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(72) **Inventeurs/Inventors:**
POGUE, SARAH L., US;
WILSON, DAVID S., US;
DOYLE, ANTHONY GERARD, AU;
BEHRENS, COLLETTE JANE, AU

(73) **Propriétaire/Owner:**
TEVA PHARMACEUTICALS AUSTRALIA PTY LTD, AU

(74) **Agent:** OSLER, HOSKIN & HARCOURT LLP

(54) **Titre : COMBINAISON DE LENALIDOMIDE ET D'UNE CONSTRUCTION DE POLYPEPTIDE, ET SES UTILISATIONS**
(54) **Title: COMBINATION OF LENALIDOMIDE OR POMALIDOMIDE AND CD38 ANTIBODY-ATTENUATED INTERFERON-ALPHA CONSTRUCTS, AND THE USE THEREOF**

(57) **Abrégé/Abstract:**
Methods for cancer treatment include administering to a cancer patient an anti- CD38 antibody-attenuated human IFN alpha-2b construct and lenalidomide or pomalidomide. Tumors that may be treated according to these methods include tumors which comprise CD-38 expressing tumor cells, including B-cell lymphoma, multiple myeloma, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, and acute lymphocytic leukemia.

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(71) Applicant: **TEVA PHARMACEUTICALS AUSTRALIA PTY LTD** [AU/AU]; Level 2, 37 Epping Road, Macquarie Park, NSW 2113 (AU).

(72) Inventors: **POGUE, Sarah, L.**; 41 Moores Road, Frazer, PA 19355 (US). **WILSON, David, S.**; 41 Moores Road, Frazer, PA 19355 (US). **DOYLE, Anthony, Gerard**; 100 Gipps Street, Drummoyne, 2047 (AU). **BEHRENS, Collette, Jane**; Level 2.37 Epping Road, Macquarie Park, 2113 (AU).

(74) Agent: **DAVIES COLLISON CAVE**; 1 Nicholson Street, Melbourne, VIC 3000 (AU).

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(54) Title: COMBINATION OF LENALIDOMIDE OR POMALIDOMIDE AND CD38 ANTIBODY-ATTENUATED INTERFERON-ALPHA CONSTRUCTS, AND THE USE THEREOF

(57) Abstract: Methods for cancer treatment include administering to a cancer patient an anti- CD38 antibody-attenuated human IFN alpha-2b construct and lenalidomide or pomalidomide. Tumors that may be treated according to these methods include tumors which comprise CD-38 expressing tumor cells, including B-cell lymphoma, multiple myeloma, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, and acute lymphocytic leukemia.

COMBINATION OF LENALIDOMIDE OR POMALIDOMIDE AND CD38 ANTIBODY-ATTENUATED INTERFERON-ALPHA CONSTRUCTS, AND THE USE THEREOF

FIELD

This disclosure relates generally to the field of cancer treatment. More specifically, this disclosure relates to a cancer therapy that synergistically combines lenalidomide or pomalidomide with an anti-CD38 antibody-attenuated interferon alpha-2b construct. The combination therapy substantially enhances tumor growth inhibition or delay relative to the tumor growth inhibition or delay exhibited by administration of either lenalidomide, pomalidomide, or the construct alone. In addition, the combination therapy may overcome lenalidomide resistance or pomalidomide resistance.

BACKGROUND

Various publications, including patents, published patent applications, technical articles, scholarly articles, and gene or protein accession numbers are cited throughout the specification.

CD38 is a 46kDa type II transmembrane glycoprotein that is involved in transmembrane signaling and cell adhesion. It is also known as cyclic ADP ribose hydrolase because it can transform NAD^+ and $NADP^+$ into cADPR, ADPR and NAADP, depending on extracellular pH. These products induce Ca^{2+} -mobilization inside the cell, which can lead to tyrosine phosphorylation and activation of the cell. CD38 is also a receptor that can interact with a ligand, CD31. Activation of receptor via CD31 leads to intracellular events including Ca^{2+} mobilization, cell activation, proliferation, differentiation and migration.

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CD38 is expressed at high levels on the surface of multiple myeloma cells, in most cases of T- and B-lineage acute lymphoblastic leukemias (ALL), some acute myelocytic leukemias, follicular center cell lymphomas and T lymphoblastic lymphomas. CD38 is also expressed on B-lineage chronic lymphoblastic leukemia (B-CLL) cells. In some cases, B-CLL patients presenting with a CD38+ clone are characterized by an unfavorable clinical course with a more advanced stage of disease, poor responsiveness to chemotherapy and shorter survival time.

Interferons, and in particular IFN-alpha, are able to increase apoptosis and decrease proliferation of certain cancer cells. IFN-alpha has been approved by the FDA for the treatment of several cancers including melanoma, renal cell carcinoma, B cell lymphoma, multiple myeloma, chronic myelogenous leukemia (CML) and hairy cell leukemia. A direct effect of IFN-alpha on the tumor cells is mediated by the IFN-alpha binding directly to the type I IFN receptor on those cells and stimulating apoptosis, terminal differentiation and/or reduced proliferation. Further, amongst the indirect effects of IFN-alpha on non-cancer cells is the ability of IFN-alpha to stimulate the immune system, which may produce an additional anti-cancer effect by causing the immune system to reject the tumor. IFN-alpha also exhibits the ability to inhibit tumor angiogenesis and, thus, may inhibit tumor growth by metabolic starvation.

The direct anti-tumor activities of IFN-alpha are mediated by type I interferon receptors on the surface of the cancer cells which, when stimulated, initiate various signal transduction pathways leading to reduced proliferation and/or the induction of terminal differentiation or apoptosis. The type I interferon receptor is, however, also present on most non-cancerous cells. Activation of the type I receptor on non-cancerous cells by IFN-alpha causes the expression of numerous pro-inflammatory cytokines and chemokines, leading to undesirable systemic toxicity. Such toxicity may cause severe flu-like symptoms, which prevents the dosing to a subject of IFN-alpha at levels that exert the maximum anti-proliferative and pro-apoptotic activity on the cancer cells.

In general, IFN may be targeted to cancer cells, for example, by linking it with a targeting antibody or targeting fragment thereof. While this approach may result in an increase in activity of the IFN against cancer cells, it does not completely address the issue of undesired activity of the IFN on healthy cells. Fusing IFN-alpha to the C-terminus of the heavy chain of an IgG may, for example, prolong the half-life of the IFN alpha, which may

prolong undesirable adverse events. Accordingly, there exists a need to improve the systemic toxicity profile of interferon while retaining one or more of its anti-tumor effects.

Both lenalidomide and pomalidomide are small molecule immune modulators, and derivatives of the anti-multiple myeloma drug thalidomide. Both lenalidomide and pomalidomide are used in the treatment and maintenance of certain cancers, including multiple myeloma and lymphoma. In many cases, tumors which are initially sensitive to lenalidomide or pomalidomide become resistant or refractory to these agents. In other cases, tumors do not respond to lenalidomide or pomalidomide therapy. There is a need in the art to overcome lenalidomide or pomalidomide-resistance or to enhance lenalidomide or pomalidomide activity, and potentially provide therapies whereby non-responsive patients may come to respond to lenalidomide or pomalidomide therapy.

SUMMARY

The disclosure features methods for treating tumors. The methods may comprise administering to a subject having a tumor an anti-CD38 antibody-attenuated IFN alpha-2b construct in an amount effective for treating the tumor and lenalidomide in an amount effective for treating the tumor. The methods may comprise administering to a subject having a tumor an anti-CD38 antibody-attenuated IFN alpha-2b construct in an amount effective for treating the tumor and pomalidomide in an amount effective for treating the tumor. The construct may enhance the anti-tumor activity of the lenalidomide or may enhance the anti-tumor activity of the pomalidomide, and/or the lenalidomide or pomalidomide may enhance the anti-tumor activity of the construct. The effective amount preferably is an amount at which both agents synergize to substantially inhibit and/or delay tumor growth when compared to tumor growth following the administration of only lenalidomide or pomalidomide or construct., The administration eliminate established tumors, and/or inhibit tumor re-establishment. The subject may be any mammal, preferably is a primate, and most preferably is a human being. Preferably, the amount of the construct and the amount of lenalidomide or pomalidomide are sufficient for the construct and the lenalidomide or pomalidomide to synergize in their therapeutic effect. Each of the construct and the lenalidomide or pomalidomide may be comprised in a composition which comprises a pharmaceutically acceptable carrier, although the construct and lenalidomide or pomalidomide may be comprised in separate compositions. The construct and the lenalidomide or pomalidomide may be administered substantially at the

same time, or may be administered sequentially. Administration may be intravenously (*e.g.*, construct), or orally (*e.g.*, lenalidomide or pomalidomide) and may be at the direction of a medical practitioner. It is believed that the construct remains in circulation longer than lenalidomide or pomalidomide does, such that a therapeutic regimen may comprise more frequent administration of lenalidomide or pomalidomide relative to the administration of the construct. In accordance with such methods, the construct may comprise any anti-CD38 antibody and any attenuated interferon alpha-2b molecule described or exemplified herein.

The tumor will comprise CD-38-expressing tumor cells. The tumor may comprise a B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia. Any such tumor may be sensitive to lenalidomide or pomalidomide alone or resistant to lenalidomide or pomalidomide alone, such that the combination therapy produces a therapeutic benefit to the subject. Multiple myeloma is highly preferred. The disclosure also features use of an anti-CD38 antibody-attenuated IFN alpha-2b construct and lenalidomide or pomalidomide as a combination therapy in the treatment of B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, or acute lymphocytic leukemia.

The anti-CD38 antibody-attenuated IFN alpha-2b construct is preferably a fusion protein comprising an anti-CD38 antibody portion comprising a heavy chain and a light chain, and an attenuated IFN alpha-2b portion, preferably with the C-terminus of the anti-CD38 antibody heavy chain fused to the N-terminus of the attenuated IFN alpha-2b directly by a peptide bond. In some aspects, the C-terminus of the anti-CD38 antibody heavy chain is fused to the N-terminus of the attenuated IFN alpha-2b via a linker peptide of five or more amino acids and, accordingly, the construct further comprises a linking peptide.

The anti-CD38 antibody portion of the construct may comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 17 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 21, optionally with the proviso that SEQ ID NO: 17 excludes the amino acid sequence of SEQ ID NO: 24 and SEQ ID NO: 21 excludes the amino acid sequence of SEQ ID NO: 25. The heavy chain variable region

and light chain variable region pairs may be chosen from the pairs set forth in any of Tables 1-4 of this disclosure.

In some aspects, the anti-CD38 antibody portion of the construct comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22. The anti-CD38 antibody may comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 21, optionally with the proviso that SEQ ID NO: 21 excludes the amino acid sequence of SEQ ID NO: 25. In some aspects, the anti-CD38 antibody portion of the construct comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 20 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 23.

The anti-CD38 antibody portion of the construct may comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, or SEQ ID NO: 28. The anti-CD38 antibody portion of the construct may comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29 or SEQ ID NO: 30. Any of SEQ ID NOs: 26, 27, or 28 may be paired with any of SEQ ID NOs: 29 or 30. In highly preferred aspects, the anti-CD38 antibody portion of the construct may comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

In some aspects, the anti-CD38 antibody-attenuated interferon alpha-2b construct comprises an anti CD-38 antibody heavy chain-attenuated aglycosylated interferon alpha-2b fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 216, and an anti-CD38 antibody light chain which comprises a variable region comprising the amino acid sequence of SEQ ID NO: 29. In some aspects, the light chain has the amino acid sequence of SEQ ID NO: 217 (variable and constant regions).

The anti-CD38 antibody portion of the construct may comprise a human IgG1 constant region. In some preferred aspects, the anti-CD38 antibody portion of the construct may comprise a human IgG4 constant region. It is preferred that the antibody comprise an IgG4 constant region or an IgG1 constant region engineered to abolish FcR binding to avoid antibody-mediated effector functions, which is believed to provide an advantage in avoiding

non-specific Fc receptor–mediated antibody binding and subsequent IFN-mediated toxicity on non-antibody-targeted cells.

The human IgG1 constant region may optionally comprise a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 according to the EU numbering system. The human IgG4 constant region may optionally comprise a proline at position 228 according to the EU numbering system, and optionally further comprises a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 according to the EU numbering system. The anti-CD38 antibody portion of the construct may comprise a Fab.

The attenuated interferon alpha-2b portion of the construct may be an attenuated human interferon alpha-2b. The attenuated interferon alpha-2b portion of the construct may comprise the amino acid sequence of any one of SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, or SEQ ID NO: 215. The attenuated interferon alpha-2b portion of the construct may include a 23 amino acid N-terminal truncation (SEQ ID NO: 4). The attenuated interferon alpha-2b portion of the construct preferably includes a 23 amino acid N-terminal truncation with an A145D substitution (SEQ ID NO: 5) or A145G substitution (SEQ ID NO: 7). The attenuated interferon alpha-2b portion of the construct may be aglycosylated, for example, a truncated (23 amino acid N-terminal truncation) human interferon alpha-2b with an amino acid deletion or substitution at position 106, which preferably is a T106A substitution, but may comprise other suitable substitutions to remove the glycosylation site (SEQ ID NO: 214). In some preferred aspects, the attenuated interferon alpha-2b portion of the construct includes the T106A substitution and the A145D substitution (SEQ ID NO: 212) or the A145G substitution (SEQ ID NO: 213). In some aspects, the attenuated interferon alpha-2b portion of the construct includes a deletion of T106 (SEQ ID NO: 215).

In highly preferred aspects of the method, the method is used to treat multiple myeloma in a human subject. In some aspects, the methods comprise administering to the subject lenalidomide and an anti-CD38 antibody-attenuated IFN alpha-2b construct comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29, and an IgG4 constant region, and comprising an attenuated IFN alpha-2b molecule comprising the amino acid sequence of SEQ ID NO: 212 or SEQ ID NO: 213. In some aspects,

the methods comprise administering to the subject pomalidomide and an anti-CD38 antibody-attenuated IFN alpha-2b construct comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29, and an IgG4 constant region, and comprising an attenuated IFN alpha-2b molecule comprising the amino acid sequence of SEQ ID NO: 212 or SEQ ID NO: 213.

