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(54) Title: IMMUNE CHECKPOINT INHIBITORS AND CYTOTOXIC T CELLS FOR THE TREATMENT OF CANCER

(57) Abstract: Provided herein are methods for treating cancer comprising conjoint administration of an immune checkpoint inhibitor and a composition comprising cytotoxic T cells (CTLs).

IMMUNE CHECKPOINT INHIBITORS AND CYTOTOXIC T CELLS FOR THE  
TREATMENT OF CANCER

## RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application 5 serial number 62/341,402, filed May 25, 2016, hereby incorporated by reference in its entirety.

## BACKGROUND

Nasopharyngeal carcinoma is a type of head and neck cancer that begins in the nasopharynx. Recently, there is emerging evidence to show that exposure to Epstein Barr 10 virus (EBV) can contribute to the pathology of nasopharyngeal carcinoma. Epstein-Barr virus associated nasopharyngeal carcinoma (NPC) is endemic in regions of South-East Asia, with incidence as high as 25–50 cases per 100,000 people in southern China. While current standard therapy is often curative for a subset with stage I or II disease, a high proportion of patients relapse and many patients are still initially diagnosed with advanced stage III or IV 15 disease, where overall 5-year survival is significantly reduced. Thus, there exists a need to develop improved therapies for NPC.

## SUMMARY

In certain aspects, provided herein are methods of treating cancer (e.g., NPC) in a subject by administering (e.g., conjointly) an immune checkpoint inhibitor and a 20 composition comprising cytotoxic T cells (CTLs) expressing a T cell receptor specific for a cancer-associated peptide presented on a class I MHC.

In some embodiments, the immune checkpoint inhibitor is a protein or polypeptide (e.g., an antibody or antigen-binding fragment thereof) that binds to an immune checkpoint protein, such as CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, 25 TIM-3, IDO, TDO, and VISTA. In some embodiments, the immune checkpoint protein is CTLA4, PD-1, PD-L1, TIM-3 or LAG-3. In some embodiments, the immune checkpoint inhibitor binds to the immune checkpoint protein such that it inhibits its activity. In some embodiments, the immune checkpoint inhibitor inhibits the interaction between the immune checkpoint protein and an associated receptor/ligand. In some embodiments, the immune 30 checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-

A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT 011, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.

In some embodiments, the cytotoxic T cells in the composition can be specific for any cancer-associated peptide presented on a class I MHC (e.g., a cancer associated peptide expressed by a tumor and/or cancer cells in the subject). In some embodiments, the cancer-associated peptide is a viral peptide. In some embodiments (e.g., when the subject has EBV-associated NPC or another EBV-associated cancer), the viral peptide is an EBV peptide. In some embodiments, the EBV peptide comprises a LMP1 peptide, a LMP2A peptide, and/or an EBNA1 peptide.

10 In some embodiments, the CTLs are allogeneic to the subject (e.g., obtained from a cell bank). In some embodiments, the CTLs are autologous to the subject. The CTLs and the immune checkpoint inhibitor may be co-administered or administered sequentially. In some embodiments, the method further comprises administering to the subject a chemotherapeutic agent.

15 In some aspects, provided herein are methods of treating cancer (e.g. nasopharyngeal carcinoma) in a subject, comprising generating peptide-specific CTLs by incubating a sample comprising CTLs and antigen-presenting cells (APCs) that present a CMV peptide, thereby inducing proliferation peptide-specific CTLs in the sample, and administering the peptide-specific CTLs to the subject in combination with an immune checkpoint inhibitor described herein. In some embodiments, the APCs are made to present the EBV peptide by incubating them with a nucleic acid construct (e.g., AdE1-LMPpoly) encoding for the EBV peptide, thereby inducing the APCs to present the EBV peptide. In some embodiments, the APCs may be B cells, antigen-presenting T cells, dendritic cells, or artificial antigen-presenting cells (e.g., a cell line expressing CD80, CD83, 41BB-L and/or CD86, such as 20 aK562 cells). In some embodiments, the EBV peptide comprises a LMP1 peptide or a fragment thereof, a LMP2A peptide or fragment thereof, and/or an EBNA1 peptide or fragment thereof. In some embodiments, the EBV peptide comprises a sequence listed in Table 1. In some embodiments, one or more immune checkpoint inhibitors are administered. The immune checkpoint inhibitors may be administered by any technique known in the art. 25 In some embodiments, the immune checkpoint inhibitor is administered intratumorally. In some embodiments, the sample comprises one or more cytokines or peripheral blood mononuclear cells (PBMCs).

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 has two panels showing the expression of immune checkpoint molecules (*i.e.*, LAG-3, TIM-3, CTLA4, or PD-1). Panel A depicts percentage of HLA-multimer positive CD8-positive lymphocytes that express PD-1, TIM-3, LAG-3 and CTLA-4. Panel B depicts the percentage of PD-1 positive, TIM-3 positive, LAG-3 positive and CTLA-4 positive lymphocytes in the CTL immunotherapy administered in NPC patients with no/minimal residual disease (N/MRD) and active-recurrent/metastatic disease (ARMD) who either showed stable disease (SD) or progressive disease (PD) following adoptive T cell therapy.

## 10 DETAILED DESCRIPTION

### General

In certain aspects, provided herein are methods to treat cancer in a subject using a combination therapy that includes administration, *e.g.*, conjoint administration, of one or more immune checkpoint inhibitors combined with cytotoxic T cell (CTL) immunotherapy.

15 In some embodiments, the cancer is EBV-associated NPC and the CTLs administered to the subject express a T cell receptor that has binding specificity for a peptide expressing and EBV epitope presented on a class I MHC.

### Definitions

20 For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The articles “*a*” and “*an*” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

25 As used herein, the term “*administering*” means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering. Such an agent can contain, for example, peptide described herein, an antigen presenting cell provided herein and/or a CTL provided herein.

30 The term “*biological sample*,” “*tissue sample*,” or simply “*sample*” each refers to a collection of cells obtained from a tissue of a subject. The source of the tissue sample may be solid tissue, as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, or aspirate; blood or any blood constituents, serum, blood; bodily fluids such as cerebral spinal

fluid, amniotic fluid, peritoneal fluid or interstitial fluid, urine, saliva, stool, tears; or cells from any time in gestation or development of the subject.

The term "*binding*" or "*interacting*" refers to an association, which may be a stable association, between two molecules, *e.g.*, between a T cell receptor (TCR) and a

5 peptide/MHC, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

As used herein, the term "*cancer*" includes, but is not limited to, solid tumors and blood borne tumors. The term cancer includes diseases of the skin, tissues, organs, bone, cartilage, blood and vessels. The term "*cancer*" further encompasses primary and metastatic

10 cancers.

The term "*epitope*" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains. Certain epitopes can be defined by a particular sequence of amino acids to which a T cell receptor or antibody is capable of binding.

15 As used herein, the phrase "*pharmaceutically acceptable*" refers to those agents, compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

20 As used herein, the phrase "*pharmaceutically-acceptable carrier*" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting an agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of

25 the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository

30 waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate;

(13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, a therapeutic that "*prevents*" a condition refers to a compound that, when administered to a statistical sample prior to the onset of the disorder or condition, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

As used herein, the term "*subject*" means a human or non-human animal selected for treatment or therapy.

