(12) STANDARD PATENT (11) Application No. **AU 2020380288 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Combination therapy to treat brain cancer

(51) International Patent Classification(s)
A61K 39/00 (2006.01) ***C07K 16/30*** (2006.01)
C07K 14/47 (2006.01)

(21) Application No: **2020380288** (22) Date of Filing: **2020.11.04**

(87) WIPO No: **WO21/092019**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/988,102	**2020.03.11**	**US**
62/930,417	**2019.11.04**	**US**
63/018,060	**2020.04.30**	**US**
63/070,987	**2020.08.27**	**US**

(43) Publication Date: **2021.05.14**
(44) Accepted Journal Date: **2024.02.01**

(71) Applicant(s)
Inovio Pharmaceuticals, Inc.;Regeneron Pharmaceuticals, Inc.

(72) Inventor(s)
BREDLAU, Amy-Lee;LOWY, Israel;SKOLNIK, Jeffrey;YAN, Jian;FERRARO, Bernadette;WALTERS, Jewell

(74) Agent / Attorney
FB Rice Pty Ltd, L 23 44 Market St, Sydney, NSW, 2000, AU

(56) Related Art
WO 2018/064588 A2
DAVID REARDON, ET AL, CANCER RESEARCH, vol. 79, no. 13_Supplement, 1 July 2019 (2019-07-01), US , DOI: 10.1158/1538-7445.AM2019-CT114

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2021 (14.05.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/092019 A1

(51) International Patent Classification:
C07K 14/47 (2006.01) *C07K 16/30* (2006.01)
A61K 39/00 (2006.01)

(21) International Application Number:
PCT/US2020/058891

(22) International Filing Date:
04 November 2020 (04.11.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/930,417	04 November 2019 (04.11.2019)	US
62/988,102	11 March 2020 (11.03.2020)	US
63/018,060	30 April 2020 (30.04.2020)	US
63/070,987	27 August 2020 (27.08.2020)	US

(71) Applicants: **INOVIO PHARMACEUTICALS, INC.** [US/US]; 660 W. Germantown Pike, Suite 110, Plymouth Meeting, PA 19462 (US). **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventors; and

(71) Applicants: **YAN, Jian** [US/US]; 503 Sheffield Drive, Wallingford, PA 19086 (US). **FERRARO, Bernadette** [US/US]; 8594 Villa La Jolla Drive, #376, La Jolla, CA 92037 (US). **WALTERS, Jewell** [GB/US]; 11854 Stoneypeak Drive, Unit 318, San Diego, CA 92128 (US).

(72) Inventors: **BREDLAU, Amy-Lee**; c/o Regeneration Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **LOWY, Israel**; c/o Regeneration Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **SKOLNIK, Jeffrey**; 1940 Cardinal Lake Drive, Cherry Hill, NJ 08003 (US).

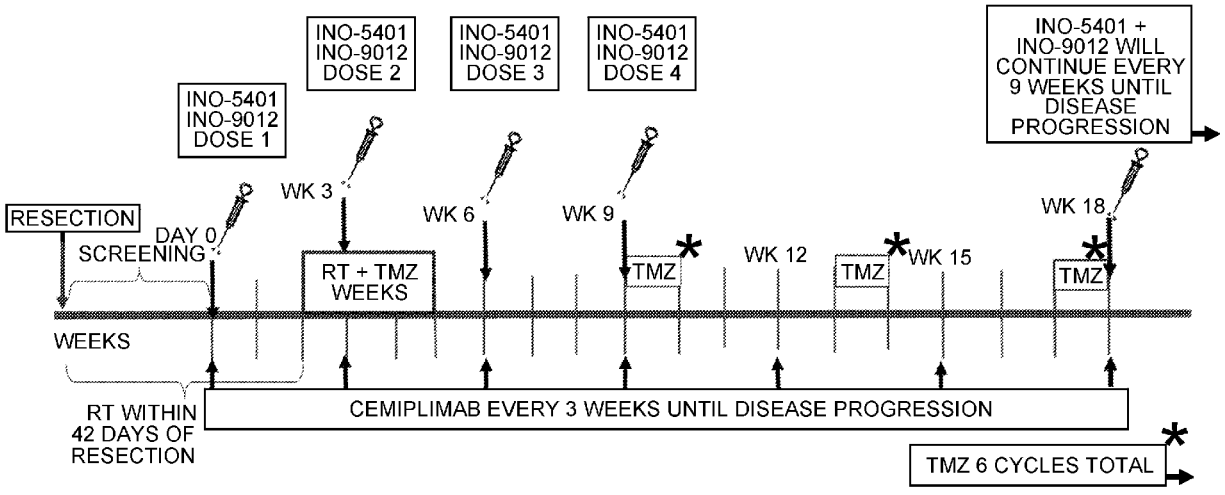
(74) Agent: **GROTH, Felicity E.**; Baker & Hostetler LLP, 2929 Arch Street, Cira Centre, 12th Floor, Philadelphia, PA 19104-2891 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM,

(54) Title: COMBINATION THERAPY TO TREAT BRAIN CANCER

Figure 1

STUDY SCHEMA



* CONTINUATION OF TEMOZOLOMIDE (TMZ) IN COHORT B (MGMT PROMOTER-UNMETHYLATED) ONLY

(57) Abstract: Provided herein are nucleic acid molecules, proteins, compositions and methods for treating brain cancer in a subject. In some embodiments, the compositions comprise cancer antigens hTERT, WT-1, and PSMA. In some embodiments, the compositions also comprise an adjuvant. The methods comprise administering to a subject in need thereof the cancer antigens. According to certain embodiments, the methods further involve administering the adjuvant and an anti-PD-1 antibody. In certain embodiments, the methods further comprise administering radiation therapy and/or a chemotherapeutic agent. In certain embodiments, the methods are clinically proven safe, clinically proven effective, or both.

WO 2021/092019 A1

[Continued on next page]

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

COMBINATION THERAPY TO TREAT BRAIN CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Application No. 63/070,987, filed August 27, 2020; U.S. Application No. 63/018,060, filed April 30, 2020; U.S. Application No. 62/988,102 filed March 11, 2020; and U.S. Application No. 62/930,417, filed November 4, 2019. Each of these applications is incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Novemer 4, 2020, is named 104409_000581_SL.txt and is 89,861 bytes in size.

TECHNICAL FIELD

[0003] The present invention relates to combination therapies and methods for treating brain cancer.

BACKGROUND

[0004] Despite advances in therapy, glioblastoma (GBM) remains one of the most deadly cancers. The current standard treatment for GBM is surgery, followed by concurrent radiation therapy (RT) and temozolomide (TMZ) chemotherapy administered daily during RT and then for 6-12 maintenance (adjuvant) cycles following the completion of RT for select patients [Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005,352:987-996].

[0005] Checkpoint inhibitors, such as programmed cell death-1 (PD-1) inhibitors, have increased response rates in many cancers, but have not yet shown clinical benefit in GBM.

[0006] Accordingly, a need exists for the identification and development of methods for the treatment of GBM to facilitate clinical management and progression of disease. Furthermore, more effective treatments are required to delay disease progression and/or decrease mortality in subjects suffering from cancer.

SUMMARY

[0007] Provided herein are vaccines and methods of their use to prevent or treat cancer.

[0007A] The present disclosure provides a method of treating brain cancer in a subject in need thereof, the method comprising administering to the subject:

an immunogenic composition comprising a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28; and

an anti-programmed cell death receptor 1 (PD-1) antibody.

[0007B] The present disclosure also provides a vaccine comprising:

an immunogenic composition comprising a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleic acid sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28;

when used in combination with an anti-programmed cell death receptor 1 (PD-1) antibody to treat brain cancer in a subject.

[0007C] The present disclosure also provides the use of a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleotide sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28 in the manufacture of a medicament to treat brain cancer in a subject, wherein the medicament is provided for administration in combination with an anti-programmed cell death receptor 1 (PD-1) antibody.

[0007D] The present disclosure also provides the use of a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleic acid sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28; and an anti-programmed cell death receptor 1 (PD-1) antibody, in the manufacture of a medicament to treat brain cancer in a subject.

[0007E] The cancer can be, for example, glioblastoma. In certain embodiments, the vaccine also includes an adjuvant, such as IL-12. In some embodiments, the methods prevent tumor growth. In some embodiments, the methods can reduce tumor growth and/or mass. In some embodiments, the methods can prevent metastasis of tumor cells. In some embodiments, the methods can increase a cellular immune response in the subject. In some embodiments, the methods increase tumor-free survival, progression-free survival, overall survival, orany combination thereof, of the subject.

[0008] In certain embodiments, IL-12 is encoded by a DNA plasmid, for example, INO-9012 or a biosimilar or bioequivalent thereof. In certain embodiments, hTERT, WT-1, and PSMA are encoded by one or more DNA plasmids, for example, INO-5401 or a biosimilar or bioequivalent thereof. In certain embodiments, the anti-PD-1 antibody is cemiplimab or a biosimilar or bioequivalent thereof. In certain embodiments, the methods further comprise administering radiation therapy and/or a chemotherapeutic agent, for example, temozolomide or a bioequivalent thereof.

[0009] In certain embodiments, the methods are clinically proven safe, clinically proven effective, or both.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods, there are shown in the drawings exemplary embodiments of the thereof; however, the methods are not limited to the specific embodiments disclosed. In the drawings:

[0011] **Figure 1** illustrates the study design for the example.

[0012] **Figure 2** shows the study population demographics for the example.

[0013] **Figure 3** shows representative MRI Images from two patients demonstrating increase in MRI signal at timepoints following first dose of INO-5401 + INO-9012 and cemiplimab- rwlc, suggestive of edema or tumor. Biopsy on several patients shows treatment-related changes with necrosis and mixed inflammation; absence of mitotic activity; and no evidence of viable tumor. The subject represented by the MRI images in the lower panel showed evidence of disease progression at Week 9 but resolution at Week 21. Subjects with similar findings on MRI who were resected showed only immune infiltrate with an absence of viable tumor.

[0013] **Figure 3** shows representative MRI Images from two patients demonstrating increase in MRI signal at timepoints following first dose of INO-5401 + INO-9012 and cemiplimab- rwlc, suggestive of edema or tumor. Biopsy on several patients shows treatment-related changes with necrosis and mixed inflammation; absence of mitotic activity; and no evidence of viable tumor. The subject represented by the MRI images in the lower panel showed evidence of disease progression at Week 9 but resolution at Week 21. Subjects with similar findings on MRI who were resected showed only immune infiltrate with an absence of viable tumor.

[0014] **Figure 4** demonstrates ELISpot results supporting the combination of INO-5401 and cemiplimab-rwlc as immunogenic- with IFN-g magnitudes above baseline to all 3 antigens in 5/11 subjects and to at least one antigen in 9 subjects obtained at the 12-month data cut-off.

[0015] **Figures 5A, 5B, and 5C** show the lytic granule loading assay results demonstrating frequencies of live, antigen-specific, activated (CD38+) CD3+CD8+ T cells with lytic potential (expressing Granzyme A, Perforin) obtained at the 12-month data cut-off. Figure 5A shows the frequencies of live, antigen specific, activated (CD38+) CD3+CD8+ T cells with lytic potential (expressing Granzyme A, Perforin) from before treatment (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc. Each subject is represented by an open circle, bars represent the mean. The difference from pre to peak, delta, is shown for each antigen graph as well as together for 8 subjects assayed (Figure 5B) and for the 5 subjects with sample available to week 12 (Figure 5C). INO-5401 is the sum of WT1, PSMA and hTERT. Box plots extend from the 25th to 75th percentile, with a horizontal line at the median, and "+" at the mean.

[0016] **Figure 6** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A, patients with the O6- methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0017] **Figure 7** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort B, patients with the O6- methylguanine methyltransferase gene promoter methylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0018] **Figure 8** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A and Cohort B, patients with the O6-methylguanine methyltransferase gene promoter unmethylated or methylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0019] **Figure 9** shows the tabular representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A, Cohort B, and both cohorts combined.

