; and (iii) a combination of 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab is administered on day 1 of each of a second 21-day cycle, a third 21-day cycle, and a fourth 21-day cycle, wherein the second 21-day cycle, the third 21-day cycle, and the fourth 21-day cycle follow in succession after the first 21-day cycle.

[0098] The following disclosure explains the invention further and additionally provides information that provides context for the claimed invention:

[0099] Dosage regimens are adjusted to provide the optimum desired response, *e.g.*, a maximal therapeutic response and/or minimal adverse effects. In some embodiments of the disclosure, the anti-PD-1 antibody is administered at a weight-based dose. For administration of an anti-PD-1 antibody, the dosage can range from at least about 0.01 mg/kg to at least about 20 mg/kg, from at least about 0.1 mg/kg to at least about 10 mg/kg, from about 0.01 mg/kg to about 5 mg/kg, from about 1 mg/kg to about 5 mg/kg, from about 2 mg/kg to about 5 mg/kg, from about 1 mg/kg to about 3 mg/kg, from about 7.5 mg/kg to about 12.5 mg/kg, or from about 0.1 mg/kg to about 30 mg/kg of the subject's body weight. For example, dosages can be at least about 0.1 mg/kg, at least about 0.3 mg/kg, at least about 1 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 5 mg/kg, or at least about 10 mg/kg body weight. In certain embodiments and according to the claimed invention, the dosage of the anti-PD-1 antibody is 3 mg/kg body weight.

[0100] In one embodiment of the disclosure, a dosage regimen for an anti-PD-1 antibody comprises about 0.3-1 mg/kg body weight, about 5 mg/kg body weight, 1-5 mg/kg body weight, or about 1-3 mg/kg body weight via intravenous administration, with the antibody being given every about 14-21 days in up to about 6-week or about 12-week cycles until complete response or confirmed progressive disease. In some embodiments, the antibody treatment, or any combination treatment disclosed herein, is continued for at least about 1 month, at least about 3 months, at least about 6 months, at least about 9 months, at least about 1 year, at least about 18 months, at least about 24 months, at least about 3 years, at least about 5 years, or at least about 10 years.

[0101] The dosing schedule is typically designed to achieve exposures that result in sustained receptor occupancy (RO) based on typical pharmacokinetic properties of an antibody. An exemplary treatment regime entails administration once per week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once a month, once every 3-6 months or longer. In certain embodiments, an anti-PD-1 antibody such as nivolumab is administered to the subject once every 2 weeks. In other embodiments, the antibody is administered once every 3 weeks. The dosage and scheduling can change during a course of treatment. The anti-PD-1 antibody can be administered in at least two doses, each of the doses is at an amount of about 0.01 mg/kg to about 5 mg/kg, *e.g.*, 3 mg/kg, at a dosing interval of every two weeks between the two doses. In some embodiments, the anti-PD-1 antibody is administered in at least three, four, five, six, or seven doses (*i.e.*, multiple doses), each of the doses is at an amount of about

0.01 mg/kg to about 5 mg/kg, e.g., 3 mg/kg, at a dosing interval of every two weeks between two adjacently given doses. The dosage and scheduling may change during a course of treatment. For example, a dosing schedule for anti-PD-1 monotherapy can comprise administering the antibody: (i) every 2 weeks in 6-week cycles; (ii) every 4 weeks for six dosages, then every three months; (iii) every 3 weeks; or (iv) 3-10 mg/kg once followed by 1 mg/kg every 2-3 weeks. Considering that an IgG4 antibody typically has a half-life of 2-3 weeks, a dosage regimen for an anti-PD-1 antibody of the disclosure comprises 0.3-10 mg/kg body weight, e.g., 1-5 mg/kg body weight, e.g., 1-3 mg/kg body weight via intravenous administration, with the antibody being given every 14-21 days in up to 6-week or 12-week cycles until complete response or confirmed progressive disease.

[0102] In particular embodiments of the disclosure, the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, or 3 weeks. In further embodiments, the anti-PD-1 antibody (e.g., nivolumab) is administered at a dose of at least about 3 mg/kg body weight once about every 2 weeks. In other embodiments, the anti-PD-1 antibody (e.g., pembrolizumab) is administered at a dose of at least about 200 mg every 3 weeks or 2 mg/kg (up to 200 mg) every three weeks. In some embodiments, the anti-PD-1 antibody (e.g., avelumab) is administered at a dose of 10 mg/kg every two weeks.

[0103] In certain embodiments of the disclosure, an anti-PD-1 antibody is administered at a flat dose. In embodiments, the flat dose of the anti-PD-1 antibody is a dose (e.g., flat dose) of at least about 100-600 mg, at least about 400-500 mg, such as, at least about 480 mg, or at least about 100-300 mg, such as, at least about 200-300 mg, at least about 220-260 mg, at least about 230-250 mg or at least about 240 mg, such as at least about 60 mg, at least about 80 mg, at least about 100 mg, at least about 120 mg, at least about 140 mg, at least about 160 mg, at least about 180 mg, at least about 200 mg, at least about 220 mg, at least about 240 mg, at least about 260 mg, at least about 280 mg, at least about 300 mg, at least about 320 mg, at least about 360 mg, at least about 400 mg, at least about 440 mg, at least about 480 mg, at least about 500 mg, at least about 550 mg, at least about 600 mg, at least about 650 mg, at least about 700 mg, at least about 750 mg, or at least about 800 mg. In one embodiment, the anti-PD-1 antibody is a dose (e.g., flat dose) of at least about 240 mg or at least about 480 mg, e.g., 240 mg to 480 mg, once about every 2 to 4 weeks. In other embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose higher than, i.e., at least about, 240 mg. In a particular embodiment, the anti-PD-1 antibody is administered a flat dose of about 360 mg once about every 3 weeks.

[0104] In certain embodiments of the disclosure, an anti-PD-1 antibody is administered at a flat dose. In embodiments, the flat dose of the anti-PD-1 antibody is a dose (e.g., flat dose) of about 100-600 mg, about 400-500 mg, such as, about 480 mg, or about 100-300 mg, such as, about 200-300 mg, about 220-260 mg, about 230-250 mg or about 240 mg, such as about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg, about 360 mg, about 400 mg, about 440 mg, about 480 mg, about 500 mg,

about 550 mg, about 600 mg, about 650 mg, about 720 mg, about 750 mg, or about 800 mg. In one embodiment, the anti-PD-1 antibody is a dose (e.g., flat dose) of about 240 mg or about 480 mg, e.g., 240 mg to 480 mg, once about every 2 to 4 weeks. In other embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose higher than, i.e., about 240 mg. In a particular embodiment, the anti-PD-1 antibody is administered a flat dose of about 360 mg once about every 3 weeks.

[0105] In some embodiments of the disclosure, the anti-PD-1 antibody is administered in a fixed dose with the anti-CD30 antibody. In some embodiments, the ratio is at least about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1 mg anti-PD-1 antibody to anti-CD30 antibody.

[0106] When used in combinations with other anti-cancer agents, the dosage of an anti-PD-1 antibody can be lowered compared to the monotherapy dose. For example, a dosage of nivolumab that is significantly lower than the typical 3 mg/kg, but not less than 0.001 mg/kg, for instance 0.1 mg/kg or less every 3 or 4 weeks, is regarded as a subtherapeutic dosage. The subtherapeutic doses of an anti-PD-1 antibody used in the methods herein are higher than 0.001 mg/kg and lower than 3 mg/kg. In some embodiments, a subtherapeutic dose is about 0.001 mg/kg to about 1 mg/kg, about 0.01 mg/kg to about 1 mg/kg, about 0.1 mg/kg to about 1 mg/kg, or about 0.001 mg/kg to about 0.1 mg/kg body weight. In some embodiments, the subtherapeutic dose is at least about 0.001 mg/kg, at least about 0.005 mg/kg, at least about 0.01 mg/kg, at least about 0.05 mg/kg, at least about 0.1 mg/kg, at least about 0.5 mg/kg, or at least about 1.0 mg/kg body weight. Receptor-occupancy data from 15 subjects who received 0.3 mg/kg to 10 mg/kg dosing with nivolumab indicate that PD-1 occupancy appears to be dose-independent in this dose range. Across all doses, the mean occupancy rate was 85% (range, 70% to 97%), with a mean plateau occupancy of 72% (range, 59% to 81%). (Brahmer et al., J Clin Oncol 28:3167-75 2010). In some embodiments, 0.3 mg/kg dosing can allow for sufficient exposure to lead to maximal biologic activity. In a particular embodiment, the anti-CD30 antibody, e.g., BV, is administered at a dose of 1.8 mg/kg once every 3 weeks.

[0107] Although higher nivolumab monotherapy dosing up to 10 mg/kg every two weeks has been achieved without reaching the maximum tolerated dose (MTD), the significant toxicities reported in other trials of checkpoint inhibitors plus anti-angiogenic therapy (see, e.g., Johnson et al., 2013; Rini et al., 2011) support the selection of a nivolumab dose lower than 10 mg/kg.

[0108] In some embodiments of the disclosure, the anti-CD30 antibody (e.g., brentuximab vedotin) is administered at a weight-based dose. For administration of an anti-CD30 antibody (e.g., brentuximab vedotin), the dosage can range from about 0.01 mg/kg to about 20 mg/kg, about 0.05 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 20 mg/kg, about 0.1 mg/kg to

about 15 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 4 mg/kg, about 0.1 mg/kg to about 3 mg/kg, about 0.1 to about 2 mg/kg, about 1 to about 10 mg/kg, about 1 to about 10 mg/kg, about 1 to about 8 mg/kg, about 1 to about 5 mg/kg, about 1 to about 3 mg/kg, about 1 to about 2 mg/kg of the subject's body weight. For example, dosages can be about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2.0 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, or about 20 mg/kg of the subject's body weight.

[0109] In some embodiments of the disclosure, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.1 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.2 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.3 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.4 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.5 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.6 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.7 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.8 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 0.9 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.0 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.1 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.2 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.3 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.4 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.5 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.6 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.7 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.8 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 1.9 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.0 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.1 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.2 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.3 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.4

mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is 2.5 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is about 5 mg/kg body weight. In other embodiments, the dosage of the anti-CD30 antibody (e.g., brentuximab vedotin) is about 10 mg/kg body weight.

[0110] In certain embodiments of the disclosure, an anti-CD30 antibody (e.g., brentuximab vedotin) is administered at a flat dose. In some embodiments, the flat dose of the anti-CD30 antibody is a dose (e.g., flat dose) of at least about 1-1500 mg, at least about 10-1000 mg, such as, at least about 50-800 mg, at least about 100-600 mg, at least about 100-400 mg or at least about 100-200 mg, such as at least about 1 mg, at least about 3 mg, at least about 5 mg, at least about 8 mg, at least about 10 mg, at least about 20 mg, at least about 30 mg, at least about 40 mg, at least about 50 mg, at least about 60 mg, at least about 70 mg, at least about 80 mg, at least about 90 mg, at least about 100 mg, at least about 110 mg, at least about 120 mg, at least about 130 mg, at least about 140 mg, at least about 150 mg, at least about 160 mg, at least about 170 mg, at least about 180 mg, at least about 190 mg, at least about 200 mg, at least about 220 mg, at least about 240 mg, at least about 260 mg, at least about 280 mg, at least about 300 mg, at least about 320 mg, at least about 340 mg, at least about 360 mg, at least about 380 mg, at least about 400 mg, at least about 420 mg, at least about 440 mg, at least about 460 mg, at least about 480 mg, at least about 500 mg, at least about 600 mg, at least about 700 mg, at least about 800 mg, at least about 900 mg, at least about 1000 mg, at least about 1100 mg, at least about 1200 mg, at least about 1300 mg, at least about 1400 mg, or at least about 1500 mg.

[0111] In certain embodiments of the disclosure, an anti-CD30 antibody (e.g., brentuximab vedotin) is administered at a flat dose. In some embodiments, the flat dose of the anti-CD30 antibody is a dose (e.g., flat dose) of about 1-1500 mg, about 10-1000 mg, such as, about 50-800 mg, about 100-600 mg, about 100-400 mg or about 100-200 mg, such as about 1 mg, about 3 mg, about 5 mg, about 8 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, about 360 mg, about 380 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, or about 1500 mg.

[0112] An exemplary treatment regime entails administration once per week, once about every 2 weeks, once about every 3 weeks, once about every 4 weeks, once about a month, once about every 3-6 months or longer. In certain embodiments, the anti-CD30 antibody (e.g., brentuximab vedotin) is administered once about every 3 weeks.

