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(54) Title: IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA

(57) **Abstract:** Disclosed herein is method for the prevention, delay of progression or treatment of hepatocellular carcinoma in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of an anti-PD-1 antibody, which is an antibody or a fragment antigen binding thereof, specifically binding to human PD-1.

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IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/524,967 and International Patent Application No. PCT/CN2017/090397, the disclosures of each of which are hereby incorporated by references in their entireties for all purposes.

FIELD OF THE INVENTION

[0002] Disclosed herein is a method for immunotherapy of a patient with hepatocellular carcinoma (HCC) comprising administering to the patient an anti-PD-1 antibody which was specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis.

BACKGROUND OF THE INVENTION

[0003] Hepatocellular carcinoma (HCC) is one of most common cancers in the world and the third highest cause of cancer-related mortality globally due to its malignancy. HCC develops in patients with chronic hepatitis, either due to chronic hepatitis B or C viral infection or due to inflammation following aflatoxin ingestion, or excessive alcohol consumption.

[0004] Most HCC patients are first diagnosed with the disease at an advanced stage or present with poor liver function, thereby preventing the use of potentially curative therapies. Treatment options for patients with advanced stage disease are limited to either chemoembolization or systemic therapies, which include sorafenib, which is the only approved first-line treatment, with modest efficacy and considerable toxicity [*Samonakis DN, Kouroumalis EA. Systemic treatment for hepatocellular carcinoma: Still unmet expectations. World J Hepatol.* ***2017****;9(2):80–90.*] Though these approaches have led to improved clinical outcomes, survival among HCC patients remains less than one year for patients with advanced stage disease, and the patients remain at high risk of disease recurrence after potentially curative surgery and ablation. As toxic chemotherapies are often not well-tolerated by these patients due to liver dysfunction, novel immunotherapies hold promise for advanced HCC. Monoclonal antibodies against the immune checkpoint inhibitory receptor, programmed cell death-1 (PD-1), have demonstrated antitumor activity across multiple malignancies [*Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med.* ***2012****;366(26):2443–2454.*], including HCC [*El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular*

carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. ***2017****;389(10088):2492–2502*]. However, the response rate in the HBV-infected group is relatively low (7%) as reported for Nivolumab [*M. Kudo, Immune Checkpoint Blockade in Hepatocellular Carcinoma: 2017 Update, Liver Cancer* ***2017****; 6:1-12*]. So far, HBV-infected HCC is associated with poor prognosis. Therefore, there is a need for a new immunotherapy for advanced HCC, in particular, with high response rate to infected HCC.

SUMMARY OF THE INVENTION

[0005] Disclosed herein is a method for immunotherapy of a patient with hepatocellular carcinoma (HCC) comprising administering to the patient a therapeutically effective amount of an anti-PD-1 antibody or an antigen binding fragment thereof. In some embodiments, the anti-PD-1antibody or antigen binding fragment thereof was specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis.

[0006] In one embodiment, the HCC is advanced HCC and/or a metastatic HCC. In other embodiments, the advanced HCC is HBV-infected HCC, or HCV-infected HCC, or HBV/HCV co-infected HCC. Preferably, the advanced HCC is advanced HBV-infected HCC, metastatic HBV-infected HCC, HCV-infected HCC, or metastatic HCV-infected HCC.

[0007] In some embodiments, the anti-PD-1 antibody is the one disclosed in **WO2015/035606A1** or US Patent No. 8,735,553, the entire contents of which are incorporated by reference herein. The antibodies disclosed in **WO2015/035606A1** and US Patent No. 8,735,553 specifically bind to Programmed Death-1 (PD-1) and inhibit PD-1-mediated cellular signaling and activities in immune cells. In some embodiments, the antibodies bind to a set of amino acid residues required for its ligand (Programmed death-ligand 1, PD-L1) binding. Especially, the anti-PD-1 antibody is a humanized monoclonal antibody comprising a heavy chain variable region (Vh) and a light chain variable region (Vk) (comprising SEQ ID No 24 and SEQ ID No 26, respectively) and a IgG4 heavy chain effector or constant domain (comprising SEQ ID NO: 88), hereinafter **Mab-1**, which specifically binds to PD-1. In some embodiments, the antibody binds to PD-1 residues including K45 and I93; or, I93, L95 and P97, and inhibits PD-1-medidated cellular signaling and activities in immune cells, the antibodies binding to a set of amino acid residues required for its ligand binding.

[0008] The method for immunotherapy disclosed herein has been proved to prevent, delay progression, alleviate, and therefore treat HCC, or even advanced HCC, in particular infected advanced HCC, and the toxicity profile of the anti-PD-1 antibodies disclosed herein demonstrate that adverse events (AEs) are generally low severity, manageable and reversible. Accordingly, the present disclosure provides PD-1 antibodies with a superior effect in HCC relative to other PD-1 antibodies.

[0010] The inventors of the present application have found that treatment with **Mab-1** was generally well tolerated in pretreated patients with advanced HCC. The preliminary safety profile and antitumor activity support continued development of **Mab-1** in patients with advanced HCC, especially in patient with infectious HCC, including HBV-infected HCC, HCV-infected HCC and HBV/HCV-coinfected HCC.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 shows the potential mechanism of T-cell clearance of the anti-PD-1 antibody used in the present application, i.e., lacking or reduced FcγR binding prevents macrophage-mediated T-cell clearance.

[0012] Figure 2 shows a schematic of the study design of the phase 1a/1b study.

[0013] Figure 3 shows best change in tumor size by hepatitis virus infection status in the phase 1a/1b study.

[0014] Figure 4 shows duration of treatment and response in the phase 1a/1b study.

[0015] Figure 5 shows baseline and most recent CT assessment in the three patients with partial response in the phase 1a/1b study.

[0016] Figure 6 shows change in tumor burden over time in the phase 1a/1b study.

[0017] Figure 7 shows change in Alpha-Fetoprotein (AFP) from baseline in the phase 1a/1b study.

[0018] Figure 8 shows the study design of the phase 3 study.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations

[0019] Throughout the detailed description and examples disclosed herein, the following abbreviations provided in Table 1 will be used:

Table 1. Abbreviations

AE	Adverse event
BID	Twice daily
CDR	Complementarity determining region
DPBS	Dulbecco's Phosphate Buffered Saline
IgG	immunoglobulin G
i.p.	Intraperitoneal or Intraperitoneally
i.v.	intravenous or intravenously
IFN-γ	Interferon-γ
mAb	Monoclonal antibodies
MTD	Maximum tolerated dose

NK	Natural killer
PD-1	Programmed Death 1 protein, Pdcd-1, or CD279
PDX	Patient-derived xenograft
p.o.	"by mouth" or "per os"
QW	Once weekly
Q2W	Once every two weeks
Q3W	Once every three weeks
Q4W	Once every four weeks
TILs	Tumor-infiltrating lymphocytes
Vh	Heavy chain variable region
Vk	Light chain variable region

Definitions

[0020] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0021] As used herein, including the appended claims, the singular forms of words such as "**a**", "**an**", and "**the**", include their corresponding plural references unless the context clearly dictates otherwise.

[0022] The term "**antibody**" herein is used in the broadest sense and specifically covers antibodies (including full length monoclonal antibodies) and antibody fragments so long as they recognize PD-1. An antibody molecule is usually monospecific, but may also be described as idiospecific, heterospecific, or polyspecific. Antibody molecules bind by means of specific binding sites to specific antigenic determinants or epitopes on antigens. "Antibody fragments" or "antigen binding fragments" comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0023] The term "**monoclonal antibody**" or "**mAb**" or "**Mab**" herein means a population of substantially homogeneous antibodies, i.e., the antibody molecules comprised in the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, which are often specific for different epitopes. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially

homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies (mAbs) may be obtained by methods known to those skilled in the art. See, for example *Kohler et al (**1975**); **U.S. Pat. No. 4,376,110**; Ausubel et al (**1987- 1999**); Harlow et al (**1988**); and Colligan et al (**1993**).* The mAbs disclosed herein may be of any immunoglobulin class including IgG, IgM, IgD, IgE, IgA, and any subclass thereof. A hybridoma producing a mAb may be cultivated *in vitro* or *in vivo*. High titers of mAbs can be obtained in *in vivo* production where cells from the individual hybridomas are injected intraperitoneally into mice, such as pristine-primed Balb/c mice to produce ascites fluid containing high concentrations of the desired mAbs. MAbs of isotype IgM or IgG may be purified from such ascites fluids, or from culture supernatants, using column chromatography methods well known to those of skill in the art.

[0024] In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "light chain" (about 25 kDa) and one "heavy chain" (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as α, δ, ε, γ, or μ, and define the antibody's isotypes as IgA, IgD, IgE, IgG, and IgM, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids.

[0025] The variable regions of each light/heavy chain (Vk/Vh) pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

[0026] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called "**complementarity determining regions (CDRs)**", which are located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR-1, CDR-1, FR-2, CDR-2, FR-3, CDR-3, and FR-4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, *Kabat, et al. National Institutes of Health, Bethesda, Md. 5th ed., NIH Publ. No. 91-3242 (**1991**); Kabat (**1978**) Adv. Prot. Chem. 32: 1-75; Kabat, et al., (**1977**) J. Biol. Chem. 252:6609-6616; Chothia, et al, (**1987**) J. Mol. Biol. 196:901-917 or Chothia, et al, (**1989**) Nature 342:878-883.*

[0027] The term "**hypervariable region**" means the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (i.e., CDR-L1, CDR-L2 and CDR-L3 in the light chain variable domain and CDR-H1, CDR-H2 and CDR-H3 in the heavy chain variable domain). See, *Kabat et al. (**1991**) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.* (defining the CDR regions of an antibody by sequence); see also *Chothia and Lesk (**1987**) J. Mol. Biol. 196: 901-917* (defining the CDR regions of an antibody by structure). The term "framework" or "FR" residues means those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

[0028] Unless otherwise indicated, "**antibody fragment**" or "**antigen binding fragment**" means antigen binding fragments of antibodies, i.e. antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, e.g. fragments that retain one or more CDR regions. Examples of antibody binding fragments include, but not limited to, Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, e.g., sc-Fv; nanobodies and multispecific antibodies formed from antibody fragments.

[0029] An antibody that "**specifically binds to**" a specified target protein is an antibody that exhibits preferential binding to that target as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is considered "specific" for its intended target if its binding is determinative of the presence of the target protein in a sample, e.g. without producing undesired results such as false positives. Antibodies, or binding fragments thereof, useful in the present invention will bind to the target protein with an affinity that is at least two fold greater, preferably at least ten times greater, more preferably at least 20- times greater, and most preferably at least 100-times greater than the affinity with non-target proteins. An antibody herein is said to bind specifically to a polypeptide comprising a given amino acid sequence, e.g. the amino acid sequence of a mature human PD-1 molecule, if it binds to polypeptides comprising that sequence but does not bind to proteins lacking that sequence.