The total number of subjects per cohort, number of events, estimation of the event (PFS6), and the 95% confidence interval (CI) in which the numerical estimate of the event (PFS6) exists are all provided.

[0020] **Figure 10A** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohort A, for patients with the O6-methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. **Figure 10B** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over eighteen months for Cohort A, for patients with the O6-methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. Median follow-up in Cohort A is 17.8 months. mITT includes any subject who received ≥1 dose of study therapy. Shading represents confidence band on point estimate for survival at that timepoint.

[0021] **Figure 11A** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohort B, for patients with the O6-methylguanine methyltransferase gene promoter methylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. **Figure 11B** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over eighteen months for Cohort B, for patients with the O6-methylguanine methyltransferase gene promoter methylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. Median follow-up in Cohort B is 15.6 months. Censored; two subjects in Cohort B withdrew consent for follow-up at Week 3. mITT includes any subject who received ≥1 dose of study therapy. Shading represents confidence bands on point estimate for survival at that timepoint.

[0022] **Figure 12** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohorts A + B combined. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis.

[0023] **Figure 13** shows the efficacy data of the overall survival at 12 months and 18 months for Cohort A, for Cohort B, and combined. The figure shows the total number of subjects who were reported alive at 12 months and at 18 months. The total number of subjects, estimation of the event (OS12 or OS18), and the 95% confidence interval (CI) in which the numerical estimate of the event (OS12 or OS18) exists are all provided. The 95% CI were calculated using the exact Clopper-Pearson method.

[0024] **Figure 14** illustrates all Adverse Events as defined by the clinical study protocol ≥ NCI CTCAE Grade 3 from the example.

Figure 15 illustrates Immune Related Adverse Events as defined by the clinical study protocol from the example.

[0025] **Figures 16A and 16B** provide ELISpot results by Cohort at the 18-month data cut-off. In Cohort A, 19/22 (86%) subjects tested to date had an IFN-g magnitude above baseline to one or more of the antigens INO-5401 (Fig. 16A). In Cohort B, 16/17 (94%) subjects tested to date had an IFN-g magnitude above baseline to one or more of the antigens in INO-5401 (Fig. 16B). Baseline values from the peak timepoint following treatment are plotted. Samples collected Q3 weeks x 4 and then Q12 weeks.

[0026] **Figures 17A and 17B** provide results of assessment of post-INO-5401 peripheral immune responses by Cohort by flow cytometry (the expansion of antigen specific CD8+ T cells with lytic potential) at the 18-month data cut-off. In Cohort A, 13/19 (68%) subjects tested to date had a frequency of CD38+GrzA+Prf+ CD8+T cells above baseline to one or more of the antigens in INO-5401 (Figure 17A). In Cohort B, 8/10 (80%) subjects tested to date had a frequency of CD38+GrzA+Prf+ CD8+T cells above baseline to one or more of the antigens in INO-5401 (Figure 17B). Baseline values from the peak timepoint following treatment are plotted. Samples were collected Q3 weeks x 4 and then Q12 weeks.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0027] The disclosed nucleic acid molecules, proteins, vaccines, and methods may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed nucleic acid molecules, proteins, vaccines, and methods are not limited to the specific nucleic acid molecules, proteins, vaccines, and methods described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed nucleic acid molecules, proteins, vaccines, and methods.

[0028] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed nucleic acid molecules, proteins, vaccines, and methods are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0029] Throughout this text, the descriptions refer to compositions and methods of using said compositions. Where the disclosure describes or claims a feature or embodiment associated with a composition, such a feature or embodiment is equally applicable to the methods of using said composition. Likewise, where the disclosure describes or claims a feature or embodiment associated

with a method of using a composition, such a feature or embodiment is equally applicable to the composition.

[0030] It is to be appreciated that certain features of the disclosed nucleic acid molecules, proteins, vaccines, and methods which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment.

[0031] Conversely, various features of the disclosed nucleic acid molecules, proteins, vaccines, and methods that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

[0032] Provided herein are vaccines and methods of their use to prevent or treat cancer. The cancer can be brain cancer, for example, glioblastoma. The vaccine preferably includes at least three cancer antigens, hTERT, WT-1, and PSMA. In certain embodiments, the vaccine also includes an adjuvant, such as IL-12, and an anti-PD-1 antibody. The methods involve administering cancer antigens hTERT, WT-1, and PSMA, an adjuvant, and a programmed death receptor-1 (PD-1) checkpoint inhibitor, such as an anti-PD-1 antibody to a subject in need thereof. In some embodiments, the methods prevent tumor growth. In some embodiments, the methods can reduce tumor growth and/or mass. In some embodiments, the methods can prevent metastasis of tumor cells. In some embodiments, the methods can increase a cellular immune response in the subject. In some embodiments, the methods increase tumor-free survival, progression-free survival, overall survival, or any combination thereof, of the subject.

[0033] In certain embodiments, IL-12 is encoded by a DNA plasmid, for example, INO-9012 or a biosimilar or bioequivalent thereof. In certain embodiments, hTERT, WT-1, and PSMA are encoded by one or more DNA plasmids, for example, INO-5401 or a biosimilar or bioequivalent thereof. In certain embodiments, the anti-PD-1 antibody is cemiplimab or a biosimilar or bioequivalent thereof. In certain embodiments, the methods further comprise administering radiation therapy and/or a chemotherapeutic agent, for example,temozolomide or a bioequivalent thereof.

[0034] In certain embodiments, the methods are clinically proven safe, clinically proven effective, or both.

[0035] The recombinant cancer antigens can induce antigen-specific T cell and/or high titer antibody responses, thereby inducing or eliciting an immune response that is directed to or reactive against the cancer or tumor expressing the antigen. In some embodiments, the induced or elicited immune response can be a cellular, humoral, or both cellular and humoral immune responses. In some embodiments, the induced or elicited cellular immune response can include induction or secretion of interferon-gamma (IFN-γ) and/or tumor necrosis factor alpha (TNF-α). In other embodiments, the induced or elicited immune response can reduce or inhibit one or more immune suppression factors that promote growth of the tumor or cancer expressing the antigen, for example, but not limited to,

factors that down regulate MHC presentation, factors that up regulate antigen-specific regulatory T cells (Tregs), PD-L1, FasL, cytokines such as IL-10 and TFG-β, tumor associated macrophages, tumor associated fibroblasts, soluble factors produced by immune suppressor cells, CTLA-4, PD-1, MDSCs, MCP-1, and an immune checkpoint molecule.

[0036] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Exemplary methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting. The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[00036A] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

[0037] The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms "a," "and" and "the" include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments "comprising," "consisting of," and "consisting essentially of" the embodiments or elements presented herein, whether explicitly set forth or not.

[0038] For recitation of numeric ranges herein, each intervening number therebetween with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

[0039] Some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given is intended to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such value.

[0040] "Adjuvant" as used herein means any molecule added to the immunogenic compositions described herein to enhance the immunogenicity of the antigens encoded by the nucleic

acid molecules and the encoding nucleic acid sequences described hereinafter.

[0041] "Biosimilar" (of an approved reference product/biological drug, i.e., reference listed drug) refers to a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components with no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity and potency, based upon data derived from

(a) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (b) animal studies (including the assessment of toxicity); and/or (c) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biosimilar. The biosimilar may be an interchangeable product that may be substituted for the reference product at the pharmacy without the intervention of the prescribing healthcare professional. To meet the additional standard of "interchangeability," the biosimilar is to be expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar and the reference product is not greater than the risk of using the reference product without such alternation or switch. The biosimilar utilizes the same mechanisms of action for the proposed conditions of use to the extent the mechanisms are known for the reference product. The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biosimilar have been previously approved for the reference product. The route of administration, the dosage form, and/or the strength of the biosimilar are the same as those of the reference product and the biosimilar is manufactured, processed, packed or held in a facility that meets standards designed to assure that the biosimilar continues to be safe, pure and potent. The biosimilar may include minor modifications in the amino acid sequence when compared to the reference product, such as N- or C-terminal truncations that are not expected to change the biosimilar performance.

[0042] The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). In a typical antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0043] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0044] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab′)2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3- CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0045] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a VH domain associated with a VL domain, the VH and VL domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain VH-VH, VH-VL or VL-VL dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric VH or VL domain.

[0046] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) VH-CH1; (ii) VH-CH2; (iii) VH-CH3; (iv) VH-CH1-CH2; (V) VH-CH1-CH2-CH3; VH-CH2-CH3; (vii) VH-CL; (Viii) VL-CH1; (ix) VL-CH2;

(x) VL-CH3; (xi) VL-CH1-CH2; (xii) VL-CH2-CH2-CH3; (xiii) VL-CH2-CH3; and (xiv) VL-CL. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen- binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric VH or VL domain (e.g., by disulfide bond(s)).

[0047] "Coding sequence" or "encoding nucleic acid" as used herein means the nucleic acids (RNA or DNA molecule) that comprise a nucleotide sequence which encodes a protein. The coding sequence can further include initiation and termination signals operably linked to regulatory elements including a promoter and polyadenylation signal capable of directing expression in the cells of an individual or mammal to which the nucleic acid is administered.

[0048] "Complement" or "complementary" as used herein means a nucleic acid can mean Watson-Crick (e.g., A-T/U and C-G) or Hoogsteen base pairing between nucleotides or nucleotide analogs of nucleic acid molecules.

[0049] "Consensus" or "consensus sequence" as used herein means a polypeptide sequence based on analysis of an alignment of multiple sequences for the same gene from different organisms. Nucleic acid sequences that encode a consensus polypeptide sequence can be prepared. Immunogenic compositions comprising proteins that comprise consensus sequences and/or nucleic acid molecules that encode such proteins can be used to induce broad immunity against an antigen.

[0050] "Electroporation," "electro-permeabilization," or "electro-kinetic enhancement" ("EP") as used interchangeably herein means the use of a transmembrane electric field pulse to induce microscopic pathways (pores) in a bio-membrane; their presence allows biomolecules such as plasmids, oligonucleotides, siRNA, drugs, ions, and water to pass from one side of the cellular membrane to the other.

[0051] "Fragment" as used herein with respect to nucleic acid sequences means a nucleic acid sequence or a portion thereof, that encodes a polypeptide capable of eliciting an immune response in a mammal that cross reacts with an antigen disclosed herein. The fragments can be DNA fragments selected from at least one of the various nucleotide sequences that encode protein fragments set forth below. Fragments can comprise at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of one or more of the nucleic acid sequences set forth below. In some embodiments, fragments can comprise at least 20 nucleotides or

more, at least 30 nucleotides or more, at least 40 nucleotides or more, at least 50 nucleotides or more, at least 60 nucleotides or more, at least 70 nucleotides or more, at least 80 nucleotides or more, at least 90 nucleotides or more, at least 100 nucleotides or more, at least 150 nucleotides or more, at least 200 nucleotides or more, at least 250 nucleotides or more, at least 300 nucleotides or more, at least 350 nucleotides or more, at least 400 nucleotides or more, at least 450 nucleotides or more, at least 500 nucleotides or more, at least 550 nucleotides or more, at least 600 nucleotides or more, at least 650 nucleotides or more, at least 700 nucleotides or more, at least 750 nucleotides or more, at least 800 nucleotides or more, at least 850 nucleotides or more, at least 900 nucleotides or more, at least 950 nucleotides or more, or at least 1000 nucleotides or more of at least one of the nucleic acid sequences set forth below.