The phrases "*therapeutically-effective amount*" and "*effective amount*" as used herein means the amount of an agent which is effective for producing the desired therapeutic effect in at least a sub-population of cells in a subject at a reasonable benefit/risk ratio applicable to any medical treatment.

"*Treating*" a disease in a subject or "*treating*" a subject having a disease refers to subjecting the subject to a pharmaceutical treatment, *e.g.*, the administration of a drug, such that at least one symptom of the disease is decreased or prevented from worsening.

As used herein, the term "*conjoint administration*" means administration of two or more agents to a subject of interest as part of a single therapeutic regimen. The administration(s) can be either simultaneous or sequential, *i.e.*, administering one agent followed by administering of a second (and/or a third one, etc.) at a later time, as long as the agents administered co-exist in the subject being treated, or at least one agent will have the opportunity to act upon the same target tissues of other agents while said target tissues are still under the influence of said other agents. In a certain embodiment, agents to be administered can be included in a single pharmaceutical composition and administered together. In a certain embodiment, the agents are administered simultaneously, including through separate routes. In a certain embodiment, one or more agents are administered continuously, while other agents are administered only at predetermined intervals (such as a single large dosage, or twice a week at smaller dosages, etc.).

#### Immune Checkpoint Inhibitors

5 In certain aspects, provided herein are methods related to treating cancer (*e.g.*, nasopharyngeal carcinoma) in a subject by administering to the subject a combination therapy, the combination therapy comprising administering to the subject both an immune checkpoint inhibitor and a composition comprising cytotoxic T cells (CTLs) expressing a T cell receptor specific for a cancer-associated peptide presented on a class I MHC.

The immune checkpoint inhibitor and CTL composition can be administered together or separately. They can be administered simultaneously or sequentially. When sequentially administered, in some embodiments the immune checkpoint inhibitor will be administered before the CTL composition (*e.g.*, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours before, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days before). When sequentially administered, in some embodiments the CTL composition will be administered before the immune checkpoint inhibitor (*e.g.*, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours before, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days before).

20 Immune checkpoint inhibition broadly refers to inhibiting the biological pathways that serve as checkpoints to prevent or downregulate an immune response. Such pathways are often used by cancer cells to avoid an anti-tumor immune response. In certain embodiments, the method includes administering to the subject one or more immune checkpoint inhibitors that target immune checkpoint proteins. Immune checkpoint proteins include, but are not limited to, CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, and VISTA. In some embodiments, one or more immune checkpoint inhibitor may target one or more immune checkpoint proteins.

25 In some embodiments, the immune checkpoint inhibitor is a protein, such as a soluble fusion protein. In some embodiments, such a protein comprises a receptor/ligand binding domain (*e.g.*, an extracellular domain) of CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA. In some embodiments, the receptor/ligand binding domain is fused to an immunoglobulin Fc domain. Such a fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different peptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini,

filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers.

Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, for example, Current Protocols in Molecular Biology, Ausubel et al., eds., John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety.

10 In certain embodiments, the immune checkpoint inhibitor is an antibody or antigen-binding fragment thereof that binds to and inhibits an immune checkpoint protein (e.g., CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA). As used herein, the term “antibody” may refer to both an intact antibody and an antigen binding fragment thereof. The term “antibody” includes, for example, 15 monoclonal antibodies, polyclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, multispecific antibodies (e.g., bispecific antibodies), single-chain antibodies and antigen-binding antibody fragments. An antigen-binding fragment of an antibody refers to one or more fragments of an antibody that retain the ability to bind to an antigen. Examples of binding fragments include Fab, Fab', F(ab')<sub>2</sub>, Fv, scFv, disulfide linked 20 Fv, Fd, diabodies, single-chain antibodies, camelid antibodies, isolated CDRH3, and other antibody fragments that retain at least a portion of the variable region of an intact antibody. Such antibody fragments can be obtained using conventional recombinant and/or enzymatic techniques and can be screened for antigen-binding in the same manner as intact antibodies.

25 In some embodiments, the immune checkpoint inhibitor is an inhibitory nucleic acid (e.g., an siRNA molecule, an shRNA molecule, an antisense RNA) that specifically binds to an mRNA that encodes an immune checkpoint inhibitor (e.g., CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA). Inhibitory nucleic acid molecules can be prepared by chemical synthesis, in vitro transcription, or digestion of long dsRNA by Rnase III or Dicer. Inhibitory nucleic acid molecules can be 30 delivered in vitro to cells or in vivo, e.g., to tumors or hypoxic tissues of a mammal. Typical delivery means known in the art can be used. For example, an interfering RNA can be delivered systemically using, for example, the methods and compositions described in PCT

Application No: PCT/US09/036223, PCT/US09/061381 PCT/US09/063927, PCT/US09/063931 and PCT/US09/063933, each of which is hereby incorporated by reference in its entirety. In certain embodiments the inhibitory nucleic acid is delivered locally. For example, when the inhibitory nucleic acid described herein is used to treat 5 cancer, delivery to a tumor can be accomplished by intratumoral injections, as described, for example, in Takahashi *et al.*, *Journal of Controlled Release* 116:90-95 (2006) and Kim *et al.*, *Journal of Controlled Release* 129:107-116 (2008), each of which is incorporated by reference in its entirety.

In yet other embodiments, the immune checkpoint inhibitor is a small organic 10 molecule, e.g., a molecule having a molecular weight under about 5 kD, preferably less than about 2 kD, and typically exclude oligonucleotides and oligopeptides. Small molecules include, for example, peptidomimetics, oligosaccharides, steroids, etc. Representative small-molecule checkpoint inhibitors are described in WO 2016/041511, WO 2015/034820, WO 2010/005958, WO 2014/159248, US Published Application 2011/0318373, and Weinmann, 15 H., *Chem. Med. Chem.* **2016**, *11*, 450-466 (and in references cited therein).

Various immune checkpoint inhibitors are known in the art. In some embodiments, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT Oll, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.

## 20 Cytotoxic T Lymphocytes

In some embodiments, the CTLs in the CTL composition administered to the subject express a T cell receptor that specifically binds to a peptide (e.g., a peptide comprising a 25 cancer-associated epitope) presented on a class I MHC. In some embodiments, the class I MHC has an  $\alpha$  chain polypeptide that is HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-g, HLA-K or HLA-L. In some embodiments, the peptide is a peptide described herein. In some embodiments, the CTLs in the sample express a TCR specific for an Epstein-Barr Virus (EBV) peptide (e.g., a LMP1 peptide, a LMP2A peptide or an EBNA1 peptide) presented on a class I MHC.

30 CTLs in the CTL compositions described herein may be generated by incubating a sample comprising CTLs with the antigen-presenting cells (APCs), thereby inducing the CTLs to proliferate. In some embodiments, the APCs that present a peptide described herein (e.g., a peptide comprising a LMP1, LMP2A, or EBNA1 epitope sequence). In some

embodiments the APCs are B cells, antigen-presenting T-cells, dendritic cells, or artificial antigen-presenting cells (*e.g.*, aK562 cells).