Also provided is a combination of lenalidomide or pomalidomide and an anti-CD38 antibody-attenuated interferon alpha-2b construct for use in the treatment of any one of B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia. Also provided is a combination of lenalidomide and an anti-CD38 antibody-attenuated interferon alpha-2b construct for use in the treatment of any one of B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia. Also provided is a combination of pomalidomide and an anti-CD38 antibody-attenuated interferon alpha-2b construct for use in the treatment of any one of B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows median tumor volume in SCID mice with a multiple myeloma tumor xenograft as a function of time following treatment with either a vehicle control, a free-non-attenuated interferon-alpha 2b (IFN-alpha), a construct including an anti-CD38 antibody fused to attenuated interferon alpha 2b (145D) alone, lenalidomide alone, a combination of free-non-attenuated interferon-alpha and lenalidomide, or a combination of the anti-CD38-attenuated interferon alpha fusion construct and lenalidomide. The anti-CD38 antibody-attenuated interferon alpha fusion construct was administered in a dose that generated sub-maximal tumor inhibition. The wild type interferon was administered at a dose of 0.5 mg/kg, which is equivalent in molar quantity to the amount of interferon administered as a component of the anti-CD38-attenuated interferon alpha 2b construct. Lenalidomide was administered daily for 21 days at 25 mg/kg via intraperitoneal injection.

Fig. 2 shows tumor volume in SCID mice with a multiple myeloma tumor xenograft as a function of time following treatment with either a vehicle control, a construct of an isotype-matched antibody (the same isotype as the anti-CD38 antibody from Fig. 1) directed to an irrelevant antigen fused to attenuated interferon alpha (145D), or a combination of the isotype-matched antibody-attenuated interferon alpha fusion construct and lenalidomide. None of these agents or combination of agents was capable of preventing tumor growth, although lenalidomide alone or in combination with an irrelevant fusion construct delayed the onset of rapid tumor growth.

Fig. 3A-3J show tumor volumes in individual SCID mice with a multiple myeloma tumor xenograft NCI-H929 as a function of time following treatment with either a vehicle control, lenalidomide alone daily at 25mg/kg via intraperitoneal injection for 21 days, an anti-CD38 antibody (A10.21) fused to an attenuated aglycosylated human interferon-alpha 2b (T106A) at a dose or dose frequency for sub-maximal tumor inhibition or various combinations of lenalidomide and anti-CD38 antibody fused to attenuated aglycosylated interferon at doses or dose frequencies for sub-maximal tumor inhibition as defined in Table 5.

Fig. 4 shows the effects on survival (Kaplan- Meier graph) of the combination of suboptimal dose levels or dosing intervals of an anti-CD38 antibody fused to attenuated aglycosylated interferon-alpha 2b and lenalidomide in SCID mice implanted with the human myeloma cell line NCI-H929.

Fig. 5 shows median tumor volume in SCID mice with a multiple myeloma tumor xenograft as a function of time following treatment with either a vehicle control, a construct including an anti-CD38 antibody fused to attenuated interferon alpha 2b (145D), pomalidomide alone, a combination of interferon-alpha and pomalidomide, or a combination of the anti-CD38-attenuated interferon alpha fusion construct and pomalidomide. Treatment with the anti-CD-38-attenuated IFN alpha2b alone caused a robust shrinkage of the tumors that was stable for the duration of the study, but animals treated with the construct alone demonstrated some tumor regrowth in 7 of the 10 mice during treatment. The combination of pomalidomide with the anti-CD38-attenuated IFN alpha2b was also able to shrink tumors, but substantially fewer mice (4 out of 10 mice) demonstrated tumor regrowth during treatment.

DETAILED DESCRIPTION

Various terms relating to aspects of disclosure are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art, unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definition provided herein.

The terms subject and patient are used interchangeably and include any mammals, including companion and farm mammals, as well as rodents, including mice, rabbits, and rats, and other rodents. Non-human primates, such as Cynomolgus monkeys, are more preferred, and human beings are highly preferred.

A molecule such as an antibody has been "isolated" if it has been altered and/or removed from its natural environment by human intervention.

As used herein, the singular forms "a," "an," and "the" include plural referents unless expressly stated otherwise.

As used herein, the term "resistance" in any respect of a cancer, tumor, malignancy, or pre-malignancy described herein refers to the cancer, tumor, malignancy, or pre-malignancy being refractory to, or failing to completely respond to or be eliminated by treatment with lenalidomide or pomalidomide, and/or to treatment with treatment with the CD38-attenuated IFN alpha 2b construct. The resistance may occur at the beginning of treatment or may take hold during treatment following a period of positive responsiveness.

"Synergy" or as used herein with respect to the tumor-treating effects of the combination of lenalidomide or pomalidomide and an anti-CD38 antibody-attenuated-interferon alpha-2b construct (e.g., synergistic tumor treatment), comprises tumor growth inhibition, including tumor suppression, tumor growth or re-growth delay, and/or substantial elimination of established tumors, and including inhibition of re-establishment of the tumor following cessation of the treatment, that is significantly greater in terms of the amount, degree, extent of inhibition, and/or rate, and/or significantly longer significantly longer in terms of the time of inhibited re-establishment relative to the tumor-treating effects of lenalidomide or pomalidomide or the anti-CD38 antibody-attenuated-interferon alpha-2b construct alone, or relative to an additive tumor treating effect of the agents in isolation. Thus, a "synergistically effective amount" of lenalidomide or pomalidomide or a "synergistically effective amount" of an anti-CD38 antibody-attenuated-interferon alpha-2b construct is an amount at which "synergy" of the lenalidomide or

pomalidomide and an anti-CD38 antibody-attenuated-interferon alpha-2b construct occurs, including an amount at which both agents synergize to substantially inhibit, delay, or suppress tumor growth, substantially eliminate established tumors, and/or substantially inhibit, delay, or suppress tumor re-establishment.

An anti-CD38 antibody-attenuated interferon alpha 2b construct comprises an antibody that specifically binds to CD38 which is joined to an attenuated interferon (IFN) alpha-2b. The antibody may be joined to the IFN alpha-2b by conjugation, cross-linking, or by fusion via a linker or via a peptide bond between the antibody and the IFN molecule.

It has been observed in accordance with the disclosure that an anti-CD38 antibody-attenuated-interferon alpha-2b construct can synergize with lenalidomide or pomalidomide to inhibit tumor growth and, in some cases, eliminate established multiple myeloma tumors *in vivo*. This synergy was superior to a mere additive effect. For example, it was further observed that the majority of tumors treated with this combination did not re-establish during or following cessation of the treatment, whereas tumors treated with either a suboptimal dose of lenalidomide or pomalidomide or a suboptimal dosage of the anti-CD38 antibody-attenuated IFN alpha2b construct alone re-established during treatment and continued to grow in volume following treatment cessation. It was further observed that this combination could overcome a pre-existing or induced resistance of the tumor to lenalidomide. Accordingly, the disclosure features combination therapies for cancer treatment, and preferably for multiple myeloma treatment. The disclosure features combination therapy systems comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, compositions comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, methods for treating cancer by administering an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide to a cancer patient, and kits comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide and instructions for using the construct and lenalidomide or pomalidomide as a combination therapy in a method for treating cancer. The disclosure also features methods for enhancing the anti-tumor activity of lenalidomide or pomalidomide treatment, by combining lenalidomide treatment with an treatment with an anti-CD38 antibody-attenuated interferon alpha-2b construct. Alternatively or in addition, the disclosure features methods for enhancing treatment with an anti-CD38

antibody-attenuated interferon alpha-2b construct by combining with lenalidomide or pomalidomide treatment. Methods described herein may be carried out *in vitro*, *ex vivo*, *in vivo*, or *in situ*.

In one aspect, the disclosure features a combination therapy comprising an anti-CD38 antibody-attenuated IFN-alpha 2b construct and lenalidomide or pomalidomide. The anti-CD38 antibody-attenuated IFN-alpha 2b construct and the lenalidomide or pomalidomide are preferably in an amount effective for treating a tumor. In some aspects, the anti-CD38 antibody-attenuated IFN-alpha 2b construct and the lenalidomide or pomalidomide are in a synergistically effective amount for treating a tumor. The tumor may be B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, or acute lymphocytic leukemia. In some aspects, a combination therapy comprises a composition comprising an anti-CD38 antibody-attenuated IFN-alpha 2b construct and a pharmaceutically acceptable carrier and a composition comprising lenalidomide or pomalidomide and a pharmaceutically acceptable carrier.

As part of the construct, the anti-CD38 antibody may be a monoclonal antibody, and more preferably is a full-length monoclonal antibody comprising a variable region heavy chain and a variable region light chain. In some aspects, an anti-CD38 antibody may comprise derivatives or fragments or portions of antibodies that retain the CD38-binding specificity, and also preferably retain most or all of the affinity, of the parent antibody molecule (*e.g.*, for CD38). For example, derivatives may comprise at least one variable region (either a heavy chain or light chain variable region). Other examples of suitable antibody derivatives and fragments include, without limitation, antibodies with polyepitopic specificity, bispecific antibodies, multi-specific antibodies, diabodies, single-chain molecules, as well as FAb, F(Ab')2, Fd, Fabc, and Fv molecules, single chain (Sc) antibodies, single chain Fv antibodies (scFv), individual antibody light chains, individual antibody heavy chains, fusions between antibody chains and other molecules, heavy chain monomers or dimers, light chain monomers or dimers, dimers consisting of one heavy and one light chain, and other multimers. Single chain Fv antibodies may be multivalent. All antibody isotypes may be used to produce antibody derivatives, fragments, and portions. Antibody derivatives,

fragments, and/or portions may be recombinantly produced and expressed by any cell type, prokaryotic or eukaryotic.

For use in the treatment of humans, non-human derived antibodies may be structurally altered to be less antigenic upon administration to a human patient, including by deimmunization, chimerization or humanization or superhumanization. In some aspects, the antibodies are humanized antibodies. Humanized antibodies are those wherein the amino acids directly involved in antigen binding, *e.g.*, the complementarity determining regions (CDR), and in some cases the framework regions (FR), or portions thereof, of the heavy and/or light chains are not of human origin, while the rest of the amino acids in the antibody are human or otherwise of human origin, *e.g.*, a human antibody scaffold. Humanized antibodies also include antibodies in which one or more residues of the human protein are modified by one or more amino acid substitutions and/or one or more FR residues of the human protein are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found in neither the human antibody or in the non-human antibody. A humanized antibody may be a super-humanized antibody, *e.g.*, as described in U.S. Pat. No. 7,732,578. The antibodies may be humanized chimeric antibodies. Humanized antibodies also include antibodies with constant region sequences, *e.g.,* variable region framework sequences, that are artificial consensus sequences based on multiple human antibodies.

In highly preferred aspects, the anti-CD38 antibodies are fully human. Fully human antibodies are those where the whole molecule is human or otherwise of human origin, or includes an amino acid sequence identical to or substantially identical to human antibody sequences. Fully human antibodies include those obtained from a human V gene library, for example, where human genes encoding variable regions of antibodies are recombinantly expressed. Fully human antibodies may be expressed in other organisms (*e.g.*, mice and xenomouse technology) or cells from other organisms transformed with genes encoding human antibodies. Fully human antibodies may nevertheless include amino acid residues not encoded by human sequences, *e.g.*, mutations introduced by random or site directed mutations.

The anti-CD38 antibodies may be full length antibodies of any class, for example, IgG1, IgG2 or IgG4. In particular embodiments the anti-CD38 antibodies are full-length IgG4 antibodies. The constant domains of such antibodies are preferably human. The variable

regions of such antibodies may be of non-human origin, or preferably are human in origin or are humanized. Antibody fragments may also be used in place of the full length antibodies.

In some aspects, the anti-CD38 antibodies may comprise non-immunoglobulin derived protein frameworks. For example, reference may be made to (Ku & Schutz, Proc. Natl. Acad. Sci. USA 92: 6552-6556, 1995) which describes a four-helix bundle protein cytochrome b562 having two loops randomized to create CDRs, which have been selected for antigen binding.

Natural sequence variations may exist among heavy and light chains and the genes encoding them, and therefore, persons having ordinary skill in the art would expect to find some level of variation within the amino acid sequences, or the genes encoding them, of the antibodies described and exemplified herein. Encompassed within the term antibody are sequence variants which maintain CD38 binding specificity and which preferably substantially maintain the affinity of the parent antibody. Such an expectation is due in part to the degeneracy of the genetic code, as well as to the known evolutionary success of conservative amino acid sequence variations, which do not appreciably alter the nature of the encoded protein. Accordingly, such variants and homologs are considered substantially the same as one another and are included within the scope of the disclosure. The antibodies thus include variants having single or multiple amino acid substitutions, deletions, additions, or replacements that retain the biological properties (*e.g.*, binding specificity and binding affinity) of the parent antibodies. The variants are preferably conservative, but may be non-conservative.

Amino acid positions assigned to complementarity determining regions (CDRs) and framework regions (FRs) may be defined according to Kabat Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., 1987 and 1991 (also referred to herein as the Kabat numbering system). In addition, the amino acid positions assigned to CDRs and FRs may be defined according to the Enhanced Chothia Numbering Scheme (http://www.bioinfo.org.uk/mdex.html). The heavy chain constant region of an antibody can be defined by the EU numbering system (Edelman, GM *et al.* (1969)., Proc. Natl. Acad. USA, 63, 78-85).

According to the numbering system of Kabat, VH FRs and CDRs may be positioned as follows: residues 1-30 (FR1), 31-35 (CDR1), 36-49 (FR2), 50-65 (CDR2), 66-94 (FR3), 95-102 (CDR3) and 103- 113 (FR4), and VL FRs and CDRs are positioned as follows: residues 1–23

(FR1), 24-34 (CDR1), 35-49 (FR2), 50-56 (CDR2), 57-88 (FR3), 89-97 (CDR3) and 98-107 (FR4). In some instances, variable regions may increase in length and according to the Kabat numbering system some amino acids may be designated by a number followed by a letter. This specification is not limited to FWRs and CDRs as defined by the Kabat numbering system, but includes all numbering systems, including the canonical numbering system or of Chothia *et al.* (1987) J. Mol. Biol. 196:901-17; Chothia *et al.* (1989) Nature 342:877-83; and/or Al-Lazikani *et al.* (1997) J. Mol. Biol. 273:927-48; the numbering system of Honnegher *et al.* (2001) J. Mol. Biol., 309:657-70; or the IMGT system discussed in Giudicelli *et al.*, (1997) Nucleic Acids Res. 25:206-11. In some aspects, the CDRs are defined according to the Kabat numbering system.

In some particular aspects, for any of the heavy chain CDR2 subdomains described herein, according to the Kabat numbering system, the five C-terminal amino acids may not participate directly in antigen binding, and accordingly, it will be understood that any one or more of these five C-terminal amino acids may be substituted with another naturally-occurring amino acid without substantially adversely affecting antigen binding. In some aspects, for any of the light chain CDR1 subdomains described herein, according to the Kabat numbering system, the four N-terminal amino acids may not participate directly in antigen binding, and accordingly, it will be understood that any one or more of these four amino acids may be substituted with another naturally-occurring amino acid without substantially adversely affecting antigen binding. For example, as described by Padlan *et al.* (1995) FASEB J. 9:133-139, the five C terminal amino acids of heavy chain CDR2 and/or the four N-terminal amino acids of light chain CDR1 may not participate in antigen binding. In some aspects, both the heavy chain CDR2 and the light chain CDR1 do not directly participate in antigen binding.