[0030] The term "**human antibody**" herein means an antibody that comprises human immunoglobulin protein sequences only. A human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, "mouse antibody" or "rat antibody" mean an antibody that comprises only mouse or rat immunoglobulin sequences, respectively.

[0031] The term "**humanized antibody**" means forms of antibodies that contain sequences from non-human (e.g., murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or

substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix "**hum**", "**hu**" or "**h**" is added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

[0032] The term "**hepatocellular carcinoma (HCC)**" has its general meaning in the art and refers to the cancer developed in hepatocytes. In general, liver cancer indicates hepatocellular carcinoma. HCC may result from excessive alcohol consumption (alcoholic steatohepatitis) or from inflammation following aflatoxin ingestion (non-alcoholic steatohepatitis, sometimes referred to as NASH). HCC may be caused by infection, such as hepatitis B virus (sometimes referred to as HBV-infected HCC) or hepatitis C virus (sometimes referred to as HCV-infected HCC) or by infection of HBV and HCV together (sometimes referred to as HBV/HCV co-infected HCC). In some embodiments, HCC is developed from chronic hepatitis B, chronic hepatitis C, aflatoxin, alcoholism, cirrhosis of the liver, nonalcoholic steatohepatitis, hemochromatosis, alpha 1-antitrypsin deficiency Wilson's disease, Type 2 diabetes, hemophilia, etc. In some embodiments, the HCC is early stage HCC, non-metastatic HCC, primary HCC, advanced HCC, locally advanced HCC, metastatic HCC, HCC in remission, or recurrent HCC.

[0033] The term "**treatment**" or "**treating"** is an approach for obtaining beneficial or desired clinical results, including, but not limited to, one or more of the following: alleviating one or more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (e.g., preventing or delaying the worsening of the disease), preventing or delaying the spread (e.g., metastasis) of the disease, preventing or delaying the recurrence of the disease, delay or slowing the progression of the disease, ameliorating the disease state, providing a remission (partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. Therefore, a reduction of pathological consequence of HCC is also included by the term "treatment". The methods disclosed herein encompass any one or more of these aspects of treatment.

[0034] The term "patient" is used interchangeably herein with the term "subject" and the like. In certain embodiments, the patient is a human patient. In particular embodiments, the patient is a human patient who has been diagnosed with, is in need of treatment for, and/or is at risk of HCC.

[0035] The term "**CDRs**" means complementarity determining region(s) in an immunoglobulin variable region, defined using the Kabat numbering system, unless otherwise indicated.

Anti-PD-1 antibody

[0036] As disclosed herein, the anti-PD-1 antibody is an antibody or a fragment antigen binding thereof, which specifically binds to human PD-1.

[0037] As disclosed herein, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain complement determinant regions (CDRs) provided in **Table 2**:

Table 2. CDRs of exemplary antibodies provided herein

a) mu317	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 12, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);
b) mu326	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 18, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
c) 317-4B6	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively);
d) 326-4A3	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 37, 38, 39, respectively); and CDR-L1, CDR--L2 and CDR-L3 (SEQ ID NOs: 40, 41, 42, respectively);
e) 317-1H	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 59, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);
f) 317-4B2	CDR-HL CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);
g) 317-4B5	CDR-Hl, CDR-H2 and CDR-H3 (SEQ ID NOs: 11 , 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);
h) 317-4B6	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 32, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);
i) 326-1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
j) 326-3B1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
or k) 326-3G1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-I 2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively).

[0038] As disclosed herein, the anti-PD-1 antibody, in some embodiments, is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain any combinations of CDRs provided in **Table 3**:

Table 3. CDRs of exemplary antibodies provided herein

(a)	CDR-H1 (SEQ ID NO 31), CDR-H2 (SEQ ID NO 12, 32, 59 or 60) and CDR-H3 (SEQ ID NO 33), CDR-L1 (SEQ ID NO 14, 34 or 61), CDR-L2 (SEQ ID NO 35) and CDR-L3 (SEQ ID NO 36); or

(b)	CDR-H1 (SEQ ID NO 37), CDR-H2 (SEQ ID NO 18, 38 or 62) and CDR-H3 (SEQ ID NO 39), CDR-L1 (SEQ ID NO 40), CDR-L2 (SEQ ID NO 41) and CDR-L3 (SEQ ID NO 42).

[0039] As disclosed herein, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) comprising sequences selected from those provided in **Table 4**:

Table 4. Vh and Vk sequences of exemplary antibodies provided herein

a) mu317 (SEQ ID NOs: 4 and 6, respectively);	p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);
b) mu326 (SEQ ID NOs: 8 and 10, respectively);	q) 317-311 (SEQ ID NOs: 70 and 26, respectively);
c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);	
d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);	r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);	s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);	t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);	u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);	v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);	w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);	x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);	y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);	z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);	aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);	ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);	ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

[0040] In some embodiments, the anti-PD-1 antibody provided herein comprises a heavy chain effector or constant domain that includes amino acid mutations that reduce binding to FcγR. The antibody may further comprise one or more mutations in the effector or constant domain that provide enhanced stability. In some embodiments, the antibody comprises an IgG4 Fc region. In some embodiments, the antibody comprises an IgG4 Fc region comprising one or more amino acid mutations that reduce binding to FcγR. For example, in some embodiments, the antibody comprises an IgG4 Fc region comprising mutations that reduce or eliminate binding to FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and/or FcγRIIIB.

[0041] In some embodiments, the antibody comprises an IgG4 Fc region having a serine to proline mutation at position 228 (EU numbering system). In some embodiments, this mutation is referred to as the S228P mutation. In some embodiments, the antibody comprises an IgG4 Fc region having a mutation at one or more of positions 233, 234, 235, 265, 309, and 409 (EU numbering system). For example, in some embodiments, the antibody comprises an IgG4 region having a mutation at 228 and at least one other position, wherein the at least one other mutation results in reduced binding to

one or more FcγR. In further embodiments, the antibody comprises an IgG4 region having a mutation at position 228 and at least two, at least 3, at least 4, at least 5, or at least 6 additional positions, wherein one or more of the additional mutations results in reduced binding to one or more FcγR. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234 and 235. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 235, and 235. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, and 265. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, and 265. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, 309, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, 309, and 409. The mutation at position 234 may be a phenylalanine to valine substitution or a phenylalanine to alanine substitution. The mutation at position 235 may be a leucine to alanine substitution. The mutation at position 233 may be a glutamic acid to proline substitution. The mutation at position 265 may be a aspartic acid to valine substitution or an aspartic acid to threonine substitution. The mutation at position 309 may be a leucine to valine substitution. The mutation at position 409 may be an arginine to a lysine, threonine, or methionine substitution. Exemplary IgG4 Fc regions are provided in **Table 5** below.

Table 5. Exemplary IgG4 Fc region sequences

IgG4 variant mutated positions	**Amino acid sequence**	**SEQ ID NO**
WT IgG4	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	107
228P	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	83

228P 233P	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***P***EFGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	91
228P 234V	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***V***FGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	92
228P 235A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEF***A***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	93
228P 234V 235A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***VA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	94
228P 234A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***A***FGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	95
228P 234A 235A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	96

228P 233P 234V 235A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	84
228P 233P 234A 235A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PAA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	97
228P 234V 235A 265A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***VA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	98
228P 234A 235A 265A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	99
228P 233P 234V 235A 265A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PVA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	85
228P 233P 234A 235A 265A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PAA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	100

228P 265A	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	101
228P 309V	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV***V***HQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	102
228P 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	103
228P 309V 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV***V***HQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	104
228P 265A 309V 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV***V***HQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	105
228P 233P 234V 235A 265T	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PVA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***T***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	86

228P 233P 234V 235A 265A 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PVA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	87
228P 233P 234V 235A 265A 309V 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PVA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV***V***HQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	88
228P 233P 234A 235A 265A 309V 409K	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCP***P***CPAP***PAA***GGPSVFLFPPKPKDTLMISRTPEVTCVVV***A***VSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV***V***HQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS***K***LTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	106

[0042] As disclosed herein, the anti-PD-1 antibody is an antibody which comprises a IgG4 heavy chain effector or constant domain comprising any of SEQ ID NOs: 83-88.

[0043] As disclosed in each of the above aspects, the anti-PD-1 antibody is an antibody which contains a F(ab) or $F(ab)_2$ comprising a domain said above, including a heavy chain variable region (Vh), a light chain variable region (Vk) and a IgG4 heavy chain effector or constant domain .

[0044] As disclosed herein, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and a IgG4 heavy chain effector or constant domain comprising a sequence selected from SEQ ID NOs: 83-88 and 91-106, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprise sequences selected from those provided in **Table 6**:

Table 6. Exemplary Vh and Vk sequences

a) mu317 (SEQ ID NOs: 4 and 6, respectively); b) mu326 (SEQ ID NOs: 8 and 10, respectively); c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);	p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively); q) 317-311 (SEQ ID NOs: 70 and 26, respectively);

d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);	r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);	s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);	t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);	u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);	v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);	w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);	x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);	y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);	z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);	aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);	ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);	ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

[0045] As disclosed herein, in some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain CDR-H1, CDR-H2, and CDR-H3 according to SEQ ID NOs: 11, 32, and 13, respectively; a light chain CDR-L1, CDR-L2, and CDR-L3 according to SEQ ID NOs: 61, 15, and 16, respectively; and an IgG4 heavy chain effector or constant domain comprising SEQ ID NO: 88.

[0046] As disclosed herein, in some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and an IgG4 heavy chain effector or constant domain comprising SEQ ID NO: 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprises SEQ ID NO: 24 and SEQ ID NO: 26, respectively.

[0047] As disclosed herein, in some embodiments, the anti-PD-1 antibody is a uniquely engineered humanized IgG4 monoclonal antibody with high affinity and binding specificity against PD-1, specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance.

[0048] The anti-PD1 antibodies and antibody fragments thereof disclosed herein may be prepared in accordance with the disclosure of **WO2015/035606A1** or **US Patent No. 8,735,553**, the entire disclosure of which is expressly incorporated herein by reference.

Methods of treatment

[0049] In the methods of treatment disclosed herein, the anti-PD-1 antibody at a certain dose was administered to the patients with HCC intravenously. In some embodiments, the patient with HCC was not previously treated with a PD-1 or PD-L1 targeting therapy. In some embodiments, the patient with HCC was previously treated with another therapeutic agent (e.g., sorafenib).