[0113] In some embodiments of the disclosure, a subtherapeutic dose of an anti-CD30 antibody (e.g., brentuximab vedotin) is used in the methods herein. The subtherapeutic

dosages of an anti-CD30 antibody (e.g., brentuximab vedotin) used in the methods herein are higher than 0.001 mg/kg and lower than 10 mg/kg. In some embodiments, the subtherapeutic dose is about 0.001 mg/kg-about 10 mg/kg, about 0.01 mg/kg-about 10 mg/kg, about 0.01 mg/kg-about 1 mg/kg, about 0.1 mg/kg-about 1 mg/kg, or about 0.001 mg/kg-about 0.1 mg/kg body weight. In some embodiments, the subtherapeutic dose is at least about 0.001 mg/kg, at least about 0.005 mg/kg, at least about 0.01 mg/kg, at least about 0.05 mg/kg, at least about 0.1 mg/kg, at least about 0.2 mg/kg, at least about 0.3 mg/kg, at least about 0.4 mg/kg, at least about 0.5 mg/kg, at least about 0.6 mg/kg, at least about 0.7 mg/kg, at least about 0.8 mg/kg, at least about 0.9 mg/kg, at least about 1 mg/kg, at least about 1.1 mg/kg, at least about 1.2 mg/kg, at least about 1.3 mg/kg, at least about 1.4 mg/kg, at least about 1.5 mg/kg, at least about 1.6 mg/kg, or at least about 1.7 mg/kg body weight.

[0114] In certain embodiments of the disclosure, at least about 0.1 mg/kg to about 5 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.1 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.2 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.3 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.4 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.5 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.6 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.7 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.8 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 0.9 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.1 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.2 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.3 mg/kg of the anti-

CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.4 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.5 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.6 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.7 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.8 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 1.9 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 2 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 3 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 4 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 5 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In certain embodiments, at least about 10 mg/kg of the anti-CD30 antibody (e.g., brentuximab vedotin) and at least about 240 mg of the anti-PD-1 antibody are administered to the subject once about every three weeks. In embodiments, the anti-CD30 antibody is brentuximab vedotin. In some embodiments, the anti-PD-1 antibody is nivolumab.

[0115] In certain embodiments of the disclosure, the combination of an anti-PD-1 antibody (e.g., nivolumab) and an anti-CD30 antibody (e.g., brentuximab vedotin) is administered intravenously to the subject once about every 3 weeks for a total of nine weeks. In some embodiments, the nine week cycle is repeated 3 or 4 times. In embodiments, the subject is treated with a combination of an anti-PD-1 antibody (e.g., nivolumab) and an anti-CD30 antibody (e.g., brentuximab vedotin) every 3 weeks for a total of nine weeks and 3 nine-week cycles are performed. In embodiments, the subject is treated with a combination of an anti-PD-1 antibody (e.g., nivolumab) and an anti-CD30 antibody (e.g., brentuximab vedotin) every 3 weeks for a total of nine weeks and 4 nine-week cycles are performed. In embodiments, a subject is treated with the anti-PD-1 antibody for 12 nine-week cycles.

[0116] In certain embodiments of the disclosure, the anti-CD30 antibody (e.g., brentuximab vedotin) is administered (e.g., intravenously) to a subject on day 1 of the first cycle (cycle 1 day

1); the anti-PD-1 antibody (e.g., Nivolumab) is administered (e.g., intravenously) to the subject on day 8 of the cycle (cycle 1 day 8); and a combination of an anti-CD30 antibody (e.g., brentuximab vedotin) and an anti-PD-1 antibody (e.g., Nivolumab) is administered (e.g., intravenously) on day 1 of each of cycles 2-4. In some embodiments, each cycle is two weeks, 15 days, three weeks, four weeks, a month, five weeks, or six weeks. In one particular embodiment, the subject is treated with about 1.8 mg/kg of an anti-CD30 antibody (e.g., brentuximab vedotin) on cycle 1 day 1 (e.g., 21 day cycle); about 3 mg/kg of an anti-PD-1 antibody (e.g., Nivolumab) on cycle 1 day 8; and a combination of an anti-CD30 antibody (e.g., brentuximab vedotin) and an anti-PD-1 antibody (e.g., Nivolumab) on day 1 of each of cycles 2-4. In one particular embodiment, the combination of an anti-CD30 antibody (e.g., brentuximab vedotin) and an anti-PD-1 antibody (e.g., Nivolumab) comprises a dose of about 1.8 mg/kg of an anti-CD30 antibody (e.g., brentuximab vedotin) and a dose of about 3 mg/kg of an anti-PD-1 antibody (e.g., Nivolumab).

[0117] Treatment is continued as long as clinical benefit is observed or until unacceptable toxicity or disease progression occurs. In certain embodiments, the anti-PD-1 antibody can be administered at the dosage that has been shown to produce the highest efficacy as monotherapy in clinical trials, e.g., about 3 mg/kg of nivolumab administered once about every three weeks (Topalian et al., 2012 N Engl JMed 366:2443-54; Topalian et al., 2012 Curr Opin Immunol 24:207-12), at a flat dose of 240 mg, or at a significantly lower dose, i.e., at a subtherapeutic dose.

[0118] In certain embodiments of the disclosure, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for a set period of time followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. In some embodiments, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for about 6 weeks followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. In some embodiments, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for about 9 weeks followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. In some embodiments, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for about 12 weeks followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. In some embodiments, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for about 24 weeks followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. In some embodiments, the subject is treated with a combination of an anti-PD-1 antibody and an anti-CD30 antibody once about every 3 weeks for about 48 weeks followed by a monotherapy of an anti-PD-1 antibody or a monotherapy of an anti-CD30 antibody. The monotherapy of the anti-PD-1 antibody can be administered by any route disclosed herein at any dose disclosed herein. In one embodiment, the monotherapy of the anti-PD-1 antibody is administered intravenously at a flat dose of 240 mg. In another embodiment, the monotherapy of the anti-PD-1 antibody is administered intravenously at a dose of 3 mg/kg or 6 mg/kg. The monotherapy of the anti-CD30 antibody can be administered

by any route disclosed herein at any dose disclosed herein. In one embodiment, the monotherapy of the anti-CD30 antibody, e.g., brentuximab vedotin, is administered intravenously at a dose of 1.8 mg/kg.

[0119] Dosage and frequency vary depending on the half-life of the antibody in the subject. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is typically administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0120] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present disclosure can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being unduly toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present disclosure employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health, and prior medical history of the patient being treated, and like factors well known in the medical arts. A composition of the present disclosure can be administered via one or more routes of administration using one or more of a variety of methods well known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

Kits

[0121] Also within the scope of the present disclosure are kits comprising an anti-PD-1 antibody and an anti-CD30 antibody for therapeutic uses. Kits typically include a label indicating the intended use of the contents of the kit and instructions for use. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit. Accordingly, this disclosure provides a kit for treating a subject afflicted with a cancer, the kit comprising: (a) a dosage ranging from about 4 mg to about 500 mg of an anti-PD-1 antibody or antigen-binding portion thereof; (b) a dosage ranging from about 0.1 mg to about 500 mg of an anti-CD30 antibody or antigen-binding portion thereof; and (c) instructions for using the anti-PD-1 antibody and the anti-CD30 antibody in any of the combination therapy methods disclosed herein. In certain embodiments, the anti-PD-1 antibody, the anti-CD30 can be co-packaged in unit dosage form. In certain embodiments for

treating human patients, the kit comprises an anti-human PD-1 antibody disclosed herein, e.g., nivolumab, pembrolizumab, MEDI0680 (formerly AMP-514), AMP-224, or BGB-A317. In other embodiments, the kit comprises an anti-human CD30 antibody disclosed herein, e.g., brentuximab vedotin. The kit for use in a method of treating relapsed or refractory Hodgkin lymphoma in a subject in need thereof according to the invention comprises: (a) a dosage of nivolumab; and (b) a dosage of brentuximab vedotin.

[0122] The present disclosure is further illustrated by the following examples

EXAMPLES

REFERENCE EXAMPLE 1

[0123] A phase 1/2 open-label, international, multicenter study (NCT02581631), is underway to investigate the safety and efficacy of nivolumab combined with BV in patients with relapsed/refractory NHL.

Background

[0124] Treatment options for patients with relapsed, refractory non-Hodgkin lymphoma (NHL) are limited. Nivolumab is a fully human IgG4 monoclonal antibody immune checkpoint inhibitor that targets programmed death receptor-1 (PD-1) to restore active T-cell immune responses against the tumor (FIG. 1). Nivolumab has approval in the United States as treatment for metastatic melanoma, metastatic non-small cell lung cancer, and advanced renal cell carcinoma. Safety and tolerability of nivolumab is consistent across both solid and hematologic tumor types. While PD-1 blockade has shown encouraging activity in aggressive B-cell and T-cell NHL—a phase 1 trial demonstrated an objective response rate (ORR) of 36% in heavily pretreated patients with relapsed, refractory diffuse large B-cell lymphoma (DLBCL)—the majority of patients either do not respond or progress after an initial response. Combination therapy with therapeutic agents such as antibody-drug conjugates can increase the frequency and durability of responses, through both direct cell killing and immunogenic consequences of cell death.

[0125] Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate that has shown anti-tumor activity in a range of lymphoid malignancies. BV works primarily by inducing cell cycle arrest and apoptotic death in CD30-expressing cells. BV may also mediate immunogenic cell death, bystander-killing effects, and antibody-dependent cellular phagocytosis (FIG. 2). Gardai SJ, et al. Cancer Res 2015;75(Suppl. 15):2469 [abstract]; Li F et al. Cancer Res 2016;76:2710-2719; and Oflazoglu E, et al. Blood 2007;110:4370-4372.

[0126] In studies of patients with CD30+ relapsed, refractory DLBCL, CD30+ relapsed, refractory peripheral T-cell lymphoma (PTCL), and CD30+ cutaneous T-cell lymphoma (CTCL) treated with BV, ORR observed was 44%, 41%, and 73%, respectively. BV is approved in the United States as treatment for cHL after autologous stem cell transplant (ASCT) failure, or after failure of ≥ 2 prior chemotherapy regimens in non-ASCT candidates, and for systemic anaplastic large cell lymphoma after failure of ≥ 1 chemotherapy regimen. BV elicits its effect by inducing cell cycle arrest and apoptotic death in CD30-expressing cells, and can also mediate immunogenic cell death, bystander effects, and antibody-dependent cellular phagocytosis. As BV can mediate immunogenic cell death, it could synergize with PD-1 blockade. We hypothesize that nivolumab and BV can induce frequent and durable responses in patients with CD30+ relapsed, refractory T-cell NHL and diffuse large B-cell lymphoma (DLBCL).

Study Rationale

[0127] Patients with relapsed, refractory NHLs after progression following systemic therapy represent an area of substantial unmet medical need. BV can provide synergy with immune checkpoint inhibitors by inducing immunogenic cell death, which can upregulate the expression of the costimulatory molecule CD86 and MHC class II antigens on antigen-presenting cells in the tumor microenvironment. We hypothesize that the complementary mechanisms of actions of nivolumab in combination with BV could provide frequent and durable responses for patients with CD30+ relapsed, refractory NHL.

Study Design

[0128] The design of the present single-arm, phase 1/2 multicenter study is shown in FIG. 3. Treatment continues in 3-week cycles until disease progression or unacceptable toxicity. Both nivolumab and BV are administered as 30-minute IV infusions. For cycles in which both treatments are given on the same day, the schedule is as follows: BV infusion, 30-minute rest, nivolumab infusion. Planned enrollment is for 96 patients: 6 in phase 1 and 90 in phase 2; recruitment will be equal across the 3 subtypes. Key inclusion and exclusion criteria are shown in Table 1.

Table 1. Key Inclusion/Exclusion Criteria

Inclusion	Exclusion
Patients with relapsed, refractory NHLs, including DLBCL, PTCL, CTCL, PMBL, and MGZL	NHL involving the CNS
Expression of CD30 on $\geq 1\%$ of tumor cells, confirmed via immunohistochemical analysis	History of progressive multifocal leukoencephalopathy
Age ≥ 15 years for patients with PMBL, ≥ 18 years for other histologies	Any active grade 3+ infection within 2 weeks prior to the first dose of BV

Inclusion	Exclusion
ECOG PS score of 0 or 1	Pre-existing neuropathy of grade >2
Tumor tissue (biopsy) for biomarker analysis	Prior BV exposure
Measurable disease according to 2014 Lugano Classification for patients with DLBCL, PTCL, PMBL, and MGZL	Prior exposure to immune checkpoint inhibitor
	Suspected or known autoimmune disease
CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IHC = immunohistochemistry	

Objectives

[0129] The primary objectives of the present study are two-fold. First, safety and tolerability of nivolumab in combination with BV will be evaluated in patients with relapsed, refractory NHLs. Second, the clinical benefit of nivolumab in combination with BV will be assessed in patients with relapsed, refractory NHLs, as measured by objective response rate (ORR; patients achieving a best overall response of either partial response or complete response).