In some aspects, chemical analogues of amino acids may be used in the antibodies described and/or exemplified herein. The use of chemical analogues of amino acids is useful, for example, for stabilizing the molecules such as if required to be administered to a subject. The analogues of the amino acids contemplated herein include, but are not limited to, modifications of side chains, incorporation of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

The anti-CD38 antibodies may comprise post-translational modifications or moieties, which may impact antibody activity or stability. These modifications or moieties include, but are not limited to, methylated, acetylated, glycosylated, sulfated, phosphorylated, carboxylated, and amidated moieties and other moieties that are well known in the art. Moieties include any chemical group or combinations of groups commonly found on immunoglobulin molecules in nature or otherwise added to antibodies by recombinant expression systems, including prokaryotic and eukaryotic expression systems.

Examples of side chain modifications contemplated by the disclosure include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal. The carboxyl group may be modified by carbodiimide activation via O-acylisourea formation followed by subsequent derivation, for example, to a corresponding amide. Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH. Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative. Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Crosslinkers may be used, for example, to stabilize 3D conformations of the anti-CD38 antibodies and anti-CD38 antibody-attenuated interferon alpha-2b constructs, using

homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In some aspects, the antibodies may be derivatized by known protecting/blocking groups to prevent proteolytic cleavage or enhance activity or stability.

The anti-CD38 antibodies may be affinity matured, or may comprise amino acid changes that decrease immunogenicity, for example, by removing predicted MHC class II-binding motifs. The therapeutic utility of the antibodies described herein may be further enhanced by modulating their functional characteristics, such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), serum half-life, biodistribution and binding to Fc receptors or the combination of any of these. This modulation can be achieved by protein-engineering, glyco-engineering or chemical methods. Depending on the therapeutic application required, it could be advantageous to either increase or decrease any of these activities. An example of glyco-engineering used the Potelligent® method as described in Shinkawa T. *et al.* (2003) J. Biol. Chem. 278: 3466-73.

The anti-CD38 antibodies may include modifications that modulate its serum half-life and biodistribution, including modifications that modulate the antibody's interaction with the neonatal Fc receptor (FcRn), a receptor with a key role in protecting IgG from catabolism, and maintaining high serum antibody concentration. Serum half-life modulating modifications may occur in the Fc region of IgG1 or IgG4, including the triple substitution of M252Y/S254T/T256E (Numbering according to the EU numbering system (Edelman, G.M. *et al.* (1969) Proc. Natl. Acad. USA 63, 78-85)), (*e.g.*, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16), as described in U.S. Pat. No. 7,083,784. Other substitutions may occur at positions 250 and 428, see *e.g.,* U.S. Pat. No 7,217,797, as well as at positions 307, 380 and 434, see, *e.g.*, WO 00/42072. Examples of constant domain amino acid substitutions which modulate binding to Fc receptors and subsequent function mediated by these receptors, including FcRn binding and serum half-life, are described in U.S. Publ. Nos. 2009/0142340, 2009/0068175, and 2009/0092599. Naked antibodies may have the heavy chain C-terminal lysine omitted or removed to reduce heterogeneity. The substitution of

S228P (EU numbering) in the human IgG4 can stabilize antibody Fab-arm exchange in vivo (Labrin *et al*. (2009) Nature Biotechnology 27:8; 767-773).

The glycans linked to antibody molecules are known to influence interactions of antibody with Fc receptors and glycan receptors and thereby influence antibody activity, including serum half-life. Hence, certain glycoforms that modulate desired antibody activities can confer therapeutic advantage. Methods for generating engineered glycoforms include but are not limited to those described in U.S. Pat. Nos. 6,602,684, 7,326,681, and 7,388,081 and PCT Publ. No. WO 08/006554. Alternatively, the antibody sequences may be modified to remove relevant glycoform-attachment sites.

The anti-CD38 antibodies preferably have a binding affinity for an epitope on CD38 that includes a dissociation constant (Kd) of less than about 1×10^{-4} M. In some embodiments, the Kd is less than about 1×10^{-5} M. In still other embodiments, the Kd is less than about 1×10^{-6} M. In other embodiments, the Kd is less than about 1×10^{-7} M. In other embodiments, the Kd is less than about 1×10^{-8} M. In other embodiments, the Kd is less than about 1×10^{-9} M. In other embodiments, the Kd is less than about 1×10^{-10} M. In still other embodiments, the Kd is less than about 1×10^{-11} M. In some embodiments, the Kd is less than about 1×10^{-12} M. In other embodiments, the Kd is less than about 1×10^{-13} M. In other embodiments, the Kd is less than about 1×10^{-14} M. In still other embodiments, the Kd is less than about 1×10^{-15} M. Affinity values refer to those obtained by standard methodologies, including surface plasmon resonance such as Biacore™ analyses or analysis using an Octet® Red 96 (Forte Bio) Dip-and-Read system.

The anti-CD38 antibodies are preferably capable of binding to CD38-positive cells. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 100 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 75 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 50 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 30 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 25 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 20 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 18 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 15 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 13 nM. The antibody may bind to a CD38-positive cell with an EC_{50} value of less than about 10 nM.

An anti-CD38 antibody may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20. An antibody may comprise a light chain comprising the amino acid sequence of SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23. In some aspects, the heavy chain amino acid sequence of SEQ ID NO: 17 excludes the amino acid sequence of SEQ ID NO: 24. In some aspects, the light chain amino acid sequence of SEQ ID NO: 21 excludes the amino acid sequence of SEQ ID NO: 25. Variants of such anti-CD38 antibodies can be engineered and expressed such that the antibodies have reduced immunogenicity, enhanced stability, and enhanced half life in circulation without a significant loss of specificity or affinity of the antibody to the CD38 antigen. These variant antibodies can be fused to an attenuated interferon.

In some aspects, the anti-CD38 antibody comprises particular heavy and light chain pairs. Any of the heavy chains having the amino acid sequences of SEQ ID NO: 17 may be paired with any light chains having the amino acid sequences of SEQ ID NO: 21. Any of the heavy chains having the amino acid sequences of SEQ ID NO: 18 may be paired with any light chains having the amino acid sequences of SEQ ID NO: 22. Any of the heavy chains having the amino acid sequences of SEQ ID NO: 19 may be paired with any light chains having the amino acid sequences of SEQ ID NO: 21. Any of the heavy chains having the amino acid sequences of SEQ ID NO: 20 may be paired with any light chains having the amino acid sequences of SEQ ID NO: 23.

In some preferred aspects, the anti-CD38 antibody comprises a heavy and light chain pair of Table 1, Table 2, or Table 3. In more preferred aspects, the anti-CD38 antibody comprises a heavy and light chain pair of Table 4. In more preferred aspects, the anti-CD38 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

Table 1. Heavy and Light Chain Variable Region Pairs

Antibody Name	Variable Heavy SEQ ID NO: (amino acid)	Variable Light SEQ ID NO: (amino acid)
A02.10	208	25
A02.11	209	25
A02.112	43	77
A02.12	43	77

A02.13	44	77
A02.16	43	104
A02.17	43	105
A02.18	43	85
A02.19	43	86
A02.2	24	77
A02.20	43	87
A02.21	43	88
A02.22	43	89
A02.23	43	90
A02.24	43	91
A02.25	43	92
A02.26	43	93
A02.27	43	94
A02.28	43	95
A02.29	43	96
A02.3	206	77
A02.30	43	97
A02.31	43	98
A02.32	43	99
A02.33	43	100
A02.43	43	101
A02.35	43	102
A02.36	43	103
A02.37	43	78
A02.38	43	123
A02.39	43	122
A02.4	207	77
A02.40	131	77
A02.41	130	77
A02.43	130	123
A02.44	131	122
A02.46	43	79
A02.47	43	80
A02.48	43	81
A02.49	43	82
A02.5	208	77
A02.50	43	83
A02.51	43	84
A02.52	43	106
A02.53	43	107
A02.54	43	108
A02.55	43	109
A02.56	43	110
A02.57	43	111
A02.58	43	112

A02.59	43	113
A02.6	209	77
A02.60	43	114
A02.61	43	115
A02.62	43	116
A02.63	43	117
A02.64	43	118
A02.65	43	119
A02.66	43	102
A02.67	43	121
A02.8	206	25
A02.9	207	25
X02.10	208	25
X02.100	24	70
X02.101	24	71
X02.102	24	72
X02.103	24	73
X02.104	24	74
X02.105	24	75
X02.106	24	76
X02.107	24	77
X02.108	41	25
X02.11	209	25
X02.110	42	25
X02.114	33	124
X02.115	33	125
X02.116	33	126
X02.117	33	127
X02.118	43	128
X02.119	43	129
X02.120	45	128
X02.121	46	128
X02.122	47	128
X02.123	48	128
X02.124	45	129
X02.125	46	129
X02.126	47	129
X02.127	48	129
X02.68	210	25
X02.69	31	25
X02.70	32	25
X02.71	33	25
X02.72	34	25
X02.73	35	25
X02.74	36	25
X02.75	37	25

X02.76	38	25
X02.77	39	25
X02.78	40	25
X02.8	206	25
X02.80	24	50
X02.81	24	51
X02.82	24	52
X02.83	24	53
X02.84	24	54
X02.85	24	55
X02.86	24	56
X02.87	24	57
X02.88	24	58
X02.89	24	59
X02.9	207	25
X02.90	24	60
X02.91	24	61
X02.92	24	62
X02.93	24	63
X02.94	24	64
X02.95	24	65
X02.96	24	66
X02.97	24	67
X02.98	24	68
X02.99	24	69

Table 2. Heavy and Light Chain Variable Region Pairs

Antibody Name	Variable Heavy SEQ ID NO: (amino acid)	Variable Light SEQ ID NO: (amino acid)
A10.1	139	167
A10.10	147	167
A10.11	148	167
A10.12	149	167
A10.13	150	167
A10.14	151	167
A10.15	152	167
A10.16	153	167
A10.17	27	171
A10.18	27	172
A10.19	27	173
A10.2	140	167
A10.20	27	174
A10.21	27	29

A10.22	27	175
A10.23	27	176
A10.24	27	177
A10.25	27	178
A10.26	27	179
A10.27	27	180
A10.28	27	181
A10.29	27	182
A10.3	28	167
A10.30	27	183
A10.31	27	184
A10.32	27	185
A10.35	154	167
A10.36	27	186
A10.38	26	167
A10.39	26	171
A10.4	141	167
A10.40	26	172
A10.41	26	173
A10.42	26	174
A10.43	26	29
A10.44	26	175
A10.45	26	176
A10.46	26	177
A10.47	26	178
A10.48	26	179
A10.49	26	180
A10.5	142	167
A10.50	26	181
A10.51	26	182
A10.52	26	183
A10.53	26	184
A10.54	26	185
A10.57	26	186
A10.59	27	167
A10.6	143	167
A10.7	144	167
A10.8	145	167
A10.9	146	167
A10A2.0 (chimeric)	132	163
A10A2.1	133	164
A10A2.10	134	166
A10A2.11	134	167
A10A2.12	134	168
A10A2.13	134	169
A10A2.14	134	170

A10A2.15	135	164
A10A2.16	135	165
A10A2.17	135	166
A10A2.18	135	167
A10A2.19	135	168
A10A2.2	133	165
A10A2.20	135	169
A10A2.21	135	170
A10A2.22	26	164
A10A2.23	26	165
A10A2.24	26	166
A10A2.25	26	167
A10A2.26	26	168
A10A2.27	26	169
A10A2.28	26	170
A10A2.29	136	164
A10A2.3	133	166
A10A2.30	136	165
A10A2.31	136	166
A10A2.32	136	167
A10A2.33	136	168
A10A2.34	136	169
A10A2.35	136	170
A10A2.36	137	164
A10A2.37	137	165
A10A2.38	137	166
A10A2.39	137	167
A10A2.4	133	167
A10A2.40	154	168
A10A2.41	137	169
A10A2.42	137	170
A10A2.43	137	164
A10A2.44	138	165
A10A2.45	138	166
A10A2.46	138	167
A10A2.47	138	168
A10A2.48	138	169
A10A2.49	138	170
A10A2.5	133	168
A10A2.50	27	164
A10A2.51	27	165
A10A2.52	27	166
A10A2.53	27	167
A10A2.54	27	168
A10A2.55	27	169
A10A2.56	27	170

A10A2.6	133	169
A10A2.7	133	170
A10A2.8	134	164
A10A2.9	134	165
X10.100	155	30
X10.101	156	30
X10.102	157	30
X10.103	158	30
X10.104	159	30
X10.105	160	30
X10.106	161	30
X10.107	162	30
X10.108	155	189
X10.109	156	189
X10.110	157	189
X10.111	158	189
X10.112	159	189
X10.113	160	189
X10.114	161	189
X10.115	162	189
X10.116	155	190
X10.117	156	190
X10.118	157	190
X10.119	158	190
X10.120	159	190
X10.121	160	190
X10.122	161	190
X10.123	162	190
X10.124	155	191
X10.125	156	191
X10.126	157	191
X10.127	158	191
X10.128	159	191
X10.129	160	191
X10.130	161	191
X10.131	162	191
X10.132	155	192
X10.133	156	192
X10.134	157	192
X10.135	158	192
X10.136	159	192
X10.137	160	192
X10.138	161	192
X10.139	162	192
X10.140	155	193
X10.141	156	193

X10.142	157	193
X10.143	158	193
X10.144	159	193
X10.145	160	193
X10.146	161	193
X10.147	162	193
X10.60	27	187
X10.61	27	188
X10.62	27	30
X10.63	27	189
X10.64	27	190
X10.65	27	191
X10.66	27	192
X10.67	27	193
X10.68	155	167
X10.69	156	167
X10.70	157	167
X10.71	158	167
X10.72	159	167
X10.73	160	167
X10.74	161	167
X10.75	162	167
X10.76	26	187
X10.77	26	188
X10.78	26	30
X10.79	26	189
X10.80	26	190
X10.81	26	191
X10.82	26	192
X10.83	26	193
X10.84	155	187
X10.85	156	187
X10.86	157	187
X10.87	158	187
X10.88	159	187
X10.89	160	187
X10.90	161	187
X10.91	162	187
X10.92	155	188
X10.93	156	188
X10.94	157	188
X10.95	158	188
X10.96	159	188
X10.97	160	188
X10.98	161	188
X10.99	162	188

Table 3. Heavy and Light Chain Variable Region Pairs

Antibody Name	Variable Heavy SEQ ID NO: (amino acid)	Variable Light SEQ ID NO: (amino acid)
X910/12-HC-L0- IFN-alpha (A145D) IgG4	130	122
X913/15-HC-L0- IFN-alpha (A145D) IgG4	131	123

Table 4. Heavy and Light Chain Variable Region Pairs

Antibody Name	Variable Heavy SEQ ID NO: (amino acid)	Variable Light SEQ ID NO: (amino acid)
X10.78	26	30
A10.21	27	29
A10.43	26	29
A10.62	27	30
A10.152	28	30

The anti-CD38 antibody may be an anti-CD38 antibody described in the art. Examples of anti-CD38 antibodies which may be used as described herein include antibodies described in U.S. Pat. Nos. 5,545,405, 7,829,673, 8,088,896, or 8,153,765, or described in U.S. Publ. Nos. 2002/0164788, 2003/0211553, 2009/0076249, 2009/0123950, or 2010/0285004.