[0050] In some embodiments, the present disclosure provides methods for treating HCC in a subject in need thereof, the method comprising administering to the subject an anti-PD-1 antibody or antigen binding fragment thereof, wherein the antibody is engineered to reduce, minimize, or eliminate FcγR binding on macrophages or other antigen presenting cells. In some embodiments, the antibody comprises an engineered IgG4 region provided herein. For example, in some embodiments, the antibody comprises an engineered IgG4 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 83-88 and 91-106. In some embodiments, the antibody comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NOs: 11, 32, and 13, respectively; light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NOs: 61, 15, and 16, respectively; and an IgG4 region that has been engineered to have reduced FcγR. In some embodiments, the antibody comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NOs: 11, 32, and 13, respectively; light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NOs: 61, 15, and 16, respectively; and an IgG4 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 83-88 and 91-106. In some embodiments, the antibody comprises heavy and light chain variable region sequences according to SEQ ID NOs: 24 and 26, respectively, and an IgG4 region that has been engineered to have reduced FcγR. In some embodiments, the antibody comprises heavy and light chain variable region sequences according to SEQ ID NOs: 24 and 26, respectively, and comprises an IgG4 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 83-88 and 91-106. In some embodiments, the anti-PD-1 antibody is **Mab-1**.

[0051] In some embodiments, the present disclosure provides an antibody provided herein for use in the treatment of HCC in a patient. In some embodiments, the present disclosure provides an antibody provided herein for use in immunotherapy in a HCC patient. In some embodiments, the present disclosure provides an antibody provided herein for use in the manufacture of a medicament for the treatment of HCC. In some embodiments, the present disclosure provides an antibody provided herein for use in the manufacture of a medicament for immunotherapy in a HCC patient.

[0052] In some embodiments, the present disclosure provides methods for treating HCC in a patient comprising administering an antibody provided herein, wherein the administration of the antibody provides improvement in: overall survival (OS), objective response rate (ORR), complete response rate (CR), partial response rate (PR), stable disease (SD), progression free survival (PFS), disease free survival (DFS), event-free survival (EFS), duration of response (DoR), time to progression (TTP), disease control rate (DCR), clinical benefit rate (CBR), or any combination thereof, relative to a patient that did not receive the antibody. In particular embodiments, the administration of the antibody provides improvement in OS.

[0053] In some embodiments, OS is defined as the time from clinical trial randomization until death from any cause. In some embodiments, ORR is defined as the percentage of patients with a tumor size reduction of a predefined amount and for a minimum period of time. In some embodiments, CR is defined as the disappearance of all signs of cancer in response to treatment. In some embodiments, PR is defined as at least 30% reduction in detectable disease (e.g., size of tumors). In some embodiments, SD is defined as neither sufficient reduction in disease to qualify as PR nor sufficient increase in disease to qualify as progressive disease (e.g., less than 25% increase to a 30% reduction in detectable disease (e.g., size of tumors)). In some embodiments, the TTP is defined as the time from randomization until tumor progression. In some embodiments, PFS is defined as the time from randomization until tumor progression or until death occurs. In some embodiments, DFS is defined as the time from randomization until recurrence of tumor or death from any cause. In some embodiments, EFS is defined as the time from randomization to disease progression, death, or discontinuation of treatment for any reason. In some embodiments, the DoR is defined as the period of time from documentation of tumor response to disease progression. In some embodiments, both DCR and CBR are defined as the percentage of patients who have achieved a complete response, partial response, or stable disease.

[0054] In some embodiments, RECIST v. 1.1 (Response Evaluation Criterial in Solid Tumors), a set of published rules that define disease response, progression, or stability in cancer patients during or following treatment, is used to evaluate patients treated with an antibody provided herein.

[0055] In some embodiments, the present disclosure provides methods for treating a patient with HCC comprising administering an antibody provided herein to the patient, wherein the method achieves ORR and/or CR and/or PR and/or DCR and/or CBR (or any other known rate-based measure of outcome for tumor patients) of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, or more.

[0056] In some embodiments, the present disclosure provides methods for treating HCC in a patient comprising administering an antibody provided herein, wherein the administration of the antibody provides a statistically significant therapeutic effect relative to a placebo treatment, or relative to another anti-tumor or anti-cancer therapy. In some embodiments, the statistically significant effect includes therapeutic efficacy in combination with a statistically significant effect on toxicity or tolerability parameters. In some embodiments, the statistically significant effect further comprises improved OS, ORR, CR, PR, SD, PFS, DFS, EFS, DoR, TTP, DCR, CBR, or any combination thereof. In some embodiments, the methods provided herein provide a statistically significant effect compared to sorafenib. In some embodiments, the method provided herein comprise administration

of about 200 mg IV Q3W of an antibody provided herein (*e.g.*, Mab-1), wherein the method provides a statistically significant effect compared to administration of about 400 mg sorafenib orally BID. In some embodiments, the method provided herein provides a statistically significant effect compared to another PD-1 or PD-L1 targeting therapy. The term "statistically significant therapeutic effect" and the like refers to an outcome of a treatment that results in a clinical or medical improvement in a subject. By "statistically significant" it is meant that the result was unlikely to have occurred by chance. Statistical significance can be determined by any method known in the art. Commonly used measures of significance include the p-value, which is the frequency or probability with which the observed event would occur, if the null hypothesis were true. If the obtained p-value is smaller than the significance level, then the null hypothesis is rejected. In simple cases, the significance level is defined at a p-value of 0.05 or less.

[0057] In some embodiments, the anti-PD-1 antibody is administered at a dose of 0.5-10 mg/kg QW, or Q2W, or Q3W, or Q4W. In some embodiments herein, the anti-PD-1 antibody is **Mab-1**, and the **Mab-1** is administrated at a dose of 0.5-10 mg/kg QW or Q2W or Q3W. Preferably, **Mab-1** is administrated at a dose of 0.5-5 mg/kg Q2W, 5-10 mg/kg Q2W, or 2-5 mg/kg Q3W. Most preferably, **Mab-1** is administrated parenterally at a dose of 0.5 mg/kg Q2W, 5 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W or 5 mg/kg Q3W.

[0058] In some embodiments, the present disclosure provides methods for treating HCC comprising administering an anti-PD-1 antibody provided herein at a dose of about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, the antibody is administered daily, every other day, every 3 days, every 4 days, every 5 days, every 6 days, or every seven days. In some embodiments, the antibody is administered weekly, every 10 days, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks. In some embodiments, the antibody is administered monthly or every other month. In some embodiments, the antibody is administered one or more times to a subject, and/or at increasing or decreasing doses of the antibody, depending on the clinical stage of the patient, the therapeutic effect achieved, and other patient characteristics. In particular embodiments, the antibody is administered to a subject QW, Q2W, Q3W, or Q4W.

[0059] In some embodiments, the route of administration of the pharmaceutical composition is according to known methods, *e.g.* through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation

devices. In certain embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

[0060] In certain embodiments, the present disclosure provides methods for treating HCC comprising administering to a subject in need thereof an anti-PD-1 antibody provided herein at a dose of about 200 mg intravenously (IV), every 3 weeks (Q3W).

EXAMPLES

Example 1 A Phase 1A/1B study of Mab-1 in patients with advanced hepatocellular carcinoma (HCC)

[0061] **Study Design-patient differentiation and enrollment**

[0062] The purpose of the study design is to enroll HCC patients by selecting tumors for recommended phase 2 dose (RP2D) determination and preliminary differentiation, consisting of phase 1A and phase 1B. The study design is detailed in **Figure 2**.

[0063] In phase 1A, **Mab-1** (unless indicated otherwise, the antibody used in the clinical trials is **Mab-1**) of 10 mg/kg Q2W was the maximum administered dose; maximum tolerated dose (MTD) was not reached. All patients in phase 1B received **Mab-1** as a 5 mg/kg IV infusion Q3W. Radiographic assessment was every 9 weeks. Results presented here include patients with advanced HCC treated with 5 mg/kg Q3W. Finally, 40 patients with HCC (n=40) were enrolled in the clinical trials.

[0064] **Key Eligibility of the Pooled HCC Population Subset**

[0065] Adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced/ metastatic HCC who had not received prior PD-1 or PD-L1 treatment were enrolled.

[0066] Specific inclusion criteria included Barcelona Clinic Liver Cancer stage C or stage B refractory/not amenable to loco-regional therapy, and not amenable to a curative treatment approach, and Child–Pugh A without encephalopathy of any grade.

[0067] Eligible patients must have a hepatitis B virus (HBV) viral load <200 IU/mL (~1000 cps/mL) and subjects with active HBV infection need to be on anti-HBV suppression for ≥3 months throughout treatment and for 6 months after.

[0068] Patients with active hepatitis C virus (HCV) infection who are untreated are not allowed on study.

[0069] **Patient Disposition**

[0070] 40 patients with advanced HCC, the majority of whom were HBV positive (n=28/40), had enrolled in this study (**Table 7**). A total of 24 patients remain on treatment at the time of the present analysis.

[0071] **Table 7: Patient demographics and disease characteristics**

		HCC Population (N=40)
Median age, years (min, max)		55.5 (28, 76)
Sex	Male/female	32/8
Race	Asian/White/other	35/3/2
Median treatment duration, days (min, max)		64 (1, 471)
Median number of prior anti-cancer treatment regimens (min, max)		2 (0, 6)
Prior anti-cancer therapy regimens, n*	0	2†
	1	16
	2	12
	≥3	10
Infection status, n	HBV	28
	HCV	2
	HBV/HCV co-infection	6
	No infection	4

*Only 1 patient was sorafenib naïve; †Both patients had received sorafenib as adjuvant therapy.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

[0072] **Preliminary Antitumor Activity**

[0073] Among the enrolled 40 advanced HCC patients, a total of 27 patients were evaluable, wherein 25 had measurable disease and at least 1 evaluable post-baseline tumor assessment; 2 died prior to the 1st scheduled date of tumor assessment.

[0074] In the clinical trials and results hereinafter, all patients received **Mab-1** as a 5 mg/kg IV infusion Q3W with radiographic assessment every 9 weeks. Across the 27 evaluable† HCC patients: 3 patients achieved at least partial response (PR) and 9 patients achieved stable disease (SD). The initial disease control rate (DCR) including partial response (PR) and stable disease (SD) is 44% as shown in **Figure 3** showing best change in tumor size by hepatitis virus infection status.

[0075] The duration of treatment with **Mab-1** and response of the patients were shown in **Figure 4**. It shows that the maximum duration was 28 weeks.

[0076] As mentioned above, three patients were found to achieve at least partial response, which was confirmed by the baseline and most recent CT assessment in the three patients with partial response in **Figure 5**.

[0077] **Figure 6** also shows that change in tumor burden over time in patients with HBV-infected HCC is promising.

[0078] **Figure 7** shows the best overall response by radiographic evidence in the HCC patients in which one patient shown to have a controlled, stable disease for over 60 weeks.