[0130] The secondary objectives are to measure the duration of response, the complete response (CR) rate and duration of CR, and the progression free survival (PFS) and overall survival rate. In addition, exploratory objectives include (i) indeterminate response (IR) per Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC); (ii) assessment of CD30 expression and PD-L1/2 status, and correlation with response, and (iii) identification of biomarkers of response or resistance to the BV and nivolumab combination regimen.

[0131] After the administration of BV and nivolumab, the patients will show improved overall response rates, increased overall survival, increased progression free survival, decreased tumor burden, decreased occurrence of drug-related adverse events or any combination thereof.

EXAMPLE 2

[0132] A phase 1/2 study (NCT02572167) is ongoing to assess the safety profile and antitumor activity of BV administered in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma (HL). Patients will be treated for up to four 21-day cycles with BV 1.8 mg/kg and nivolumab 3 mg/kg. Patients will be administered 1.8 mg/kg BV on Cycle 1 Day 1, and 3 mg/kg nivolumab on Cycle 1 Day 8. For cycles 2 through 4, BV and nivolumab will be administered on Day 1 of each cycle at the same doses, e.g., 1.8 mg/kg BV and 3 mg/kg nivolumab. Both BV and nivolumab will be administered by IV injection. After completion of the

Cycle 4 response assessment (EOT), patients will be eligible to undergo ASCT. Responses were assessed using the 2014 Lugano classification (Cheson et al., J Clin Oncol 2014;32(27):3059-68).

[0133] There will be two parts to this study. In Part 1, the safety of combination treatment will be evaluated by a Safety Monitoring Committee (SMC) prior to expansion of enrollment to evaluate treatment effect in Part 2. Part 2 of the study will further characterize safety and evaluate the antitumor activity of BV combined with nivolumab by enrolling patients at the recommended dose schedule determined in Part 1. Key inclusion and exclusion criteria are shown in Table 2. Patients were excluded if they previously received more than one line of anti-cancer therapy; BV or any immuno-oncology therapy affecting the PD-1, CTLA4, or CD137 pathways; and/or Allogeneic or autologous stem cell transplant (ASCT).

Table 2. Key Inclusion/Exclusion Criteria

Inclusion	Exclusion
Relapsed or refractory Hodgkin lymphoma following failure of standard frontline chemotherapy for the treatment of classical Hodgkin lymphoma	Previously treated with BV, immune-oncology agents, or received an allogeneic or autologous stem cell transplant
	Documented history of a cerebral vascular event
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	History of another invasive malignancy that has not been in remission for at least 3 years
Age 18 years or older	History of progressive multifocal leukoencephalopathy (PML)

[0134] The primary outcome measures of the present study are two-fold. First, safety and tolerability of nivolumab in combination with BV will be evaluated in patients with relapsed or refractory HL. Second, the clinical benefit of nivolumab in combination with BV will be assessed in patients with relapsed or refractory HL, as measured by complete response (CR) rate (CRR; patients achieving a best overall response of complete response) following the completion of study treatment, AE incidence, and severity.

[0135] The secondary outcome measures are to measure objective response rate (ORR), the duration of response, the duration of complete response (CR) and objective response, and the progression free survival (PFS) post-autologous stem cell transplant. In addition, exploratory objectives include assessment of CD30 expression and correlation with response and to identification of biomarkers of response or resistance to the BV and nivolumab combination regimen.

[0136] After the administration of BV and nivolumab, the patients will show improved overall response rates, increased overall survival, increased progression free survival, decreased tumor burden, decreased occurrence of drug-related adverse events or any combination

thereof.

Results

[0137] Target enrollment of approximately 55 adult patients with classical Hodgkin lymphoma (cHL) that had relapsed or was refractory (RR) to frontline chemotherapy was met and patient information is provided below in Tables 3 and 4.

Table 3. Patient Characteristics

Patient demographics and disease characteristics		N = 62
Median age, years (range)		36 (18-69)
Gender (M/F)		30/32
Disease status relative to frontline tx, n (%)		
	Primary refractory	28 (45)
	Relapsed, remission duration $\leq$ 1 year	19 (31)
Bulky disease at baseline, n (%)		8 (13)
Extranodal disease at baseline, n (%)		16 (26)
Disease stage at initial diagnosis, n (%)		
	I/II	37 (60)
	III/IV	24 (39)
	Unknown	1 (2)
Median prior therapies ^a (range)		1 (1-3)
Prior chemotherapy regimens, n (%)		
	ABVD	56 (90)
	BEACOPP	2 (3)
	Stanford V	2(3)
	Other ^b	6(10)
Prior radiation		9(15)

Table 4. Patient Disposition

Patient disposition ^c		N = 62
		n (%)
Received $\geq$ 1 dose of both study drugs, n (%)		61 (98)
Remain on tx		0
Completed tx		58 (94)
Reason for tx discontinuation ^d		
	Patient decision	2 (3)

Patient disposition ^c		N = 62
		n (%)
	Adverse event	1 (2)
	Investigator decision	1 (2)
Received alternative salvage regimen		12 (19)
	ICE ^e	9(15)
	GEMOX	1 (2)
	BeGEV	1 (2)
	Nivolumab	1 (2)
a Includes radiation b ABVD + AVD (3 pts), ABVE-PC (2 pts), R-ABVD (1 pt) c 1 pt discontinued before receiving study drug d Pts who did not receive study drug still provided a reason for tx discontinuation e 2 of 9 pts who received ICE also received other regimens; 1 pt received 3 other salvage regimens: carboplatin/gemcitabine/decadron (not evaluable), followed by BV (PD), followed by gemcitabine/oxaliplatin (PD), and 1 pt had HL and FL and received bendamustine/rituximab		

[0138] Initially, twenty-five patients (60% female) with a median age of 32 years (range, 18-69) were enrolled to date. Sixty percent of patients have relapsed disease, 36% have primary refractory disease (failure to achieve complete response (CR) with frontline therapy, or relapse within 3 months of completing frontline therapy), and 1 patient (4%) has unknown status. At the time of enrollment, 32% of patients presented with extranodal disease and 16% with bulky disease.

[0139] Currently, sixty-two patients (52% female) with a median age of 36 years (range, 18-69) have been enrolled to date. Thirty-one percent of patients have relapsed disease, and forty-five percent of patients have primary refractory disease. At the time of enrollment, 26% of patients presented with extranodal disease and 13% with bulky disease.

[0140] At the time of the previous data extract, 23 patients had received treatment. An increased incidence of infusion-related reactions (IRRs) was observed at the start of combination treatment in Cycle 2 during the BV infusion leading to 1 dose delay. Premedication with corticosteroids (hydrocortisone 100 mg or equivalent) and antihistamines at Cycles 2-4 was instituted through a protocol amendment.

[0141] At the time of the previous data extract, six patients have completed combination treatment, and all have achieved an objective response rate (ORR, 100%), with 3 of 6 achieving a complete metabolic response (CmR, 50%). All 6 patients have proceeded directly to ASCT. The median number of CD34⁺ cells collected was 12.9 × 10⁶ cells/kg (range, 5-26) in a mean number of 1.7 apheresis sessions (range, 1-2).

[0142] Currently, fifty-nine patients (95%) have completed combination treatment, with a high objective response rate (85%) with 63% complete responses (FIGs. 5A and 5B). Additional information about patient responses is provided in Table 5 below. Thirty-seven patients have proceeded to ASCT.

Table 5.

		N = 59
		n (%)
Complete response (CR)		37 (63)
	Deauville ≤ 2	29 (49)
	Deauville 3	7 (12)
	Deauville 5 ^a	1 (2)
Partial response (PR)		13 (22)
	Deauville 4	7 (12)
	Deauville 5	6 (10)
No metabolic response (SD)		5 (8)
	Deauville 5	5 (8)
Progressive disease (PD)		3 (5)
	Deauville 5	2 (3)
	Missing	1 (2)
Clinical Progression (CP)		1 (2)
^a 1 patient had uptake in lymph node, but no evidence of disease was found on biopsy		

[0143] Priming of the immune system was indicated by an increase in pro-inflammatory cytokine and chemokine levels after BV dosing with high levels maintained following concurrent BV and nivolumab administration (FIGs. 6A-6D).

[0144] Additionally, an initial reduction in some T helper subsets (including Tregs) (FIG. 7A) and activated and proliferating CD4⁺ T cells (FIGs. 7B and 7C) after single agent BV administration, is followed by an expansion after combination dosing.

[0145] BV and nivolumab in combination were well tolerated in patients with relapsed refractory cHL. Potential immune-mediated AEs requiring steroids occurred in <10% of patients (FIG. 8). And although IRRs occurred relatively frequently (41% of patients), most frequently during the Cycle 2 BV infusion and required dose interruptions in 25% of patients, the maximum severity was Grade 3 which occurred in less than 5% of patients (FIG. 9).

[0146] Mandatory premedication with low-dose corticosteroids (hydrocortisone 100 mg or

equivalent) and antihistamine at Cycles 2-4 was instituted. The rate of IRRs at Cycle 2 was equivalent before and after instituting premedication, i.e., 5 of 15 patients (33%) developed IRRs without premedication, whereas 15 of 45 patients (33%) developed IRRs with premedication. The rate of IRRs at Cycles 3-4 was low irrespective of premedication requirements.

[0147] Pre-ASCT treatment-emergent AEs occurred in 98% of patients at the following frequencies: Grade 1 (25%), Grade 2 (36%), Grade 3 (33%; anemia most frequent at 8%), and Grade 4 (5%). Treatment-related SAEs occurred in 5 patients (8%): pneumonitis and pyrexia each occurred in 2 patients; and colitis, malaise, nausea, pneumonia, respiratory failure, and sepsis each occurred in 1 patient. No unusual post-ASCT toxicities were reported.

[0148] Systemic steroids for potential immune-mediated AEs were required in 7% of patients. Each of the following was experienced by 1 patient: Grade 4 pneumonitis and colitis (related to BV and nivolumab, 2 patients or 3%), Grade 2 pneumonitis (id.), Grade 3 diarrhea and Grade 2 colitis, and Grade 3 AST elevation.

[0149] Preliminary biomarker data indicate a BV-induced decrease in the percentage of CD4⁺ T regulatory (T_{reg}) cells at Cycle 1 Day 8, with no effect on proliferating CD8⁺ T cells. At Cycle 1, nivolumab induced a robust expansion of T cells one week after dosing (2 weeks after BV dosing), with no significant change observed in the percentage of CD4⁺ Th1 cells compared to baseline for most patients (5 of 6, 83%).

[0150] Early data suggest the combination of BV and nivolumab is an active and well-tolerated salvage therapy in patients with relapsed or refractory (R/R) Hodgkin lymphoma (HL). While an elevated incidence of IRRs has been observed, toxicities with this regimen appear to be tolerable overall. The preliminary antitumor activity suggests this combination can be a promising option for R/R HL patients.

[0151] The promising activity of the BV and nivolumab combination supports further exploration of this novel regimen for RR cHL patients.

EXAMPLE 3

[0152] A randomized, open-label, Phase 3 trial of nivolumab plus brentuximab vedotin versus brentuximab vedotin alone in participants with relapsed refractory or ineligible for autologous stem cell transplant (ASCT) advanced stage classical Hodgkin Lymphoma is planned.