As part of the construct, the anti-CD38 antibody preferably is joined to an attenuated form of IFN alpha 2b. IFN alpha-2b attenuation relates to the biologic activity of interferon achieved by binding to an interferon receptor on a cell surface. Attenuation may be achieved by introducing certain amino acid changes into the interferon protein sequence.

An attenuated interferon molecule is joined to an anti-CD38 antibody such that the antibody may serve as a delivery vehicle for the attenuated interferon, delivering it to CD38-positive cells with a resulting diminution of off- target interferon activity caused by the attenuated interferon molecule. An anti-CD38 antibody-attenuated interferon alpha-2b construct includes, but is not limited to, any antibody described or exemplified herein that binds specifically to CD38 that is joined to an attenuated IFN alpha-2b protein, including an

IFN alpha-2b of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 211, SEQ ID NO: 212, or SEQ ID NO: 213.

Human CD38 comprises the amino acid sequence of SEQ ID NO: 1, and cynomolgus monkey CD38 comprises the amino acid sequence of SEQ ID NO: 2.

The anti-CD38 antibody is employed as delivery vehicles for the attenuated interferon alpha-2b. Without intending to be limited to any particular theory or mechanism or action, it is believed that the antibody, as a delivery vehicle, compensates for the diminished capacity of the interferon molecule to bind to its receptor (its attenuation). In this sense, the attenuated interferon has reduced capacity to interact with its receptor on healthy cells, and particularly cells that do not express CD38. It is believed that by bringing the attenuated interferon into proximity with its receptor on CD38-positive cells, the antibodies may enhance the capacity of the attenuated interferon to bind to its relevant receptor and induce a therapeutic effect, while exhibiting a diminished capacity to induce undesirable effects on healthy cells that do not express CD38. Joining the attenuated interferon to an anti-CD38 antibody does not significantly affect the capacity of the antibody to specifically bind to CD38 on cells expressing CD38, including cells *in vivo*.

The antibodies may be fused to attenuated ligands, for example, to form antibody-attenuated ligand constructs, which show an elevated antigen-specificity index (ASI) with respect to activating signaling pathways due to the action of the attenuated ligand on a cell surface receptor. These constructs are based on the observation that, in the context of an antibody-ligand construct, the ligand portion can be mutated in such a way that the ligand activity on antigen-negative cells is dramatically attenuated, while the ligand activity on antigen-positive cells is only modestly, if at all, attenuated. Such constructs display one, two, three, four or five orders of magnitude greater potency on antigen-positive cells compared to antigen negative cells than does the free ligand. In some aspects, the antibody-attenuated ligand construct retains at least 1%, at least 10%, at least 20%, at least 30%, at least 40% or at least 50% of the potency on antigen-positive cells as the non-attenuated free (i.e., not attached to an antibody) ligand. In some aspects, the antibody-attenuated ligand construct retains at least 30%, at least 50%, at least 75% or at least 90% of the maximal activity of the non-attenuated free (i.e. not attached to an antibody) ligand. Maximal activity includes the amount of signaling activity (or downstream effect thereof) at

the high, plateau portion of a dose-response curve, where further increases in the agent does not further increase the amount of response.

In some aspects, the antibody fusion to and inclusion of an attenuating mutation(s) in the interferon ligand increases the antigen-specificity index (ASI) by greater than 10-fold, preferably greater than 50-fold, preferably greater than 100-fold, preferably greater than 1000-fold, or preferably greater than 10,000 fold, relative to an antibody without a fusion. The ASI comprises the fold-increased potency in signaling activity of the antibody-IFN ligand construct relative to the free non-mutated polypeptide ligand on target antigen-positive cells, multiplied by the fold decreased potency in signaling activity relative to the free non-mutated polypeptide ligand on target antigen-negative cells. Potency may be quantitatively represented by the EC_{50} value, which is the mathematical midpoint of a dose-response curve, in which the dose refers to the concentration of ligand or antibody-ligand construct in an assay, and response refers to the quantitative response of the cells to the signaling activity of the ligand at a particular dose. Thus, for example, when a first compound is shown to possess an EC_{50} (expressed for example in Molar units) that is 10-fold lower than a second compound's EC_{50} on the same cells, typically when measured by the same method, the first compound is said to have a 10-fold higher potency. Conversely, when a first compound is shown to possess an EC_50 that is 10-fold higher than a second compound's EC_{50} on the same cells, typically when measured by the same method, the first compound is said to have a 10-fold lower potency.

The interferon alpha-2b ligand joined to the anti-CD38 antibody preferably comprises alterations in its amino acid sequence, including point mutations and/or deletions that render the interferon less active in stimulating its respective receptors on cells that lack cell surface expression of the CD38 antigen to which the antibody binds. A preferred variant of interferon alpha comprises an amino acid change at position 168 of the interferon alpha 2b amino acid sequence of SEQ ID NO: 8. For example, the amino acid at position 168, which is an alanine in the parent IFN-alpha2b molecule (SEQ ID NO: 8), is preferably changed to a glycine (Gly/G) (SEQ ID NO: 6) or aspartic acid (Asp/D) (SEQ ID NO: 3). In some preferred aspects, the IFN-alpha2b is truncated at its N-terminus when the IFN-alpha2b is fused to an IgG heavy chain constant domain such as the human IgG1 or human IgG4 heavy chain constant domain. The truncated IFN-alpha2b does not have the twenty three N-terminal amino acids of SEQ ID NO: 8 (Met 1 through Gly 23 are deleted), and the truncated

IFN-alpha2b comprises the amino acid sequence of SEQ ID NO: 4. The truncated IFN-alpha2b may also comprise the amino acid change at what was formerly position 168, but which becomes position 145 in the truncated protein (*e.g.*, alanine 168 becomes alanine 145). In the truncated IFN-alpha2b, the alanine is preferably changed to a glycine (Gly/G) (SEQ ID NO: 7) or aspartic acid (Asp/D) (SEQ ID NO: 5). Interferon with the A145D alteration (SEQ ID NO: 3 or SEQ ID NO: 5) is particularly preferred as the attenuated interferon joined to the antibodies of the disclosure. Any of these point-mutated, attenuated versions of IFN-alpha may be joined to any antibody described herein, for example, as an antibody-attenuated interferon construct. In some aspects, joining an unmutated IFN alpha-2b protein, such as SEQ ID NO: 8, to an anti-CD38 antibody attenuates the biologic activities of the interferon molecule. In this disclosure, attenuated interferon, attenuated IFN alpha-2b, IFN alpha-2b A145D, and IFN alpha-2b A145G are used interchangeably.

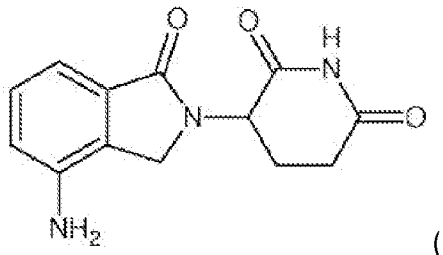
In highly preferred aspects, the anti-CD38 antibody is fused to an attenuated interferon alpha 2b comprising the amino acid sequence of SEQ ID NO: 211, SEQ ID NO: 212, or SEQ ID NO: 213. In these attenuated interferon alpha 2b molecules, the N-terminal 23 amino acids of the parent interferon alpha 2b molecule are deleted, resulting in a truncation variant having 165 amino acids such that amino acid number 24 of the parent interferon alpha 2b molecule becomes amino acid number 1 of the truncation variant. In these truncation variants, certain additional amino acids may be substituted. For example, the threonine at position 106 may be changed to an alanine (T106A) in order to remove a glycosylation site (aglycosylated interferon alpha 2b) (*e.g.*, SEQ ID NO: 211). Additionally, the alanine at position 145 of the truncation variant may be changed to aspartic acid (SEQ ID NO: 212) or may be changed to glycine (SEQ ID NO: 213).

In some aspects, the linkage between the antibody and the interferon comprises a fusion, for example, a peptide bond between the N- or the C-terminus of the interferon and the N- or C-terminus of the heavy or the light chain of the antibody. In one preferred aspect, no linker is present between the antibody and the interferon (other than the ribosomally synthesized peptide bond between the last C-terminal amino acid of the first component of the fusion protein and the N-terminal amino acid of the second component of the fusion protein), and the antibody and interferon are thus directly fused. It is believed that direct fusion, without an intervening linker peptide, provides at least a measurable degree of attenuation of the interferon protein, and it is also believed that this attenuation

is additive with the attenuation of the interferon protein that stems from the mutations introduced into the interferon protein, including those described or exemplified herein. For example, in some aspects, the anti-CD38 antibody-attenuated interferon alpha-2b construct comprises the amino acid sequence of SEQ ID NO: 216 (heavy chain and interferon) and the amino acid sequence of SEQ ID NO: 217 (light chain).

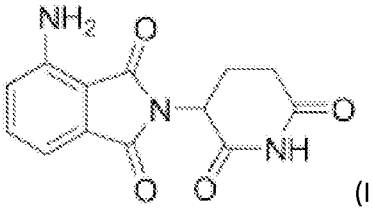
In some aspects, the construct includes an intervening stretch of amino acids between the last C-terminal amino acid of the first protein of the construct and the N-terminal amino acid of the second protein of the construct. The number of amino acids in such a peptide linker may be anywhere from 1 to 50 in length, preferably 1-20 in length. The sequences of such linkers could include sequences primarily consisting of glycine and serine, for example, such as the sequence $(G_4S)n$, where n can be any number from 1 to about 10, and preferably is 1 to about 4.

As a therapeutic modality, and as part of a therapy or treatment regimen, the anti-CD38 antibody-attenuated interferon alpha-2b construct is paired with lenalidomide. Lenalidomide, also known as (RS)-3-(4-Amino-1-oxo 1,3-dihydro-2H-isoindol- 2-yl)piperidine-2,6-dione, has the chemical formula, Formula I:



(I).

As an alternative therapeutic modality, and as part of a therapy or treatment regimen, the anti-CD38 antibody-attenuated interferon alpha-2b construct may be paired with pomalidomide. Thus, pomalidomide may be substituted for lenalidomide in any of the systems, kits, methods, compositions, or uses described or exemplified herein. Pomalidomide, also known as (RS)-4-Amino-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione, has the chemical formula, Formula II:



(II).

In some aspects, an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide are each comprised in a composition. The composition may be used in accordance with a combination therapy. A combination therapy may comprise a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a separate composition of lenalidomide or pomalidomide, or may comprise a composition of both agents together. A composition may comprise at least one of any suitable auxiliary, such as, but not limited to one or more, diluents, binders, stabilizers, buffers, salts, lipophilic solvents, preservatives, adjuvants, or other suitable carrier and/or excipient. Pharmaceutically acceptable auxiliaries are preferred. The anti-CD38 antibody-attenuated interferon alpha-2b construct and/or lenalidomide or pomalidomide may be formulated with an acceptable carrier such as a pharmaceutically acceptable carrier. Suitable carriers include any media that does not interfere with the biological activity of the antibody and/or the interferon and preferably is not toxic to a host to which it is administered. The carrier may be an aqueous solution, such as water, saline, or alcohol, or a physiologically compatible buffer, such as Hanks's solution, Ringer's solution, or physiological saline buffer. The carrier may contain formulatory agents, such as suspending, stabilizing and/or dispersing agents

Pharmaceutical excipients and additives useful in the composition include but are not limited to proteins, peptides, amino acids, lipids, and carbohydrates (*e.g.*, sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and other known sugars; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination any suitable weight or volume. Exemplary protein excipients include serum albumin, such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and other known proteins. Representative amino acids which can also function in a buffering capacity include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, and

aspartame. One preferred amino acid is histidine. A second preferred amino acid is arginine.

Carbohydrate excipients suitable for use in the composition include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, and sorbose; disaccharides, such as lactose, sucrose, trehalose, and cellobiose; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, and starches; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), and myoinositol. Preferred carbohydrate excipients for use in the disclosure are mannitol, trehalose, and raffinose.

The compositions may include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts, such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the compositions are organic acid salts, such as citrate.

The compositions may include polymeric excipients/additives, such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (*e.g.*, cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin), polyethylene glycols, antimicrobial agents, antioxidants, antistatic agents, surfactants (*e.g.*, polysorbates such as "TWEEN® 20" and "TWEEN® 80"), lipids (*e.g.*, phospholipids, fatty acids), steroids (*e.g.*, cholesterol), and chelating agents (*e.g.*, EDTA).

The compositions may be formulated in sustained release vehicles or depot preparations. For example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well-known examples of delivery vehicles suitable for use as carriers for hydrophobic drugs.

The compositions may be formulated for administration to a subject in any suitable dosage form. The compositions may be formulated for oral, buccal, nasal, transdermal, parenteral, injectable, intravenous, subcutaneous, intramuscular, rectal, or vaginal administrations. The compositions may be formulated in a suitable controlled-release vehicle, with an adjuvant, or as a depot formulation. Lenalidomide is preferably in a solid dosage form such as a pill or tablet. The construct is preferably in a liquid dosage form for parenteral administration.

Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions.

A combination therapy system comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct paired with lenalidomide or pomalidomide may be used, for example, to inhibit, reduce, decrease, block, or prevent proliferation of a cell that expresses CD38 on its surface. A combination therapy comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct paired with lenalidomide or pomalidomide may be used, for example, to induce, facilitate, or enhance apoptosis of a cell that expresses CD38 on its surface. The cell that expresses CD38 may be a lymphocyte, an autoimmune lymphocyte, or a tumor cell such as a leukemia cell, a multiple myeloma cell, or a lymphoma cell. Preferably, a cell that expresses CD38 is a tumor cell, and the tumor cell may be resistant to lenalidomide or pomalidomide, including resistance arising after an initial period of positively responsive treatment, such that the tumor responds positively to the combination therapy.