[0079] **Tolerability Profile**

[0080] Adverse events (AEs) associated with administration of **Mab-1** disclosed herein was also studied.

[0081] Treatment-related AEs occurred in 21 of the 40 patients with HCC (**Table 8**). All but one of these events were grade ≤2. The most common events were rash (n=8) and pruritus (n=5).

[0082] **Table 8: Treatment-related adverse events**

HCC Population (N=40)		
	All grades	**Grade ≥3**
Any treatment-related AE	21	1
Rash	8	0
Pruritus	5	0
AST increased	3	0
Fatigue	2	0
Hypothyroidism	2	0
Decreased appetite	2	0
Acute hepatitis*	1	1
ALT increased	1	0
Blood creatine increased	1	0
Blood creatinine increased	1	0
QT prolongation	1	0
Skin reaction	1	0
Chills	1	0
Feeling hot	1	0
Nausea	1	0
Vomiting	1	0
Arthralgia	1	0
Proteinuria	1	0
Cough	1	0
Hypertension	1	0
Data presented as n. **Bold** font indicates events that are possibly immune related. *Acute hepatitis was fatal (grade 5).		

[0083] Two patients discontinued treatment due to any treatment-emergent AE, one of which was a grade 5 AE considered related to treatment by the investigator. A 49-year-old Asian male with HBV and HCC widely metastatic to brain, liver and lung, developed evidence of progression (disturbed consciousness, abdominal pain, and changes on chest x-ray) shortly following the first and only dose of Mab-1. The patient died approximately 5 weeks after entering the study, despite treatment with methylprednisolone and entecavir. Viral serology was negative; no autopsy was performed. The cause of death was attributed to acute hepatitis and confounded by rapid disease progression.

[0084] These results confirmed that the antibody disclosed herein (**Mab-1**) is tolerable; its toxicity profile demonstrates that adverse events (AEs) are generally low severity, manageable, and reversible.

[0085] In this early report more than half of patients remained on study (n=24/40); median treatment duration was 64 days (range: 1–471 days); rate of treatment discontinuation due to a treatment-related AE was low (n=1/40. Adverse events reported in this cohort were consistent with the overall safety profile observed in the study and were generally of low severity, manageable, and reversible. Most patients had underlying viral infection (HBV+, n=28; HCV+/HBV+, n=6; HCV+, n=2). Tumor reductions meeting the definition of "partial response" (*i.e.*, defined as at least 30% reduction in tumor burden) were observed in 3 patients; and nine patients achieved stable disease, some of whom also had significant reductions in AFP.

Example 2 A Phase 2 study of Mab-1 in patients with unresectable hepatocellular carcinoma (HCC)

[0086] **Study design**

[0087] A Phase 2 study is designed to evaluate the efficacy, safety/tolerability, and pharmacokinetics (PK) of **Mab-1** in patients with previously treated HCC. Safety/tolerability assessments will include monitoring of adverse events (AEs), including immune-related AEs.

[0088] **Study Population**

[0089] Adult patients, aged ≥18 years, will be enrolled if:

(a) histologically confirmed HCC;

(b) with Barcelona Clinic Liver Cancer (BCLC) Stage C, or BCLC stage B not amenable to locoregional therapy or relapsed after locoregional therapy, and not amenable to a curative treatment approach;

(c) has received at least 1 line of systemic therapy for unresectable HCC;

(d) has at least 1 measurable lesion as defined per RECIST v1.1;

(e) child-Pugh score A;

(f) Easter Cooperative Oncology Group (ECOG) Performance Status ≤ 1;

(g) adequate organ function.

[0090] Patients will be excluded if:

(a) known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC histology;

(b) prior therapies targeting PD-1 or PD-L1;

(c) has known brain or leptomeningeal metastasis;

(d) tumor thrombus involving main trunk of portal vein or inferior vena cava;

(e) loco-regional therapy to the liver within 4 weeks before enrollment;

(f) medical history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc;

(g) have received, within 28 days or 5 half-lives (whichever is shorter) of the first study drug administration: any chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin) or any investigational therapies; within 14 days of the first study drug administration: sorafenib, regorafenib, or any Chinese herbal medicine or Chinese patent medicines used to control cancer;

(h) active autoimmune diseases or history of autoimmune diseases that may relapse;

(i) with any condition requiring systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 14 days before study drug administration.

[0091] **Treatment**

[0092] Patients will be treated with **Mab-1** 200 mg IV Q3W.

Example 3 A phase 3 study to compare the efficacy and safety of Mab-1 versus sorafenib as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC)

[0093] **Study design**

[0094] A phase 3 study is designed to evaluate the efficacy and safety of **Mab-1** compared with sorafenib as a first-line treatment of advanced HCC (**Figure 8**).

[0095] The primary object will be to compare overall survival (OS) between the two treatment groups. Objective response rate (ORR), as assessed by blinded independent review committee per RECIST v1.1, is a key secondary objective. Other secondary objectives will include a comparison of **Mab-1** and sorafenib in terms of various efficacy assessments (progression free survival [PFS],

duration of response [DoR], time to progression [TTP], disease control rate [DCR], and clinical benefit rate [CBR]), measures of health-related quality of life, and safety and tolerability.

[0096] **Study Population**

[0097] Adult patients, aged ≥18 years, will be enrolled if:

(a) unresectable, histologically confirmed HCC,

(b) an Eastern Cooperative Oncology Group (ECOG) score ≤1, Child-Pugh A classification,

(c) Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC, Stage B disease that is not amenable to, or has progressed after, loco-regional therapy, and is not amenable to a curative treatment approach,

(d) not received prior systemic therapy.

[0098] Patients will be excluded if:

(a) known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC histology,

(b) tumor thrombus involving the main trunk of the portal vein or inferior vena cava,

(c) received loco-regional therapy to the liver or any prior immunotherapy within 28 days prior to randomization, or any Chinese herbal medicine or patent medicine used to control cancer within 14 days of randomization,

(d) grade 2 or higher hepatic encephalopathy (at screening or prior history),

(e) pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites at screening.

[0099] **Treatment**

[0100] Patients will be randomized 1:1 to receive **Mab-1** 200 mg IV Q3W or sorafenib 400 mg orally twice daily (BID), with randomization stratified by the presence of macrovascular invasion, the presence of extrahepatic spread, ECOG performance status, etiology, and geography. Treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons.

[0101] **Study assessments and statistical analysis**

(a) Tumor response will be evaluated every 9 weeks during Year 1 and every 12 weeks from Year 2 onwards, in accordance with RECIST v1.1.

(b) The primary efficacy endpoint of OS for **Mab-1** versus sorafenib will be assessed for non-inferiority.

(c) Secondary endpoints (such as ORR, PFS, DoR, and TTP assessed by a blinded independent review committee) will be evaluated for treatment comparisons

(d) All tests will be performed at one-sided α=0.025 (or 2-sided α=0.05).

(e) Safety and tolerability (a secondary endpoint) will be assessed by monitoring adverse events (AEs), including immune-related AEs, and through physical examinations, vital signs, and electrocardiograms.

(f) The European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ-HCC18) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 will be used to assess health-related quality of life between the two treatment arms using a mixed model. The European Quality of Life 5-Dimensions will also be summarized.

[0102] The foregoing examples and description of certain embodiments should be taken as illustrating, rather than as limiting the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. All such variations are intended to be included within the scope of the present invention. All references cited are incorporated herein by reference in their entireties.

[0103] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country.

[0104] In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "**comprise**" or variations such as "**comprises**" or "**comprising**" is used in an inclusive sense, i.e., to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0105] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS

1. A method for immunotherapy of a patient with hepatocellular carcinoma (HCC) comprising administering to the patient a therapeutically effective amount of an anti-PD-1 antibody or a fragment antigen binding thereof, which was specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis.

2. The method of Claim 1, wherein the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain complement determinant regions (CDRs) listed as follows:

a) mu317 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 12, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);

b) mu326 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 18, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);

c) 317-4B6 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively);

d) 326-4A3 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 37, 38, 39, respectively); and CDR-L1, CDR--L2 and CDR-L3 (SEQ ID NOs: 40, 41, 42, respectively);

e) 317-1H CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 59, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);

f) 317-4B2 CDR-HL CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);

g) 317-4B5 CDR-Hl, CDR-H2 and CDR-H3 (SEQ ID NOs: 11 , 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);

h) 317-4B6 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 32, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);

i) 326-1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);

j) 326-3B1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively); or

k) 326-3G1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-I 2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively).

3. The method of Claim 1, wherein the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain any combinations of CDRs listed as follows:

(a) CDR-H1 (SEQ ID NO 31), CDR-H2 (SEQ ID NO 12, 32, 59 or 60) and CDR-H3 (SEQ ID NO 33),
CDR-L1 (SEQ ID NO 14, 34 or 61), CDR-L2 (SEQ ID NO 35) and CDR-L3 (SEQ ID NO 36); or

(b) CDR-H1 (SEQ ID NO 37), CDR-H2 (SEQ ID NO 18, 38 or 62) and CDR-H3 (SEQ ID NO 39),
CDR-L1 (SEQ ID NO 40), CDR-L2 (SEQ ID NO 41) and CDR-L3 (SEQ ID NO 42).

4. The method of any one of Claims of 2-3, wherein the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) comprising:

a) mu317 (SEQ ID NOs: 4 and 6, respectively);
b) mu326 (SEQ ID NOs: 8 and 10, respectively);
c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);
d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);
p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);
q) 317-311 (SEQ ID NOs: 70 and 26, respectively);
r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

5. The method of any one of Claims 2-3, wherein the anti-PD-1 antibody is an antibody which contains a IgG4 heavy chain effector or constant domain comprising any of SEQ ID NOs: 83-88 or 91-106.

6. The method of any one of Claims 2-3, wherein the anti-PD-1 antibody is an antibody which contains a F(ab) or F(ab)2 comprising a domain of any one claims of 2-5.

7. The method according to Claim 1, wherein the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and a IgG4 heavy chain effector or constant domain comprising SEQ ID NOs: 87 or 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprise:

a) mu317 (SEQ ID NOs: 4 and 6, respectively);
b) mu326 (SEQ ID NOs: 8 and 10, respectively);
c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);
d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);
p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);
q) 317-311 (SEQ ID NOs: 70 and 26, respectively);
r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

8. The method according to claim 1, wherein the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and an IgG4 heavy chain effector or constant domain comprising SEQ ID NO: 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprises SEQ ID NO: 24 and SEQ ID NO: 26, respectively.

9. The method of any one of Claims 1-8, wherein the HCC is an advanced HCC and/or a metastatic HCC.

10. The method of any one of Claims 1-8, wherein the HCC is a virus infection related HCC.

11. The method of Claim 10, wherein the HCC is HBV-infected HCC, HCV-infected HCC, or HBV/HCV co-infected HCC.

12. The method of any one of Claims 1-8, wherein the HCC is an advanced HBV-infected HCC, metastatic HBV-infected HCC, HCV-infected HCC, or metastatic HCV-infected HCC.