Background

[0153] The programmed death-1 (PD-1) cell surface membrane receptor is a member of the

CD28 family of T-cell co-stimulatory receptors. PD-1 expression is a marker of T cell exhaustion and is associated with immune evasion in tumors. Hodgkin Lymphoma (HL) is characterized by genetic predisposition for over expression of programmed death (PD)-1 ligands. There are multiple mechanisms identified for upregulation of PD-L1 and PD-L2 in HL. Additionally CD30 is a cell membrane protein of the tumor necrosis factor family. CD30 is highly expressed in HL on the Reed Sternberg cells. Given the abundant expression of PD-1 ligands and CD30 in HL, the two proteins provide opportunity to target specific molecules associated with tumor growth and progression. Ongoing trials with the combination of brentuximab vedotin (BV) and nivolumab appear promising. Nivolumab and BV have demonstrated encouraging single agent activity in the treatment of relapsed HL. Since both drugs are effective as single agents, it is likely that the combination may have better efficacy as compared to either agent alone. A Phase 1/2 trial of the BV and nivolumab combination is ongoing in adults with Relapsed/Refractory Hodgkin Lymphoma after failure of first-line therapy. In this study, patients have been treated for a total of 4 cycles with combination regimen. Overall, the combination has been well tolerated with none of the participants requiring dose discontinuation due to toxicities. All patients were able to tolerate 4 cycles of combination regimen. The majority of adverse events including immune-related adverse events were low grades (1 and 2). Preliminary results are indicative of a highly efficacious regimen in a sample size n= 20, with an Objective Overall Response Rate of 90% and Complete Metabolic Response of 62%. Similar findings have been observed in another ongoing trial. The preliminary data from the E4412 trial with a sample size (N=10) for relapsed/refractory patients has demonstrated an ORR of 100% and CR of 63%. Although the studies are ongoing and numbers are small, preliminary findings are suggestive of an effective and tolerable regimen in a refractory patient population with high unmet need.

[0154] It is therefore anticipated that combination therapy could potentially be more effective in the salvage treatment setting than administration of either agent alone. The combination may result in demonstrating higher clinical benefit, which can translate into improved disease control in a patient population where outcome is poor. Moreover, both agents are well tolerated, have few overlapping toxicities, and can be infused in the outpatient setting.

Study Population

[0155] Males and females, ages 18 and above with relapsed/refractory cHL and with one of the following:

1. a) Autologous Stem Cell Transplant (ASCT) ineligible patients

Chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy) or any significant coexisting medical condition (cardiac, renal, pulmonary, or hepatic dysfunction) are likely to have a negative impact on tolerability of ASCT. Note: Sponsor review and approval of participants < 65 years of age who are not ASCT candidates is required before randomization. Participants must have received at least 2 prior chemotherapy regimens (BV can be included as one regimen).

2. b) Patients after failure of ASCT:

- Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT
- Documented relapsed disease (after CR) or disease progression (after PR or SD)

[0156] Both for a) and b), participants who are naive to BV or who were sensitive to the most recent BV treatment are eligible. Participants must demonstrate BV sensitivity as defined by documented PR or CR from the most recent BV treatment, and by no disease progression during the most recent BV treatment or no early relapse within 3 months after last dose of the most recent BV based on medical record. For b), prior treatment with BV may have been as a single agent or in combination with chemotherapy and may have occurred during any line of therapy (e.g., induction, salvage, or consolidation post-ASCT). Of note, documentation of response following consolidation therapy with BV is not required, as it is assumed that the patients are in remission at the time of consolidation.

[0157] Other key inclusion criteria include ECOG PS 0-1 and biopsy confirmation of cHL prior to initiation of study drug. Key exclusion criteria include known CNS lymphoma, nodular lymphocyte-predominant HL, and active interstitial pneumonitis or CT evidence of Grade 1 pneumonitis.

Objectives and Endpoints

[0158] The primary and secondary objectives of the study, and the endpoints of the study, are set forth in Table 6 below. The primary objectives in the study will be measured by the primary endpoint of PFS assessed by BICR. The secondary objectives in the study will be measured by: (1) CRR, ORR, DOR, and DOCR assessed by BICR; (2) PFS assessed by investigator; and (3) OS.

Table 6. Objectives/Endpoints

Objectives		Endpoints	
Primary			
	• To compare progression free survival of nivolumab+BV vs. BV based on BICR assessments		• Progression Free Survival (PFS): defined as time from date of randomization to death, or disease progression.

Secondary		
	• To compare the complete response rate of nivolumab+BV vs. BV based on BICR assessments	• Complete Response Rate (CRR): defined as proportion of participants who have achieved complete response (Lugano 2014 conference)
	• To assess objective response rate and duration of response based on BICR	• Objective Response Rate (ORR): defined as the proportion of participants who have achieved complete response or partial response (Lugano 2014 classification)
	• To assess duration of complete response based on BICR	
	• To assess overall survival of participants treated with nivolumab + BV vs BV	• Duration of response or duration of complete response (DOR or DOCR): defined as the time from first response or complete response to the date of initial objectively documented progression as determined using the 2014 Lugano classification or death due to any cause
	• To assess PFS based on investigator assessments	
		• Overall Survival (OS): defined as the time between the date of randomization and the date of death.
		• PFS defined as the above but assessed by investigator.

[0159] The primary endpoint PFS based on BICR assessment will be compared in two randomized arms via a two-sided, log-rank test stratified by the same factors used in randomization. Participants who die without a reported progression will be considered to have progressed on the date of their

Overall Design

[0160] This is a 1:1 randomized, open-label phase 3 study in advanced cHL participants ≥ 18 years old who are relapsed refractory or ineligible for autologous stem cell transplant (ASCT). Patients will be balanced in the 2 groups in regards to prior therapies. Approximately 340 participants will be treated in one of two arms: (1) nivolumab 360 mg IV every 3 weeks until progression or unacceptable toxicity (except for patients in CR who can discontinue at 2 years) plus BV 1.8 mg/kg IV every 3 weeks for 16 cycles, or until progression or unacceptable toxicity, whichever occurs first, or (2) BV alone 1.8 mg/kg every 3 weeks for 16 cycles, or until progression or unacceptable toxicity, whichever occurs first. Treatment may also be discontinued if the participant meets other criteria for discontinuation of study drug outlined in

Section 8.1 of the protocol. Participants receiving nivolumab who achieve CR may discontinue treatment after a maximum of 2 years of therapy, provided that there is no prohibitive toxicity. Participants can be BV- naïve, or can have prior BV treatment as a single agent or in combination in any line of therapy. Randomization stratification will be performed on the following two factors: (1) Prior ASCT status (YES/NO); (2) Prior BV use (YES/NO). Participants will be balanced based on the stratification factors per arm.

[0161] Participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 21-day dosing period will constitute a cycle.

[0162] Any participant who discontinues the study treatment prior to progression will be followed for progression, then survival, in the follow up phase of the study.

[0163] Approximately 400 participants will be screened and then, with an estimated screen failure rate of 15%, the planned sample size for this study will be approximately 340 randomized participants. The sample size of the study accounts for the primary efficacy endpoint, PFS. PFS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided) with 90% power.

[0164] Sample size determination for PFS provides approximately 340 participants will be randomized to nivolumab + BV and BV arms in a 1:1 ratio, i.e., such that 170 participants will be assigned to the nivolumab + BV arm, and 170 participants will be assigned to the BV arm. For the comparison of PFS between the two treatment arms, the study requires at least 187 PFS events to ensure that a two-sided 5% type I error sequential test procedure will have 90% power to detect a hazard ratio (HR) of 0.62, corresponding to a median PFS of 15 vs 9.3 months for the nivolumab + BV and BV arms, respectively.

[0165] One formal PFS interim analysis will be conducted when at least 131 PFS events (70% of the final PFS events) have been observed and also requires a minimum follow-up of 9 months from Last Patient First Visit (LPFV).

[0166] Assuming an accrual rate of 10 participants enrolled per month, the accrual will take approximately 30.5 months. The final analysis for PFS is expected to take place 46 months after the first participant's randomization date (30.5 months of accrual + 15.5 months of follow-up). This projection is based on an assumption that the progression free survival rates are 28% and 45.4% at 24 months in BV arm and nivolumab + BV arm, and very few events will occur after two years of treatment in both arms. The interim analysis for PFS is expected to take place 40 months after the first participant's randomization date.

[0167] East version 6.3 was used for sample size/power computations.

[0168] The treatment arms and duration are shown in FIG. 10. The study treatment includes (1) a Randomized Investigational Arm: Nivolumab (360 mg flat dose) every 3 weeks until progression or unacceptable toxicity + BV (1.8 mg/kg) every 3 weeks for 16 cycles,

progression, or unacceptable toxicity, whichever occurs first; and (2) a Randomized Control Arm: BV (1.8 mg/kg) every 3 weeks for 16 cycles, progression, or unacceptable toxicity, whichever occurs first. Further information about preparations and routes of administration for nivolumab and BV is provided in Table 7 below.

Table 7.

Study Drug		
Medication	Potency	IP/Non-IP
Nivolumab (BMS-936558) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP
Brentuximab Vedotin Powder for Solution for Injection	50 mg	IP

[0169] Other medications used as support medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

EXAMPLE 4

BV-killed A20 mouse lymphoma immunization confers anti-tumor protection

[0170] A20 mouse lymphoma cells were transfected with plasmid constructs encoding human *TNFRSF8* (NM_001243.4) and sgRNA/Cas9 for control under the endogenous promoter of murine *Tnfrsf8*. Fluorescence activated cell sorting (FACS) yielded a clonal population of A20 cells that stably expressed human CD30, to be referenced as A20^{hCD30}, in order to be susceptible to brentuximab vedotin treatment.

[0171] A20^{hCD30} cells were cultured in RPMI 1640 with 10% FBS, 10mM HEPES, 1mM sodium pyruvate, penicillin (100 U/ml), and streptomycin (100 µg/ml). A20^{hCD30} cells were treated with 1µg/ml BV or 100 nM mc-vc-MMAE for 4 days. In order to prepare dying cells for immunization, treated A20^{hCD30} cells were overlaid atop Histopaque, and centrifuged at 2000g for 30 minutes. Dead and dying cells were pelleted underneath the Histopaque layer, and viability was assessed to be <20% live cells by trypan blue exclusion. Flash-frozen A20^{hCD30} cells were prepared by submerging cells in liquid nitrogen for 10 seconds, followed by immersion in 37°C water until completely thawed. The liquid nitrogen freeze-thaw process was repeated 5 times. Dead and dying A20^{hCD30} cells were resuspended in PBS and 2×10⁶ cells were injected into the peritoneum of immune-competent Balb/c mice. 7 days later, mice received a second immunization with dead and dying cells prepared in the same manner.

[0172] 14 days after initial immunization, mice were subcutaneously implanted with 5×10^6 wild-type A20 cells and monitored for tumor growth. As shown in FIG. 11, mice that were immunized with BV-killed or mc-vc-MMAE-killed A20^{hCD30} cells delayed tumor growth, and increased survival of tumor-bearing mice. As these effects occurred in the absence of any administered therapeutic, the presence of cells killed by BV or MMAE were sufficient to generate long-lasting protective immune memory against subsequent A20 lymphoma challenge.

T cell transfer provides protective immunity

[0173] Immune-competent Balb/c mice were immunized with BV-killed or flash-frozen-killed A20^{hCD30} cells as previously described. 16 weeks after initial immunization, spleens were harvested from immunized mice or naive Balb/c mice, and manually homogenized. Splenic homogenates were combined from 4 mice per immunization, and CD3⁺ T cells were isolated using EasySep Mouse T cell Enrichment Kit (Stem Cell Technologies). 1×10^6 CD3⁺ T cells were administered intravenously into A20 tumor-bearing mice.

[0174] 4×10^6 wild-type A20 cells were subcutaneously implanted into immunodeficient NOD/SCID/y-chain-deficient (NSG) mice. 5 days after implant, mice harboring tumors $\sim 100 \text{ mm}^3$ were randomized, and received 1×10^6 T cells from mice as described above. As shown in FIG. 12A, NSG mice that received T cells from mice immunized with BV-killed cells slowed tumor growth, as well as increased CD8 T cells within the tumor (FIG. 12B). The capacity of T cells to provide robust anti-tumor immunity long after immunization demonstrates that tumor death from BV elicits strong immune memory that is mediated by T cells.

PD-1 inhibition potentiates protective immunity conferred by BV

[0175] Balb/c mice were immunized with BV- or MMAE-killed A20^{hCD30} cells as described above. 14 days after initial immunization, mice were subcutaneously implanted with 5×10^6 wild-type A20 cells. Anti-murine PD-1 (1mg/kg, BioLegend) was administered intravenously on days 6, 9, 14, and 17 after A20 tumor challenge. Immunization with BV- or MMAE-killed A20^{hCD30} cells conferred protective anti-tumor immunity. As shown in FIG. 13, combination with anti-PD-1 therapy augmented protective immunity and improved tumor clearance and survival.

[0176] T cell and NK cell infiltration into autologous tumors in a humanized mouse model.