Dendritic cells for use in the process may be prepared by taking peripheral blood mononuclear cells (PBMCs) from a patient sample and adhering them to plastic. Generally the monocyte population sticks and all other cells can be washed off. The adherent population is then differentiated with IL-4 and GM-CSF to produce monocyte derived dendritic cells. These cells may be matured by the addition of IL-1 $\beta$ , IL-6, PGE-1 and TNF- $\alpha$  (which upregulates the important co-stimulatory molecules on the surface of the dendritic cell) and are then transduced with one or more of the peptides provided herein.

APCs that present one or more peptides described herein may be generated by contacting an APC with a peptide comprising a CTL epitope and/or with a nucleic acid encoding a peptide comprising a CTL epitope. In some embodiments, the APCs are irradiated. In some embodiments, the APCs that present a peptide described herein (*e.g.*, a peptide comprising a LMP1, LMP2A, or EBNA1 epitope sequence). A cell presenting a peptide described herein can be produced by standard techniques known in the art. For example, a cell may be pulsed to encourage peptide uptake. In some embodiments, the cells are transfected with a nucleic acid encoding a peptide provided herein. Provided herein are methods of producing antigen-presenting cells (APCs), comprising pulsing a cell with the peptides described herein. Exemplary examples of producing antigen-presenting cells can be found in WO2013088114, hereby incorporated in its entirety.

In some embodiments, the methods provided herein include steps of generating, activating and/or inducing proliferation of T cells (*e.g.*, CTLs) that recognize one or more of the CTL epitopes described herein. In some embodiments, a sample comprising CTLs (*i.e.*, a PBMC sample) is incubated in culture with an APC provided herein (*e.g.*, an APC that presents a peptide comprising a CTL epitope (*e.g.*, EBV epitope) on a class I MHC complex). In some embodiments, the APCs are autologous to the subject from whom the T cells were obtained. In some embodiments, the APCs are not autologous (*i.e.* allogeneic) to the subject from whom the T cells were obtained. In some embodiments, the sample containing T cells is incubated two or more times with APCs provided herein. In some embodiments, the T cells are incubated with the APCs in the presence of at least one cytokine. In some embodiments, the cytokine is IL-4, IL-7 and/or IL-15. Exemplary methods

for inducing proliferation of T cells using APCs are provided, for example, in U.S. Pat. Pub. No. 2015/0017723, which is hereby incorporated by reference.

In some aspects, provided herein are methods comprising the administration of samples, comprising immune checkpoint inhibitors and CTLs to a subject in order to treat and/or prevent cancer. In some embodiments, the method includes administering to the subject an effective amount of a composition comprising CTLs one or more immune checkpoint inhibitors, provided herein. In some embodiments, the composition includes a combination of multiple (e.g., two or more) CTLs and/or immune checkpoint inhibitors provided herein. In some embodiments, the T cells are autologous to the subject. In some embodiments, the T cells are allogeneic to the subject. In some embodiments, the CTLs are stored in a cell bank before they are administered to the subject.

In some embodiments, the methods provided herein include selecting allogeneic CTLs from a cell bank (e.g., a pre-generated third party donor derived bank of epitope specific CTLs) for adoptive immunotherapy by determining the level expression of a biomarker within the CTL population. In some embodiments, the level of expression of two or more biomarkers is determined. In some embodiments, the method further includes selecting allogeneic CTLs because they express a TCR restricted to a class I MHC that is encoded by an HLA allele that is present in the subject. In some embodiments, the CTLs are selected if the CTLs and subject share at least 2 (e.g., at least 3, at least 4, at least 5, at least 6) HLA alleles and the CTLs are restricted through a shared HLA allele. In some embodiments, the method comprises testing the TCR repertoire of the pre-generated third-party-donor-derived epitope-specific T cells (*i.e.*, allogeneic T cells) with flow cytometry. In some embodiments epitope-specific T cells are detected using a tetramer assay, an ELISA assay, a western blot assay, a fluorescent microscopy assay, an Edman degradation assay and/or a mass spectrometry assay (e.g., protein sequencing). In some embodiments, the TCR repertoire is analyzed using a nucleic acid probe, a nucleic acid amplification assay and/or a sequencing assay.

#### Peptides

In some embodiments, the methods and compositions provided herein relate to peptide specific CTLs. In some embodiments, the methods include the generation of such CTLs, for example, by incubating a sample comprising CTLs (*i.e.*, a PBMC sample) with antigen-presenting cells (APCs) that present one or more of the CTL epitopes described

herein (e.g., APCs that present a peptide described herein comprising a CTL epitope on a class I MHC complex).

In some embodiments, the peptides provided herein comprise a sequence of any EBV viral protein (e.g., a sequence of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous amino acids of any EBV protein). In some embodiments, the peptides provided herein comprise no more than 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 contiguous amino acids of the EBV viral protein.

In some embodiments, the peptides provided herein comprise a sequence of LMP1 (e.g., a sequence of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous amino acids of LMP1). In some embodiments, the peptides provided herein comprise no more than 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 contiguous amino acids of LMP1. An exemplary LMP1 amino acid sequence is provided below (SEQ ID NO: 1):

```
1 mdldlergpp gprpprgpp lssyialall llllallfwl yiimsnwtgg
15 allvlyafal
61 mlviiiliif ifrrdllicpl galcllllmi tlllialwnl hgqalylgiv
lfifgcclvl
121 giwvyfleil wrlgatiwql lafflaffld illliialyl qgnwwtllvd
llwlllflai
20 181 liwmyyhgqr hsdehhhdds 1phpqqatdd ssnhsdsnsn egrhhllvsg
agdapplcsg
241 nlgapggpd ngpqdpdntd dngpqdpdnt ddngphdplp qdpdntddng
pqdpdntddn
25 301 gphdplphnp sdsagndggp pnltteevenk ggdrgppsmt dggggdphlp
tlllgtsgsg
361 gddddphgpv qlsyyd
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In some embodiments, the peptides provided herein comprise a sequence of LMP2A (e.g., a sequence of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous amino acids of LMP2A). In some embodiments, the peptides provided herein comprise no more than 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 contiguous amino acids of LMP2A. An exemplary LMP2A amino acid sequence is provided below (SEQ ID NO: 2):