[0052] "Fragment" or "immunogenic fragment" with respect to polypeptide sequences means a polypeptide capable of eliciting an immune response in a mammal that cross reacts with an antigen disclosed herein. The fragments can be polypeptide fragments selected from at least one of the various amino acid sequences below. Fragments of consensus proteins can comprise at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% of a consensus protein. In some embodiments, fragments of consensus proteins can comprise at least 20 amino acids or more, at least 30 amino acids or more, at least 40 amino acids or more, at least 50 amino acids or more, at least 60 amino acids or more, at least 70 amino acids or more, at least 80 amino acids or more, at least 90 amino acids or more, at least 100 amino acids or more, at least 110 amino acids or more, at least 120 amino acids or more, at least 130 amino acids or more, at least 140 amino acids or more, at least 150 amino acids or more, at least 160 amino acids or more, at least 170 amino acids or more, at least 180 amino acids or more of a protein sequence disclosed herein.

[0053] As used herein, the term "genetic construct" refers to the DNA or RNA molecules that comprise a nucleotide sequence which encodes a protein. The coding sequence includes initiation and termination signals operably linked to regulatory elements including a promoter and polyadenylation signal capable of directing expression in the cells of the individual to whom the nucleic acid molecule is administered. As used herein, the term "expressible form" refers to gene constructs that contain the necessary regulatory elements operably linked to a coding sequence that encodes a protein such that when present in the cell of the individual, the coding sequence will be expressed.

[0054] The term "homology," as used herein, refers to a degree of complementarity. There can be partial homology or complete homology (i.e., identity). A partially complementary sequence that at least partially inhibits a completely complementary sequence from hybridizing to a target nucleic acid is referred to using the functional term "substantially homologous." When used in

reference to a double-stranded nucleic acid sequence such as a cDNA or genomic clone, the term "substantially homologous," as used herein, refers to a probe that can hybridize to a strand of the double-stranded nucleic acid sequence under conditions of low stringency. When used in reference to a single-stranded nucleic acid sequence, the term "substantially homologous," as used herein, refers to a probe that can hybridize to (i.e., is the complement of) the single-stranded nucleic acid template sequence under conditions of low stringency.

[0055] "Identical" or "identity" as used herein in the context of two or more nucleic acids or polypeptide sequences means that the sequences have a specified percentage of residues that are the same over a specified region. The percentage can be calculated by optimally aligning the two sequences, comparing the two sequences over the specified region, determining the number of positions at which the identical residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the specified region, and multiplying the result by 100 to yield the percentage of sequence identity. In cases where the two sequences are of different lengths or the alignment produces one or more staggered ends and the specified region of comparison includes only a single sequence, the residues of single sequence are included in the denominator but not the numerator of the calculation. When comparing DNA and RNA, thymine (T) and uracil (U) can be considered equivalent. Identity can be performed manually or by using a computer sequence algorithm such as BLAST or BLAST 2.0.

[0056] "Substantially complementary" as used herein means that a first sequence is at least 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the complement of a second sequence over a region of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 180, 270, 360, 450, 540, or more nucleotides or amino acids, or that the two sequences hybridize under stringent hybridization conditions.

[0057] "Substantially identical" as used herein means that a first and second sequence are at least 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical over a region of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 180, 270, 360, 450, 540 or more nucleotides or amino acids, or with respect to nucleic acids, if the first sequence is substantially complementary to the complement of the second sequence.

[0058] The term "therapeutically effective amount" refers to a therapeutically effective amount of a biologic, compound, or composition that can produce a therapeutic effect in a human subject. A therapeutically effective amount is an amount that can treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic effect. A therapeutically effective amount is an amount that results in one or more of: (a) a reduction in the severity or duration of a symptom or an indication of

a cancer, e.g., glioblastoma; (b) inhibition of tumor growth, or an increase in tumor necrosis, tumor shrinkage and/or tumor disappearance; (c) delay in tumor growth and development; (d) inhibition of tumor metastasis; (e) prevention of recurrence of tumor growth; (f) increase in survival of a subject with a cancer; and/or (g) a reduction in the use or need for conventional anti-cancer therapy (e.g., reduced or eliminated use of chemotherapeutic or cytotoxic agents) as compared to an untreated subject or a subject administered the anti-cancer therapy as monotherapy.The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0059] As used herein, "therapeutic effect" is a consequence of a medical treatment of any kind, the results of which are judged to be desirable and beneficial. This is true whether the result was expected, unexpected, or even an unintended consequence of the treatment. A therapeutic effect may also be an objectively identifiable improvement as noted by the clinician or other qualified observer.

[0060] "Variant" used herein with respect to a nucleic acid means (i) a portion or fragment of a referenced nucleotide sequence; (ii) the complement of a referenced nucleotide sequence or portion thereof; (iii) a nucleic acid that is substantially identical to a referenced nucleic acid or the complement thereof; or (iv) a nucleic acid that hybridizes under stringent conditions to the referenced nucleic acid, complement thereof, or a sequences substantially identical thereto. A variant may be a nucleic acid sequence that is substantially identical over the full length of the full gene sequence or a fragment thereof. The nucleic acid sequence may be 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical over the full length of the gene sequence or a fragment thereof.

[0061] "Variant" with respect to a polypeptide is one that differs in amino acid sequence by the insertion, deletion, or conservative substitution of amino acids, but retains at least one biological activity of the reference polypeptide. Variant can also mean a protein with an amino acid sequence that is substantially identical to a referenced protein with an amino acid sequence that retains at least one biological activity. A variant may be an amino acid sequence that is substantially identical over the full length of the amino acid sequence or fragment thereof. The amino acid sequence may be 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical over the full length of the amino acid sequence or a fragment thereof.

[0062] "Vector" as used herein means a nucleic acid sequence containing an origin of replication. A vector can be a viral vector, bacteriophage, bacterial artificial chromosome or yeast artificial chromosome. A vector can be a DNA or RNA vector. A vector can be a self- replicating extrachromosomal vector, and in one embodiment, is an expression plasmid. The vector can contain or include one or more heterologous nucleic acid sequences.

[0063] "Immune response" as used herein means the activation of a host's immune system, e.g., that of a mammal, in response to the introduction of antigen. The immune response can be in the form of a cellular or humoral response, or both.

[0064] "Nucleic acid" or "oligonucleotide" or "polynucleotide" as used herein means at least two nucleotides covalently linked together. The depiction of a single strand also defines the sequence of the complementary strand. Thus, a nucleic acid also encompasses the complementary strand of a depicted single strand. Many variants of a nucleic acid can be used for the same purpose as a given nucleic acid. Thus, a nucleic acid also encompasses substantially identical nucleic acids and complements thereof. A single strand provides a probe that can hybridize to a target sequence under stringent hybridization conditions. Thus, a nucleic acid also encompasses a probe that hybridizes under stringent hybridization conditions.

[0065] Nucleic acids can be single stranded or double-stranded or can contain portions of both double-stranded and single-stranded sequence. The nucleic acid can be DNA, both genomic and cDNA, RNA, or a hybrid, where the nucleic acid can contain combinations of deoxyribo- and ribo-nucleotides, and combinations of bases including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine hypoxanthine, isocytosine and isoguanine. Nucleic acids can be obtained by chemical synthesis methods or by recombinant methods.

[0066] "Operably linked" as used herein means that expression of a gene is under the control of a promoter with which it is spatially connected. A promoter can be positioned 5' (upstream) or 3' (downstream) of a gene under its control. The distance between the promoter and a gene can be approximately the same as the distance between that promoter and the gene it controls in the gene from which the promoter is derived. As is known in the art, variation in this distance can be accommodated without loss of promoter function.

[0067] A "peptide," "protein," or "polypeptide" as used herein can mean a linked sequence of amino acids and can be natural, synthetic, or a modification or combination of natural and synthetic.

[0068] "Promoter" as used herein means a synthetic or naturally-derived molecule which is capable of conferring, activating or enhancing expression of a nucleic acid in a cell. A promoter can comprise one or more specific transcriptional regulatory sequences to further enhance expression and/or to alter the spatial expression and/or temporal expression of same. A promoter can also comprise distal enhancer or repressor elements, which can be located as much as several thousand base pairs from the start site of transcription. A promoter can be derived from sources including viral, bacterial, fungal, plants, insects, and animals. A promoter can regulate the expression of a gene component constitutively, or differentially with respect to cell, the tissue or organ in which expression occurs or, with respect to the developmental stage at which expression occurs, or in response to external stimuli such as physiological stresses, pathogens, metal ions, or inducing agents.

Representative examples of promoters include the bacteriophage T7 promoter, bacteriophage T3 promoter, SP6 promoter, lac operator-promoter, tac promoter, SV40 late promoter, SV40 early promoter, RSV-LTR promoter, CMV IE promoter, SV40 early promoter or SV40 late promoter and the CMV IE promoter.

[0069] "Signal peptide" and "leader sequence" are used interchangeably herein and refer to an amino acid sequence that can be linked at the amino terminus of a protein set forth herein. Signal peptides/leader sequences typically direct localization of a protein. Signal peptides/leader sequences used herein can facilitate secretion of the protein from the cell in which it is produced. Signal peptides/leader sequences are often cleaved from the remainder of the protein, often referred to as the mature protein, upon secretion from the cell. Signal peptides/leader sequences are linked at the amino terminus (i.e., N terminus) of the protein.

[0070] As used herein, the expression "a subject in need thereof" means a human or non-human mammal that exhibits one or more symptoms or indications of brain cancer, and/or who has been diagnosed with brain cancer, including for example glioblastoma, and who needs treatment for the same. In many embodiments, the term "subject" may be interchangeably used with the term "patient". For example, a human subject may be diagnosed with a primary or a metastatic tumor and/or with one or more symptoms or indications including, but not limited to, unexplained weight loss, general weakness, persistent fatigue, loss of appetite, fever, night sweats, bone pain, shortness of breath, swollen abdomen, chest pain/pressure, enlargement of spleen, and elevation in the level of a cancer- related biomarker (e.g., CA125). The expression includes subjects with primary or established tumors. The term includes subjects with primary or metastatic tumors (advanced malignancies). For example, the expression includes subjects who have been newly diagnosed. In some embodiment, the expression includes subjects for whom treatment in accordance with the disclosed methods is an initial treatment (e.g.,"first line" treatment, wherein the patient has not received prior systemic treatment for the cancer). In certain embodiments, the expression includes subjects for whom treatment in accordance with the disclosed methods is "second-line" treatment, wherein the patient has been previously treated with "standard-of-care" therapy including, but not limited to chemotherapy, surgery and radiation.

[0071] As used herein, the term "treat", "treating", or the like, means to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, to delay or inhibit tumor growth, to reduce tumor cell load or tumor burden, to promote tumor regression, to cause tumor shrinkage, necrosis and/or disappearance, to prevent tumor recurrence, to prevent or inhibit metastasis, to inhibit metastatic tumor growth, and/or to increase duration of survival of the subject.

[0072] As used herein, the phrase 'in combination with" means that the cancer antigens hTERT, PSMA, and WT-1 are administered to the subject at the same time as, just before, or just after

administration of the adjuvant, the programmed death receptor-1 (PD-1) checkpoint inhibitor, radiation therapy, and/or chemotherapeutic agent. In certain embodiments, the cancer antigens are administered as a co-formulation with the adjuvant.

[0073] As used herein, unless otherwise noted, the term "clinically proven" (used independently or to modify the terms "safe" and/or "effective") shall mean that it has been proven by a clinical trial wherein the clinical trial has met the approval standards of U.S. Food and Drug Administration, EMA or a corresponding national regulatory agency. For example, proof may be provided by the clinical trial described in the example provided herein.