[0177] Epstein Barr virus (EBV) transformed lymphoblastoid cell Lines (LCL) were implanted subcutaneously into NSG mice. When LCL tumor volumes reached 250 mm^3 , mice received a

single suboptimal dose of BV or control hlgG-MMAE (1mg/kg, i.p). Three days following dosing, 2.0×10^6 autologous peripheral blood mononuclear cells (PBMC) were adoptively transferred to mice via tail vein injection. Eleven days following transfer of PBMC, tumors were harvested, weighed, and manually dissociated through a 70 μ m cell strainer. Following centrifugation, individual tumor cell pellets were resuspended in 4ml of RPMI +10% FCS, and 200ul of the cell suspension was used for staining and analysis by flow cytometry (FACS). Tumor cell suspensions were stained with Zombie Aqua Viability Dye (Biolegend) followed by staining with fluorescently labeled antibodies targeting human CD19, CD2, CD8, CD4, CD56, human CD45, PD-L1, PD-1, and murine CD45.1 (1:50 dilution, Biolegend) in staining buffer (SB: PBS, 2%FCS, 1% NRS, 0.05% NaN₃) at 4°C for 30 minutes. Cells were washed and resuspended in 120 μ l of SB for plate-based FACS using an Attune NXT flow cytometer. All events were collected from 80 μ l of sample, and FACS-measured cell concentrations were used to calculate numbers of infiltrating immune cells. CD8⁺ T cells were identified as viability dye^{neg}, hCD45⁺, mCD45.1⁻, CD2⁺, CD8⁺ cells. NK cells were identified as viability dye^{neg}, hCD45⁺, mCD45.1⁻, CD2⁺, CD56⁺ cells. FIG. 14A shows calculated cell counts relative to tumor mass, or alternatively, as a calculated total cell count (FIG. 14B). FIG. 14C shows CD8⁺ T cells recovered from tumors expressed increased levels of PD-1, and LCL tumor cells expressed heightened levels of PD-L1 relative to their resting/normal PBMC counterparts (FIG. 14D). Treatment of mice harboring established LCL tumors with a suboptimal dose of BV enhanced intratumoral accumulation of human cytotoxic cells consistent with the induction of an anti-tumor inflammatory response.

[0178] BV enhances immune-mediated tumor clearance alone and in combination with Nivolumab in the humanized LCL tumor model.

[0179] Epstein Barr virus (EBV) transformed lymphoblastoid cell lines (LCL) were implanted subcutaneously into NSG mice. When LCL tumors averaged 250mm³, mice received a single suboptimal dose of BV or control hlgG-MMAE (1 mg/kg, i.p). Three days following dosing, 2×10^6 autologous PBMC were adoptively transferred to mice via tail vein injection. Mice received two doses of nivolumab (10 mg/kg, i.p.) 2 and 7 days after adoptive transfer of PBMC. FIG. 15A shows treatment group tumor volume over time, relative to untreated (no drug) control. Notably, mice receiving a suboptimal dose of BV without the addition of PBMC (solid line, top) did not reject tumors and were removed from the study when tumors exceeded 2000 mm³. All other treatment groups received autologous PBMC and showed tumor regression, highlighting the role of immune-mediated tumor clearance in this model. A single, suboptimal dose of BV administered 3 days prior to transfer of PBMC resulted in enhanced immune-mediated tumor clearance compared to mice receiving control hlgG-MMAE or nivolumab alone. Importantly, mice receiving a combination of BV and nivolumab showed the most rapid tumor clearance of any treatment group. The significance of these differences is reflected in a comparison of mean tumor volumes at day 50, during active tumor clearance (FIG. 15B). Taken together, results obtained from this humanized model support the conclusion that in addition to direct tumor cell killing, BV drives an inflammatory response that enhances immune-

mediated cellular cytotoxicity and pairs well with nivolumab.

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ANVENDELSE AF ET ANTI-PD-1-ANTISTOF I KOMBINATION MED ET ANTI-CD30- ANTISTOF I
LYMFOMBEHANDLING

PATENTKRAV

1. Nivolumab til anvendelse i en fremgangsmåde til behandling af et recidiverende eller refraktært
5 Hodgkins lymfom hos et individ med behov derfor, hvor individet får indgivet en kombination af:
 - (a) en dosis på 3 mg/kg nivolumab og
 - (b) en dosis på 1,8 mg/kg brentuximab-vedotin;

hvor (i) dosen af brentuximab-vedotin indgives til individet på dag 1 af en første 21-dages cyklus;
(ii) dosen af nivolumab indgives til individet på dag 8 af den første 21-dages cyklus; og (iii) en kombination
10 af 1,8 mg/kg brentuximab-vedotin og 3 mg/kg nivolumab indgives på dag 1 af hver af en anden 21-dages
cyklus, en tredje 21-dages cyklus og en fjerde 21-dages cyklus, hvor den anden 21-dages cyklus, den tredje
21-dages cyklus og den fjerde 21-dages cyklus følger efter hinanden efter den første 21-dages cyklus.
2. Nivolumab til anvendelse ifølge krav 1, hvor Hodgkins lymfomet omfatter én eller flere celler, der
udtrykker CD30.
- 15 3. Nivolumab til anvendelse ifølge krav 2, hvor mindst 1 % af Hodgkins lymfomcellerne udtrykker
CD30.
4. Nivolumab til anvendelse ifølge et hvilket som helst af kravene 1 til 3, hvor nivolumab og
brentuximab-vedotin indgives sekventielt.
5. Nivolumab til anvendelse ifølge et hvilket som helst af kravene 1 til 4, hvor Hodgkins lymfomet
20 omfatter én eller flere celler, der udtrykker PD-L1, PD-L2, eller både PD-L1 og PD-L2.
6. Kit til anvendelse i en fremgangsmåde til behandling af recidiverende eller refraktært Hodgkins
lymfom hos et individ med behov derfor ifølge et hvilket som helst af kravene 1 til 5 omfattende:
 - (a) en dosis nivolumab; og
 - (b) en dosis brentuximab-vedotin.