```
1 mgslempmg agppspggdp dgddggnnnsq ypsasgsdgn tptppndeer
esnepppyy
```

61 edldwgngdr hsdyqplgnq dpslylqlqh dgndglpppp ysprddssqh  
 iyeeagrgsm  
 121 npvclpviva pylfwlaaia ascftasvst vvtatglals llllaavass  
 yaaaqrkllt  
 5 181 pvtvlavvt ffaicltwri edppfnsslif allaaagglq giyvlvmlvl  
 lilayrrrwr  
 241 rltvcggimf lacvlvlivd avlqlspllg avtvvsmtll llafvlwlss  
 pgglgtlgaa  
 301 lltlaaalal laslilgtln lttmfllml1 wtlvvllics scsscpkti  
 10 llarlflyi  
 361 ailllasali aggsilqtnf ksksstefip nlfcmllliv agilfilail  
 tewgsgnryt  
 421 gpvfmclgg1 ltmvagavwl tvmtnllsa wntagflif ligfalfgvi  
 rccryccyyt  
 15 481 ltleserpp tpyrntv

In some embodiments, the peptides provided herein comprise a sequence of EBNA1 (e.g., a sequence of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous amino acids of EBNA1). In some embodiments, the peptides provided herein comprise no more than 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 contiguous amino acids of EBNA1. An exemplary EBNA1 amino acid sequence is provided below (SEQ ID NO: 3):

1 pffhpvgdead yfeylqeggp dgepdvppga ieqgpaddpg egpstgprgg  
 gdggrrkkgg  
 61 wfgkhrgqgg snpkfeniae glrvllarsh vertteegtw vagvfvygg  
 25 ktslynlrrg  
 121 talaipqcrltplsrlpfgm apgpgpqpgp lresivcyfm vflqthifae  
 vlkdaikdlv  
 181 mtkpaptcni kvtvcsfddg vdippwfppm vegaaaegdd gddgdeggdg degeegqe

In some embodiments, the peptide comprises the sequence of an epitope listed in  
 30 Table 1.

**Table 1. Exemplary EBV viral protein epitopes**

Peptide Sequence	HLA Restriction	SEQ ID No:
PYLFWLAAI	A*2301/A*2402/03	4
SSSSCPLSKI	A*1101	5
TYGPVFMCL	A*2402	6

RRRWRRRLTV	B*27/02/04/05/06/09	7
LLSAWILTA	A*0203	8
LTAGFLIFL	A*0206	9
CLGGLLTMV	A*0201	10
VMSNTLLSAW	A*25/A*26	11
MSNTLLSAW	B*58	12
IEDPPFNSL	B*4001	13
YLLEMILWRL	A*02	14
YLQQNWWTL	A*02	15
ALLVLYSFA	A*02	16
IALYLYQQNW	B*57/B*58	17
FLYALALLL	A*0201	18
WTLVVLLI	A*24	19
CPLSKILL	B*0801	20
HPVGEADYFNEY	B*35	21
RPQKRPSCI	B*0702	22
IPQCRLTPL	B*0702	23
LSRLPFGMA	B*5701	24
YNLRRGTAL	B*0801	25
VLKDAIKDL	A*0203	26
FVYGGSKTSL	C*0303/C*0304	27
FVYGGSKTSLY	A*26	28
HPVGEADYF	B*53	29
LQTHIFAEV	A*0206	30
FMVFLQTHI	A*0201	31

In some embodiments, the peptides provided herein comprise two or more of the CTL epitopes (e.g., viral epitopes). In some embodiments, the peptides provided herein comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 CTL epitopes. For example, in some embodiments, the peptides provided herein comprise two or more of the CTL epitopes connected by linkers (e.g., polypeptide linkers).

In some embodiments, the sequence of the peptides comprise a viral protein sequence except for 1 or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) conservative sequence modifications. As used herein, the term “conservative sequence modifications” is intended to refer to amino acid modifications that do not significantly affect or alter the interaction between a T cell receptor (TCR) and a peptide containing the amino acid sequence presented on an MHC. Such conservative modifications include amino acid substitutions, additions (e.g., additions of amino acids to the N or C terminus of the peptide) and deletions (e.g., deletions of amino acids from the N or C terminus of the peptide). Conservative amino acid

substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., 5 lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or 10 more amino acid residues of the peptides described herein can be replaced with other amino acid residues from the same side chain family and the altered peptide can be tested for retention of TCR binding using methods known in the art. Modifications can be introduced into an antibody by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis.

In some embodiments, the peptides provided herein comprise a sequence that is at 15 least 80%, 85%, 90%, 95% or 100% identical to a protein sequence (e.g., the sequence of a fragment of a viral protein). To determine the percent identity of two amino acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). The amino acid residues at 20 corresponding amino acid positions are then compared. When a position in the first sequence is occupied by the same amino acid residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be 25 introduced for optimal alignment of the two sequences.

The peptides provided herein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques, and can be produced by recombinant DNA techniques, and/or can be chemically synthesized using standard peptide synthesis techniques. The peptides described herein can be produced in 30 prokaryotic or eukaryotic host cells by expression of nucleotides encoding a peptide(s) of the present invention. Alternatively, such peptides can be synthesized by chemical methods. Methods for expression of heterologous peptides in recombinant hosts, chemical synthesis of

peptides, and *in vitro* translation are well known in the art and are described further in Maniatis et al., Molecular Cloning: A Laboratory Manual (1989), 2nd Ed., Cold Spring Harbor, N. Y.; Berger and Kimmel, Methods in Enzymology, Volume 152, Guide to Molecular Cloning Techniques (1987), Academic Press, Inc., San Diego, Calif.; Merrifield, J. (1969) *J. Am. Chem. Soc.* 91:501; Chaiken I. M. (1981) *CRC Crit. Rev. Biochem.* 11:255; Kaiser et al. (1989) *Science* 243:187; Merrifield, B. (1986) *Science* 232:342; Kent, S. B. H. (1988) *Annu. Rev. Biochem.* 57:957; and Offord, R. E. (1980) *Semisynthetic Proteins*, Wiley Publishing, which are incorporated herein by reference.

In certain aspects, provided herein are nucleic acid molecules encoding the peptides described herein. In some embodiments, the nucleic acid molecule is a vector. In some embodiments, the nucleic acid molecule is a viral vector, such as an adenovirus based expression vector, that comprises the nucleic acid molecules described herein. In some embodiments, the vector provided herein encodes a plurality of epitopes provided herein (e.g., as a polyepitope). In some embodiments, the vector provided herein encodes at least 2, 10 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 epitopes provided herein (e.g., epitopes provided in Table 1).

In some embodiments, the vector is AdE1-LMPpoly. The AdE1-LMPpoly vector encodes a polyepitope of defined CTL epitopes from LMP1 and LMP2 fused to a Gly-Ala repeat-depleted EBNA1 sequence. The AdE1-LMPpoly vector is described, for example, in Smith et al., *Cancer Research* 72:1116 (2012); Duraiswamy et al., *Cancer Research* 64:1483-9 (2004); and Smith et al., *J. Immunol.* 117:4897-906, each of which is hereby incorporated by reference.

As used herein, the term “vector,” refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a 25 “plasmid”, which refers to a circular double-stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication, episomal mammalian vectors). Other vectors (e.g., non- 30 episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby be replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes. Such vectors are

referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In some embodiments, provided herein are nucleic acids operably linked to one or more regulatory sequences (e.g., a promotor) in an expression vector. In some embodiments, the cell transcribes the nucleic acid provided herein and thereby expresses a peptide described 5 herein. The nucleic acid molecule can be integrated into the genome of the cell or it can be extrachromosomal.