[0074] The term "clinically proven safe", as it relates to a dose, dosage regimen, treatment or method with cancer antigens hTERT, PSMA, WT1 (for example, administered as INO-5401 or a biosimilar or bioequivalent thereof) in combination with the adjuvant, such as IL-12 (for example, administered as INO-9012 or a biosimilar or bioequivalent thereof) and a programmed death receptor-1 (PD-1) checkpoint inhibitor, such as an anti-PD-1 antibody (e.g., the anti-PD-1 antibody REGN2810 or a biosimilar or bioequivalent thereof), refers to a favorable risk:benefit ratio with an acceptable frequency and/or acceptable severity of treatment-emergent adverse events (referred to as AEs or TEAEs) compared to the standard of care or to another comparator. An adverse event is an untoward medical occurrence in a patient administered a medicinal product. One index of safety is the National Cancer Institute (NCI) incidence of adverse events (AE) graded per Common Toxicity Criteria for Adverse Events CTCAE v4.03.

[0075] The terms "clinically proven efficacy" and "clinically proven effective" as used herein in the context of a dose, dosage regimen, treatment or method refer to the effectiveness of a particular dose, dosage or treatment regimen. Efficacy can be measured based on change in the course of the disease in response to an agent of the present invention. For example, a combination of cancer antigens hTERT, PSMA, WT1, and adjuvant, (for example, INO-5401 or a biosimilar or bioequivalent thereof in combination with INO-9012 or a biosimilar or bioequivalent thereof) with a PD-1 checkpoint inhibitor, such as an anti-PD-1 antibody (e.g., the anti-PD-1 antibody cemiplimab or a biosimilar or bioequivalent thereof), is administered to a patient in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease. For

example, the combination of cancer antigens hTERT, PSMA, WT1, and adjuvant, (for example, INO-5401 or a biosimilar or bioequivalent thereof in combination with INO-9012 or a biosimilar or bioequivalent thereof) with an anti-PD-1 antibody (e.g., the anti-PD-1 antibody cemiplimab or a biosimilar or bioequivalent thereof), may be administered to achieve an improvement in a patient's condition related to brain cancer, such as glioblastoma (GBM). Improvement may be indicated by an improvement in an index of disease activity, by amelioration of clinical symptoms or by any other measure of disease activity.

[0076] As used herein, "INO-5401" refers to an immunologic composition of three DNA plasmids: a DNA plasmid comprising an insert encoding hTERT operably controlled by a promoter, a DNA plasmid comprising an insert encoding WT1 operably controlled by a promoter, and a DNA plasmid comprising an insert encoding PSMA operably controlled by a promoter.

[0077] As used herein, the term "radiation therapy", also referred to as "XRT," means using ionizing radiation to kill cancer cells, generally as part of anti-cancer therapy. X-rays, gamma rays or charged particles (e.g., protons or electrons) are used to generate ionizing radiation.

[0078] Radiation therapy may be delivered by a machine placed outside the patient's body (external- beam radiation therapy), or by a source placed inside a patient's body (internal radiation therapy or brachytherapy), or through systemic radioisotopes delivered intravenously or orally (systemic radioisotope therapy). Radiation therapy may be planned and administered in conjunction with imaging-based techniques such a computed tomography (CT), magnetic resonance imaging (MRI) to accurately determine the dose and location of radiation to be administered. In various embodiments, radiation therapy is selected from the group consisting of total all-body radiation therapy, conventional external beam radiation therapy, stereotactic radiosurgery, stereotactic body radiation therapy, 3-D conformal radiation therapy, intensity- modulated radiation therapy, image-guided radiation therapy, tomotherapy, brachytherapy, and systemic radiation therapy. Depending upon the intent, in certain embodiments, radiation therapy is curative, adjuvanating or palliative. In specific embodiments, the term "radiation therapy" refers to hypofractionated radiation therapy. Hypofractionated radiation therapy refers to a radiation treatment schedule in which the total dose of radiation is divided into large doses and treatments are given once a day or less often. Hypofractionated radiotherapy may provide more radiation per dose in fewer doses than standard radiotherapy. In various embodiments, each fraction comprises 2-20 Gy. For example, a radiation dose of 50 Gy may be split up into 10 fractions, each comprising 5 Gy. In certain embodiments, the 2 or more fractions are administered on consecutive or sequential days. In certain other embodiments, the 2 or more fractions are administered once in 2 days, once in 3 days, once in 4 days, once in 5 days, once in 6 days, once in 7 days, or in a combination thereof.

[0079] According to certain embodiments, provided herein are methods for treating cancer, such as brain cancer (for example, glioblastoma) in a subject. The disclosed methods comprise administering to the subject an immunogenic composition of cancer antigens human telomerase reverse transcriptase (hTERT), Wilms Tumor-1 (WT-1), and prostate specific membrane antigen (PSMA); an adjuvant; and an anti-programmed cell death receptor 1 (PD-1) antibody or antibody-binding fragment thereof.

[0080] Disclosed herein are optimized consensus sequences of cancer antigens hTERT, WT-1, and PSMA. In one embodiment, the antigen encoded by the optimized consensus sequence is capable of eliciting an immune response in a mammal. In one embodiment, the antigen encoded by the optimized consensus sequence can comprise an epitope(s) that makes it particularly effective as an immunogen against which an immune response can be induced.

[0081] In one embodiment is provided an optimized consensus PSMA designed to break tolerance to native human PSMA. In one embodiment, a human optimized consensus PSMA encoding sequence is as set forth in SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO: 21, or SEQ ID NO: 29. In one embodiment, a human optimized consensus PSMA encoded antigen has an amino acid sequence as set forth in SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO: 28.

[0082] In one embodiment, an optimized consensus WT-1 is designed to break tolerance to native human WT-1. In one embodiment, a human optimized consensus WT-1 encoding sequence is as set forth in SEQ ID NO:15 or SEQ ID NO: 27. In one embodiment, a human optimized consensus WT-1 encoded antigen has an amino acid sequence as set forth in SEQ ID NO:16 or SEQ ID NO: 26.

[0083] In one embodiment, an optimized consensus TERT is designed to break tolerance to native human TERT. In one embodiment, a human optimized consensus TERT encoding sequence is as set forth in SEQ ID NO:17 or SEQ ID NO:19. In one embodiment, a human optimized consensus TERT encoded antigen has an amino acid sequence as set forth in SEQ ID NO:18 and SEQ ID NO:20.

[0084] The disclosed vaccines may further comprise an adjuvant. In certain embodiments, the disclosed methods of treatment further comprise administering to the subject an adjuvant. In certain embodiments, the adjuvant is IL12. IL12 may be included in a vaccine in the form of its p35 and p40 subunits. The adjuvant IL 12 may be administered to the subject as its p35 and p40 subunits. The IL12 p35 and p40 subunits may be encoded by the same expression vector or by separate expression vectors. In one embodiment, the IL12 p35 encoding sequence is as set forth in SEQ ID NO:22. In one embodiment, the IL12 p35 subunit has an amino acid sequence as set forth in SEQ ID NO:23. In one embodiment, the IL12 p40 encoding sequence is as set forth in SEQ ID NO:24. In one embodiment, the IL12 p40 subunit has an amino acid sequence as set forth in SEQ ID NO:25.

[0085] The cancer antigens TERT, WT-1, PSMA, and/or adjuvant can be present in the vaccine or administered to the subject as the polypeptide, fragment thereof, variant thereof, nucleic

acid sequence encoding the polypeptide, fragment or variant thereof, or any combination thereof. The cancer antigen can be any form that induces an immune response in a subject. The nucleic acid sequence can be DNA, RNA, cDNA, a variant thereof, a fragment thereof, or a combination thereof. The nucleic acid sequence can also include additional sequences that encode linker or tag sequences that are linked to the antigen by a peptide bond. The amino acid sequence can be a protein, a peptide, a variant thereof, a fragment thereof, or a combination thereof.

[0086] The cancer antigens TERT, WT-1, PSMA, and/or adjuvant can be included in a vaccine or administered to the subject as the polypeptide, fragment thereof, variant thereof, nucleic acid sequence encoding the polypeptide, fragment or variant thereof, or any combination thereof. The cancer antigen can be any form that induces an immune response in a subject. The nucleic acid sequence can be DNA, RNA, cDNA, a variant thereof, a fragment thereof, or a combination thereof. The nucleic acid sequence can also include additional sequences that encode linker or tag sequences that are linked to the antigen by a peptide bond. The amino acid sequence can be a protein, a peptide, a variant thereof, a fragment thereof, or a combination thereof.

[0087] The cancer antigens TERT, WT-1, PSMA and/or IL-12 can be included in a vaccine or administered as one or more nucleic acid molecules, for example but not limited to, an expression vector(s). An expression vector can be a circular plasmid or a linear nucleic acid. An expression vector is capable of directing expression of a particular nucleotide sequence in an appropriate subject cell. An expression vector can have a promoter operably linked to the antigen-encoding nucleotide sequence, which may be operably linked to termination signals. An expression vector can also contain sequences required for proper translation of the nucleotide sequence. The expression vector comprising the nucleotide sequence of interest may be chimeric, meaning that at least one of its components is heterologous with respect to at least one of its other components. The expression of the nucleotide sequence in the expression cassette may be under the control of a constitutive promoter or of an inducible promoter, which initiates transcription only when the host cell is exposed to some particular external stimulus. In the case of a multicellular organism, the promoter can also be specific to a particular tissue or organ or stage of development.

[0088] In one embodiment, the nucleic acid is an RNA molecule. Accordingly, in one embodiment, the invention provides an RNA molecule encoding one or more polypeptides of interest. The RNA may be plus-stranded. Accordingly, in some embodiments, the RNA molecule can be translated by cells without needing any intervening replication steps such as reverse transcription. A RNA molecule useful with the invention may have a 5′ cap (e.g. a 7- methylguanosine). This cap can enhance in vivo translation of the RNA. The 5′ nucleotide of a RNA molecule useful with the invention may have a 5′ triphosphate group. In a capped RNA this may be linked to a 7-methylguanosine via a 5′-to-5′ bridge. A RNA molecule may have a 3′ poly-A tail. It may also include

a poly-A polymerase recognition sequence (e.g., AAUAAA) near its 3′ end. A RNA molecule useful with the invention may be single- stranded. In some embodiments, the RNA molecule is a naked RNA molecule. In one embodiment, the RNA molecule is comprised within a vector.

[0089] In one embodiment, the RNA has 5' and 3' UTRs. In one embodiment, the 5' UTR is between zero and 3000 nucleotides in length. The length of 5' and 3' UTR sequences to be added to the coding region can be altered by different methods, including, but not limited to, designing primers for PCR that anneal to different regions of the UTRs. Using this approach, one of ordinary skill in the art can modify the 5' and 3' UTR lengths required to achieve optimal translation efficiency following transfection of the transcribed RNA.

[0090] The 5' and 3' UTRs can be the naturally occurring, endogenous 5' and 3' UTRs for the gene of interest. Alternatively, UTR sequences that are not endogenous to the gene of interest can be added by incorporating the UTR sequences into the forward and reverse primers or by any other modifications of the template. The use of UTR sequences that are not endogenous to the gene of interest can be useful for modifying the stability and/or translation efficiency of the RNA. For example, it is known that AU-rich elements in 3' UTR sequences can decrease the stability of RNA. Therefore, 3' UTRs can be selected or designed to increase the stability of the transcribed RNA based on properties of UTRs that are well known in the art.

[0091] In one embodiment, the 5' UTR can contain the Kozak sequence of the endogenous gene. Alternatively, when a 5' UTR that is not endogenous to the gene of interest is being added by PCR as described above, a consensus Kozak sequence can be redesigned by adding the 5' UTR sequence. Kozak sequences can increase the efficiency of translation of some RNA transcripts, but does not appear to be required for all RNAs to enable efficient translation. The requirement for Kozak sequences for many RNAs is known in the art. In other embodiments, the 5' UTR can be derived from an RNA virus whose RNA genome is stable in cells. In other embodiments, various nucleotide analogues can be used in the 3' or 5' UTR to impede exonuclease degradation of the RNA.

[0092] In one embodiment, the RNA has both a cap on the 5' end and a 3' poly(A) tail which determine ribosome binding, initiation of translation and stability of RNA in the cell.