DRAWINGS

FIG. 1

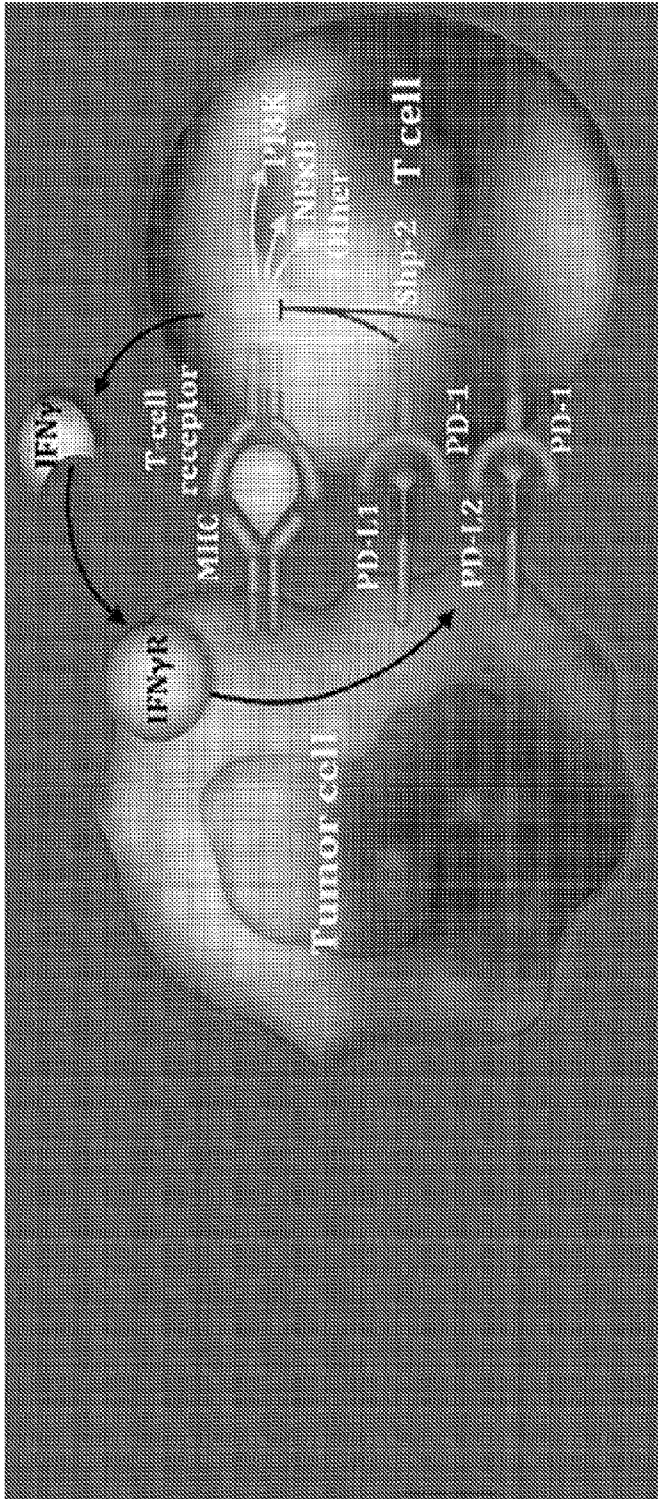


FIG. 2

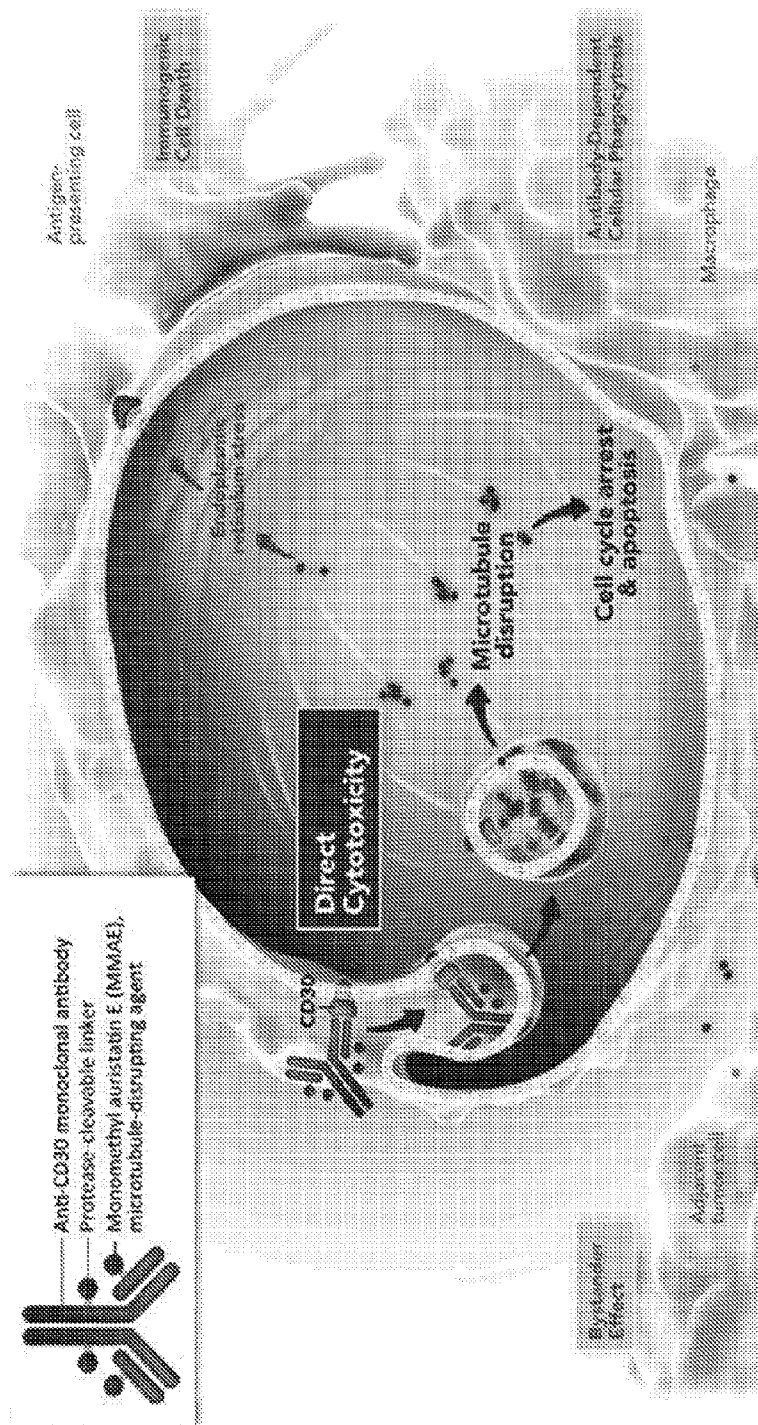
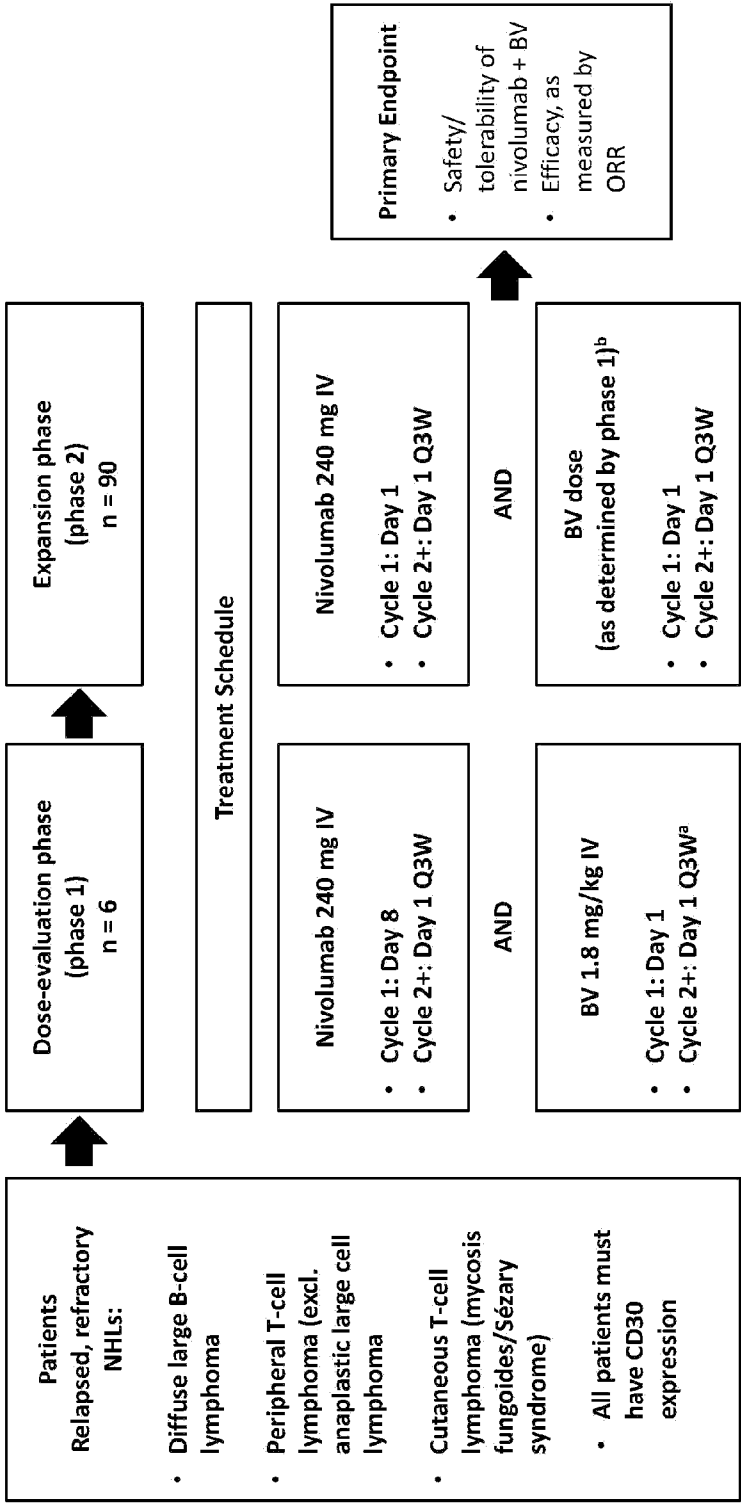


FIG. 3



^a Cycle 2+ BV dose can be reduced to 1.2 mg/kg if DLT is observed.

^b If <1 of the patients in phase 1 experience DLT, the phase 2 cohort will be given BV 1.8 mg/kg. If >2 patients experience DLT, a reduced dose of BV 1.2 mg/kg will be administered DLT = dose-limiting toxicity; Q3W = every 3 weeks