In some embodiments, provided herein are cells that contain a nucleic acid described herein (e.g., a nucleic acid encoding a peptide described herein). The cell can be, for example, prokaryotic, eukaryotic, mammalian, avian, murine and/or human. In some 10 embodiments, the cell is a mammalian cell. In some embodiments the cell is an APC (e.g. an antigen-presenting T cell, a dendritic cell, a B cell, or an aK562 cell). In the present methods, a nucleic acid described herein can be administered to the cell, for example, as nucleic acid without delivery vehicle, in combination with a delivery reagent. In some embodiments, any nucleic acid delivery method known in the art can be used in the methods described herein. 15 Suitable delivery reagents include, but are not limited to, e.g., the Mirus Transit TKO lipophilic reagent; lipofectin; lipofectamine; cellfectin; polycations (e.g., polylysine), atelocollagen, nanoplexes, and liposomes. In some embodiments of the methods described herein, liposomes are used to deliver a nucleic acid to a cell or subject. Liposomes suitable for use in the methods described herein can be formed from standard vesicle-forming lipids, 20 which generally include neutral or negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of factors such as the desired liposome size and half-life of the liposomes in the blood stream. A variety of methods are known for preparing liposomes, for example, as described in Szoka *et al.* (1980), *Ann. Rev. Biophys. Bioeng.* 9:467; and U.S. Pat. Nos. 4,235,871, 4,501,728, 25 4,837,028, and 5,019,369, the entire disclosures of which are herein incorporated by reference.

#### Therapeutic Methods

In some embodiments, the provided herein are methods of treating a cancer in a 30 subject by administering to the subject a combination therapy described herein.

In some embodiments, the methods provided herein can be used to treat any cancer. For example, in some embodiments, the methods and CTLs described herein may be used to

treat any cancerous or pre-cancerous tumor. In some embodiments, the cancer includes a solid tumor. In some embodiments, cancers that may be treated by methods and compositions provided herein include, but are not limited to, cancer cells from the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, 5 kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; 10 transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiolo-alveolar 15 adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometrioid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous 20 adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; mammary paget's disease; acinar cell carcinoma; adenosquamous carcinoma; 25 adenocarcinoma w/squamous metaplasia; malignant thymoma; malignant ovarian stromal tumor; malignant thecoma; malignant granulosa cell tumor; and malignant roblastoma; sertoli cell carcinoma; malignant leydig cell tumor; malignant lipid cell tumor; malignant paraganglioma; malignant extra-mammary paraganglioma; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading 30 melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; malignant blue nevus; sarcoma; fibrosarcoma; malignant fibrous histiocytoma; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal

rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; malignant mixed tumor; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; malignant mesenchymoma; malignant brenner tumor; malignant phyllodes tumor; synovial sarcoma; malignant mesothelioma; dysgerminoma; embryonal carcinoma; malignant teratoma;

5 malignant struma ovarii; choriocarcinoma; malignant mesonephroma; hemangiosarcoma; malignant hemangioendothelioma; kaposi's sarcoma; malignant hemangiopericytoma; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; malignant chondroblastoma; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; malignant odontogenic tumor; ameloblastic odontosarcoma; malignant ameloblastoma;

10 ameloblastic fibrosarcoma; malignant pinealoma; chordoma; malignant glioma; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendrolioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; malignant meningioma; neurofibrosarcoma; malignant neurilemmoma;

15 malignant granular cell tumor; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma; paragranuloma; small lymphocytic malignant lymphoma; diffuse large cell malignant lymphoma; follicular malignant lymphoma; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell

20 leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.

In some embodiments, the methods provided herein are used to treat EBV associated cancer. In some embodiments, the EBV-associated cancer is EBV-associated NPC. In some 25 embodiments, the EBV associated cancer is post-transplant lymphoproliferative disorder (PTLD), NK/T cell lymphoma, EBV+ gastric cancer, or EBV+ leiomyosarcoma.

In some embodiments, the combination therapy further comprises a 30 chemotherapeutic agent (e.g., alkylating agents or agents with an alkylating action, such as cyclophosphamide (CTX; e.g., CYTOXAN®), chlorambucil (CHL; e.g., LEUKERAN®), cisplatin (Cis P; e.g., PLATINOL®) busulfan (e.g., MYLERAN®), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; e.g., VEPESID®), 6-

mercaptopurine (6MP), 6-thioguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5-FU), capecitabine (e.g. XELODA®), dacarbazine (DTIC), and the like; antibiotics, such as actinomycin D, doxorubicin (DXR; e.g., ADRIAMYCIN®), daunorubicin (daunomycin), bleomycin, mithramycin and the like; alkaloids, such as vinca alkaloids such as vincristine (VCR), vinblastine, and the like; and other antitumor agents, such as paclitaxel (e.g., TAXOL®) and paclitaxel derivatives, the cytostatic agents, glucocorticoids such as dexamethasone (DEX; e.g., DECADRON®) and corticosteroids such as prednisone, nucleoside enzyme inhibitors such as hydroxyurea, amino acid depleting enzymes such as asparaginase, leucovorin and other folic acid derivatives, and similar, diverse antitumor agents. The following agents may also be used as additional agents: arnifostine (e.g., ETHYOL®), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, lomustine (CCNU), doxorubicin lipo (e.g., DOXIL®), gemcitabine (e.g., GEMZAR®), daunorubicin lipo (e.g., DAUNOXOME®), procarbazine, mitomycin, docetaxel (e.g., TAXOTERE®), aldesleukin, carboplatin, oxaliplatin, cladribine, 15 camptothecin, CPT 11 (irinotecan), 10-hydroxy 7-ethyl-camptothecin (SN38), floxuridine, fludarabine, ifosfamide, idarubicin, mesna, interferon beta, interferon alpha, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil).

20 Actual dosage levels of the active ingredients in the pharmaceutical compositions provided herein may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

25 The selected dosage level will depend upon a variety of factors including the activity of the particular agent employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

30 The CTLs and the immune checkpoint inhibitors described herein may be co-administered or administered sequentially. The immune checkpoint inhibitors may be administered by any technique known in the art. In some embodiments, the immune checkpoint inhibitor is

administered intratumorally. In some embodiments, the immune checkpoint inhibitor is administered intravenously. In some embodiments, the immune checkpoint inhibitor is administered parenterally.