[0093] In one embodiment, the RNA is a nucleoside-modified RNA. Nucleoside-modified RNA have particular advantages over non-modified RNA, including for example, increased stability, low or absent innate immunogenicity, and enhanced translation.

[0094] The expression vector may be a circular plasmid, which may transform a target cell by integration into the cellular genome or exist extrachromosomally (e.g., autonomous replicating plasmid with an origin of replication). The vector can be pVAX, pcDNA3.0, or provax, or any other expression vector capable of expressing DNA encoding the antigen and enabling a cell to translate the sequence to an antigen that is recognized by the immune system.

[0095] Also provided herein is a linear nucleic acid immunogenic composition, or linear expression cassette ("LEC"), that is capable of being efficiently delivered to a subject via electroporation and expressing one or more desired antigens. The LEC may be any linear DNA devoid of any phosphate backbone. The DNA may encode one or more antigens. The LEC may contain a promoter, an intron, a stop codon, and/or a polyadenylation signal. The expression of the antigen may be controlled by the promoter. The LEC may not contain any antibiotic resistance genes and/or a phosphate backbone. The LEC may not contain other nucleotide sequences unrelated to the desired antigen gene expression. The LEC may be derived from any plasmid capable of being linearized. The plasmid may be capable of expressing the antigen. The plasmid can be pNP (Puerto Rico/34) or pM2 (New Caledonia/99). The plasmid may be WLV009, pVAX, pcDNA3.0, or provax, or any other expression vector capable of expressing DNA encoding the antigen and enabling a cell to translate the sequence to an antigen that is recognized by the immune system. The LEC can be pcrM2. The LEC can be pcrNP. pcrNP and pcrMR can be derived from pNP (Puerto Rico/34) and pM2 (New Caledonia/99), respectively.

[0096] The vector can comprise heterologous nucleic acid encoding the above described antigens and can further comprise an initiation codon, which can be upstream of the one or more cancer antigen coding sequence(s), and a stop codon, which can be downstream of the coding sequence(s) of the above described antigens.

[0097] The vector may have a promoter. A promoter may be any promoter that is capable of driving gene expression and regulating expression of the isolated nucleic acid. Such a promoter is a cis-acting sequence element required for transcription via a DNA dependent RNA polymerase, which transcribes the antigen sequence described herein. Selection of the promoter used to direct expression of a heterologous nucleic acid depends on the particular application. The promoter may be positioned about the same distance from the transcription start in the vector as it is from the transcription start site in its natural setting. However, variation in this distance may be accommodated without loss of promoter function.

[0098] The initiation and termination codon can be in frame with the coding sequence(s) of the above described antigens. The vector can also comprise a promoter that is operably linked to the coding sequence(s) of the above described antigens. The promoter operably linked to the coding sequence(s) of the above described antigens can be a promoter from simian virus 40 (SV40), a mouse mammary tumor virus (MMTV) promoter, a human immunodeficiency virus (HIV) promoter such as the bovine immunodeficiency virus (BIV) long terminal repeat (LTR) promoter, a Moloney virus promoter, an avian leukosis virus (ALV) promoter, a cytomegalovirus (CMV) promoter such as the CMV immediate early promoter, Epstein Barr virus (EBV) promoter, or a Rous sarcoma virus (RSV) promoter. The promoter can also be a promoter from a human gene such as human actin, human

myosin, human hemoglobin, human muscle creatine, or human metallothionein. The promoter can also be a tissue specific promoter, such as a muscle or skin specific promoter, natural or synthetic. Examples of such promoters are described in US patent application publication no. US20040175727, the contents of which are incorporated herein in its entirety.

[0099] The vector can also comprise a polyadenylation signal, which can be downstream of the coding sequence(s) of the above described antigens and/or antibodies. The polyadenylation signal can be a SV40 polyadenylation signal, LTR polyadenylation signal, bovine growth hormone (bGH) polyadenylation signal, human growth hormone (hGH) polyadenylation signal, or human β-globin polyadenylation signal. The SV40 polyadenylation signal can be a polyadenylation signal from a pCEP4 vector (Invitrogen, San Diego, CA).

[0100] The vector can also comprise an enhancer upstream of the above described antigens.

[0101] The enhancer can be necessary for expression. The enhancer can be human actin, human myosin, human hemoglobin, human muscle creatine or a viral enhancer such as one from CMV, HA, RSV or EBV.

[0102] The vector may include an enhancer and an intron with functional splice donor and acceptor sites. The vector may contain a transcription termination region downstream of the structural gene to provide for efficient termination. The termination region may be obtained from the same gene as the promoter sequence or may be obtained from different genes.

[0103] The disclosed methods may comprise administration of a plurality of copies of a single nucleic acid molecule such as a single plasmid, or a plurality of copies of two or more different nucleic acid molecules such as two or more different plasmids. For example, the methods may comprise administration of two, three, four, five, six, seven, eight, nine or ten or more different nucleic acid molecules.

[0104] The nucleic acid molecules used in accordance with the disclosed methods, such as plasmids, may collectively contain coding sequence for a single antigen or for multiple antigens. As an example, in one embodiment, the antigens are multiple antigens selected from TERT and one or more additional cancer antigens. In one exemplary embodiment, the antigens are TERT and WT-1. In one exemplary embodiment, the antigens are TERT and PSMA. In one exemplary embodiment, the antigens are PSMA and one or more additional cancer antigens. In one exemplary embodiment, the antigens are PSMA and WT-1. In another exemplary embodiment, the antigens are TERT, WT-1 and PSMA.

[0105] The vector can further comprise elements or reagents that inhibit it from integrating into the chromosome. The vector can comprise a mammalian origin of replication in order to maintain the vector extrachromosomally and produce multiple copies of the vector in a cell. The vector can be pVAX1, pCEP4 or pREP4 from Invitrogen (San Diego, CA), which can comprise the Epstein Barr

virus origin of replication and nuclear antigen EBNA-1 coding region, which can produce high copy episomal replication without integration. The vector can be pVAX1 or a pVax1 variant with changes such as the variant plasmid described herein. The variant pVax1 plasmid is a 2998 base pair variant of the backbone vector plasmid pVAX1 (Invitrogen, Carlsbad CA). The CMV promoter is located at bases 137-724. The T7 promoter/priming site is at bases 664-683. Multiple cloning sites are at bases 696-811.

[0106] Bovine GH polyadenylation signal is at bases 829-1053. The Kanamycin resistance gene is at bases 1226-2020. The pUC origin is at bases 2320-2993.

[0107] Based upon the sequence of pVAX1 available from Invitrogen, the following mutations were found in the sequence of pVAX1 that was used as the backbone for plasmids 1-6 set forth herein:

C>G241 in CMV promoter

C>T 1942 backbone, downstream of the bovine growth hormone polyadenylation signal (bGHpolyA)

A> - 2876 backbone, downstream of the Kanamycin gene

C>T 3277 in pUC origin of replication (Ori) high copy number mutation (see Nucleic Acid Research 1985)

G>C 3753 in very end of pUC Ori upstream of RNASeH site

Base pairs 2, 3 and 4 are changed from ACT to CTG in backbone, upstream of CMV promoter. The backbone of the vector can be pAV0242. The vector can be a replication defective adenovirus type 5 (Ad5) vector.

[0108] The vector can also comprise a regulatory sequence, which can be well suited for gene expression in a mammalian or human cell into which the vector is administered. The one or more cancer antigen sequences disclosed herein can comprise a codon, which can allow more efficient transcription of the coding sequence in the host cell.

[0109] The vector can be pSE420 (Invitrogen, San Diego, Calif.), which can be used for protein production in Escherichia coli (E. coli). The vector can also be pYES2 (Invitrogen, San Diego, Calif.), which can be used for protein production in Saccharomyces cerevisiae strains of yeast. The vector can also be of the MAXBAC™ complete baculovirus expression system (Invitrogen, San Diego, Calif.), which can be used for protein production in insect cells. The vector can also be pcDNA I or pcDNA3 (Invitrogen, San Diego, Calif.), which may be used for protein production in mammalian cells such as Chinese hamster ovary (CHO) cells. The vector can be expression vectors or systems to produce protein by routine techniques and readily available starting materials including Sambrook et al., Molecular Cloning and Laboratory Manual, Second Ed., Cold Spring Harbor (1989), incorporated fully herein by reference.

[0110] Exemplary DNA plasmids encoding the cancer antigens hTERT, WT-1, and/or PSMA are disclosed in U.S. Application No. 62/899,543, filed September 12, 2019, the entire contents of which are disclosed herein by reference.

[0111] In accordance with the disclosed methods, the subject may be administered about 5 nanograms to about 20 mg of a nucleic acid molecule(s) encoding an antigen or antigens. In some embodiments, the subject may be administered about 5 mg to about 15 mg of a nucleic acid molecule(s) encoding an antigen or antigens. In some embodiments, the subject may be administered about 9 mg to about 11 mg of a nucleic acid molecule(s) encoding an antigen or antigens. In some embodiments, the subject may be administered about 10 mg of a nucleic acid molecule(s) encoding an antigen or antigens.

[0112] The DNA plasmid(s) can be delivered via a variety of routes. Typical delivery routes include parenteral administration, e.g., intradermal, intramuscular or subcutaneous delivery. Other routes include oral administration, intranasal, and intravaginal routes. For the DNA of the vaccine in particular, the vaccine can be delivered to the interstitial spaces of tissues of an individual (Felgner et al., U.S. Pat. Nos. 5,580,859 and 5,703,055, the contents of all of which are incorporated herein by reference in their entirety). The DNA plasmid(s) can also be administered to muscle, or can be administered via intradermal or subcutaneous injections, or transdermally, such as by iontophoresis. Epidermal administration of the DNA plasmid(s) can also be employed. Epidermal administration can involve mechanically or chemically irritating the outermost layer of epidermis to stimulate an immune response to the irritant (Carson et al., U.S. Pat. No. 5,679,647, the contents of which are incorporated herein by reference in its entirety).

[0113] The DNA plasmid(s) can be a liquid preparation such as a suspension, syrup or elixir. The vaccine can also be a preparation for parenteral, subcutaneous, intradermal, intramuscular or intravenous administration (e.g., injectable administration), such as a sterile suspension or emulsion.

[0114] The DNA plasmid(s) can be incorporated into liposomes, microspheres or other polymer matrices (Felgner et al., U.S. Pat. No. 5,703,055; Gregoriadis, Liposome Technology, Vols. I to III (2nd ed. 1993), the contents of which are incorporated herein by reference in their entirety). Liposomes can consist of phospholipids or other lipids, and can be nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

[0115] The DNA plasmid(s) can be administered via electroporation, such as by a method described in U.S. Pat. No. 7,664,545, the contents of which are incorporated herein by reference. The electroporation can be by a method and/or apparatus described in U.S. Pat. Nos. 6,302,874; 5,676,646; 6,241,701; 6,233,482; 6,216,034; 6,208,893; 6,192,270; 6,181,964; 6,150,148;

6,120,493; 6,096,020; 6,068,650; and 5,702,359, the contents of which are incorporated herein by reference in their entirety. The electroporation may be carried out via a minimally invasive device.

[0116] The minimally invasive electroporation device ("MID") may be an apparatus for injecting the vaccine described above and associated fluid into body tissue. The device may comprise a hollow needle, DNA cassette, and fluid delivery means, wherein the device is adapted to actuate the fluid delivery means in use so as to concurrently (for example, automatically) inject DNA into body tissue during insertion of the needle into the said body tissue. This has the advantage that the ability to inject the DNA and associated fluid gradually while the needle is being inserted leads to a more even distribution of the fluid through the body tissue. The pain experienced during injection may be reduced due to the distribution of the DNA being injected over a larger area.