FIG. 4

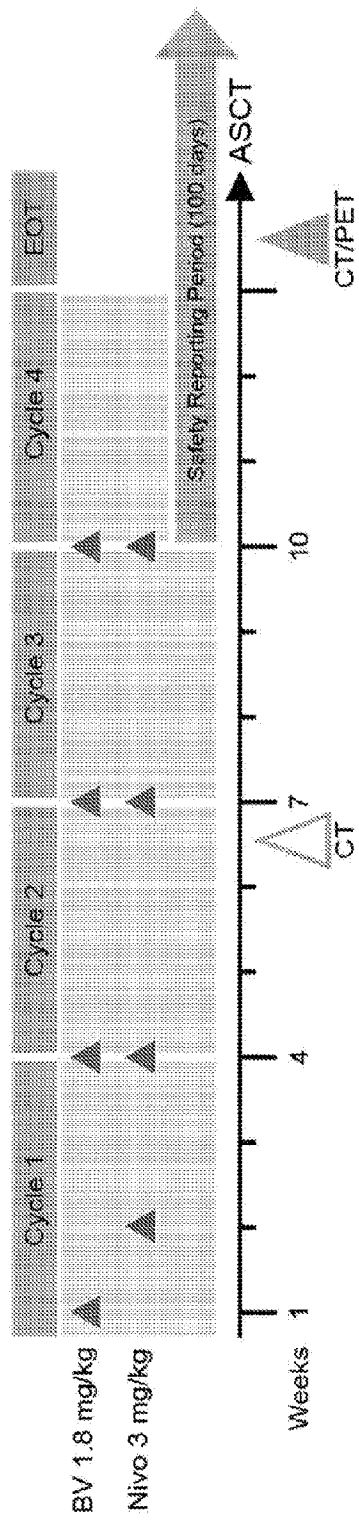


FIG. 5A

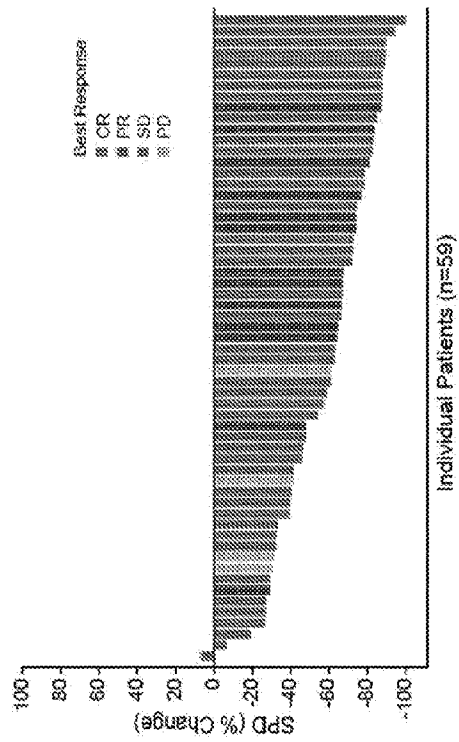


FIG. 5B

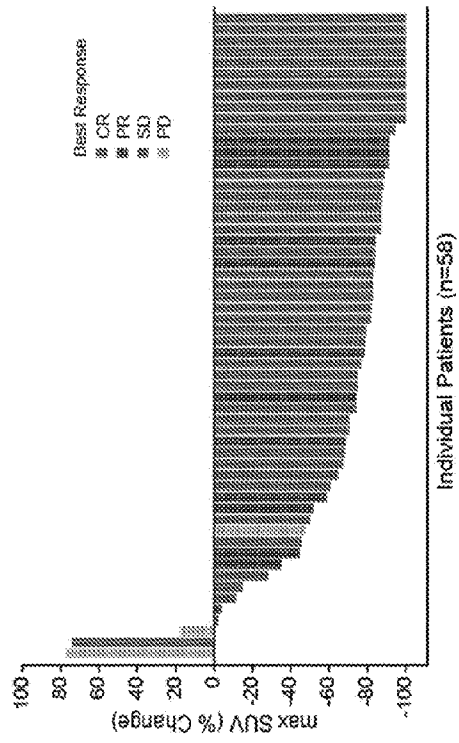


FIG. 6B

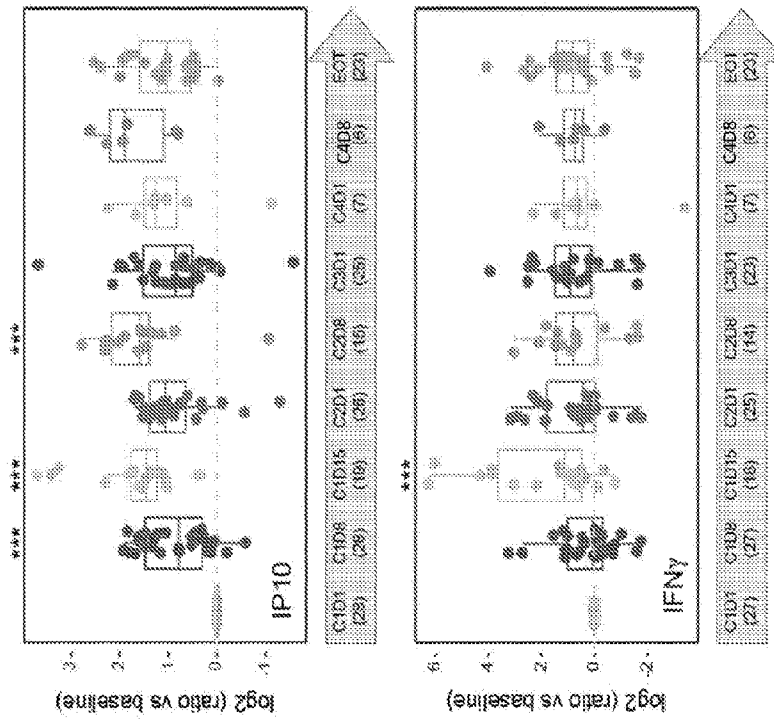


FIG. 6D

FIG. 6A

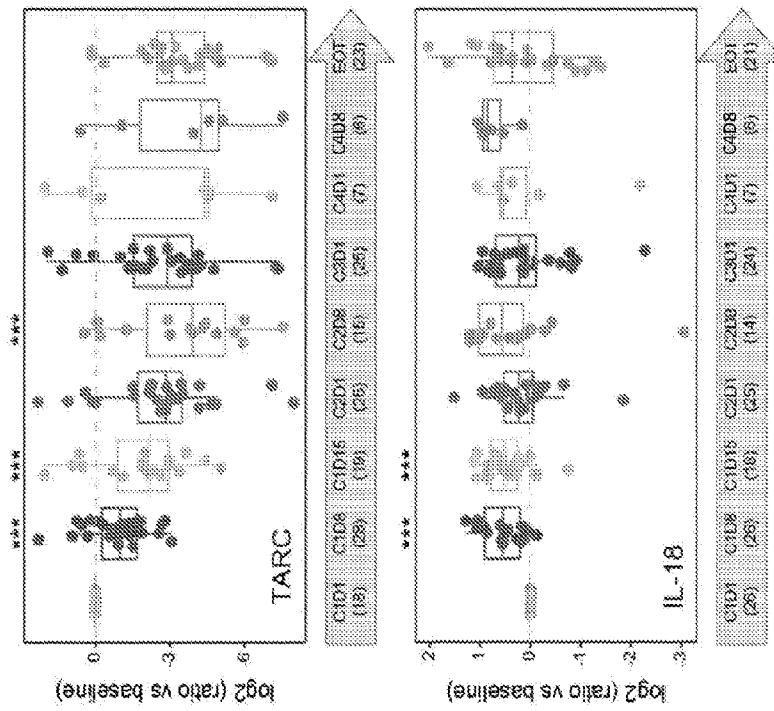


FIG. 6C

FIG. 7A

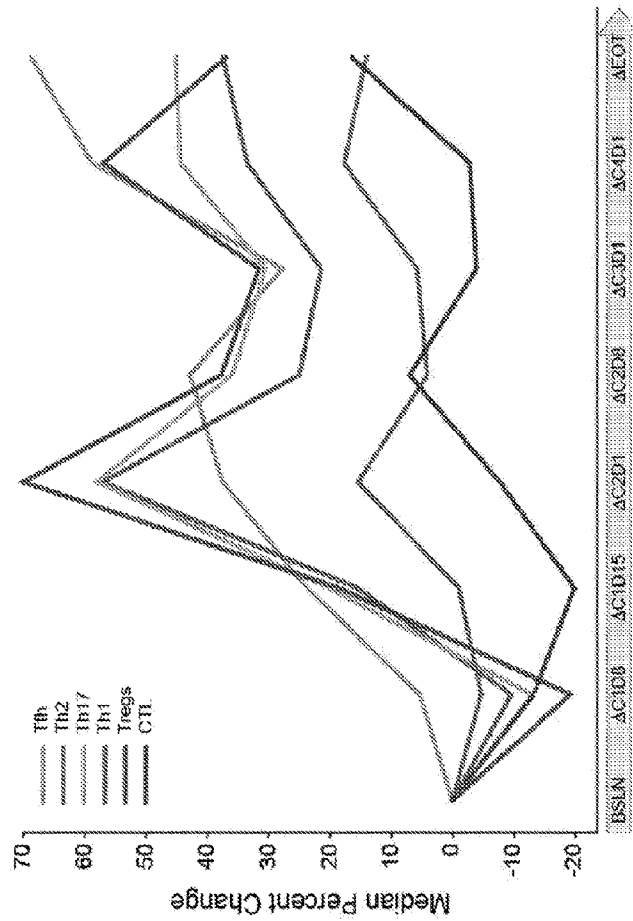


FIG. 7B

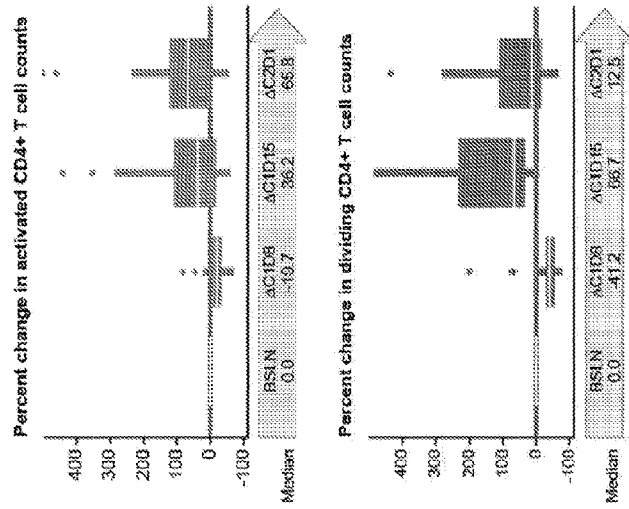


FIG. 7C

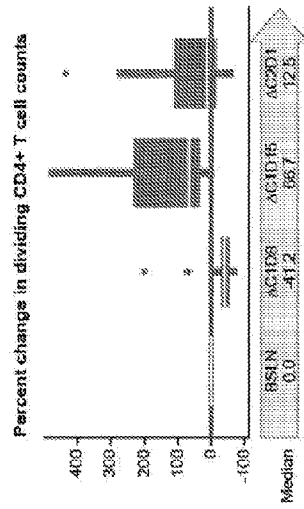


FIG. 8

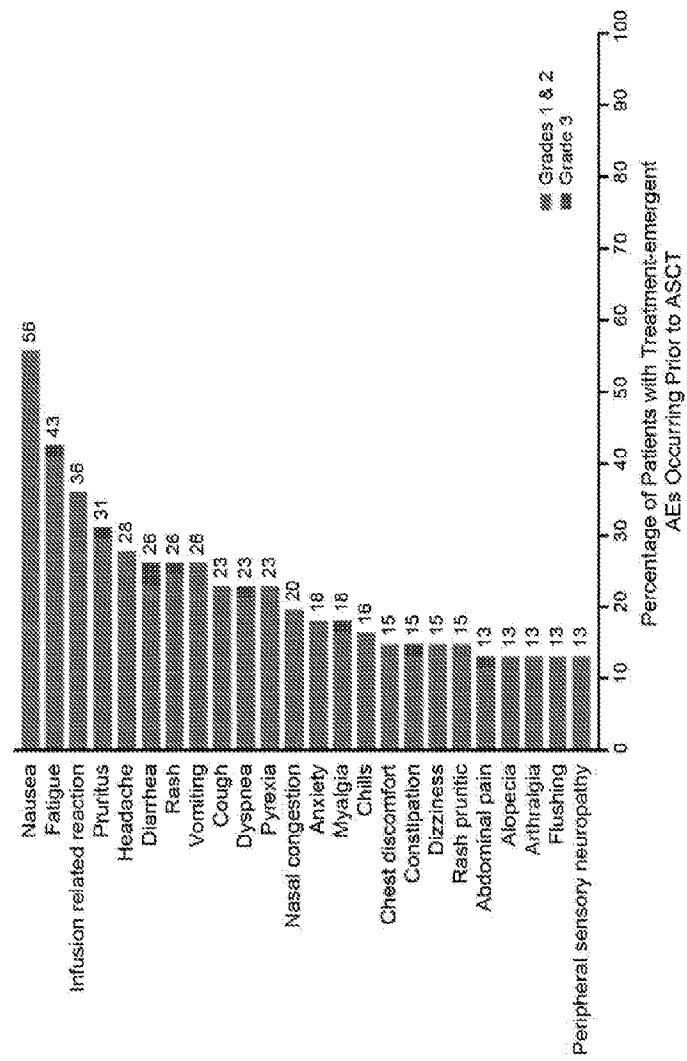


FIG. 9

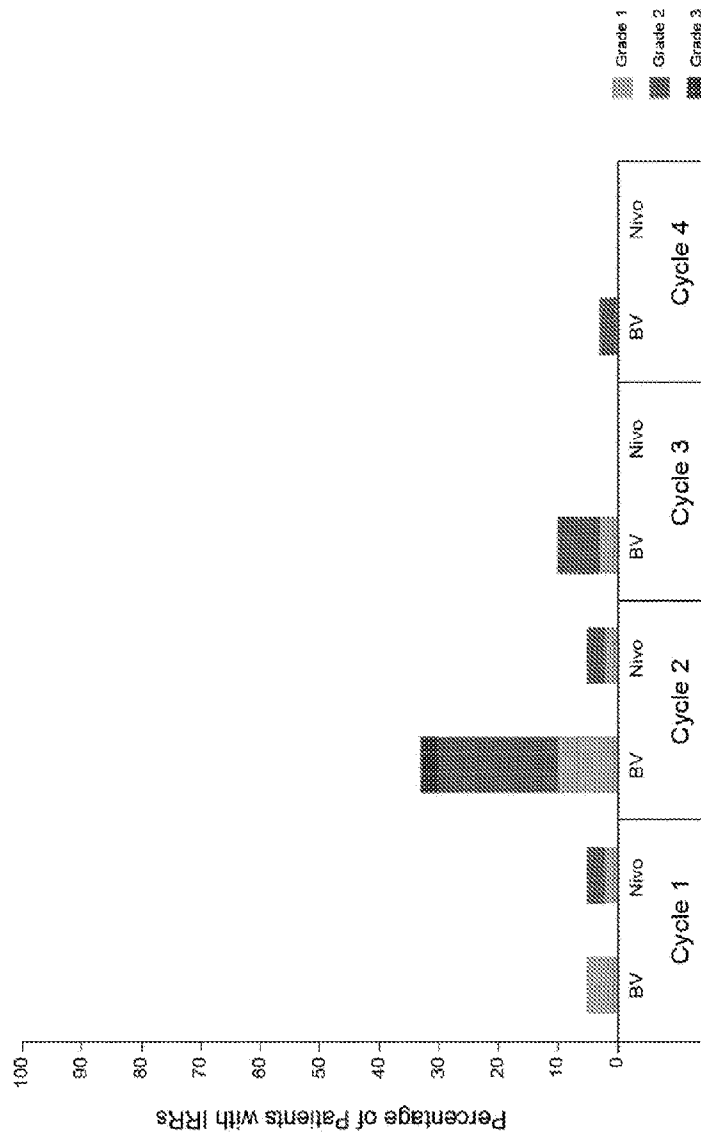
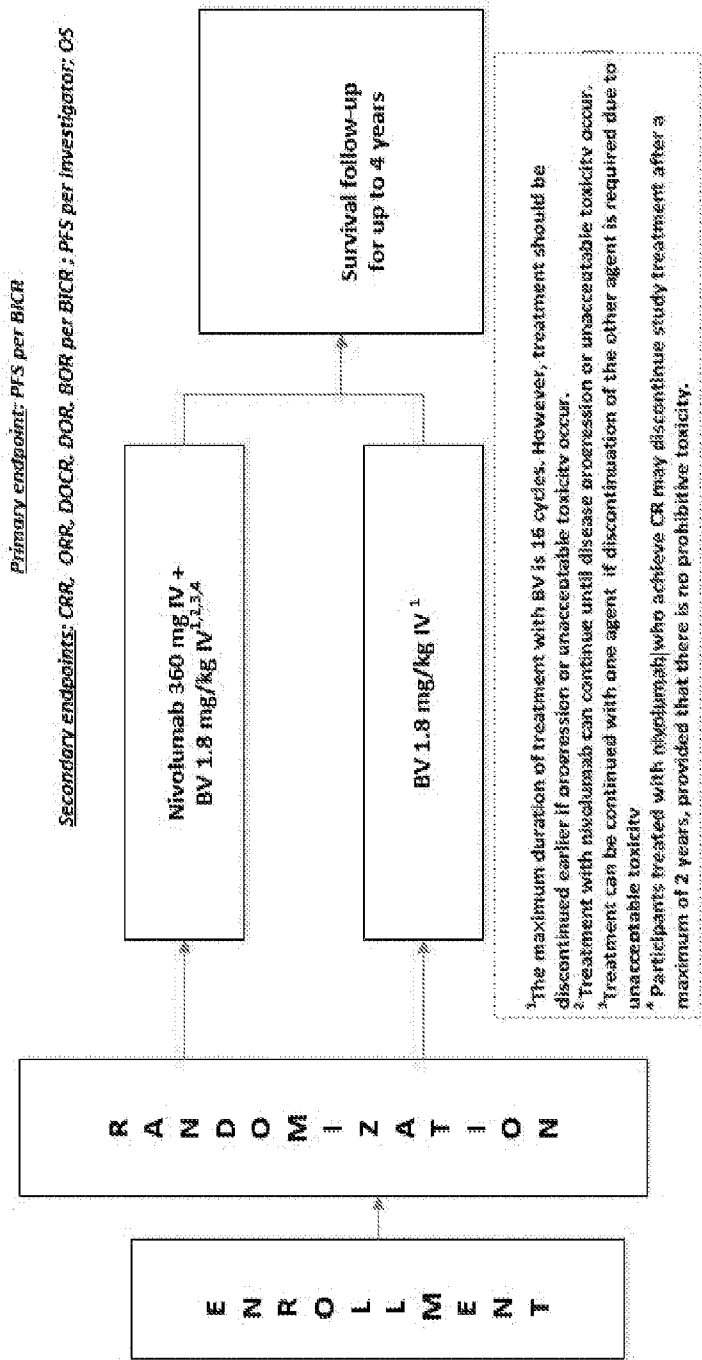


FIG. 10



Abbreviations: BV = brentuximab vedotin; BICR = Blinded Independent Central Review; PFS = progression-free survival; CRR = complete response rate; OS = overall survival; ORR = objective response rate; DOCR = duration of complete response; DOR = duration of response; BOR = best overall response