13. The method of any one of Claims 1-8, wherein the HCC is an advanced HBV-infected HCC, or metastatic HBV-infected HCC.

14. The method of Claim 9, wherein the HCC is not treated by prior PD-1 or PD-L1.

15. The method of any one of Claims 1-14, wherein the anti-PD-1 antibody is administered parenterally at a dose of 0.5-10 mg/kg QW, or Q2W, or Q3W, or Q4W.

16. The method of any one of Claims 1-14, wherein the anti-PD-1 antibody is administrated at a dose of 0.5-10 mg/kg QW or Q2W or Q3W.

17. The method of any one of Claims 1-14, wherein the Anti-PD-1 antibody is administrated at a dose of 0.5-10 mg/kg Q2W or Q3W.

18. The method of any one of Claims 1-14, wherein the anti-PD-1 antibody is administrated parenterally at a dose of 0.5-5 mg/kg Q2W, 5-10 mg/kg Q2W, or 2-5 mg/kg Q3W.

19. The method of any one of Claims 1-14, wherein the anti-PD-1 antibody is administrated parenterally at a dose of 0.5 mg/kg Q2W, 5 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W or 5 mg/kg Q3W.

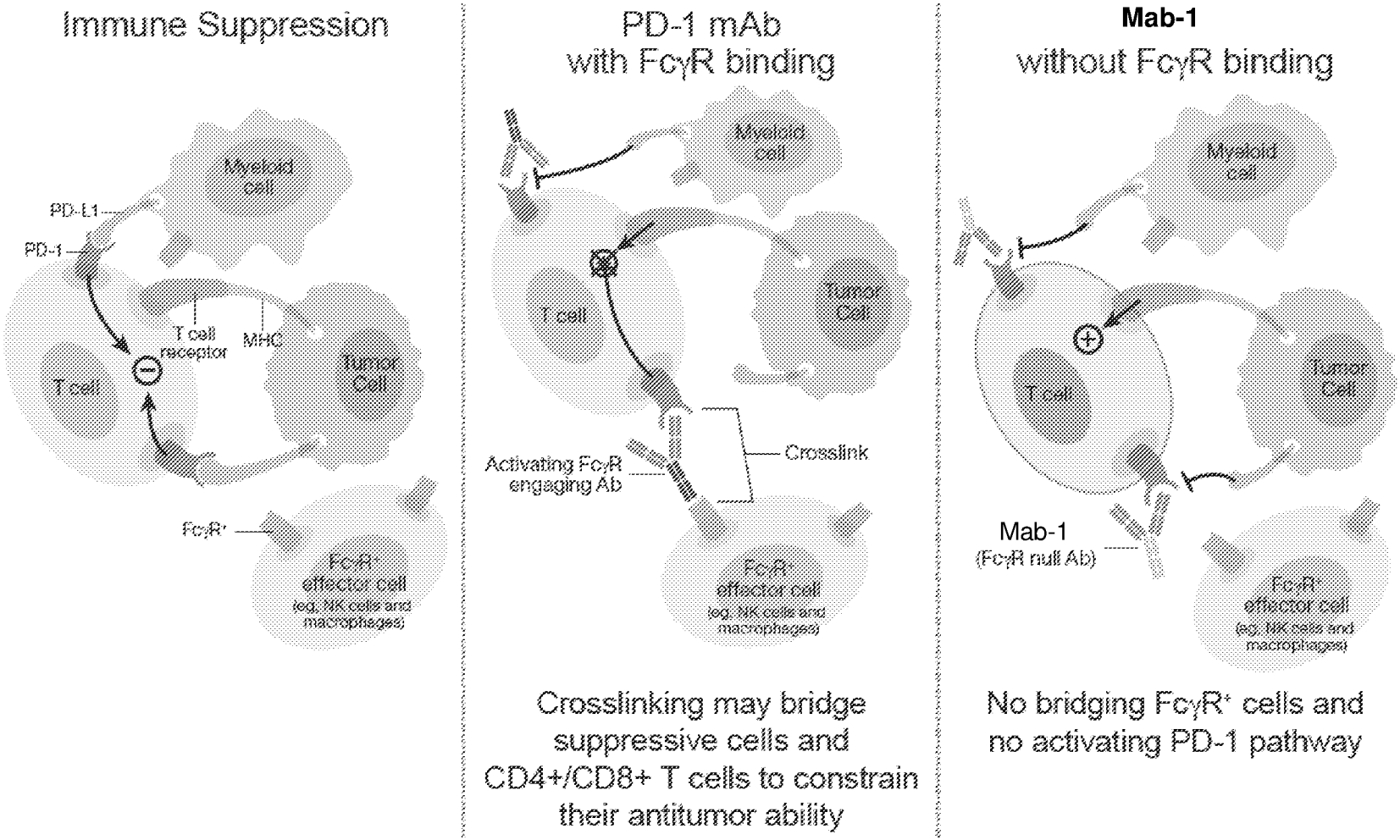
20. The method of any one of Claims 1-14, wherein the anti-PD-1 antibody is administered parenterally at a dose of about 200 mg.

21. The method of claim 20, wherein the anti-PD-1 antibody is administered Q3W.

22. The method of Claim 1, wherein the patient with HCC has a HBV viral load <200 IU/mL (~1000 cps/mL).

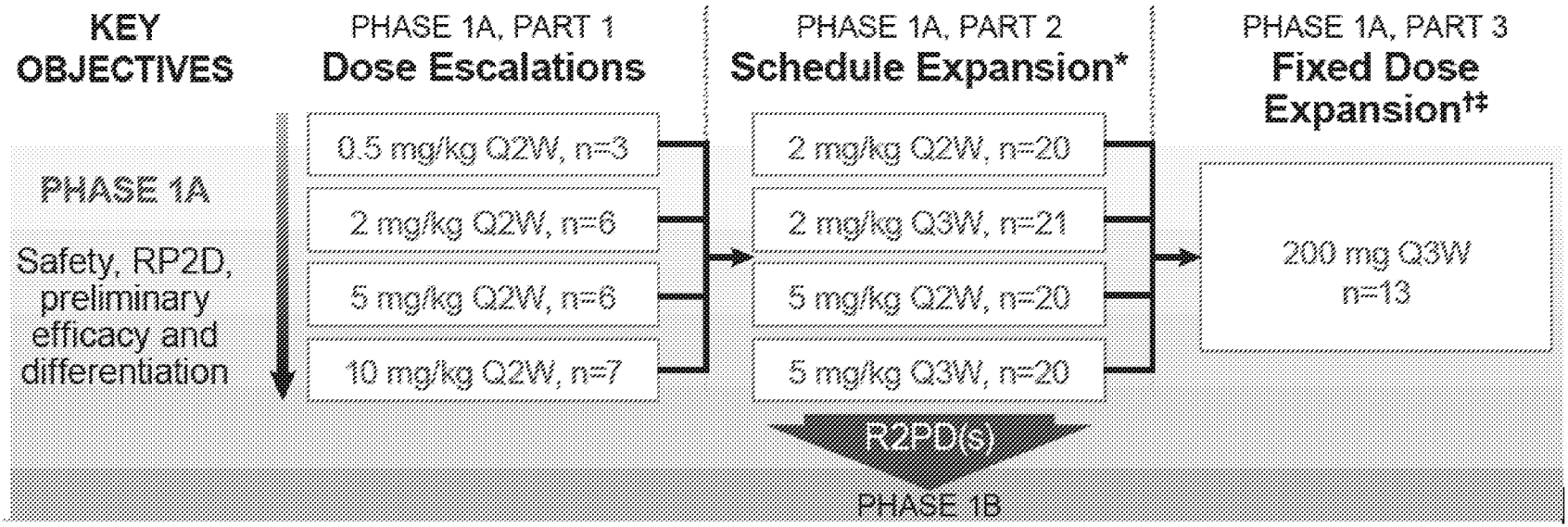
23. The method of Claim 1, wherein the patient with HCC has active HBV infection need to be on anti-HBV suppression for $\geqslant$3 months throughout treatment and for 6 months after.

Figure 1: Lack of FcγR Binding Prevents Macrophage-Mediated T-Cell Clearance



Adapted from Dahan et al. *Cancer Cell.* 2015;28:285–295.

Figure 2: Schematic of the Study Design



PHASE 1B Efficacy and safety in HCC patients (n=40)

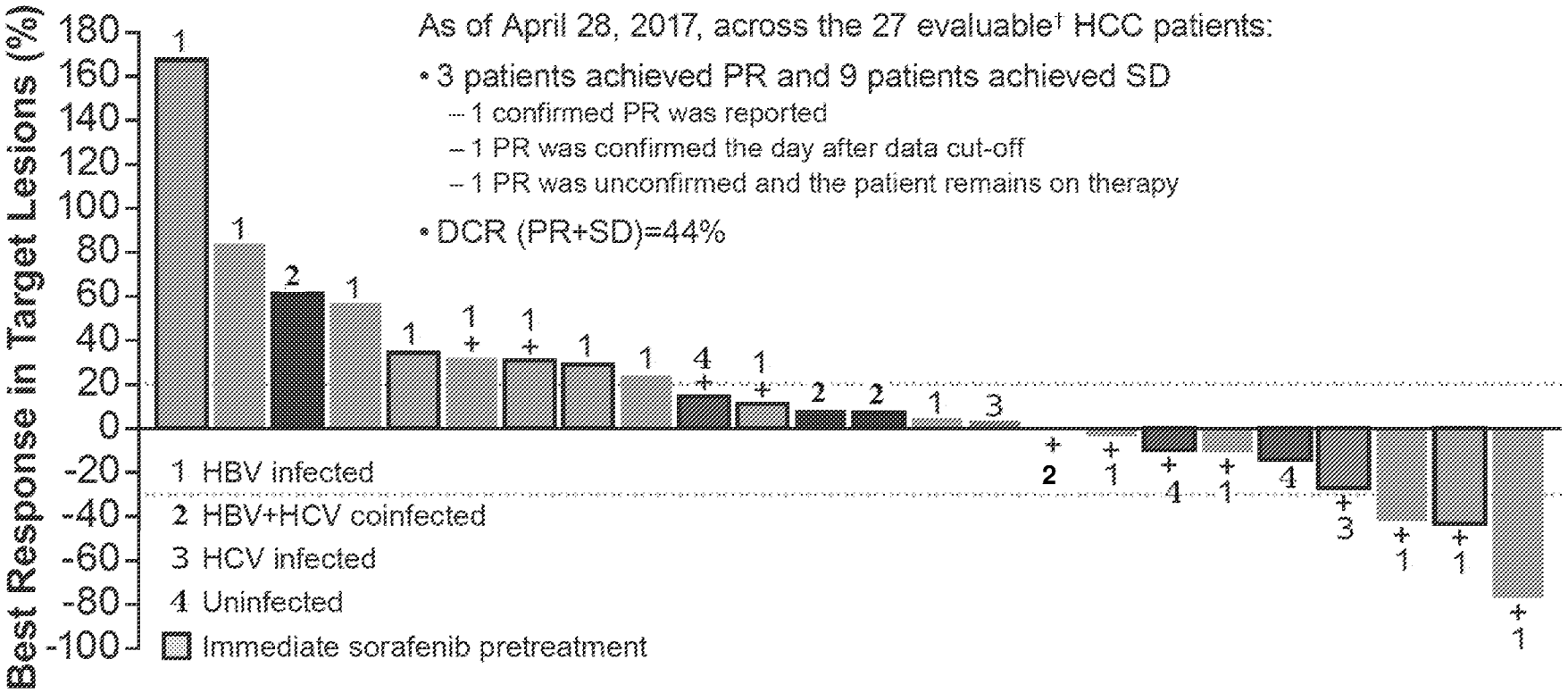
*In select tumors for RP2D determination and preliminary differentiation.