[0117] The MID may inject the DNA plasmid(s) into tissue without the use of a needle. The MID may inject the vaccine as a small stream or jet with such force that the vaccine pierces the surface of the tissue and enters the underlying tissue and/or muscle. The force behind the small stream or jet may be provided by expansion of a compressed gas, such as carbon dioxide through a micro-orifice within a fraction of a second. Examples of minimally invasive electroporation devices, and methods of using them, are described in published U.S. Patent Application No. 20080234655; U.S. Pat. Nos. 6,520,950; 7,171,264; 6,208,893; 6,009,347; 6,120,493; 7,245,963; 7,328,064; and 6,763,264, the contents of each of which are herein incorporated by reference.

[0118] The MID may comprise an injector that creates a high-speed jet of liquid that painlessly pierces the tissue. Such needle-free injectors are commercially available. Examples of needle-free injectors that can be utilized herein include those described in U.S. Pat. Nos. 3,805,783; 4,447,223; 5,505,697; and 4,342,310, the contents of each of which are herein incorporated by reference.

[0119] A desired vaccine in a form suitable for direct or indirect electrotransport may be introduced (e.g., injected) using a needle-free injector into the tissue to be treated, usually by contacting the tissue surface with the injector so as to actuate delivery of a jet of the agent, with sufficient force to cause penetration of the vaccine into the tissue. For example, if the tissue to be treated is mucosa, skin or muscle, the agent is projected towards the mucosal or skin surface with sufficient force to cause the agent to penetrate through the stratum corneum and into dermal layers, or into underlying tissue and muscle, respectively.

[0120] Needle-free injectors are well suited to deliver DNA plasmid(s) to all types of tissues, particularly to skin and mucosa. In some embodiments, a needle-free injector may be used to propel a liquid that contains the DNA plasmid(s) to the surface and into the subject's skin or mucosa. Representative examples of the various types of tissues that can be treated using the invention methods include pancreas, larynx, nasopharynx, hypopharynx, oropharynx, lip, throat, lung, heart,

kidney, muscle, breast, colon, prostate, thymus, testis, skin, mucosal tissue, ovary, blood vessels, or any combination thereof.

[0121] The MID may have needle electrodes that electroporate the tissue. By pulsing between multiple pairs of electrodes in a multiple electrode array, for example set up in rectangular or square patterns, provides improved results over that of pulsing between a pair of electrodes. Disclosed, for example, in U.S. Pat. No. 5,702,359 entitled "Needle Electrodes for Mediated Delivery of Drugs and Genes" is an array of needles wherein a plurality of pairs of needles may be pulsed during the therapeutic treatment. In that application, which is incorporated herein by reference as though fully set forth, needles were disposed in a circular array, but have connectors and switching apparatus enabling a pulsing between opposing pairs of needle electrodes. A pair of needle electrodes for delivering recombinant expression vectors to cells may be used. Such a device and system is described in U.S. Pat. No. 6,763,264, the contents of which are herein incorporated by reference. Alternatively, a single needle device may be used that allows injection of the DNA and electroporation with a single needle resembling a normal injection needle and applies pulses of lower voltage than those delivered by presently used devices, thus reducing the electrical sensation experienced by the patient.

[0122] The MID may comprise one or more electrode arrays. The arrays may comprise two or more needles of the same diameter or different diameters. The needles may be evenly or unevenly spaced apart. The needles may be between 0.005 inches and 0.03 inches, between 0.01 inches and 0.025 inches; or between 0.015 inches and 0.020 inches. The needle may be 0.0175 inches in diameter. The needles may be 0.5 mm, 1.0 mm, 1.5 mm, 2.0 mm, 2.5 mm, 3.0 mm, 3.5 mm, 4.0 mm, or more spaced apart.

[0123] The MID may consist of a pulse generator and a two or more-needle injectors that deliver the DNA plasmid(s) and electroporation pulses in a single step. The pulse generator may allow for flexible programming of pulse and injection parameters via a flash card operated personal computer, as well as comprehensive recording and storage of electroporation and patient data. The pulse generator may deliver a variety of volt pulses during short periods of time. For example, the pulse generator may deliver three 15-volt pulses of 100 ms in duration. An example of such a MID is the Elgen 1000 system by Inovio Biomedical Corporation, which is described in U.S. Pat. No. 7,328,064, the contents of which are herein incorporated by reference.

[0124] The MID may be a CELLECTRA® (Inovio Pharmaceuticals, Blue Bell Pa.) device and system, which is a modular electrode system, that facilitates the introduction of a macromolecule, such as a DNA, into cells of a selected tissue in a body or plant. The modular electrode system may comprise a plurality of needle electrodes; a hypodermic needle; an electrical connector that provides a conductive link from a programmable constant-current pulse controller to

the plurality of needle electrodes; and a power source. An operator can grasp the plurality of needle electrodes that are mounted on a support structure and firmly insert them into the selected tissue in a body or plant. The macromolecules are then delivered via the hypodermic needle into the selected tissue. The programmable constant-current pulse controller is activated and constant-current electrical pulse is applied to the plurality of needle electrodes. The applied constant-current electrical pulse facilitates the introduction of the macromolecule into the cell between the plurality of electrodes. Cell death due to overheating of cells is minimized by limiting the power dissipation in the tissue by virtue of constant-current pulses. The CELLECTRA® device and system is described in U.S. Pat. No. 7,245,963, the contents of which are herein incorporated by reference.

[0125] The MID may be an Elgen 1000 system (Inovio Pharmaceuticals). The Elgen 1000 system may comprise device that provides a hollow needle; and fluid delivery means, wherein the apparatus is adapted to actuate the fluid delivery means in use so as to concurrently (for example automatically) inject fluid, the described DNA plasmid(s) herein, into body tissue during insertion of the needle into the said body tissue. The advantage is the ability to inject the fluid gradually while the needle is being inserted leads to a more even distribution of the fluid through the body tissue. It is also believed that the pain experienced during injection is reduced due to the distribution of the volume of fluid being injected over a larger area.

[0126] In addition, the automatic injection of fluid facilitates automatic monitoring and registration of an actual dose of fluid injected. This data can be stored by a control unit for documentation purposes if desired.

[0127] It will be appreciated that the rate of injection could be either linear or non-linear and that the injection may be carried out after the needles have been inserted through the skin of the subject to be treated and while they are inserted further into the body tissue.

[0128] Suitable tissues into which fluid may be injected by the apparatus of the present invention include tumor tissue, skin or liver tissue but may be muscle tissue.

[0129] The apparatus further comprises needle insertion means for guiding insertion of the needle into the body tissue. The rate of fluid injection is controlled by the rate of needle insertion. This has the advantage that both the needle insertion and injection of fluid can be controlled such that the rate of insertion can be matched to the rate of injection as desired. It also makes the apparatus easier for a user to operate. If desired means for automatically inserting the needle into body tissue could be provided.

[0130] A user could choose when to commence injection of fluid. Ideally however, injection is commenced when the tip of the needle has reached muscle tissue and the apparatus may include means for sensing when the needle has been inserted to a sufficient depth for injection of the fluid to commence. This means that injection of fluid can be prompted to commence automatically

when the needle has reached a desired depth (which will normally be the depth at which muscle tissue begins). The depth at which muscle tissue begins could for example be taken to be a preset needle insertion depth such as a value of 4 mm which would be deemed sufficient for the needle to get through the skin layer.

[0131] The sensing means may comprise an ultrasound probe. The sensing means may comprise a means for sensing a change in impedance or resistance. In this case, the means may not as such record the depth of the needle in the body tissue but will rather be adapted to sense a change in impedance or resistance as the needle moves from a different type of body tissue into muscle. Either of these alternatives provides a relatively accurate and simple to operate means of sensing that injection may commence. The depth of insertion of the needle can further be recorded if desired and could be used to control injection of fluid such that the volume of fluid to be injected is determined as the depth of needle insertion is being recorded.

[0132] The apparatus may further comprise: a base for supporting the needle; and a housing for receiving the base therein, wherein the base is moveable relative to the housing such that the needle is retracted within the housing when the base is in a first rearward position relative to the housing and the needle extends out of the housing when the base is in a second forward position within the housing. This is advantageous for a user as the housing can be lined up on the skin of a patient, and the needles can then be inserted into the patient's skin by moving the housing relative to the base.

[0133] As stated above, it is desirable to achieve a controlled rate of fluid injection such that the fluid is evenly distributed over the length of the needle as it is inserted into the skin. The fluid delivery means may comprise piston driving means adapted to inject fluid at a controlled rate. The piston driving means could for example be activated by a servo motor. However, the piston driving means may be actuated by the base being moved in the axial direction relative to the housing. It will be appreciated that alternative means for fluid delivery could be provided. Thus, for example, a closed container which can be squeezed for fluid delivery at a controlled or non-controlled rate could be provided in the place of a syringe and piston system.

[0134] The apparatus described above could be used for any type of injection. It is however envisaged to be particularly useful in the field of electroporation and so it may further comprises means for applying a voltage to the needle. This allows the needle to be used not only for injection but also as an electrode during, electroporation. This is particularly advantageous as it means that the electric field is applied to the same area as the injected fluid. There has traditionally been a problem with electroporation in that it is very difficult to accurately align an electrode with previously injected fluid and so users have tended to inject a larger volume of fluid than is required over a larger area and to apply an electric field over a higher area to attempt to guarantee an overlap

between the injected substance and the electric field. Using the present invention, both the volume of fluid injected and the size of electric field applied may be reduced while achieving a good fit between the electric field and the fluid.

[0135] Upon administration of nucleic acid molecule(s) encoding cancer antigens hTERT, PSMA, and WT-1 to the subject, the transfected cells will express and secrete one or more of the cancer antigens. These secreted proteins, or synthetic antigens, will be recognized as foreign by the immune system, which will mount an immune response that can include: antibodies made against the one or more cancer antigens, and T-cell response specifically against the one or more cancer antigens. In some examples, a mammal administered the immunogenic composition discussed herein will have a primed immune system and when challenged with the one or more cancer antigens as disclosed herein, the primed immune system will allow for rapid clearing of subsequent cancer antigens as disclosed herein, whether through the humoral, cellular, or both cellular and humoral immune responses.

[0136] The recombinant cancer antigen can induce antigen-specific T cell and/or high titer antibody responses, thereby inducing or eliciting an immune response that is directed to or reactive against the cancer or tumor expressing the antigen. In some embodiments, the induced or elicited immune response can be a cellular, humoral, or both cellular and humoral immune responses. In some embodiments, the induced or elicited cellular immune response can include induction or secretion of interferon-gamma (IFN-γ) and/or tumor necrosis factor alpha (TNF-α). In other embodiments, the induced or elicited immune response can reduce or inhibit one or more immune suppression factors that promote growth of the tumor or cancer expressing the antigen, for example, but not limited to, factors that down regulate MHC presentation, factors that up regulate antigen-specific regulatory T cells (Tregs), PD-L1, FasL, cytokines such as IL-10 and TFG-β, tumor associated macrophages, tumor associated fibroblasts, soluble factors produced by immune suppressor cells, CTLA-4, PD-1, MDSCs, MCP-1, and an immune checkpoint molecule.

[0137] The disclosed vaccines may further comprise an anti-PD-1 antibody. The disclosed methods of treatment may further comprise administering to the subject an anti-PD-1 antibody. According to certain embodiments of the present invention, the anti-PD-1 antibody comprises a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising the amino acid sequences of any of the anti-PD-1 antibodies as set forth in US Patent Publication No. 20150203579, hereby incorporated in its entirety. In certain exemplary embodiments, the anti-PD-1 antibody that can be used in the context of the disclosed methods comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising

the amino acid sequence of SEQ ID NO: 2. According to certain embodiments, the anti-PD-1 antibody comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In yet other embodiments, the anti-PD-1 antibody comprises an HCVR comprising SEQ ID NO: 1 and an LCVR comprising SEQ ID NO: 2. In certain embodiments, the methods of the present invention comprise the use of an anti-PD-1 antibody, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9. In some embodiments, the anti-PD-1 antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 10. An exemplary antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and a light chain comprising the amino acid sequence of SEQ ID NO: 10 is the fully human anti-PD-1 antibody known as REGN2810 and also known as cemiplimab or cemiplimab-rwlc.