FIG. 11

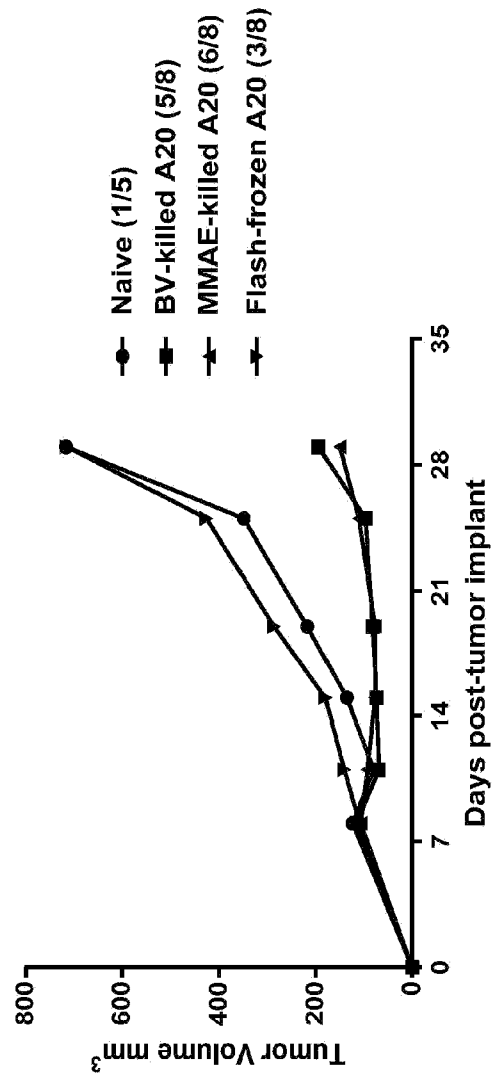


FIG. 12A

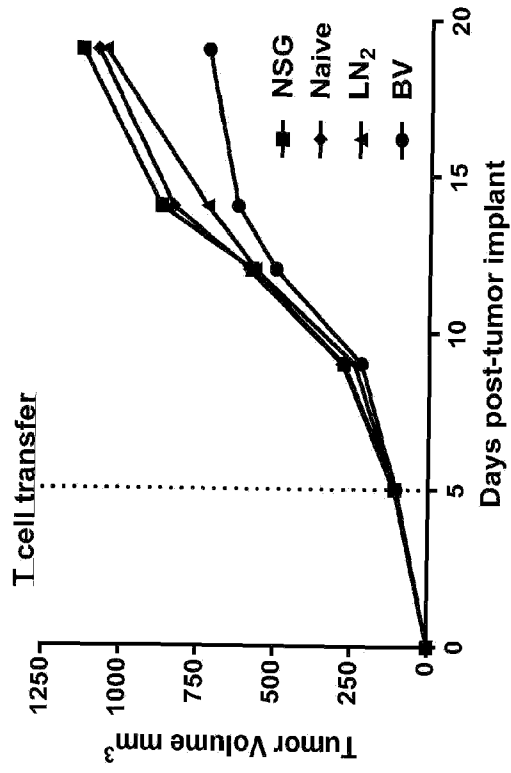


FIG. 12B

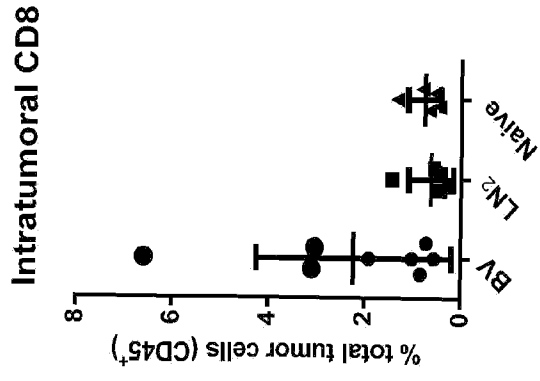


FIG. 13

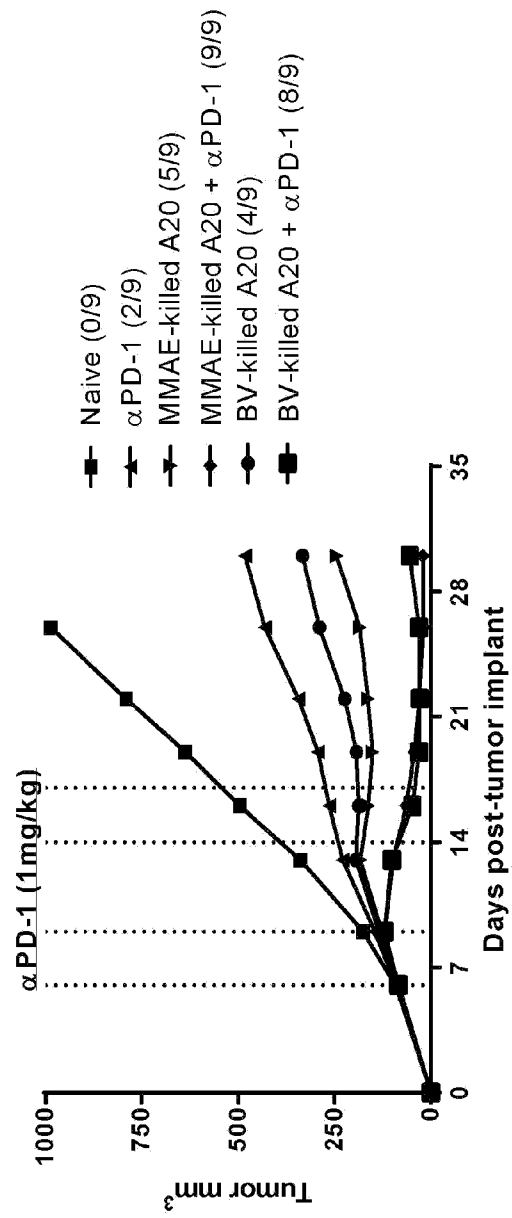


FIG. 14A

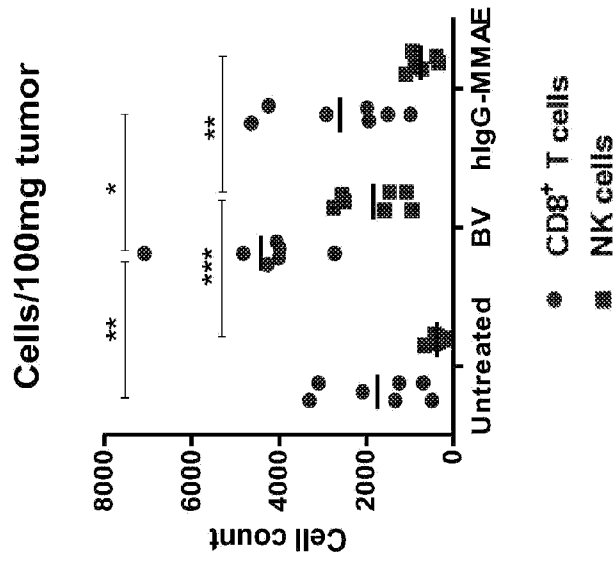


FIG. 14B

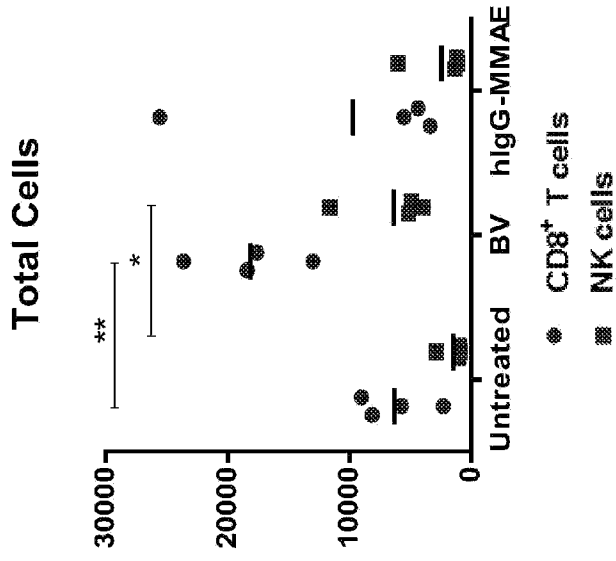


FIG. 14C

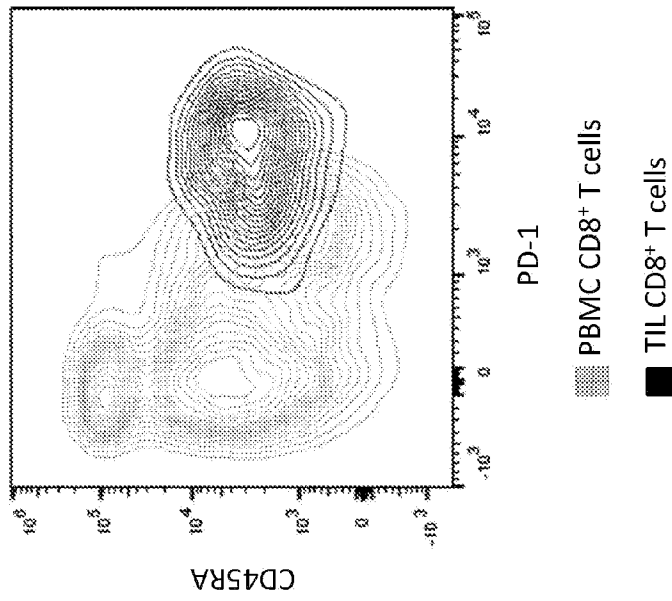


FIG. 14D

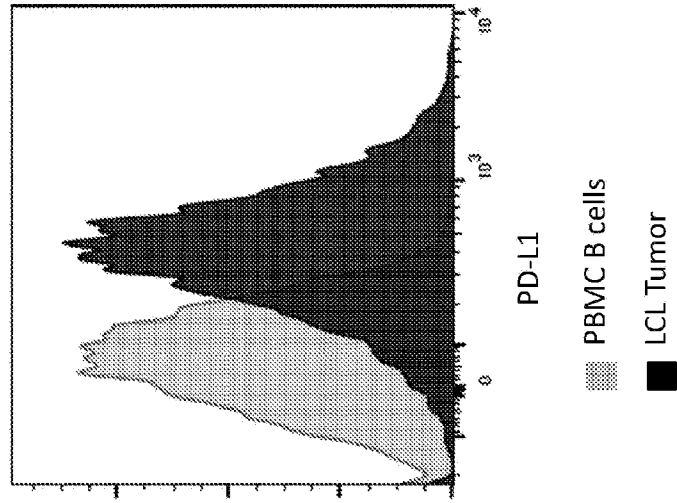


FIG. 15A

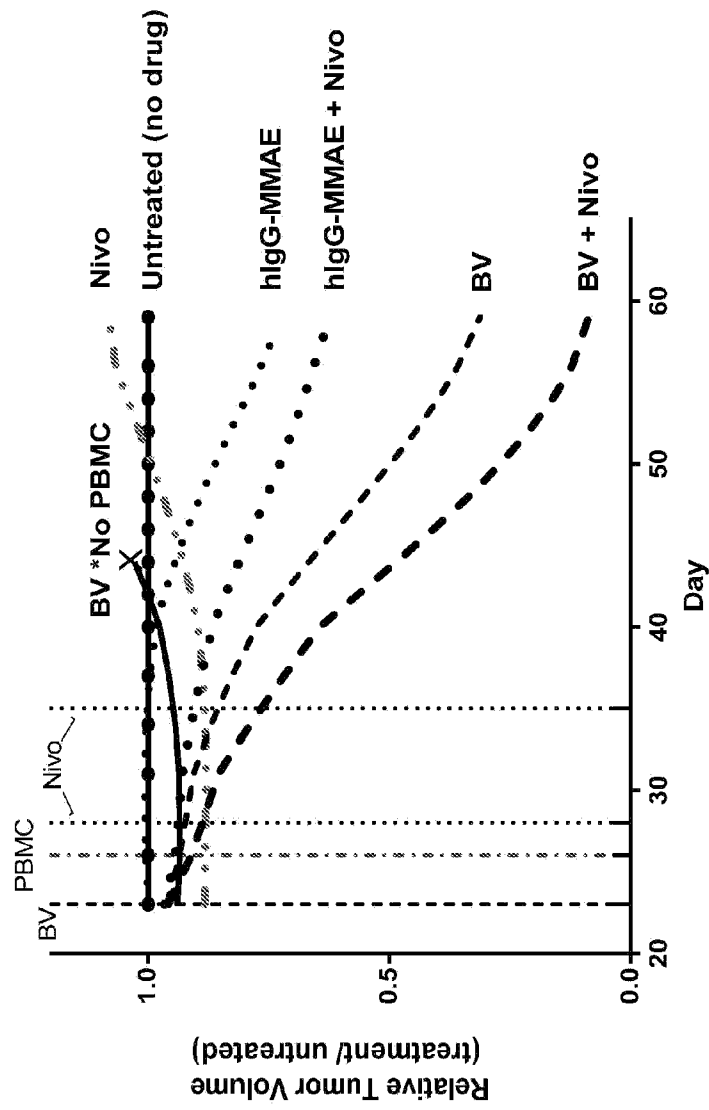


FIG. 15B

Group	Day 50 Mean+/- SEM tumor volume (mm ³)	p-values (one-tailed t- test)			
Untreated	694 +/- 77	0.44			
hIgG-MMAE	669 +/- 154	0.19	0.23		
Nivolumab	792 +/- 68	0.09	0.21	0.02	
hIgG-MMAE + Nivo	531 +/- 81	0.008	0.05	0.003	0.08
BV	345 +/- 95	0.0001	0.003	0.0001	0.002
BV + Nivo	160 +/- 49				0.06

UntreatedhIgG-MMAENivolumabhIgG-MMAE + NivoBV