†In select tumors at fixed doses that do not exceed the exposure of MTD.

‡Conducted in parallel with phase 1B.

Abbreviations: MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Figure 3: Best Change in Tumor Size by Hepatitis Virus Infection Status*

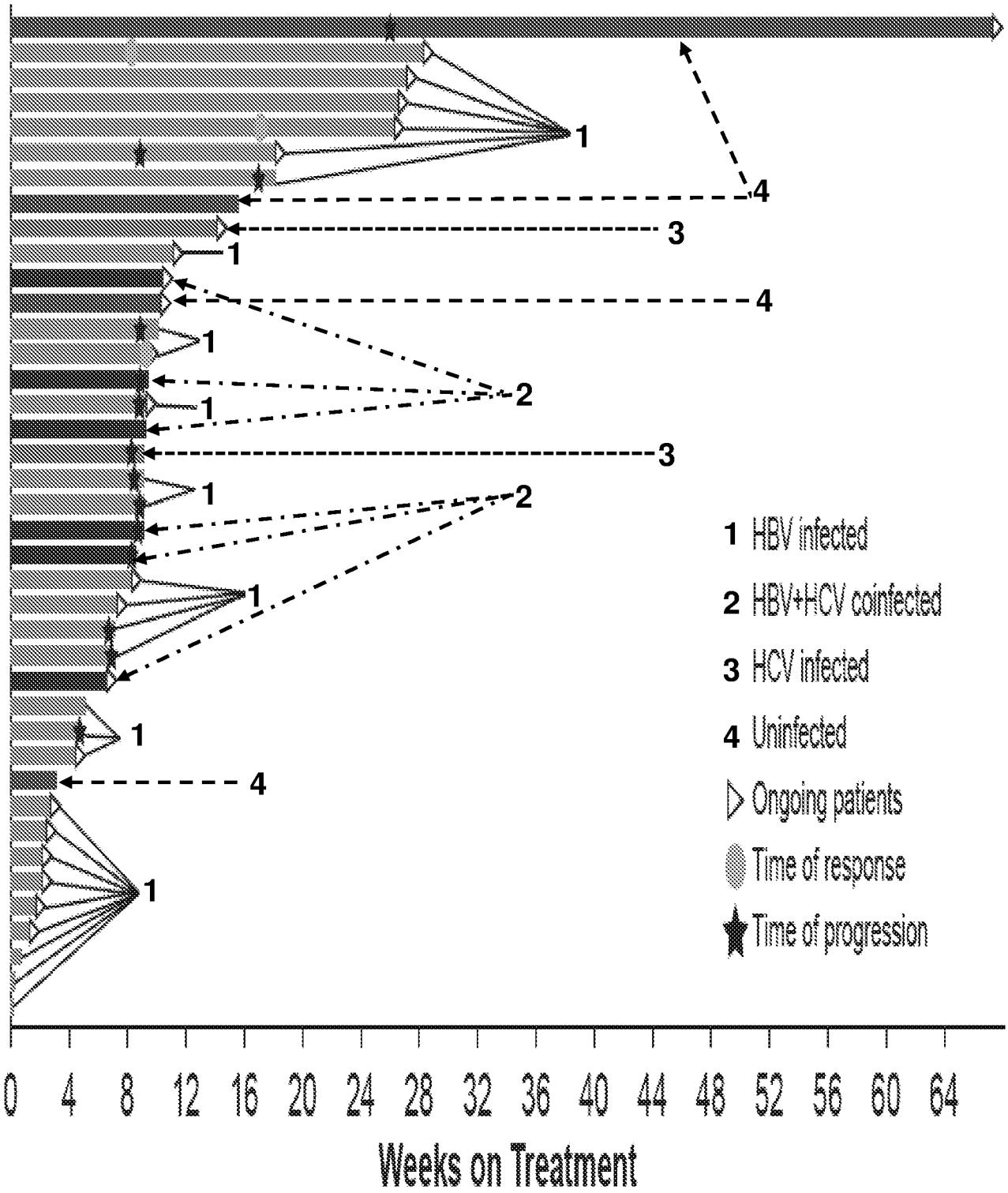


+ indicates patient still on treatment.

*Includes 24 of 25 evaluable patients with at least 1 post-baseline assessment; 1 patient had no post-baseline target lesion measurement; †Evaluable is defined as patient who had at least 1 tumor assessment after enrollment on study or had progressed or died prior to the initial tumor assessment.

Abbreviations: DCR, disease control rate; PR, partial response; SD, stable disease.

Figure 4: Duration of Treatment and Response



Each line represents an individual patient.

Figure 5: Baseline and Most Recent CT Assessment in the Three Patients with Partial Response