[0138] According to certain exemplary embodiments, the methods of the present invention comprise the use of REGN2810, or a biosimilar or bioequivalent thereof. The term "bioequivalent", as used herein, refers to anti-PD-1 antibodies or PD-1-binding proteins or fragments thereof that are pharmaceutical equivalents or pharmaceutical alternatives whose rate and/or extent of absorption do not show a significant difference with that of REGN2810 when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. In the context of the invention, the term refers to antigen-binding proteins that bind to PD-1 which do not have clinically meaningful differences with REGN2810 in their safety, purity and/or potency.

[0139] According to certain embodiments of the present invention, the anti-human PD-1 antibody comprises a HCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 1.

[0140] According to certain embodiments of the present invention, the anti-human PD-1 antibody comprises a LCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 2.

[0141] According to certain embodiments of the present invention, the anti-human PD-1 antibody comprises a HCVR comprising an amino acid sequence of SEQ ID NO: 1 having no more than 5 amino acid substitutions. According to certain embodiments of the present invention, the anti-human PD-1 antibody comprises a LCVR comprising an amino acid sequence of SEQ ID NO: 2 having no more than 2 amino acid substitutions.

[0142] Sequence identity may be measured by any method known in the art (e.g., GAP, BESTFIT, and BLAST).

[0143] The present invention also includes use of anti-PD-1 antibodies in methods to treat cancer, wherein the anti-PD-1 antibodies comprise variants of any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein having one or more conservative amino acid substitutions. For example, the present invention includes use of anti-PD-1 antibodies having HCVR, LCVR and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein.

[0144] The amount of anti-PD-1 antibody administered to a subject according to the disclosed methods can be a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" of anti-PD-1 antibody is an amount that results in one or more of: (a) a reduction in the severity or duration of a symptom or an indication of a cancer, e.g., glioblastoma; (b) inhibition of tumor growth, or an increase in tumor necrosis, tumor shrinkage and/or tumor disappearance; (c) delay in tumor growth and development; (d) inhibition of tumor metastasis; (e) prevention of recurrence of tumor growth; (f) increase in survival of a subject with a cancer; and/or (g) a reduction in the use or need for conventional anti-cancer therapy (e.g., reduced or eliminated use of chemotherapeutic or cytotoxic agents) as compared to an untreated subject or a subject administered the antibody as monotherapy.

[0145] In the case of an anti-PD-1 antibody or antigen-binding fragment thereof, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, from about 1 mg to about 500 mg, from about 10 mg to about 450 mg, from about 50 mg to about 400 mg, from about 75 mg to about 350 mg, or from about 100 mg to about 300 mg of the antibody. For example, in various embodiments, the amount of the anti-PD-1 antibody is about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-PD-1 antibody. In one embodiment, 250 mg of an anti-PD-1 antibody is administered according to the methods of the present invention. In one embodiment, 200 mg of an anti-PD-1 antibody is administered according to the methods of the present invention. In one

embodiment, 350 mg of an anti-PD- 1 antibody is administered according to the methods of the present invention.

[0146] The anti-PD-1 antibody may be administered to the subject in multiple doses, e.g., as part of a specific therapeutic dosing regimen. For example, the therapeutic dosing regimen may comprise administering one or more doses of an anti-PD-1 antibody to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently.

[0147] In some embodiments, the anti-PD-1 antibody is contained within a pharmaceutical composition. The pharmaceutical compositions of the invention may be formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0148] Various delivery systems are known and can be used to administer the anti-PD-1 antibody, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262: 4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[0149] The anti-PD-1 antibody can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering the anti- PD-1 antibody. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition of the anti-PD-1 antibody. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical

composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0150] In certain situations, the anti-PD-1 antibody can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Fla. In yet another embodiment, a controlled release system can be placed in proximity of the target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0151] Injectable preparations of the anti-PD-1 antibody may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0152] In certain embodiments, the anti-PD-1 antibody is formulated in a pharmaceutical composition for use in intravenous administration.

[0153] In certain embodiments, the methods further comprise administering radiation therapy to the subject. In certain embodiments, the one or more doses of radiation therapy are administered to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently.

[0154] In certain embodiments, the radiation therapy is hypofractionated radiation therapy. In some embodiments, the subject is administered 20-60 Gy in 2-20 fractions. In certain embodiments, the hypofractionated radiation therapy comprises 15 fractions. In certain embodiments, the 15

fractions are administered on 15-25 consecutive days. In certain embodiments, the 15 fractions are administered on 21 consecutive days.

[0155] In certain embodiments, the methods further comprise administering a chemotherapeutic agent to the subject, for example, temozolomide (TMZ). The chemotherapeutic agent can be administered with the radiation therapy. For example, TMZ is administered at a daily dose of 75 mg/m^2 concomitant with hypofractionated radiation therapy. In some embodiments, subjects having a tumor with a methylated MGMT promoter will be administered maintenance therapy of the chemotherapeutic agent. For example, following radiation therapy, subjects having a tumor with a methylated MGMT promoter may receive TMZ at a starting dose of 150 mg/m^2/day for 6 cycles on the first 5 days of a 28-day cycle (5 days "on," 23 days "off") with increased each maintenance cycle by 50 mg/m^2/dose to a maximum of 200 mg/m^2/dose, in the absence of hematologic toxicity. In some embodiments, the maintenance therapy will start approximately three to five weeks, preferably about 4 weeks, after the last dose of radiation therapy.

[0156] In particular embodiments, the disclosed methods can mediate clearance or prevent growth of tumor cells by inducing (1) humoral immunity via B cell responses to generate antibodies that block monocyte chemoattractant protein-1 (MCP-1) production, thereby retarding myeloid derived suppressor cells (MDSCs) and suppressing tumor growth; (2) increase cytotoxic T lymphocyte such as CD8+ (CTL) to attack and kill tumor cells; (3) increase T helper cell responses; (4) and increase inflammatory responses via IFN-γ and TFN-α; or (5) any combination of the aforementioned. The methods can increase progression-free survival by 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, and 45%. The methods can reduce tumor mass by 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, and 60% after immunization. The methods can prevent and block increases in monocyte chemoattractant protein 1 (MCP- 1), a cytokine secreted by myeloid derived suppressor cells. The methods can increase tumor survival by 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, and 60%.

[0157] The disclosed methods can increase a cellular immune response in a subject by about 50-fold to about 6000-fold, about 50-fold to about 5500-fold, about 50-fold to about 5000- fold, about 50-fold to about 4500-fold, about 100-fold to about 6000-fold, about 150-fold to about 6000-fold, about 200-fold to about 6000-fold, about 250-fold to about 6000-fold, or about 300-fold to about 6000-fold as compared to a cellular immune response in a subject not administered the method or administered a standard-of-care treatment method. In some embodiments the methods can increase the cellular immune response in the subject by about 50-fold, 100-fold, 150-fold, 200-fold, 250-fold, 300-fold, 350-fold, 400-fold, 450-fold, 500- fold, 550-fold, 600-fold, 650-fold, 700-fold, 750-fold,

800-fold, 850-fold, 900-fold, 950-fold, 1000-fold, 1100-fold, 1200-fold, 1300-fold, 1400-fold, 1500-fold, 1600-fold, 1700-fold, 1800-fold, 1900-fold, 2000-fold, 2100-fold, 2200-fold, 2300-fold, 2400-fold, 2500-fold, 2600-fold, 2700-fold, 2800-fold, 2900-fold, 3000-fold, 3100-fold, 3200-fold, 3300-fold, 3400-fold, 3500-fold, 3600-fold, 3700-fold, 3800-fold, 3900-fold, 4000-fold, 4100-fold, 4200-fold, 4300-fold, 4400-fold, 4500-fold, 4600-fold, 4700-fold, 4800-fold, 4900-fold, 5000-fold, 5100-fold, 5200-fold, 5300-fold, 5400-fold, 5500-fold, 5600-fold, 5700-fold, 5800-fold, 5900-fold, or 6000-fold as compared to the cellular immune response in the subject not administered the method or administered a standard-of-care treatment method.

[0158] In some embodiments, the methods can increase tumor-free survival, reduce tumor mass, increase progression-free survival, increase overall survival, or a combination thereof in the subject. The methods can increase tumor-free survival by 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, and 60% in the subject. The methods can reduce tumor mass by 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, and 70% in the subject. The methods can increase progression-free survival by 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, and 60% in the subject. The methods can increase overall survival by 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, and 60% in the subject.

[0159] In certain embodiments, the methods are clinically proven safe, clinically proven effective, or both.

EXAMPLE

Objectives

[0160] **Primary Objective:** To evaluate the safety and tolerability of INO-5401 and INO-9012 delivered by intramuscular (IM) injection followed by EP with CELLECTRA® 2000 in combination with cemiplimab-rwlc in adult subjects with newly-diagnosed GBM.

[0161] Primary Endpoint(s) and Assessments:

- Incidence of adverse events (AE) graded per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03, classified by system organ class, preferred term, severity, and relationship to

trial treatment.

- Clinically significant changes in safety laboratory parameters from baseline.

[0162] Secondary Objectives:

▪To evaluate preliminary clinical efficacy and immunogenicity of INO-5401 and INO- 9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with cemiplimab-rwlc in adult subjects with newly-diagnosed GBM.

▪To evaluate preliminary immunogenicity of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly-diagnosed GBM.

[0163] Secondary Endpoint(s) and Assessments:

- Overall survival at 18 months (OS18);
- Antigen-specific cellular immune responses assessed by:
  - Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMC) by ELISpot;
  - T-cell phenotype (e.g. activation and cytolytic cell, myeloid derived suppressor cell frequency (MDSC)) in PBMC by Flow Cytometry;
  - T cell receptor (TCR) sequencing from PBMCs to assess diversity and putative antigen specificity;
- Antigen-specific humoral responses (e.g. B cell activation/antibody secretion).

[0164] Exploratory Objective(s):

▪To explore correlative association between clinical efficacy and tumor genetics and/or biomarkers.

▪To further evaluate efficacy of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 and hypofractionated radiation therapy in adult subjects with newly-diagnosed GBM. Exploratory Endpoint(s):

▪Tumor infiltrating lymphocytes (TILs) and immunosuppressive elements, where feasible;

▪Expression of tumor oncoproteins, including but not limited to tumor expression of hTERT, WT1, and PSMA by IHC, immunofluorescence (IF) or genome sequencing;

▪MicroRNA signatures in blood plasma and/or sera;

▪Circulating tumor cells, circulating endothelial cells, and/or circulating cancer associated macrophage-like cells from peripheral blood where feasible;

- Assessment of tumor-associated antigen (TAA)-specific peripheral T cells by RNAseq;
- Assessment of cytokine profiles from plasma and/or sera;
- Progression-Free Survival, as assessed by RANO (Response Assessment in Neurooncology) criteria and Immunotherapy Response Assessment in Neuro- oncology (iRANO) criteria;
- Overall Survival (OS).

[0165] *Study Design*

[0166] The study described in this example corresponds to ClinicalTrials_gov identifier NCT03491683. The data presented herein as associated with this study reflects the state of this study as of the time of this filing. In this study, antigen-specific T cell-generating therapy, INO-5401, combined with INO-9012, followed by electroporation with the CELLECTRA® 2000 device, together with a PD-1 checkpoint inhibitor, cemiplimab-rwlc, was given to patients with newly-diagnosed GBM, together with radiation and temozolomide, in order to evaluate tolerability, immunogenicity and anti-tumor activity of the combination. Ethics Approval by NYU Ethics Board; approval number i17-00764.

[0167] This is a Phase 1/2, open-label, multi-center trial to evaluate the safety, immunogenicity, and preliminary efficacy of INO-5401 and INO-9012 in combination with cemiplimab (also known as REGN2810) in subjects with newly-diagnosed GBM. All patients provided written informed consent.