A combination therapy system comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct paired with lenalidomide or pomalidomide may be used to treat a patient having a tumor that comprises and/or is mediated, at least in part, by cells that express CD38 on their surface. In some aspects, methods for treating a tumor generally comprise administering to a patient in need of treatment of the tumor an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide. Each of the construct and lenalidomide or pomalidomide are administered in an amount effective to treat the tumor in the patient. Each of the construct and lenalidomide or pomalidomide may be comprised in a composition, with each agent comprised in either a separate composition or comprised in the same composition. The combination therapy produces a synergy of the construct with the lenalidomide or pomalidomide such that there is one or more of an enhanced inhibition or reduction of proliferation of cells in the tumor, an enhanced induction of apoptosis of cells in the tumor, and/or an enhanced killing of CD38-positive cells in the tumor, relative to tumor cells of the same type that were treated by either an anti-CD38 antibody-attenuated interferon alpha-2b construct or lenalidomide or pomalidomide, but not both. In some aspects, the tumor cells may be resistant to

lenalidomide or pomalidomide, including resistance arising after an initial period of positively responsive treatment, such that the tumor responds positively to the combination therapy. Thus, for example, the combination therapy kills tumor cells that have ceased positively responding to treatment with lenalidomide or pomalidomide alone.

In accordance with tumor treatment, the combination therapy of an anti-CD38 antibody-attenuated interferon alpha-2b construct paired with lenalidomide or pomalidomide may inhibit or prevent regrowth and re-establishment of the tumor. Such an inhibition of regrowth and re-establishment may be measured over a period of time, for example, a period of at least about one year, a period of at least about 2 years, a period of at least about 3 years, a period of at least about 5 years, or a period greater than 5 years.

As a combination therapy, an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or composition comprising an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition comprising lenalidomide or pomalidomide may be administered to a tumor by administering the anti-CD38 antibody-attenuated interferon alpha-2b construct, or composition thereof, and lenalidomide or composition thereof, to the blood, for example, via subcutaneous or intravenous administration. The anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide may be administered such that each agent diffuses via blood flow to and/or into the tumor cells. By administering the anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide to the tumor, the patient to which the anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide is treated.

Thus, a combination therapy comprises administering to a patient having a tumor and in need of treatment an amount of an anti-CD38 antibody-attenuated interferon alpha-2b construct and an amount of lenalidomide or pomalidomide that is effective to treat the tumor in the patient, *e.g.*, a synergistically effective amount. The tumor may be a lenalidomide-resistant tumor, or may comprise cells that are resistant to lenalidomide or pomalidomide, including resistance arising after an initial period of positively responsive treatment, such that the tumor responds positively to the combination therapy. The anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide may be administered substantially at the same time, for example, co-administered by way of a composition comprising these agents together, or by administering separate

compositions of each agent at the same time. The anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide may be administered sequentially, with the anti-CD38 antibody-attenuated interferon alpha-2b construct administered before the lenalidomide, or vice versa.

Tumors that may be treated with a combination therapy of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide include, but are not limited to, lenalidomide-resistant forms of, AIDS related cancers, acoustic neuroma, acute lymphocytic leukemia, acute myeloid leukemia, adenocystic carcinoma, adrenocortical cancer, agnogenic myeloid metaplasia, alopecia, alveolar soft-part sarcoma, anal cancer, angiosarcoma, aplastic anemia, astrocytoma, ataxia-telangiectasia, basal cell carcinoma (skin), bladder cancer, bone cancers, bowel cancer, brain stem glioma, brain and CNS tumors, breast cancer, CNS tumors, carcinoid tumors, cervical cancer, childhood brain tumors, childhood cancer, childhood leukemia, childhood soft tissue sarcoma, chondrosarcoma, choriocarcinoma, chronic lymphocytic leukemia, chronic myeloid leukemia, colorectal cancers, cutaneous T-Cell lymphoma, dermatofibrosarcoma-protuberans, desmoplastic-small-round-cell-tumor, ductal carcinoma, endocrine cancers, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, extra-hepatic bile duct cancer, eye cancer, eye: melanoma, retinoblastoma, fallopian tube cancer, fanconi anemia, fibrosarcoma, gall bladder cancer, gastric cancer, gastrointestinal cancers, gastrointestinal-carcinoid-tumor, genitourinary cancers, germ cell tumors, gestational-trophoblastic-disease, glioma, gynecological cancers, hematological malignancies, hairy cell leukemia, head and neck cancer, hepatocellular cancer, hereditary breast cancer, histiocytosis, Hodgkin's disease, human papillomavirus, hydatidiform mole, hypercalcemia, hypopharynx cancer, intraocular melanoma, islet cell cancer, Kaposi's sarcoma, kidney cancer, Langerhan's-cell-histiocytosis, laryngeal cancer, leiomyosarcoma, leukemia, Li-Fraumeni syndrome, lip cancer, liposarcoma, liver cancer, lung cancer, lymphedema, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, male breast cancer, malignant-rhabdoid-tumor-of-kidney, medulloblastoma, melanoma, merkel cell cancer, mesothelioma, metastatic cancer, mouth cancer, multiple endocrine neoplasia, mycosis fungoides, myelodysplastic syndromes, multiple myeloma, myeloproliferative disorders, nasal cancer, nasopharyngeal cancer, nephroblastoma, neuroblastoma, neurofibromatosis, nijmegen breakage syndrome, non-melanoma skin cancer, non-small-cell-lung-cancer-(NSCLC), ocular

cancers, esophageal cancer, oral cavity cancer, oropharynx cancer, osteosarcoma, ostomy ovarian cancer, pancreas cancer, paranasal cancer, parathyroid cancer, parotid gland cancer, penile cancer, peripheral-neuroectodermal-tumors, pituitary cancer, polycythemia vera, prostate cancer, rare-cancers-and-associated-disorders, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, Rothmund-Thomson syndrome, salivary gland cancer, sarcoma, schwannoma, Sezary syndrome, skin cancer, small cell lung cancer (SCLC), small intestine cancer, soft tissue sarcoma, spinal cord tumors, squamous-cell-carcinoma-(skin), stomach cancer, synovial sarcoma, testicular cancer, thymus cancer, thyroid cancer, transitional-cell-cancer-(bladder), transitional-cell-cancer-(renal-pelvis-/-ureter), trophoblastic cancer, urethral cancer, urinary system cancer, uroplakins, uterine sarcoma, uterus cancer, vaginal cancer, vulva cancer, Waldenstrom's-macroglobulinemia and Wilms' tumor. In an embodiment the tumor is selected from a group of multiple myeloma or non-Hodgkin's lymphoma.

In preferred aspects, a combination therapy of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide is used for treatment of multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia in a patient having multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia, including a lenalidomide-resistant form of multiple myeloma, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia. In some highly preferred aspects, a combination therapy of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide is used for treatment of multiple myeloma, leukemia, or lymphoma in a patient having multiple myeloma, leukemia, or lymphoma, including a lenalidomide-resistant form of multiple myeloma, leukemia, or lymphoma. In some highly preferred aspects a combination therapy of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide is used for treatment of multiple myeloma in a patient having multiple myeloma, including a lenalidomide-resistant form of multiple myeloma. Lenalidomide resistance includes resistance arising after an initial period of positively responsive

treatment to lenalidomide, such that the tumor responds positively to the combination therapy.

Use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of tumors are provided. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of B-cell lymphoma. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of multiple myeloma. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of non-Hodgkin's lymphoma. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of chronic myelogenous leukemia. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of chronic lymphocytic leukemia. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of acute lymphocytic leukemia. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or

pomalidomide, as a combination therapy in the treatment of early stage multiple myeloma. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of pre-multiple myeloma. The disclosure also features use of an anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide, or a composition of an anti-CD38 antibody-attenuated interferon alpha-2b construct and a composition of lenalidomide or pomalidomide, as a combination therapy in the treatment of acute lymphocytic leukemia Waldenström's macroglobulinemia.

In one aspect, the disclosure features kits. The kits comprise an anti-CD38 antibody-attenuated interferon alpha-2b construct, lenalidomide or pomalidomide, and instructions for using the construct and lenalidomide in a combination therapy for the treatment of cancer, including lenalidomide-resistant cancer. The anti-CD38 antibody-attenuated interferon alpha-2b construct and lenalidomide or pomalidomide may each be in separate dosage forms, may each be in a composition as described herein, or may be together in a composition as described herein, or may be separate but intended to be combined or mixed together in a suitable carrier prior to administration to a patient having cancer. In some aspects, the kits comprise a pharmaceutically acceptable carrier and instructions for mixing the anti-CD38 antibody-attenuated interferon alpha-2b construct with the carrier, and instructions for mixing the lenalidomide or pomalidomide with the carrier. The pharmaceutically acceptable carrier for the anti-CD38 antibody-attenuated interferon alpha-2b construct may be the same as or different from the pharmaceutically acceptable carrier for the lenalidomide or pomalidomide. The anti-CD38 antibody-attenuated interferon alpha-2b construct and the lenalidomide or pomalidomide preferably are present in the kit in an amount effective for the treatment of cancer in a patient having the cancer, e.g., a synergistically effective amount, including an amount effective for synergistically treating lenalidomide-resistant cancer, or the kit may include instructions for establishing and/or administering a synergistically effective amount for the treatment of cancer. For parenteral administration, the kit may comprise a device to infuse the anti-CD38 antibody-attenuated interferon alpha-2b construct and/or lenalidomide or pomalidomide, or composition thereof, into a subject, including but not limited to a syringe and needle, or catheter.

Lenalidomide resistance include resistance arising after an initial period of positively responsive treatment, such that the tumor responds positively to the combination therapy.

In any of the systems, compositions, kits, methods, and usages described or exemplified in this document, a synergistically effective amount of either or both of the anti-CD38 antibody-attenuated interferon alpha-2b construct and the lenalidomide or pomalidomide may relate to the inclusion of the other agent in the pair. For example, a synergistically effective amount of lenalidomide or pomalidomide may be a function of the synergistically effective amount of the anti-CD38 antibody-attenuated interferon alpha-2b construct, or a synergistically effective amount of the anti-CD38 antibody-attenuated interferon alpha-2b construct may be a function of the synergistically effective amount of lenalidomide or pomalidomide. The anti-CD38 antibody-attenuated interferon alpha-2b construct and the lenalidomide or pomalidomide synergize to produce an enhanced tumor killing effect relative to the tumor killing effect of each agent alone. A synergistically effective amount may vary, for example, according to the age, gender, the overall health of the patient, the physical characteristics of the patient, the type of the tumor, the stage of the tumor, and other factors that would be expected to be known to a practitioner who would administer an anti-CD38 antibody-attenuated interferon alpha-2b construct and the lenalidomide or pomalidomide as a combination therapy to a patient.

The following examples are provided to describe the disclosure in greater detail. They are intended to illustrate, not to limit, the disclosure.

Example 1

Cell Line Model of Anti-CD38 Antibody-attenuated IFN alpha-2b Construct + Lenalidomide Combination Therapy

In these experiments, 8-12 week-old female CB.17 severe combined immunodeficient (SCID) mice were implanted with 0.2 ml of 50% MATRIGEL® matrix-containing 10 million NCI-H929 multiple myeloma cells subcutaneously in the flank. When tumors reached an average size of 200-300 mm^3, mice were pair matched into different groups and then treated with vehicle (PBS), free-non-attenuated interferon alpha (IFN-alpha) at 0.5mg/kg, a suboptimal dose of an anti-CD38 antibody-IFN alpha-2b-145D construct (2.5mg/kg, molar equivalent to 0.5 mg/kg IFN; ip, biweekly, which was determined by previous *in vivo* efficacy studies), an isotype-matched antibody-IFN alpha-2b-145D

construct (isotype matched to the anti-CD38 antibody, with no anti-CD38 specificity), lenalidomide alone (2.5mg/kg), a combination of free-non-attenuated interferon alpha and lenalidomide, a combination of lenalidomide and a suboptimal dose of the anti-CD38 antibody-IFN alpha-2b-145D construct, or a combination of the isotype control antibody-IFN alpha-2b-145D construct and lenalidomide. The amount of the anti-CD38 antibody-attenuated IFN alpha-2b construct administered was normalized to an IFN-alpha molar equivalent of the 0.5 mg/kg of free interferon administered to the animals. The results of these experiments are shown in Fig. 1 and Fig. 2. An animal was terminated if the tumor grew to a volume of greater than 2000 mm^3 before the study was completed.

Fig. 2 shows the less than synergistic effect of non-attenuated interferon alpha (free interferon, not part of a construct) and lenalidomide. The combination of interferon and lenalidomide delayed tumor growth relative to interferon or lenalidomide alone, but eventually tumor growth initiated, with rapid increase in tumor volume within about a month of commencing treatment.

In contrast, Fig. 1 shows the synergistic effect of the combination of an anti-CD38 antibody-attenuated IFN alpha-2b construct and lenalidomide. Although each of the construct, lenalidomide, and interferon alpha, when used alone, delayed tumor growth relative to the vehicle control, eventually tumor growth initiated and accelerated within two weeks to about a month. In contrast, the combination of the construct and lenalidomide demonstrated a suppression of tumor growth for the entire duration of the experiment. The effect was both significant and markedly different from the additive effects of interferon and lenalidomide such that the presence of the anti-CD38 antibody-attenuated interferon alpha-2b construct could overcome the initiation of tumor growth observed even when an isotype control antibody construct was used.

Example 2

Cell Line Model of Anti-CD38 Antibody-attenuated aglycosylated IFN alpha-2b Construct + Lenalidomide Combination Therapy

In this experiment, 8-12 week-old female CB.17 severe combined immunodeficient (SCID) mice were implanted with 1 x 10^7 H929 multiple myeloma tumor cells in 50% Matrigel® subcutaneously in the flank. Tumor volume was measured by calipers biweekly. When tumors reached an average size of 170-350 mm^3, mice were randomized and

treatment commenced. An animal was terminated if the tumor grew to a volume of greater than 2000mm^3 before the study was completed at day 60.

In this example, dose level and inter-dosing interval of administration of an anti-CD38 antibody fused to attenuated aglycosylated interferon-alpha 2b (A10.21 (T106A)) in combination with lenalidomide was investigated. A10.21 (T106A) is an anti-CD38 IgG4 antibody x10.21 fused to an aglycosylated attenuated IFN alpha 2b having the substitutions A145D and T106A. The treatment regimen and results are summarized in Table 5 and the data for individual animals are shown in Figure 3A to 3J. Ten animals were assigned to each of groups 1 to 10. Treatment may cause "partial regression" (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume was 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 mm^3 for one or more of these three measurements. In a CR response, the tumor volume was less than 13.5 mm^3 for three consecutive measurements during the study. Any animal with a CR response at the end of the study was additionally classified as a tumor free survivor (TFS).

Table 5. Combination therapy treatment regimen and results summary.