In some embodiments, the subject has been exposed to a virus (e.g. EBV) such that 5 virus particles are detectable in the subject's blood. In some embodiments, the method further comprises measuring viral load in the subject (e.g., before or after administering the peptide specific CTLs to the subject). Determining viral load in a subject may be a good prognostic marker for immunotherapy effectiveness. In some embodiments, selecting CTLs further comprises determining the number of viral DNA copies in the subject (e.g. in a tissue 10 or blood sample). In some embodiments, viral load is measured two or more times.

In some embodiments, the method further includes selecting allogeneic CTLs for combination therapy because they express a TCR restricted to a class I MHC that is encoded by an HLA allele that is present in the subject. In some embodiments, the CTLs are selected if the CTLs and subject share at least 2 (e.g., at least 3, at least 4, at least 5, at least 6) HLA 15 alleles and the CTLs are restricted through a shared HLA allele. In some embodiments, the method comprises testing the TCR repertoire of the pre-generated third-party-donor-derived epitope-specific T cells (*i.e.*, allogeneic T cells) with flow cytometry. In some embodiments epitope-specific T cells are detected using a tetramer assay, an ELISA assay, a western blot assay, a fluorescent microscopy assay, an Edman degradation assay and/or a mass 20 spectrometry assay (e.g., protein sequencing). In some embodiments, the TCR repertoire is analyzed using a nucleic acid probe, a nucleic acid amplification assay and/or a sequencing assay. In some embodiments, the allogeneic CTLs are obtained from a cell bank.

#### **Exemplification:**

##### Example 1: Immune checkpoint protein expression in NPC patients

25 Fifty-two patients were enrolled in a study applying LMP1&2 and EBNA1-specific CTL immunotherapy for the treatment of EBV-associated NPC, including 41 with active progressive disease following palliative chemotherapy and 11 patients with minimal or no residual disease (N/MRD) following standard radio/chemotherapeutic treatment.

Twenty active disease patients and 9 N/MRD patients received the minimum 2 doses 30 (range 2-8 doses) and a median total of  $1.1 \times 10^8$  cells (range:  $5.7 \times 10^7$  to  $2.4 \times 10^8$ ). The clinical characteristics of the patients who received adoptive T cell therapy are provided in

Table 1 and 2. Of the remaining 23 patients, 1 patient died after the administration of a single dose, T cell therapy was manufactured for 5 patients but not administered due to illness, 12 failed to meet release criteria due to low specificity or cell yield and 5 were withdrawn prior to the commencement of T cell manufacture.

5 To generate LMP/EBNA1 specific T cells 100-300mL of peripheral blood was harvested and used to generate peripheral blood mononuclear cells (PBMC). The AdEB1-LMPpoly vector was then used to infect 30% of the PBMC (MOI of 10:1) that were then irradiated and co-cultured with the remaining PBMC for two weeks. Cultures were supplemented with fresh growth medium and 120IU/mL of recombinant IL-2 every 3-4 days  
10 (Komtur Pharmaceuticals, Frieburg, Germany). Cultured T cells were tested for antigen specificity using intracellular cytokine analysis and microbial contamination prior to release for infusion.

15 FACS profiling was performed to characterize the expression of immune checkpoint proteins by the T cells administered to the subjects. MHC tetramers were generated in house. T cells were incubated for 20 minutes at 4°C with APC-labelled MHC class I tetramers specific for the HLA A11-restricted epitope SSCSSCPLSKI (LMP2A), the HLA A24 restricted epitope TYGPVFMCL (LMP2A) and the HLA Cw03 restricted epitope FVYGGSKTSL (EBNA1). Cells were then incubated for a further 30 minutes with one or more of the following antibodies: PE-conjugated anti-TIM-3, FITC conjugated anti-LAG-  
20 3, BV786-conjugated anti-PD-1 and BV421-conjugated anti-CTLA4. Cells were acquired using a BD LSR Fortessa with FACSDiva software (BD Biosciences) and post-acquisition analysis was performed using FlowJo software (TreeStar).

25 Figure 1 shows the expression of immune checkpoint molecules (*i.e.*, LAG-3, TIM-3, CTLA4, or PD-1). Panel A depicts percentage of HLA-multimer positive CD8-positive lymphocytes that express PD-1, TIM-3, LAG-3 and CTLA-4. Panel B depicts the percentage of PD-1 positive, TIM-3 positive, LAG-3 positive and CTLA-4 positive lymphocytes in the CTL immunotherapy administered in NPC patients with no/minimal residual disease (N/MRD) and active-recurrent/metastatic disease (ARMD) who either showed stable disease (SD) or progressive disease (PD) following adoptive T cell therapy.

30

Example 2: Adoptive transfer of EBV-CTls and Checkpoint Inhibitor Therapy in NPC Patients

Patients with platinum resistant or recurrent EBV-associated nasopharyngeal carcinoma (NPC) are treated with adoptive transfer of allogeneic Epstein-Barr virus cytotoxic T lymphocytes (EBV-CTLs) in combination with a checkpoint inhibitor (Pembrolizumab). Up to a total of 48 subjects with metastatic, platinum-resistant or recurrent EBV-associated NPC are enrolled in the study.

#### *Study Protocol and Dosing*

The study has two parts: Cohort 1 is enrolled as the Phase 1B portion of the study to determine the Phase 2 dose; Cohort 2 is enrolled as the Phase 2 portion of the study to examine the clinical benefits of combined adoptive cellular and checkpoint inhibitor therapies for NPC. The protocol will enroll 48 subjects in total. Phase 1B (Cohort 1) will enroll 12 subjects whose disease progressed despite prior PD1 inhibitor therapy, and Phase 2 (Cohort 2) will enroll 36 subjects naïve to PD1 inhibitor therapy.

Allogeneic third-party EBV-CTLs are selected for each subject from the bank of available EBV-CTLs based on matching  $\geq 2$  HLA alleles, at least one of which is a restricting HLA allele, shared between the EBV-CTLs source material (donor) and the subject. High resolution HLA typing will be performed during screening to facilitate selection of the EBV-CTLs cell product. Historical HLA typing will be acceptable if performed at high resolution (DNA based versus serologic assessment).

In the Phase 1B (Cohort 1), EBV-CTLs are administered at doses ranging from 500,000 to 200,000,000 T-cells per infusion intravenously on Day 1, Day 8, and Day 15 of a 21 Day Cycle to six subjects with advanced NPC. The subject population is selected based on previous Phase 1 safety and efficacy data which showed adequate EBV CTL expansion and antitumor activity in patients with advanced NPC. Likewise, pembrolizumab is administered to Cohort 1 subjects at a dose of 200 mg IV Q3 weeks to adults (adults are greater than or equal to 18 years old) and at 2mg/kg IV Q3 weeks to pediatric subjects (less than 18 years old).

If less than 2 of the initial 6 Phase 1B Cohort 1 subjects experience dose limiting toxicity in the first 21 days, dose reduction of EBV-CTLs occurs, and the subsequent 6 subjects are treated with the combination of EBV-CTLs and pembrolizumab at the recommended dose level.

Screening will begin up to 28 days prior to dosing (Cycle 1 Day 1). Subjects will be treated with EBV-CTLS in combination with pembrolizumab until disease progression or an unacceptable toxicity is observed.

Study Participants

5 Summary of Subject Enrollment Criteria is as follows:

Inclusion criteria: A patient will be considered eligible to participate in this study if all of the following inclusion criteria are satisfied:

1. Males and females  $\geq$  2 years of age
2. Patients with advanced or metastatic NPC who are considered platinum refractory/resistant, defined as having at least one prior platinum-based chemotherapeutic regimen with a subsequent platinum-free interval of  $<$  12 months, having progression during platinum-based therapy, or having persistent disease after a platinum-based therapy, are eligible