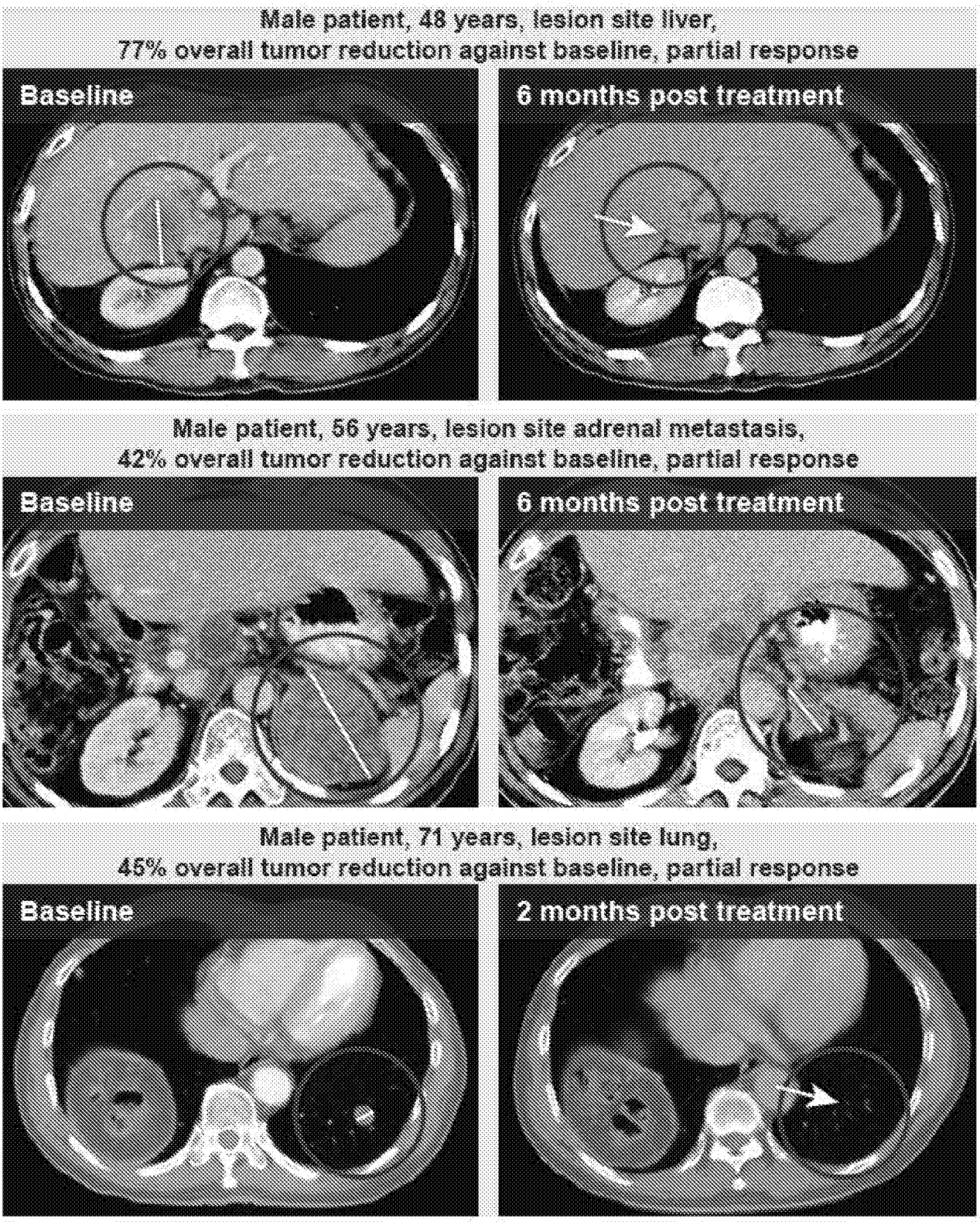


Figure 6: Change in Tumor Burden Over Time

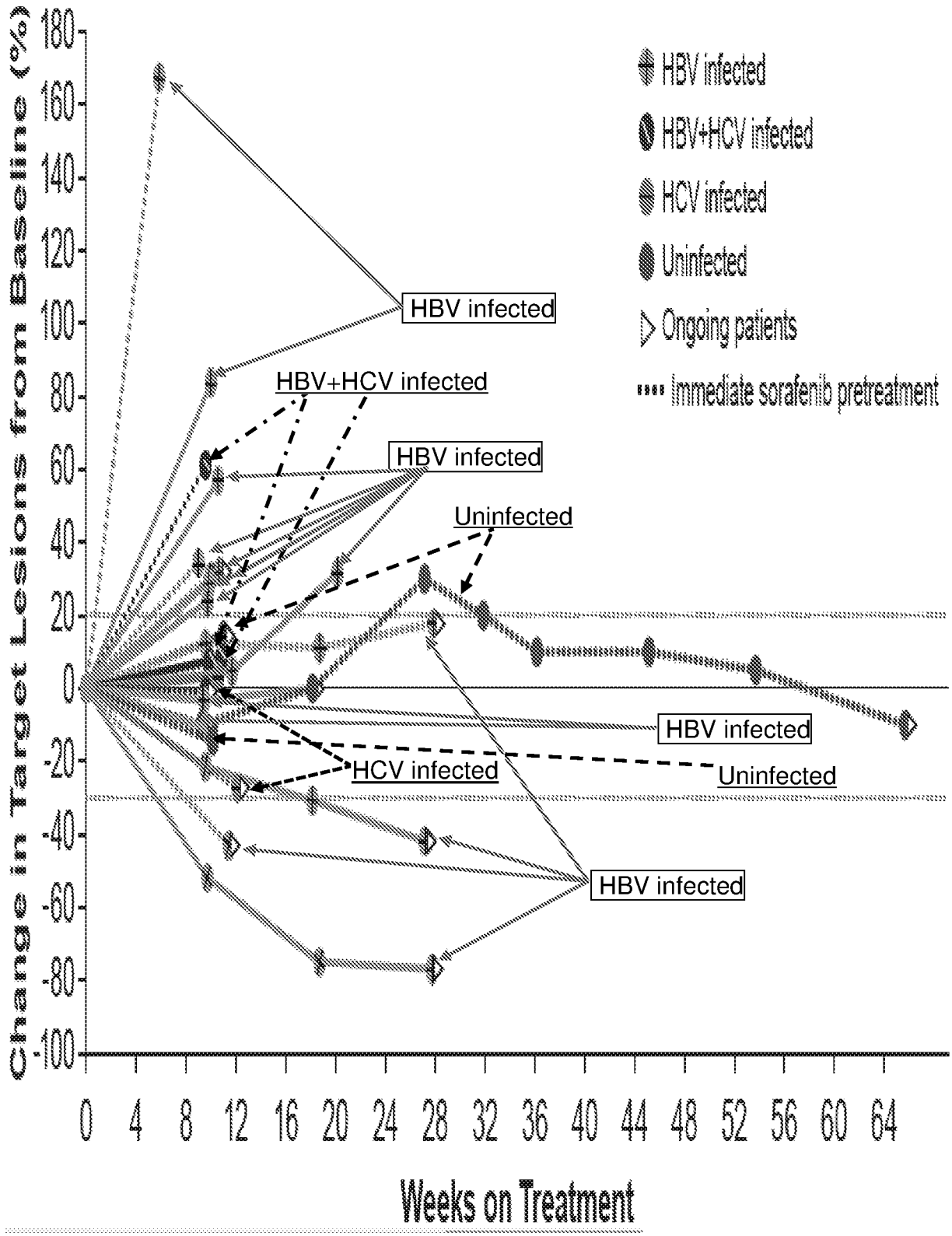


Figure 7: Change in Alpha-Fetoprotein (AFP) from Baseline

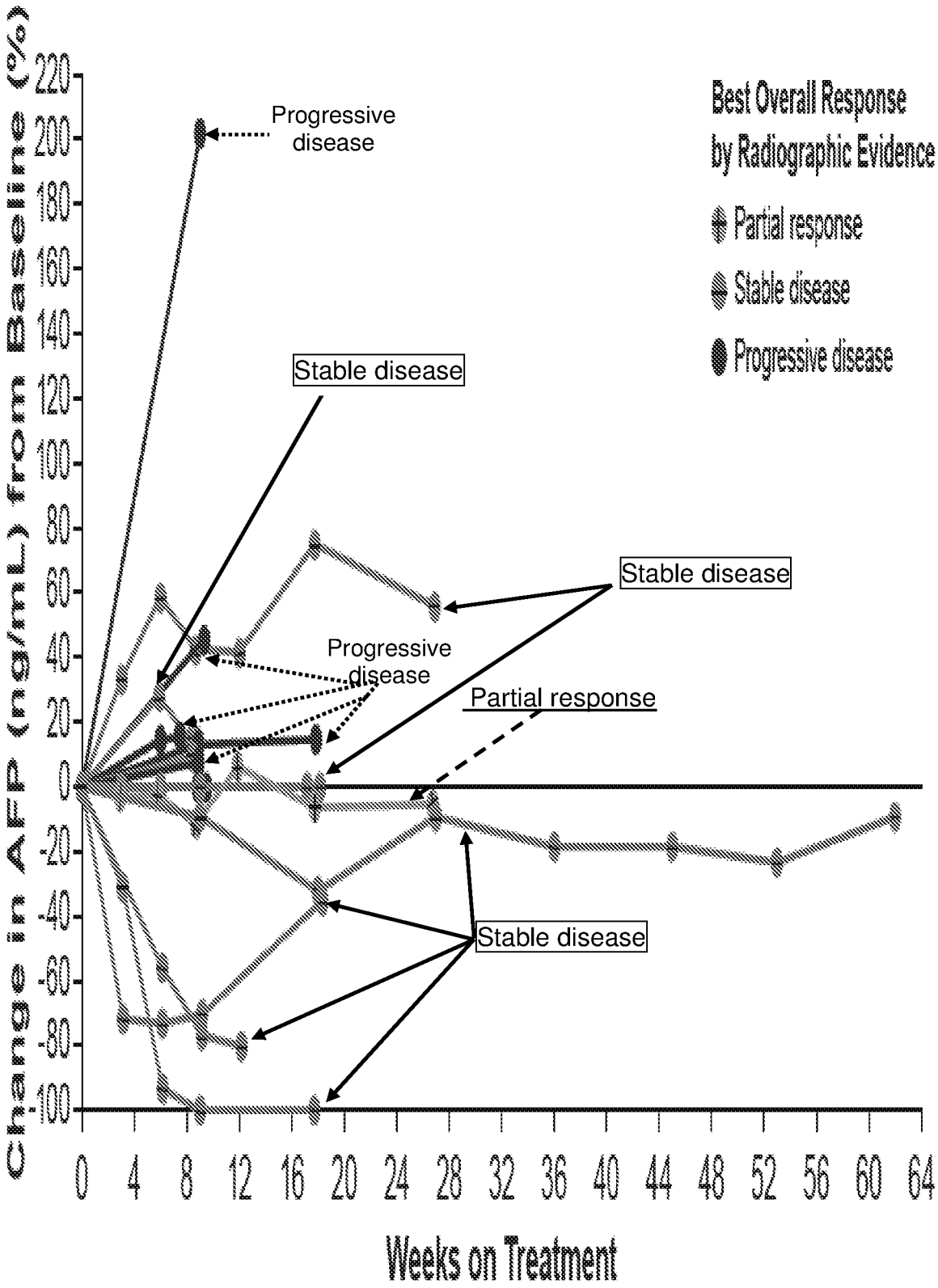
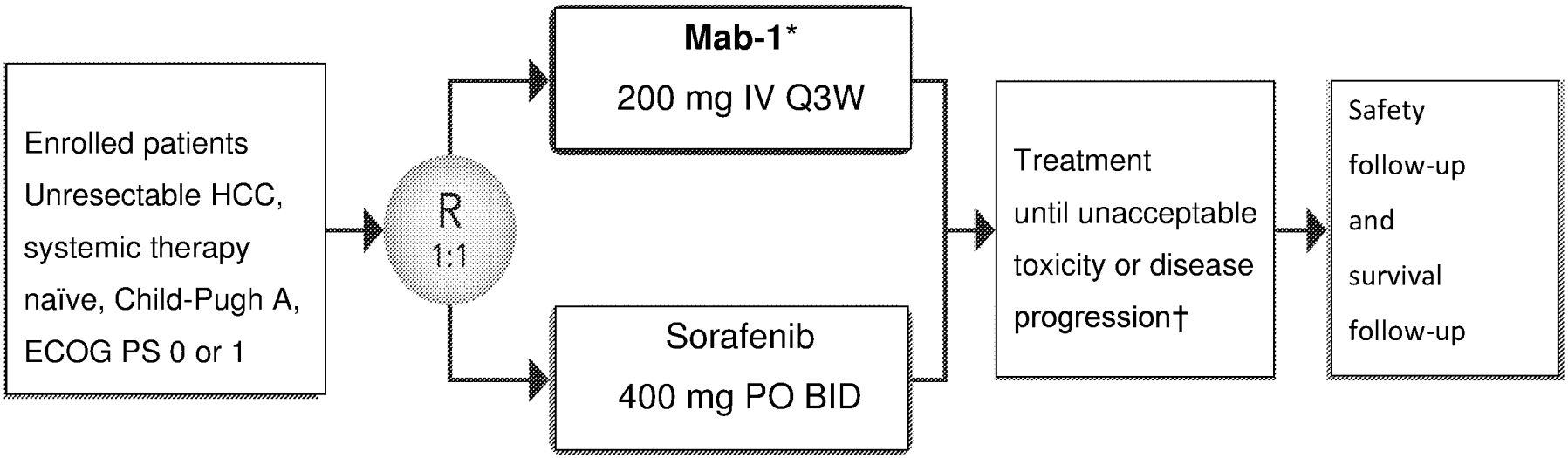


Figure 8: Study Design



Randomization stratified by: macrovascular invasion (present vs absent); extrahepatic spread (present vs absent); ECOG PS (0 vs 1); etiology (HCV vs other [includes HBV]); geography (Asia vs Japan vs Rest of World).

*The initial infusion (Cycle 1, Day 1) will be administered over 60 minutes; if well tolerated, subsequent infusions may be administered over 30 minutes. After **Mab-1** infusion, patients will be monitored for 2 hours during Cycles 1 and 2, and for ≥30 minutes from Cycle 3 onward.

†Treatment beyond the initial investigator-assessed disease progression will be permitted in both treatment arms if pseudo progression is suspected or there is reasonable belief that the patient could derive benefit from the treatment.

Abbreviations: BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenously; PO, orally; Q3W, once every 3 weeks; R, randomization.