Group	Treatment 1				Treatment 2				MTV (n) Day 60	PR	CR	TFS
	Agent	mg/kg	Route	Schedule	Agent	mg/kg	Route	Schedule				
1#	Vehicle	-	ip	bi wk for 29 days	-	-	-	-	-	0	0	0
2	lenalidomide	25	ip	q d x21	-	-	-	-	726 (1)	1	0	0
3	A10.21 (T106A)	0.3	ip	bi wk for 29 days	-	-	-	-	425 (4)	0	0	0
4	A10.21 (T106A)	0.3	ip	bi wk for 29 days	lenalidomide	25	ip	qd x 21	405 (8)	8	0	0
5	A10.21 (T106A)	1	ip	bi wk for 29 days	-	-	-	-	70 (10)	2	4	4
6	A10.21 (T106A)	1	ip	bi wk for 29 days	lenalidomide	25	ip	qd x 21	0 (10)	1	9	9

7	A10.21 (T106A)	1	ip	q4 wk for 29 days	-	-	-	-	100 8 (5)	0	0	0
8	A10.21 (T106A)	1	ip	q4 wk for 29 days	lenalidomide	25	ip	qd x 21	304 (10)	5	3	1
9	A10.21 (T106A)	3	ip	q4 wk for 29 days	-	-	-	-	2 (8)	1	6	5
10	A10.21 (T106A)	3	ip	q4 wk for 29 days	lenalidomide	25	ip	qd x 21	0 (10)	0	10	10

- Control Group (vehicle)
Study Endpoint - Earliest of 60 days or tumor volume greater than 2000mm^3
MTV (n) - Median Tumor Volume at study end (number of surviving animals used for calculation)
PR - No. of Partial Regressions
CR - No. of Complete Regressions
TFS - No. of Tumor Free Survivors

Table 5 and Fig. 3 show the synergistic effect of the combination of a sub-optimal dosage of an anti-CD38 antibody fused to attenuated aglycosylated interferon-alpha 2b (T106A) and lenalidomide. The combination of lenalidomide and an anti-CD38 antibody fused to an attenuated aglycosylated interferon-alpha2b allowed a reduction of the dose levels and an increase in dosing intervals of the construct which was required to effectively inhibit tumor growth. Although the construct or lenalidomide when used alone delayed tumor growth relative to vehicle control, tumor growth eventually recommenced. In contrast, the combination of the A10.21 antibody-attenuated aglycosylated IFN alpha2b (T106A) construct and lenalidomide demonstrated suppression of tumor growth for an extended period of time. Furthermore, tumor-free survival at 60 days was achieved in (i) all animals treated with 3mg/kg A10.21 (T106A) once every 4 weeks for 29 days in combination with lenalidomide or (ii) all animals treated with 1mg/kg A10.21 (T106A) biweekly for 29 days in combination with lenalidomide. The Kaplan-Meier Survival Plot (Fig. 4) shows improved survival at Day 60 (the longest interval studied) with the combination of these compounds over lenalidomide alone. Accordingly, the combination of these compounds

facilitates less frequent dosing and administration of lower dosage levels of either or both of lenalidomide and anti-CD-38-attenuated IFN alpha2b.

Example 3

Pomalidomide Study

These experiments were undertaken to determine the efficacy of the combination of a non-curative dosage regime of an anti-CD38 antibody fused to attenuated interferon-alpha 2b and a non-curative dosage regime of pomalidomide in the H929 human multiple myeloma xenograft model in female CB17 SCID mice. Pomalidomide, like lenalidomide, is a derivative and an analog of thalidomide with increased potency against multiple myeloma and reduced toxicity.

In brief, sixty female CB.17 SCID mice were injected with 1 x 10^7 H929 tumor cells subcutaneously in the right flank. Treatment with pomalidomide and an anti-CD38 antibody fused to attenuated interferon-alpha 2b began when tumors reached an average volume of 150 mm^3. The endpoint for the study was when tumor volume reached 2000 mm^3. Cohorts were divided as follows, as summarized in Table 6: Group 1, Vehicle (PBS); Group 2, Pomalidomide alone (2.5mg/kg); Group 3, Anti-CD38- attenuated IFNα- (40ug/dose); Group 4, Anti-isotype-IFNα-attenuated (40ug/dose), Group 5, Pomalidomide (2.5mg/kg) plus anti-CD38- attenuated IFNa (40μg/dose); and Group 6, Pomalidomide (2.5mg/kg) plus anti-isotype- attenuated IFNα- (40μg/dose), Pomalidomide administration started at day 1 and ended on day 21; antibody-interferon fusion construct administration started on day 1 and ended on day 28.

Table 6. Groups, Drugs and Treatment.

Gr.	N	Regimen 1				Regimen 2			
		Agent	mg/kg	Route	Schedule	Agent	mg/kg	Route	Schedule
1	10	Vehicle (PBS)	40*	ip	biwk x 4	-	-	-	-

2	10	Pomalidomide	2.5	ip	qd x 21	-	-	-	-
3	10	Anti CD38-attenuated IFNalpha2b (h10A2-IFN-145D)	40*	ip	biwk x 4	-	-	-	-
4	10	Isotype control (KLH-IFN-145D)	40*	ip	biwk x 4	-	-	-	-
5	10	Pomalidomide	2.5	ip	qd x 21	Anti CD38-attenuated IFNalpha2b (h10A2-IFN-145D)	40*	ip	biwk x 4
6	10	Pomalidomide	2.5	ip	qd x 21	Isotype control (KLH-IFN-145D)	40*	ip	biwk x 4

40*=40µg dose/mouse, which is approximately 2mg/kg

Pomalidomide treatment alone did not substantially slow tumor growth at the dosage used. The anti-CD38-attenuated IFN alpha2b treatment alone caused a robust shrinkage of tumors for the duration of the study. Seven of 10 mice showed minimal tumor regrowth (Fig. 5). In contrast in mice treated with the combination of pomalidomide and anti-CD38-attenuated IFN alpha2b only 4 of 10 showed minimal regrowth, with 6 of 10 mice apparently having their tumors cured. Mice treated with pomalidomide and irrelevant isotype control antibody-attenuated IFN alpha2b had their tumors stabilized for a period of approximately 10 days, but then tumors started growing, albeit at a rate somewhat slower than vehicle controls.

The disclosure is not limited to the embodiments described and exemplified above, but is capable of variation and modification within the scope of the appended claims.

The embodiments of the present invention for which an exclusive property or privilege is claimed are defined as follows:

1. A combination of (i) a construct comprising an antibody which specifically binds to CD38 and which comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29, and that is fused to an attenuated interferon alpha 2b and (ii) lenalidomide or pomalidomide, for use in the treatment of a CD38-positive B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia.

2. The combination for use according to claim 1, wherein the antibody comprises a human IgG4 constant region.

3. The combination for use according to claim 2, wherein the human IgG4 constant region comprises a proline at position 228 according to the EU numbering system.

4. The combination for use according to claim 3, wherein the human IgG4 constant region further comprises a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 of the constant region according to the EU numbering system.

5. The combination for use according to claim 1, wherein the antibody comprises a human IgG1 constant region.

6. The combination for use according to claim 5, wherein the human IgG1 constant region comprises a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 of the constant region according to the EU numbering system.

DateReçue/DateReceived 2022-06-27

7. The combination for use according to any one of claims 1 to 6, wherein the attenuated interferon alpha-2b comprises the amino acid sequence of SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 212, or SEQ ID NO: 213.

8. The combination for use according to any one of claims 1 to 7, wherein the attenuated interferon alpha-2b comprises the amino acid sequence of SEQ ID NO: 212 or SEQ ID NO: 213.

9. The combination for use according to any one of claims 1 to 8, wherein the attenuated interferon alpha-2b comprises the amino acid sequence of SEQ ID NO: 212.

10. The combination for use according to any one of claims 1 to 4, wherein the construct comprises a human IgG4 constant region and the attenuated interferon alpha-2b comprises the amino acid sequence of SEQ ID NO: 212.

11. The combination for use according to claim 10, wherein the human IgG4 constant region further comprises a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 of the constant region according to the EU numbering system.

12. The combination for use according to any one of claims 1 to 11, wherein the combination comprises lenalidomide and the construct, and the combination is for use in the treatment of a CD38-positive B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia.

DateReçue/DateReceived 2022-06-27

13. The combination for use according to any one of claims 1 to 11, wherein the combination comprises pomalidomide and the construct, and the combination is for use in the treatment of a CD38-positive B-cell lymphoma, multiple myeloma, early stage multiple myeloma, pre-multiple myeloma, Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia.

DateReçue/DateReceived 2022-06-27

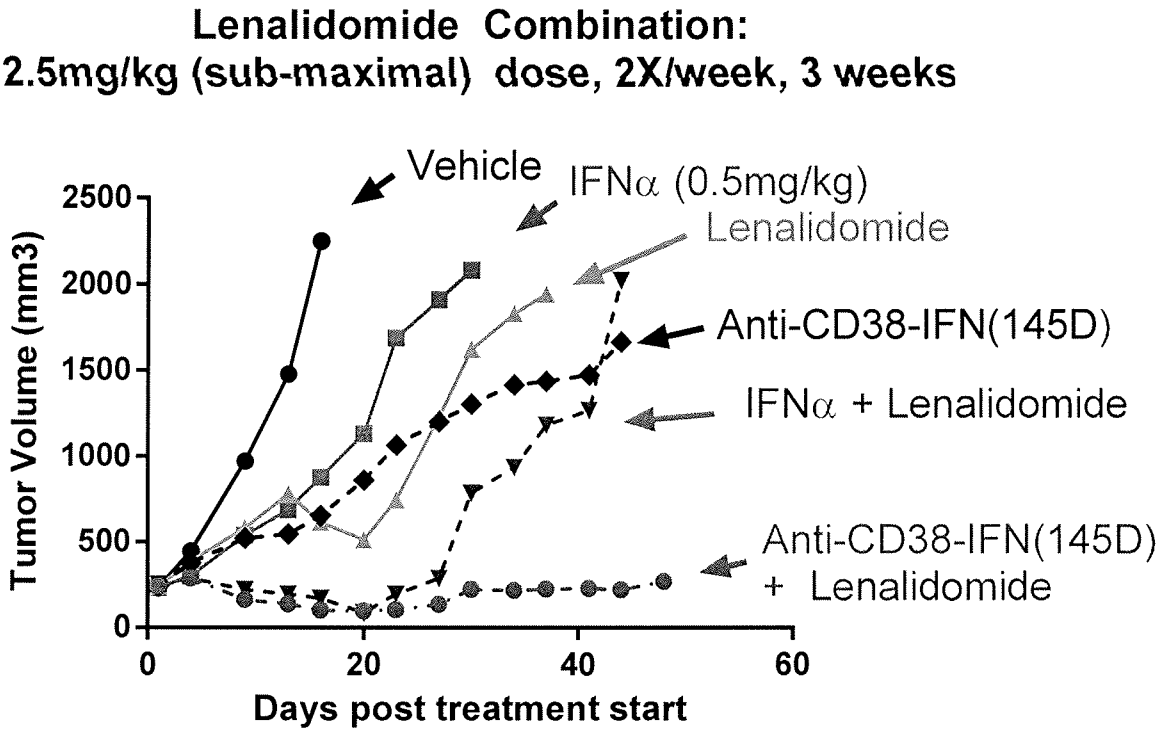

Lenalidomide Combination:
*2.5mg/kg (sub-maximal) dose, 2X/week, 3 weeks
Vehicle
IFNα (0.5mg/kg)
Lenalidomide
Anti-CD38-IFN(145D)
IFNα + Lenalidomide
Anti-CD38-IFN(145D)
+ Lenalidomide
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
20
40
60
Days post treatment start

Fig. 1

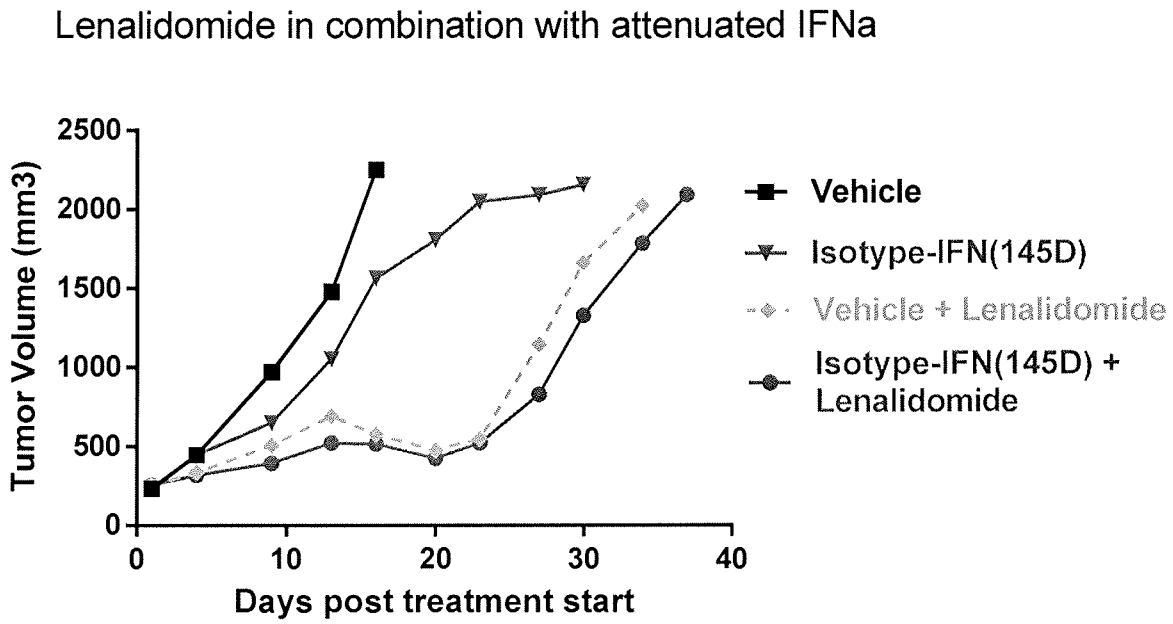

Lenalidomide in combination with attenuated IFNa
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
10
20
30
40
Days post treatment start
Vehicle
Isotype-IFN(145D)
Vehicle + Lenalidomide
Isotype-IFN(145D) + Lenalidomide