3. Patients with NPC in whom the EBV-genome or antigens have been demonstrated in tissue biopsy samples
4. Histologically or cytologically-confirmed EBV-associated locally recurrent, metastatic or persistent NPC (WHO type II/III) and meeting the following corresponding requirements for the cohort of the study they will enroll into:
  - a. Phase 1B (Cohort 1): patients who have received prior treatment with pembrolizumab anti-PD1, who have not received prior treatment with anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40 or anti-CTLA-4 antibodies
  - b. Phase 2 (Cohort 2): patients who have not received prior treatment with pembrolizumab or other anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA 4 antibodies
5. Life expectancy  $\geq$  4 months at time of screening
6. Measurable disease using RECIST 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions
7. Patients in Phase 1B must have a biopsy at baseline and on treatment of a metastatic lesion that can be biopsied with acceptable clinical risk (as judged by the investigator), and must agree to undergo biopsy.
8. Patients must agree to submit prior biopsy material for biomarker assessment.

9. Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 1$  for patients aged  $> 16$  years; Lansky score  $\geq 70$  for patients aged  $\leq 16$  years.

10. Adequate organ function per the following (unless deemed to be caused by the underlying EBV-driven

5 process which EBV-CTLs are intended to treat, or its prior therapy):

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500 / \mu\text{L}$
Platelets	$\geq 100,000 / \mu\text{L}$
Hemoglobin	$\geq 9 \text{ g/dL}$ or $\geq 5.6 \text{ mmol/L}$
<b>Renal</b>	
Creatinine <b>OR</b> Measured or calculated* creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN OR}$ $\leq 60 \text{ mL/min}$ for subject with creatinine levels $> 1.5 \times$ institutional ULN
<b>Hepatic</b>	
Total bilirubin	$\leq 1.5 \times \text{ULN OR}$ Direct bilirubin $\leq \text{ULN}$ for subjects with total bilirubin levels $> 1.5 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN OR}$ $\leq 5 \times \text{ULN}$ for subjects with liver metastases
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5 \times \text{ULN}$ unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

\* Creatinine clearance should be calculated per institutional standard.

11. Willing and able to provide written informed consent

10 **Exclusion criteria:** A patient will not be eligible to participate in the study if any of the following criteria are met:

1. Has disease that is suitable for local therapy administered with curative intent.

2. Need for methotrexate or extracorporeal photopheresis

3. Need for vasopressor or ventilator support

4. Antithymocyte globulin or similar anti-T cell antibody therapy  $\leq 4$  weeks prior to  
15 Cycle 1 Day 1

5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial

treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

6. Patients with history or evidence of interstitial lung disease
7. Patients with an active infection requiring systemic therapy
5. Patients with history of (non-infectious) pneumonitis that required steroids or current pneumonitis
9. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.
10. Pregnancy or breastfeeding; females of childbearing potential must have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy must be confirmed negative within 72 hours of first dose for the patient to be eligible.
11. Full resolution of immunotherapy related adverse effects and no treatment for these adverse events (AEs) for at least 4 weeks prior to enrollment
15. 12. No history of severe immunotherapy related adverse effects (CTCAE Grade 4; CTCAE Grade 3 requiring treatment > 4 weeks)
13. Patients who have received any non-oncology vaccine therapy used for prevention of infectious diseases for up to 30 days prior to enrollment. Examples include, but are not limited to: measures, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are acceptable.
20. 14. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
25. 15. Female of childbearing potential or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception (abstinence is acceptable) for the course of the study through 120 days after the last study dose.
16. Inability to comply with study procedures
30. 17. Chemotherapy, targeted small molecule therapy, hormonal therapy, or radiation therapy within 2 weeks of Cycle 1 Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent. Subjects

with  $\leq$  Grade 2 neuropathy or  $\leq$  Grade 2 alopecia are an exception to this criterion and may qualify for the study.

18. Antibody/biologic therapy within 5 half-lives or 4 weeks (whichever is longer) of Cycle 1 Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- 5
19. Patient with carcinomatous meningitis and/or active CNS metastases, unless metastases are treated and stable and the patient does not require systemic steroids  
NOTE: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging (using the identical imaging modality for each assessment, either MRI or CT scan) for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
- 10
20. Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 15
21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 20
22. Known history of HIV, known active Hepatitis B (e.g. HBsAg reactive), Hepatitis C (e.g. HCV RNA is detected).
23. Prior treatment with any investigational product within 4 weeks of Cycle 1 Day 1
24. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- 25
25. Prior treatment with EBV T-cells

The following are indications of efficacy of treatment:

- 30
- 1) The change in NPC disease progression and other clinically relevant outcomes, as measured by complete response (CR) rate, duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

2) Increases in immune response rate (irRR = irCR + irPR) and/or duration of response (DOirR).

5 All publications, patents, patent applications and sequence accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method of treating cancer in a subject, the method comprising administering to the subject an immune checkpoint inhibitor and a composition comprising cytotoxic T cells (CTLs) expressing a T cell receptor specific for a cancer-associated peptide presented on a class I MHC.
- 5 2. The method of claim 1, wherein the immune checkpoint inhibitor is a protein or polypeptide that binds to an immune checkpoint protein.
3. The method of claim 2, wherein the immune checkpoint protein is CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA.
- 10 4. The method of claim 3, wherein the immune checkpoint protein is PD-1, PD-L1, TIM-3, LAG-3 or CTLA4.
5. The method of claim 1, wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof that binds to an immune checkpoint protein.
6. The method of claim 5, wherein the immune checkpoint protein is CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA.
- 15 7. The method of claim 6, wherein the immune checkpoint protein is PD-1, PD-L1, TIM-3, LAG-3 or CTLA4.
8. The method of claim 1, wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-20 936559, BMS-936558, MK-3475, CT 011, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.
9. The method of any one of claims 1 to 8, wherein the cancer-associated peptide is a viral peptide.
10. The method of claim 9, wherein the viral peptide is an Epstein-Barr Virus (EBV) peptide.