SEQUENCE LISTING

<110> BeiGene Ltd.
Wang, Lai
Li, Kang
Qi, Qinzhou
Hou, Jeannie
Wu, Zhong

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gccttccccg aggaccgcag ccagcccggc caggactgcc gcttccgtgt cacacaactg 240

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        35                  40                  45


Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
    50                  55                  60


Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65                  70                  75                  80


Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
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            100                 105                 110


Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
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35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Arg Ser Gln Val Phe Leu
65 70 75 80

Arg Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
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cgtttcactg gcagtggata tgggacggat ttcattttca ccatcagcac tgtgcaggct 240

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35 40 45

Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Thr Gly
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Ser Gly Tyr Gly Thr Asp Phe Ile Phe Thr Ile Ser Thr Val Gln Ala
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35 40 45

Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Glu Glu Phe
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Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
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Gln Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
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Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
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Gly Val Ile Tyr Ala Asp Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100   105   110

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35 40 45

Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
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Gly Trp Ile Asn Asn Asn Asn Ala Glu Pro Thr Tyr Ala Gln Asp Phe
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Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
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Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


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20 25 30

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Gly Val Ile Tyr Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
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Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
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Thr Val Thr Val Ser Ser
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            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45


Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
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Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
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            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Tyr Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
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Thr Val Thr Val Ser Ser
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            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45


Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60


Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65                  70                  75                  80


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<400> 47
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acctgcactg tctctgggtt ttcattaacc agctatggtg tacactggat ccggcagccc 120

ccagggaagg gactggagtg gctgggggtc atatgggccg gtggaagcac aaattataat 180

ccctccctca agagtcgact gaccatatca aaagacaact ccaagagcca ggtttccctg 240

aagatgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agcctatggt 300

aactactggt acatcgatgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> 48
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-1 pro-Vh

<400> 48

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Ser Leu
65 70 75 80

Lys Met Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 49
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> 317-1 cDNA-Vk

<400> 49
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgca aggccagcca gagtgtgagt aatgatgtag cttggtacca gcagaaacca 120

ggacagcctc ctaagctgct cattaactat gcatttcatc gcttcactgg ggtccctgac 180

cgattcagtg gcagcgggta tgggacagat ttcactctca ccatcagcag cctgcaggct 240

gaagatgtgg cagtttatta ctgtcaccag gcttatagtt ctccgtacac gtttggcggg 300

gggaccaagc tggagatcaa a 321

<210> 50
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-1 pro-Vk

<400> 50

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

```
Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45

Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Val Tyr Tyr Cys His Gln Ala Tyr Ser Ser Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  51
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  326-3B1 pro-Vh

<400>  51

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45
```

```
Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Asp Phe
    50                  55                  60

Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser
```

<210> 52
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3B1 pro-Vk

<400> 52

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
            20                  25                  30

Gly Tyr Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80
```

```
Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
                85                  90                  95


Glu Tyr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  53
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  326-3G1 pro-Vh

<400>  53

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Asp Phe
    50                  55                  60


Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110
```

Ser Ser

<210> 54
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3G1 pro-Vk

<400> 54

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Tyr Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Tyr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 55
<211> 342
<212> DNA
<213> Artificial Sequence

<220>

<223> 326-1 cDNA-Vh

<400> 55
caggtgcagc tggtgcagag cggcagcgag ctgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc aactacggca tgaactgggt gagacaggcc 120

cccggccagg gcctggagtg gatgggctgg atcaacaaca acaacggcga gcccacctac 180

gcccagggct tcagaggcag attcgtgttc agcctggaca ccagcgccag caccgcctac 240

ctgcagatca gcagcctgaa gaccgaggac accgccgtgt acttctgcgc cagagacgtg 300

atggactact ggggccaggg caccaccgtg accgtgagca gc 342

<210> 56
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-1 pro-Vh

<400> 56

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
100 105 110

Ser Ser

<210> 57
<211> 330
<212> DNA
<213> Artificial Sequence

<220>
<223> 326-1 cDNA-Vk

<400> 57
gacattgtgc tgacccagtc tccagcctcc ttggccgtgt ctccaggaca gagggccacc 60

atcacctgca gagccagtga aagtgttgat aattatggct atagttttat gcactggtat 120

cagcagaaac caggacaacc tcctaaactc ctgatttacc gtgcatccaa cctagaatct 180

ggggtcccag ccaggttcag cggcagtggg tctaggaccg atttcaccct cacaattaat 240

cctgtggaag ctaatgatac tgcaaattat tactgtcagc aaagtaaaga atatccgacg 300

ttcggcggag ggaccaaggt ggagatcaaa 330

<210> 58
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-1 pro-Vk

<400> 58

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

```
Gly Tyr Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
                85                  90                  95


Glu Tyr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  59
<211>  16
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  317-1 H-CDR2 or CDR-H2

<400>  59

Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1               5                   10                  15


<210>  60
<211>  16
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  317-4B2 H-CDR2 or CDR-H2

<400>  60

Val Ile Tyr Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1               5                   10                  15
```

<210> 61
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-4B2 L-CDR1 or CDR-L1

<400> 61

Lys Ser Ser Glu Ser Val Ser Asn Asp Val Ala
1 5 10

<210> 62
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-1 H-CDR2 or CDR-H2

<400> 62

Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Gly Phe Arg
1 5 10 15

Gly

<210> 63
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3G1 H-CDR2 or CDR-H2

<400> 63

Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Asp Phe Arg
1 5 10 15

Gly

<210> 64
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-3A1 pro-Vh

<400> 64

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 65
<211> 118

<212> PRT
<213> Artificial Sequence

<220>
<223> 317-3C1 pro-Vh

<400> 65

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 66
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-3E1 pro-Vh

<400> 66

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Ser Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 67
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-3F1 pro-Vh

<400> 67

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

```
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210>  68
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  317-3G1 pro-Vh

<400>  68

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Ser Gln Val Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210>  69
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  317-3H1 pro-Vh

<400>  69

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
```

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 70
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-3I1 pro-Vh

<400> 70

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

```
Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210>  71
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  317-4B1 pro-Vh

<400>  71

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100                 105                 110
```

Thr Val Thr Val Ser Ser
        115

<210> 72
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-4B3 pro-Vh

<400> 72

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20   25   30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Val Ile Asn Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr
            100   105   110

Thr Val Thr Val Ser Ser
        115

<210> 73
<211> 118

<212> PRT
<213> Artificial Sequence

<220>
<223> 317-4B4 pro-Vh

<400> 73

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Pro Tyr Ile Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 74
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 317-4A2 pro-Vk

<400> 74

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys His Gln Ala Tyr Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 75
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3A1 pro-Vh

<400> 75

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 76
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3C1 pro-Vh

<400> 76

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Asp Phe
50 55 60

```
Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
            100                 105                 110


Ser Ser
```

<210> 77
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3D1 pro-Vh

<400> 77

```
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Gly Phe
    50                  55                  60


Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110


Ser Ser



<210>  78
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  326-3E1 pro-Vh

<400>  78

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Asp Phe
    50                  55                  60


Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
            100                 105                 110
```

Ser Ser

<210> 79
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3F1 pro-Vh

<400> 79

```
Gln Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Asn Asn Asn Asn Gly Glu Pro Thr Tyr Ala Gln Gly Phe
    50                  55                  60


Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
            100                 105                 110


Ser Ser
```

<210> 80
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-3B N55D pro-Vh

<400> 80

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Asn Asn Asp Gly Glu Pro Thr Tyr Ala Gln Asp Phe
50 55 60

Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 81
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> 326-4A1 pro-Vk

<400> 81

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Tyr Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Pro Val Glu Ala Glu Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Tyr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 82
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> 326-4A2 pro-Vk

<400> 82

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

```
Gly Tyr Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
                85                  90                  95


Glu Tyr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  83
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  huIgG4mt1 pro

<400>  83

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
```

```
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  84
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  huIgG4mt2 pro

<400>  84

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
```

```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
```

```
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  85
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  huIgG4mt6 pro

<400>  85

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
```

```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
```

```
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  86
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  huIgG4mt8 pro

<400>  86

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
```

```
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Thr Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
```

```
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 87
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> huIgG4mt9 pro

<400> 87

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
```

```
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
```

```
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  88
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  huIgG4mt10 pro

<400>  88

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110
```

```
Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300
```

```
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 89
<211> 367
<212> PRT
<213> Artificial Sequence

<220>
<223> OS8 pro

<400> 89

```
Met Glu Arg His Trp Ile Phe Leu Leu Leu Leu Ser Val Thr Ala Gly
1               5                   10                  15


Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg
            20                  25                  30


Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Arg Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn
65                  70                  75                  80


Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser
                85                  90                  95


Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110
```

```
Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp
        115                 120                 125


Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr Gln Ser
145                 150                 155                 160


Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys
                165                 170                 175


Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser
            180                 185                 190


Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser
        195                 200                 205


Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser Tyr Ser
    210                 215                 220


Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
225                 230                 235                 240


Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu
                245                 250                 255


Glu Ile Asn Ser Ser Val Val Pro Val Leu Gln Lys Val Asn Ser Thr
            260                 265                 270


Thr Thr Lys Pro Val Leu Arg Thr Pro Ser Pro Val His Pro Thr Gly
        275                 280                 285


Thr Ser Gln Pro Gln Arg Pro Glu Asp Cys Arg Pro Arg Gly Ser Val
    290                 295                 300
```

Lys Gly Thr Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305 310 315 320

Leu Ala Gly Ile Cys Val Ala Leu Leu Leu Ser Leu Ile Ile Thr Leu
325 330 335

Ile Cys Tyr His Arg Ser Arg Lys Arg Val Cys Lys Cys Pro Arg Pro
340 345 350

Leu Val Arg Gln Glu Gly Lys Pro Arg Pro Ser Glu Lys Ile Val
355 360 365

<210> 90
<211> 304
<212> PRT
<213> Artificial Sequence

<220>
<223> P3Z pro

<400> 90

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

```
Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Arg
            180                 185                 190

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
        195                 200                 205

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
    210                 215                 220

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
225                 230                 235                 240

Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
                245                 250                 255

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
            260                 265                 270

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
        275                 280                 285
```

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
290 295 300

<210> 91
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-233P

<400> 91

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Glu Phe Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320
```

Leu Ser Leu Ser Leu Gly Lys
325

<210> 92
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-234V

<400> 92

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Val Phe Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

```
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 93
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-235A

<400> 93

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Phe Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
```

```
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 94
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-234V-235A

<400> 94

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                  10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 95
<211> 327

<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-234A

<400> 95

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                  10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Ala Phe Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  96
<211>  327
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> IgG4 Fc region 228P-234A-235A

<400> 96

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
```

```
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 97
<211> 327
<212> PRT
<213> Artificial Sequence

<220>

<223> IgG4 Fc region 228P-233P-234A-235A

<400> 97

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                  10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Pro Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
```

```
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  98
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG4 Fc region 228P-234V-235A-265A
```

<400> 98

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                  10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
```

```
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 99
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-234A-235A-265A

<400> 99

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110


Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
```

```
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  100
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG4 Fc region 228P-233P-234A-235A-265A

<400>  100

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15
```

```
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
```

```
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 101
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-265A

<400> 101

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15
```

```
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
```

```
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  102
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG4 Fc region 228P-309V

<400>  102

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
```

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  103
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG4 Fc region 228P-409K

<400>  103

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
```

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325


<210>  104
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG4 Fc region 228P-309V-409K

<400>  104

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
```

```
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 105
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-265A-309V-409K

<400> 105

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
```

```
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 106
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG4 Fc region 228P-233P-234A-235A-265A-309V-409K

<400> 106

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
```

```
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
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<211> 327
<212> PRT
<213> Homo sapiens

<400> 107

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Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
```

```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110


Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
```

```
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325
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