Fig. 2

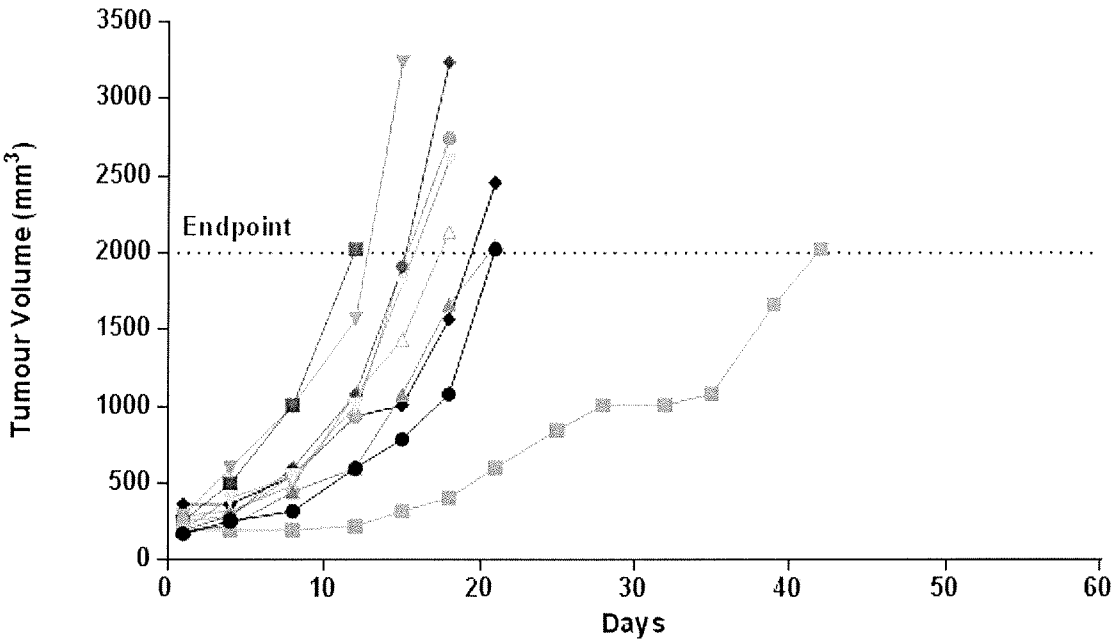

Tumour Volume (mm3)
Endpoint
Days
0
500
1000
1500
2000
2500
3000
3500
0
10
20
30
40
50
60

Fig. 3A

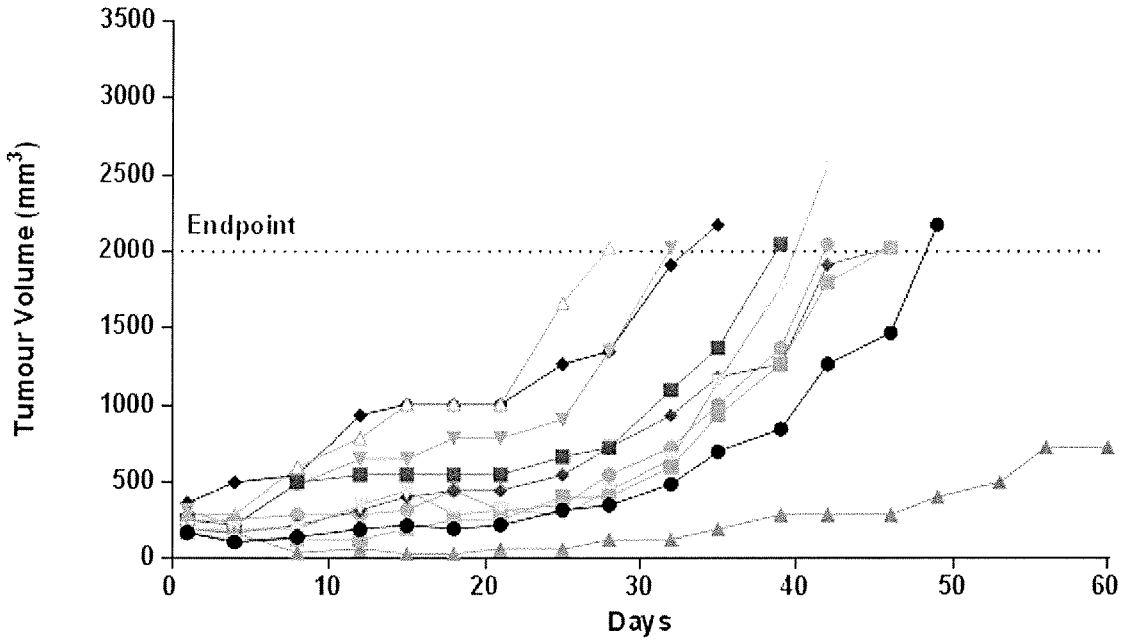
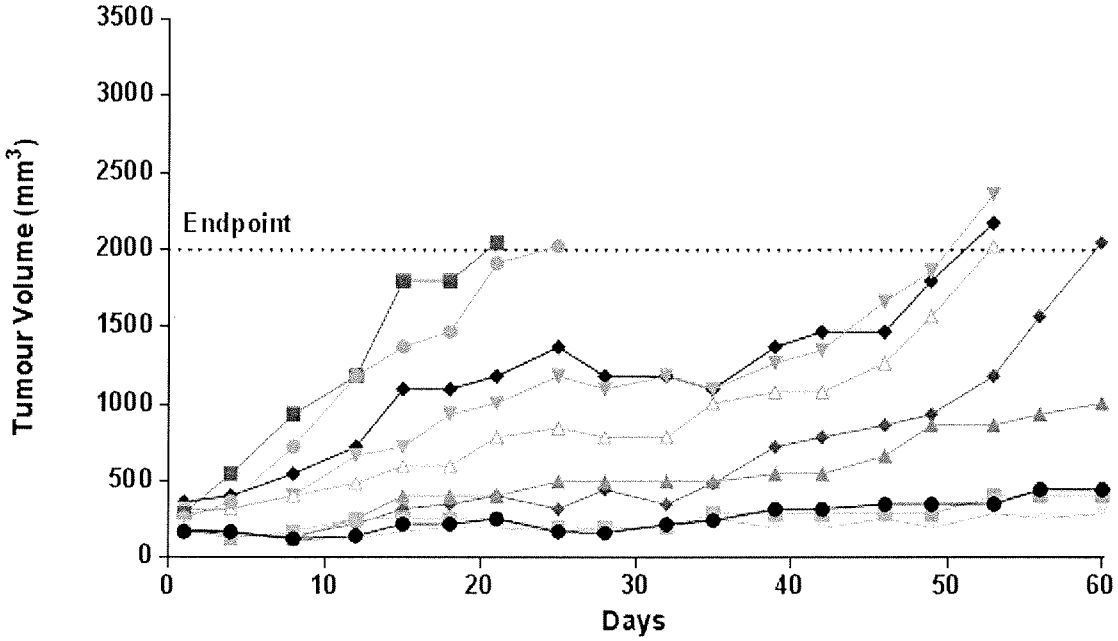

Tumour Volume (mm3)
Endpoint
Days
0
500
1000
1500
2000
2500
3000
3500
0
10
20
30
40
50
60

Fig. 3B


Tumour Volume (mm3)
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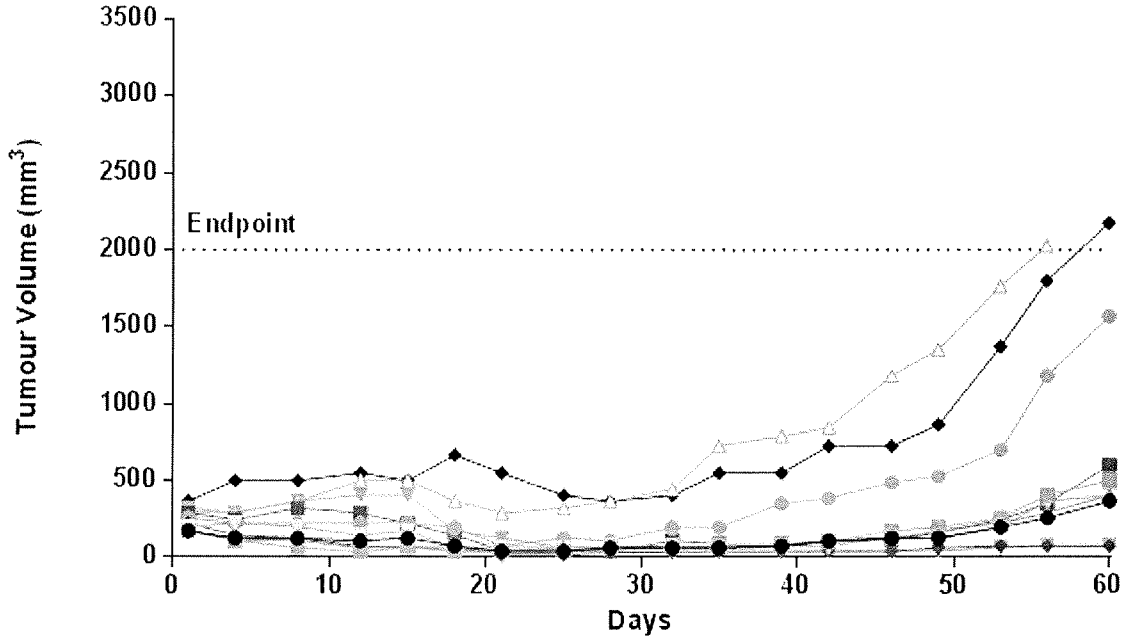
3000
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3C


Tumour Volume (mm3)
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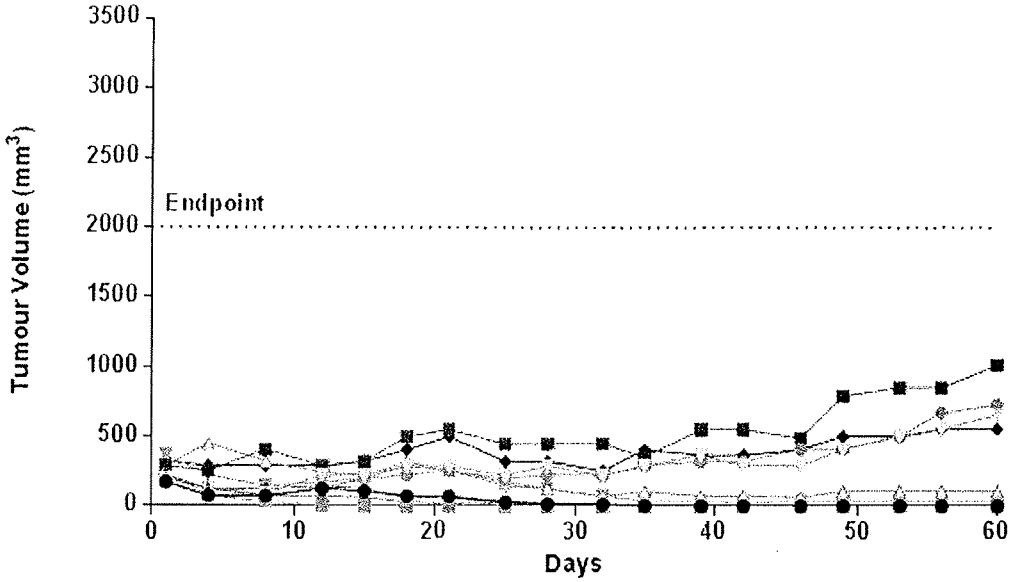
3000
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3D


Tumour Volume (mm3)
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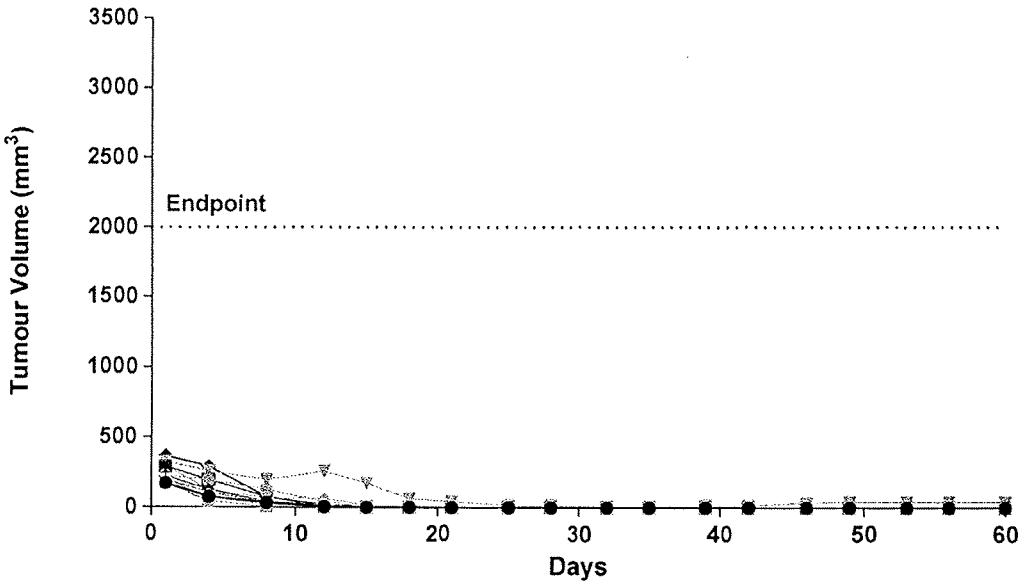
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3E


Tumour Volume (mm3)
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2500
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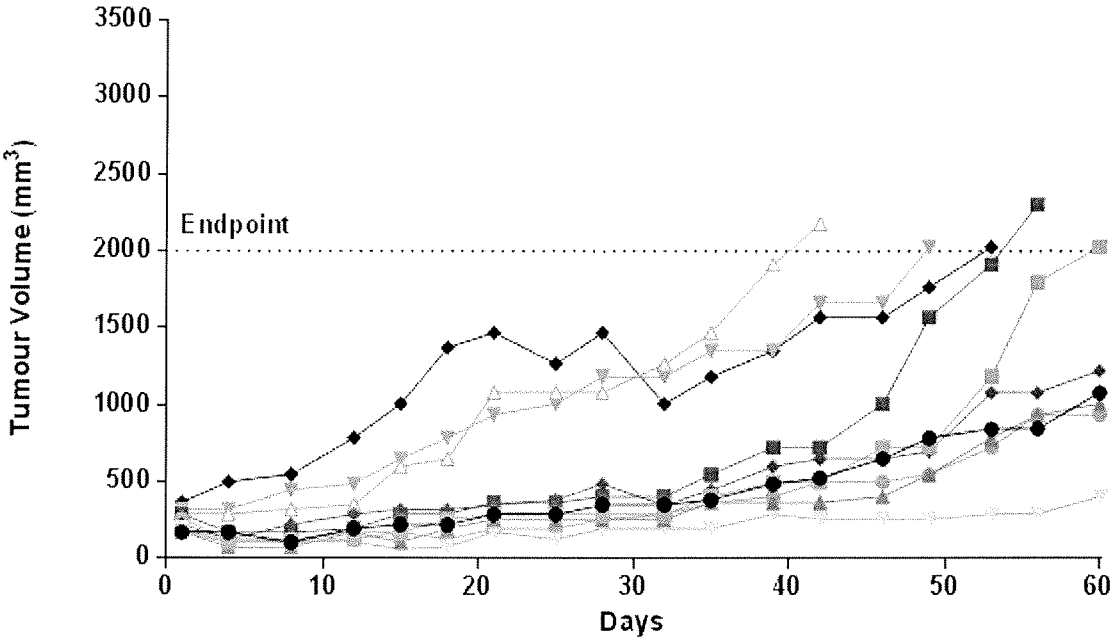
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3F