- 25 11. The method of claim 10, wherein the EBV peptide comprises a LMP1 peptide.
12. The method of claim 10, wherein the EBV peptide comprises a LMP2A peptide.
13. The method of claim 10, wherein the EBV peptide comprises an EBNA1 peptide.
14. The method of any one of claims 1 to 13, wherein the cancer is nasopharyngeal carcinoma (NPC).
- 30 15. The method of any one of claims 1 to 14, wherein the CTLs are autologous to the subject.

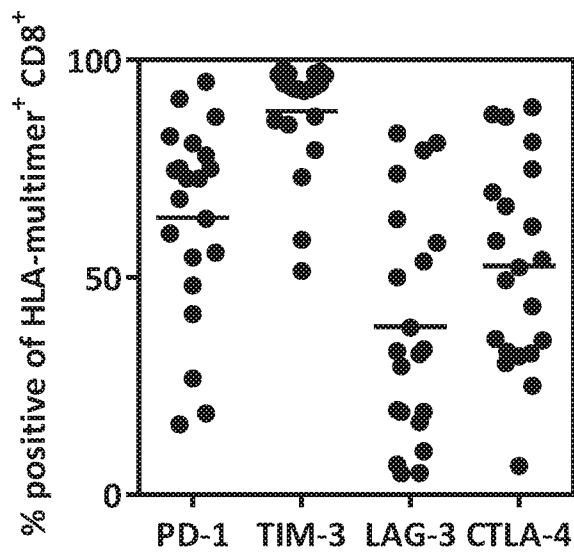
16. The method of any one of claims 1 to 14, wherein the CTLs are allogeneic to the subject.
17. The method of claim 16, wherein the CTLs are obtained from a cell bank.
18. The method of any one of the preceding claims, wherein the CTLs and the immune 5 checkpoint inhibitor are co-administered.
19. The method of any one of the preceding claims, wherein the CTLs and the immune checkpoint inhibitor are administered sequentially.
20. The method of any one of claims 1 to 19, further comprising administering to the subject a chemotherapeutic agent.
- 10 21. A method of treating or preventing cancer in a subject comprising:
  - (a) incubating a sample comprising CTLs and antigen-presenting cells (APCs) that present a CMV peptide thereby inducing proliferation peptide-specific CTLs in the sample,
  - (b) administering the peptide specific CTLs to the subject in combination with an immune checkpoint inhibitor.
- 15 22. The method of claim 21, wherein the nucleic acid construct is a viral vector.
23. The method of claim 22, wherein the viral vector is AdEl-LMPpoly.
24. The method of any one of claims 21 to 23, wherein the cancer is nasopharyngeal carcinoma (NPC).
25. The method of any one of claims 21 to 24, wherein the immune checkpoint protein is 20 CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG-3, TIM-3, IDO, TDO, or VISTA.
26. The method of claim 25, wherein the immune checkpoint protein is PD-1, PD-L1, TIM-3, LAG-3 or CTLA4.
27. The method of any one of claims 21 to 26, wherein the immune checkpoint inhibitor 25 is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT 011, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.
28. The method of any one of claims 21 to 27, wherein the CTLs and the immune 30 checkpoint inhibitor are co-administered.
29. The method of any one of claims 21 to 27, wherein the CTLs and the immune checkpoint inhibitor are administered sequentially.
30. The method of any one of claims 21 to 29, wherein the APCs are B cells.

31. The method of any one of claims 21 to 29, wherein the APCs are antigen-presenting T-cells.
32. The method of any one of claims 21 to 29, wherein the APCs are dendritic cells.
33. The method of any one of claims 21 to 29, wherein the APCs are aK562 cells.
- 5 34. The method of any one of claims 21 to 33, wherein the sample comprises peripheral blood mononuclear cells (PBMCs).

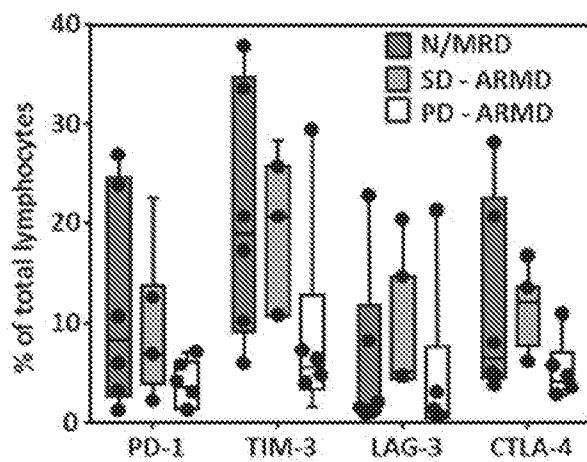
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Figure 1

(A)



(B)



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2017/000740

## A. CLASSIFICATION OF SUBJECT MATTER

A61K 35/17 (2015.01) C12N 5/0783 (2010.01) A61K 39/395 (2006.01) A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases: PATENW, MEDLINE, CAPLUS, EMBASE, Esp@cenet, Pubmed, and internal databases provided by IP Australia

Keywords: Adoptive T cell therapy, CTL, Checkpoint, PD-1, PD-L1, CTLA-4, B7-H, KIR, BTLA, LAG-3, TIM, Vista, A2AR, Yervoy, Ipilimumab, Opdivo, Nivolumab, Pembrolizumab, Keytruda, Pidilizumab, Cancer, tumour, carcinoma, EBV, LMP, EBNA, and similar terms, as well as the Applicant's and Inventor's names.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

Further documents are listed in the continuation of Box C  See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search  
6 November 2017

Date of mailing of the international search report  
06 November 2017

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).		PCT/IB2017/000740
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/083174 A2 (EMORY UNIVERSITY et al.) 10 July 2008 See pp. 2, 21, 28, 66, 70, 79, 84, 87-89, 93, Examples 23-25, and Claims	1-7, 9-10, 15, 18-22, 25-32, and 34
Y	See pp. 2, 21, 28, 66, 70, 79, 84, 87-89, 93, Examples 23-25, and Claims	12, 17, 23, 24, and 33
X	WO 2002/086083 A2 (MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH) 31 October 2002 See pp. 2, 10-17, 22, 27-28, Examples and Claims	1, 9-10, 13, 15-16, 18, 20-22, 25-26, 28, 30, 32 and 34
Y	See pp. 2, 10-17, 22, 27-28, Examples and Claims	12, 17, 23, 24, and 33
X	WO 2010/065959 A1 (NORTHEASTERN UNIVERSITY) 10 June 2010 See pp. 6-7, 61, 69-70, 78-81, and Claims	1-3, 9-10, 15, and 20
Y	See pp. 6-7, 61, 69-70, 78-81, and Claims	12 and 17
X	WO 2015/069770 A1 (COGNATE BIOSERVICES, INC. et al.) 14 May 2015 See [0022-0032], [0071], [0095], [00142-146], and Claims	1-8, 15-16, and 18-20
Y	See [0022-0032], [0071], [0095], [00142-146], and Claims	17
X	WO 2014/039983 A1 (THE TRUSTEES OF DARTMOUTH COLLEGE) 13 March 2014 See [0546-7], Examples 24- 26, and Claims	1-7, 9-11, 13-15, and 18-20
Y	See [0546-7], Examples 24- 26, and Claims	12 and 17
X	WO 2016/044530 A1 (THE JOHNS HOPKINS UNIVERSITY ) 24 March 2016 See pp. 10-11, 27 and Claims	1-10, 15-16, and 18-19
Y	See pp. 10-11, 27 and Claims	12 and 17
X	WO 2015/157636 A1 (H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, INC. et al.) 15 October 2015 See pp. 11, 33, 38-40 and Claims	1-8, 15, and 19-20
Y	See pp. 11, 33, 38-40 and Claims	17
X	Mahvi, D. et al. 2015 "CTLA-4 blockade plus adoptive T cell transfer promotes optimal melanoma immunity in mice", J. Immunother. Vol. 38, No. 2, pp. 54-61 See Abstract, Methods and Discussion	1-7, 16, and 19
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Y	See pp. 4797-9	17
X	Shin, J. et al 2016 (April) "Enhanced Anti-tumor Reactivity of Cytotoxic T Lymphocytes Expressing PD-1 Decoy" Immune Network. Vol. 16, No. 2, pp. 134-139 See Results and Discussion	1-4, 16, and 18
Y	See Results and Discussion	17
X	Shin, J. et al. 2012 "Positive conversion of negative signaling of CTLA4 potentiates antitumor efficacy of adoptive T-cell therapy in murine tumor models", Blood. Vol. 119, No. 24, pp. 5678-5687 See pp. 5680, 5683-5684, and Discussion	1-4, 16, and 18
Y	See pp. 5680, 5683-5684, and Discussion	17

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).		DOCUMENTS CONSIDERED TO BE RELEVANT
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Y	See pp. 567-8 and 570	12, 23, 24
X	Manzo, T. et al. 2015 "Antigen-specific T cell therapies for cancer", Human Molecular Genetics, 2015, Vol. 24, No. R1, pp. R67-R73 See pp. R68-R70	1-34
Y	See pp. R68-R70	12, 17, 24
X	WO 2013/088114 A1 (CELL MEDICA LIMITED et al.) 20 June 2013 See pp. 21, Examples and Claims	1-34
Y	See pp. 21, Examples and Claims	12, 24, 33

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Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. <b>PCT/IB2017/000740</b>	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
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Information on patent family members

International application No.

**PCT/IB2017/000740**

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

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<b>INTERNATIONAL SEARCH REPORT</b> Information on patent family members		International application No. <b>PCT/IB2017/000740</b>	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/IB2017/000740**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
<b>Publication Number</b>	<b>Publication Date</b>	<b>Publication Number</b>	<b>Publication Date</b>
		US 2015017723 A1	15 Jan 2015
<b>End of Annex</b>			