Tumour Volume (mm3)
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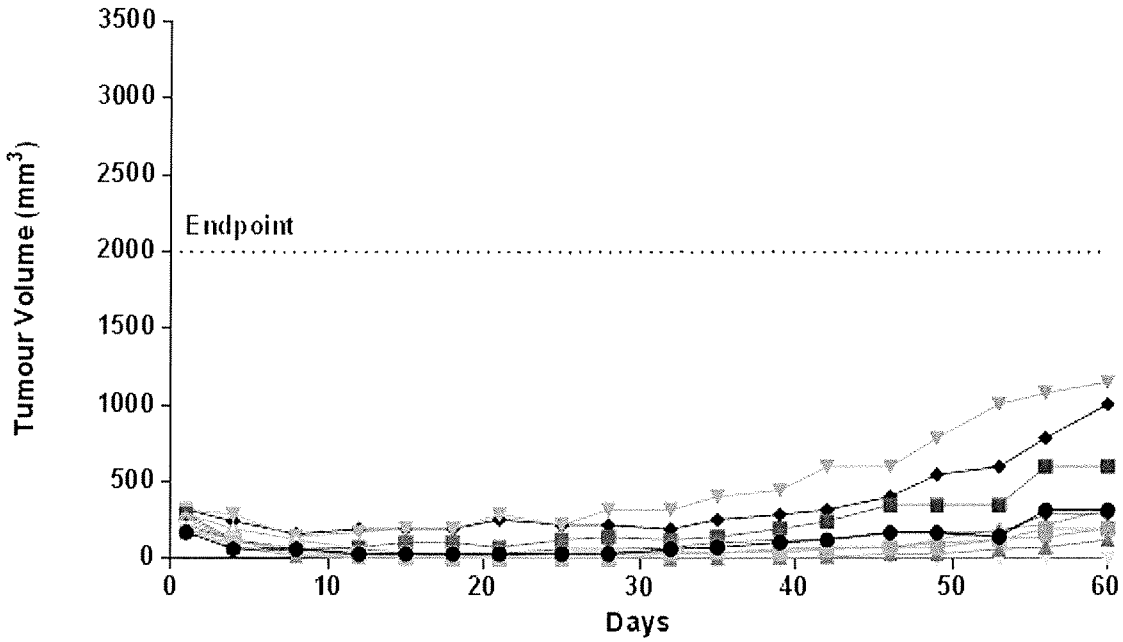
3000
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3G


Tumour Volume (mm3)
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3000
2500
2000
1500
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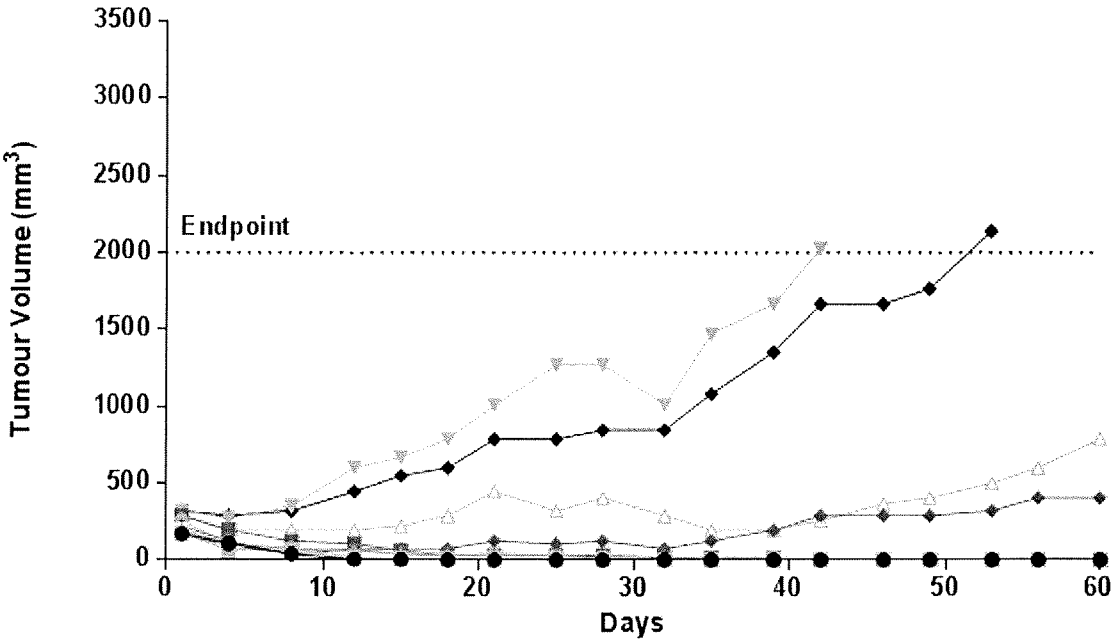
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3H


Tumour Volume (mm3)
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3000
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3I

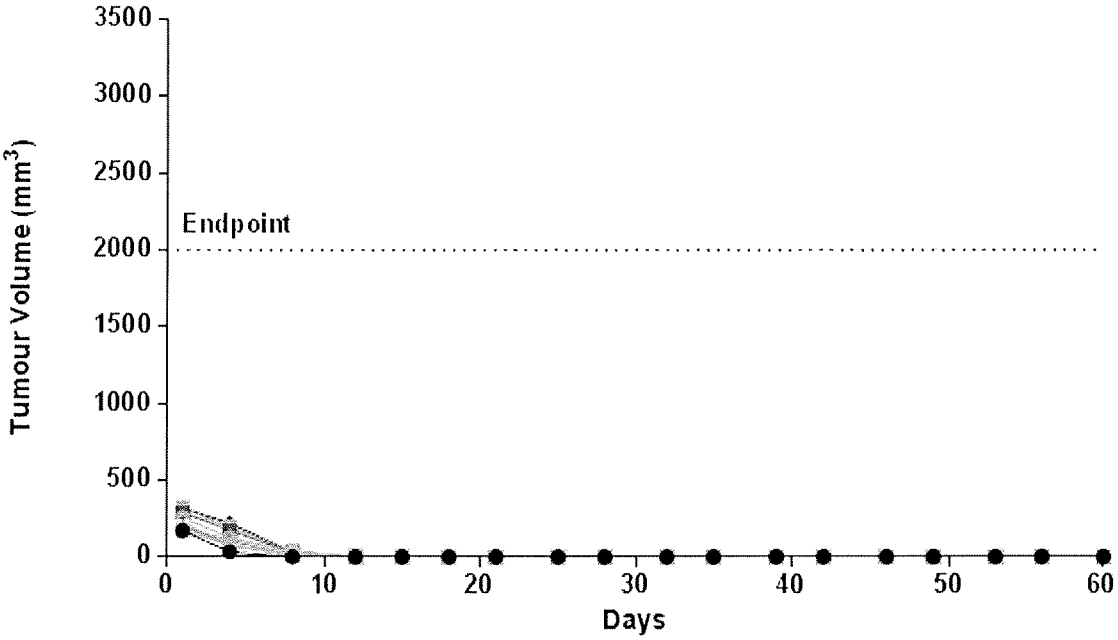
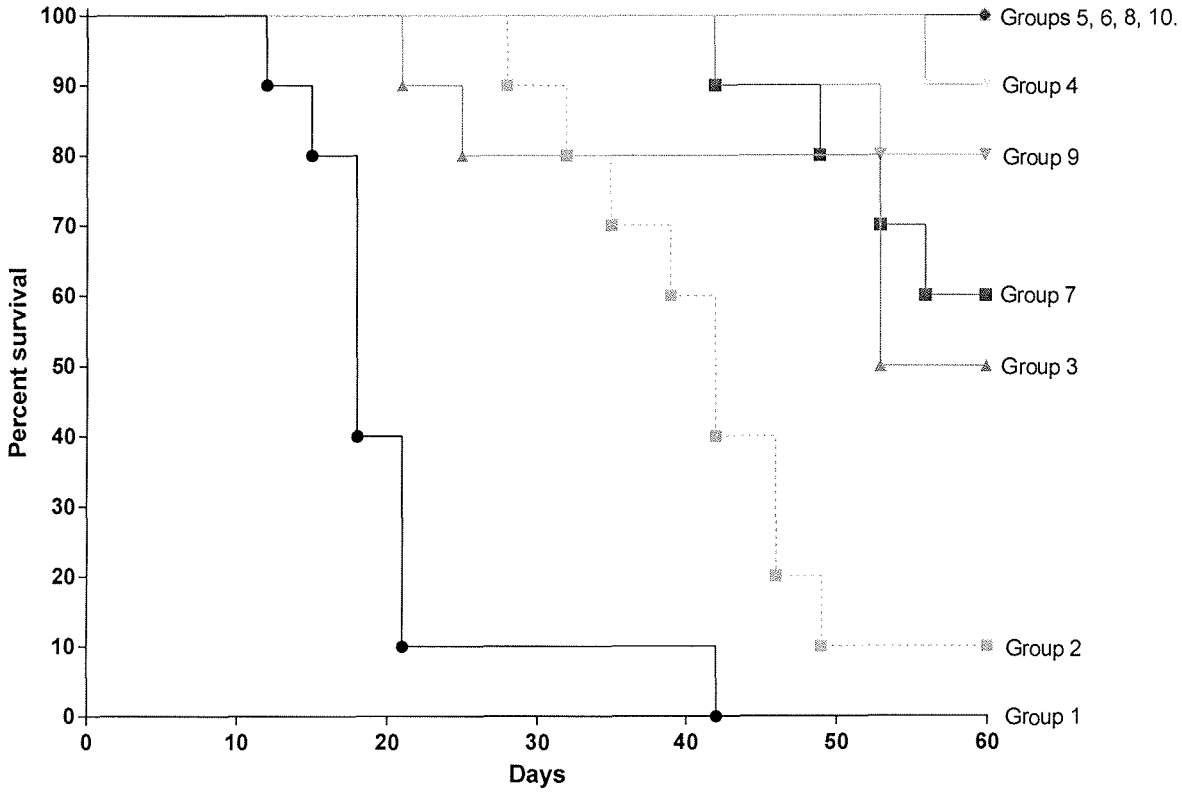

Tumour Volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
Endpoint
0
10
20
30
40
50
60
Days

Fig. 3J



- Group 1: vehicle (ip, biwk for 29 days)
- Group 2: lenalidomide (25 mg/kg, ip, qd x 21)
- Group 3: A10.21 (T106A) (0.3mg/kg, ip, biwk for 29 days)
- Group 4: A10.21 (T106A) (0.3mg/kg, ip, biwk for 29 days), lenalidomide (25 mg/kg, ip, qd x 21)
- Group 5: A10.21 (T106A) (1.0mg/kg, ip, biwk for 29 days)
- Group 6: A10.21 (T106A) (1.0mg/kg, ip, biwk for 29 days), lenalidomide (25 mg/kg, ip, qd x 21)
- Group 7: A10.21 (T106A) (1.0mg/kg, ip, q4wk for 29 days)
- Group 8: A10.21 (T106A) (1.0mg/kg, ip, q4wk for 29 days), lenalidomide (25 mg/kg, ip, qd x 21)
- Group 9: A10.21 (T106A) (3.0mg/kg, ip, q4wk for 29 days)
- Group 10: A10.21 (T106A) (3.0mg/kg, ip, q4wk for 29 days), lenalidomide (25 mg/kg, ip, qd x 21)

Fig. 4

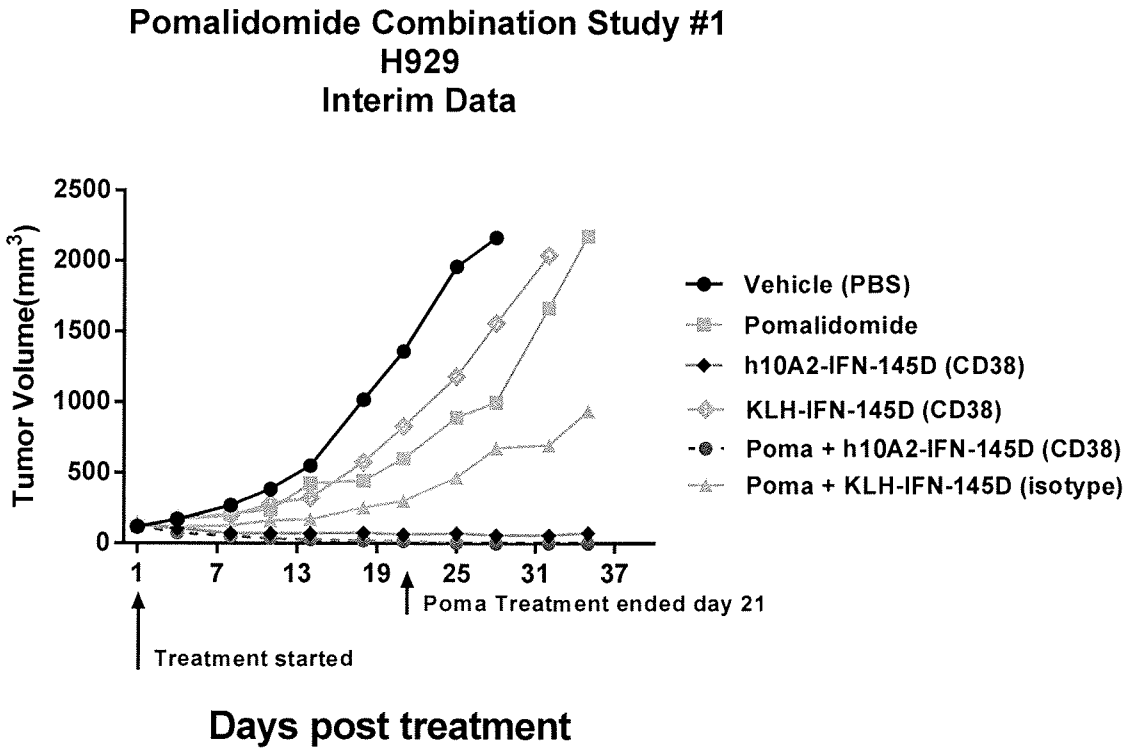

Pomalidomide Combination Study #1
H929
Interim Data
Tumor Volume(mm3)
2500
2000
1500
1000
500
0
1
7
13
19
25
31
37
Poma Treatment ended day 21
Treatment started
Days post treatment
Vehicle (PBS)
Pomalidomide
h10A2-IFN-145D (CD38)
KLH-IFN-145D (CD38)
Poma + h10A2-IFN-145D (CD38)
Poma + KLH-IFN-145D (isotype)

Fig. 5