[0168] Subjects started immunotherapy with REGN2810 upon definitive histopathological diagnosis of GBM and adequate recovery from surgical intervention. Subjects were assigned to a cohort based on the results of the MGMT gene methylation assay performed in a CLIA-certified laboratory, which was available prior to the completion of RT. The start of immunotherapy is designated as Day 0. REGN2810 was administered intravenously (IV) every three weeks until disease progression defined by iRANO (Immune Response Assessment in Neuro-Oncology), unacceptable toxicity, withdrawal of consent, or death.

[0169] On Day 0, subjects received INO-5401 and INO-9012 intramuscularly (IM) followed by electroporation (EP). INO-5401 and INO-9012 were administered, followed by EP, every three weeks for four doses, and then every 9 weeks until disease progression defined by iRANO, unacceptable toxicity, withdrawal of consent, or death.

[0170] Temozolomide was administered to all subjects both with and without MGMT promoter methylation, unless clinically contraindicated, during radiation therapy. Radiation therapy (RT) began no later than 42 days after surgical intervention. Radiation therapy started approximately

1 to 2 weeks after Day 0, and was continue(d) for approximately three weeks. Temozolomide (TMZ) was given daily during radiation therapy (TMZ/RT). Subjects with MGMT promoter methylation received maintenance (adjuvant) TMZ for 6 cycles, following recovery from TMZ/RT. Maintenance (adjuvant) TMZ was administered for the first 5 days of a 28-day cycle. This study had two cohorts: Cohort A, consisting of subjects with an unmethylated MGMT promoter, and Cohort B consisting of subjects with a methylated MGMT promoter.

[0171] *Study Population*

[0172] Each potential subject satisfied all of the following criteria to be enrolled in the study: Overview of Patient Eligibility

[0173] Adults with newly-diagnosed GBM who are post-definitive surgery, and are able to receive standard therapy. Estimated Number of Subjects: 52. Cohort A: MGMT promoter unmethylated (N=32 for 30 evaluable subjects). Cohort B: MGMT promoter methylated (N=20 for 19 evaluable subjects).

[0174] *Inclusion Criteria:*

- Subjects must provide written IRB approved informed consent in accordance with institutional guidelines;
- Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures;
- Newly-diagnosed brain cancer with histopathological diagnosis of glioblastoma (GBM);
- Karnofsky Performance Status (KPS) rating of ≥70 at baseline;
- Receipt of dexamethasone equivalent dose ≤2 mg per day, stable or decreased for ≥ three days prior to Day 0;
- Recovery from the effects of prior GBM surgery as defined by the Investigator;
- ECG with no clinically significant findings as assessed by the Investigator performed within 28 days of signing the informed consent form (ICF);
- Adequate organ function as demonstrated by hematological, renal, hepatic parameters as defined in the Table below, obtained within 28 days prior to the first trial treatment;

Absolute neutrophil count (ANC)	≥1500/mm^3
Platelets	≥100,000/mm^3
Hemoglobin	≥9 g/dL
Creatinine OR Measured or calculated creatinine clearance or GFR*	≤ 1.5 X upper limit of normal (ULN), OR ≥50 mL/min for subject with creatinine level > 1.5 X institutional ULN
Total bilirubin	≤ 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN

*Creatinine clearance should be calculated per Cockcroft-Gault equation

- Agree that, during the trial, men will not father a child, and women cannot be or become pregnant if they are of child-bearing potential. Subjects must be of non-child bearing potential (≥12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone [FSH], if not on hormone replacement); or surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females); or agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post- ovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with an expected failure rate of < 1% per year include male sterilization and hormonal implants. Alternatively, proper use of combined oral or injected hormonal contraceptives and certain intrauterine devices (IUDs) or two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year (barrier methods must always be supplemented with the use of aspermicide);
- Ability to tolerate magnetic resonance imaging (MRI).

[0175] *Exclusion Criteria*:

- Presence of greater than 1 cm x 1 cm residual tumor enhancement on post- operative MRI;
- Multifocal disease or leptomeningeal disease (LM) disease on post-operative MRI;
- Are not able to start radiation within 42 days of surgical resection of their tumor;
- Receive dexamethasone equivalent dose >2 mg per day;
- Prior treatment with an agent that blocks the PD-1/PD-L1 pathway at any point in the past;
- Receipt of previous approved or investigative immune modulatory agent (for example, anti-TNF, therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or

erythropoietin), or agents that target cytotoxic T- lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI3K-delta, or OX-40) within 28 days of receiving the first dose oftreatment;

- Have received prior treatment with idelalisib at any point in the past;
- Past, current or planned treatment with tumor treatment fields (Optune; NovoTTF); oncolytic viral treatment; or prior exposure to an investigational agent or device, including Gliadel wafer (Carmustine) implant for chemotherapy; within 28 days of receiving the first dose of treatment;
- Allergy or hypersensitivity to REGN2810 or to any of its excipients;
- History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments;
- Ongoing or recent (within 5 years) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs), with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment;
- Diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, other than dexamethasone for the underlying disease under investigation, as noted in the inclusion criteria;
- Positive serological test for human immunodeficiency virus (HIV), or a history of HIV infection; or positive tests for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating active or chronic infection, as these infections may interfere with the ability to mount an appropriate immune response to vaccination;
- Current malignancy at another site, with the exception of adequately treated basal or squamous cell skin cancers, or carcinoma of the cervix in situ, with no evidence of disease within 3 years. Cancer survivors who have undergone curative therapy for a prior malignancy, have no evidence of disease for 3 years and are deemed at low risk for recurrence are eligible for the trial;
- Receipt of any vaccine within 4 weeks prior to first dose of trial treatment with the exception of the inactivated influenza vaccine, which may be given up to 2 weeks prior;
- History of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results (e.g. chronic renal failure, angina, myocardial ischemia or infarction, New York Heart Association (NYHA) class III/ IV cardiac disease); or any cardiac pre-excitation syndromes (such as Wolff- Parkinson-White; cardiomyopathy, or clinically significant arrhythmias);
- History of pneumonitis within the last 5 years;

- Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs, excluding over-the-counter aspirin or non-steroidal anti-inflammatory drugs, such as ibuprofen) within 2 weeks of Day 0;
- Fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
  - Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
  - Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
  - Metal implants or implantable medical device within the intended treatment site (i.e. EP area);
- Active drug or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to trial requirements;
- Imprisonment, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
- Pregnant or current breastfeeding;
- As determined by the Investigator, any medical or psychological or non- medical condition that might interfere with the subject's ability to participate or affect the safety of the subject.

[0176] *Dosage and Administration*

Investigational Drug Products

Product	Formulation	Unit
INO-5401	10.0 ± 0.5 mg/mL total plasmid (pGX1108, pGX1404, pGX1434; 1:1:1 w/w) in 165 mM sodium chloride and 16.5 mM sodium citrate	1.4 mL/ 2-mL vial
INO-9012	10.0 ± 0.5 mg/mL pGX6001 in water for injection	0.2 mL/ 2-mL vial
REGN2810	REGN2810 is supplied as a sterile liquid solution of 5.5 mL in a 10 mL glass vial (50 mg/mL) for IV administration. REGN2810 may also be supplied as a sterile liquid solution of 7.44 mL in a 10 mL glass vial (50 mg/mL) for IV administration.	5.5 mL/ 10-mL vial Or 7.44 mL/ 10-mL vial

[0177] The active pharmaceutical ingredients (APIs) in INO-5401 are DNA plasmid sequences that were designed and constructed using proprietary synthetic consensus (SynCon®) technology. This process involves synthetically deriving consensus genes across multiple strains and

optimizing DNA inserts at the genetic level to allow high expression in human cells. The INO-5401 plasmids are as follows:

▪pGX1108, a plasmid for expression of prostate-specific membrane antigen (PSMA; SEQ ID NO: 28). 3 mg of pGX1108 will be present in each 10 mg dose of trial treatment (INO-5401 + INO-9012).

▪pGX1404, a plasmid for expression of Wilms' tumor gene-1 (WT1) antigen (SEQ ID NO: 26) . 3 mg of pGX1404 will be present in each 10 mg dose of trial treatment.

▪pGX1434, a plasmid for expression of human telomerase reverse transcriptase (hTERT) (SEQ ID NO: 20). 3 mg of pGX1434 will be present in each 10 mg dose of trial treatment.

[0178] The API in drug product INO-9012 is pGX6001, a DNA plasmid for expression of human IL-12 p35 and p40 subunit proteins. 1 mg of pGX6001 will be present in each 10 mg dose of trial treatment. Both DNA plasmid products INO-5401 and INO-9012, are administered using a syringe and the investigational CELLECTRA® 2000 electroporation (EP) device.

[0179] Cemiplimab-rwlc (REGN2810) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kDa based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in Fc portion of the molecule.

[0180] The REGN2810 heavy chain possesses an IgG4 isotype-constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody. Antibody generation by VelocImmune® mice is carried out using standard techniques after immunization with PD-1. The genes encoding the heavy and light chains of REGN2810 were introduced into CHO cells, and a stable expression cell line with a higher titer (Cell Line 2) was developed for this antibody. For both cell lines, the recombinant CHO cells were grown in suspension culture and chemically induced to initiate antibody expression and secretion into the cell culture medium. Antibody is harvested via filtration and purified though a series of preparative column chromatographic and filtration steps to generate drug substance. Drug substance is then formulated and sterile-filtered to produce the final drug product.

[0181] REGN2810 (50 mg/mL) is formulated in an aqueous buffered solution at pH 6.0 containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80. REGN2810 is supplied as a sterile liquid solution of 5.5 mL in a 10 or 20 mL glass vial for IV administration. A maximum volume of 5.0 mL can be withdrawn from each vial containing 250 mg of REGN2810. Seven mLs are needed to provide a 350 mg dose of REGN2810, thus 2 vials must be used when supplied with the 5 mL vials. REGN2810 (50 mg/mL) may also be supplied as a sterile

liquid solution of 7.44 mL in a 10 or 20 mL glass vial for IV administration. A maximum volume of 7.0 mL can be withdrawn from each vial containing 350 mg of REGN2810.

[0182] *Treatment*

[0183] Subjects who meet all of the inclusion criteria and none of the exclusion criteria started immunotherapy with REGN2810 and INO-5401 + INO-9012 on Day 0. REGN2810 was administered IV every three weeks at a dose of 350 mg per dose, in the absence of dose holding, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. INO-5401 and INO-9012 IM followed by EP was administered every three weeks for four doses, and then every 9 weeks, at a dose of 10 mg/DNA per dose, in the absence of dose holding, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. RT began no later than 42 days after surgical intervention and approximately 1 to 2 weeks after Day 0. RT continued for approximately three weeks. The total dose of RT was 40 Gy given over 3 weeks.

[0184] Daily TMZ with radiation therapy (TMZ/RT) began no later than 42 days after surgical intervention and approximately 2 weeks after Day 0. TMZ/RT continued for approximately three weeks. TMZ was given at a dose of 75 mg/m^2/dose, in the absence of dose reduction. Subjects should then received maintenance (adjuvant) TMZ for an additional 6 cycles. Cohort B received TMZ following radiotherapy for up to six cycles. Maintenance (adjuvant) TMZ was administered to subjects in Cohort B for the first 5 days of a 28-day cycle at 150-200 mg/m^2/dose, following peripheral blood count recovery from TMZ/RT per standard guidelines TMZ treatment.

[0185] Day 0 (first dose of INO 5401, INO 9012 and REGN2810) was at least 14 days after completion of resection of primary tumor and the subject has recovered from surgery, but no later than post-operative day 28.

[0186] For subjects who discontinued one therapy (either INO-5401 + INO-9012 or REGN2810) for reasons other than progression, the other therapy was allowed to continue after consultation with the Medical Monitor.

[0187] **Figure 1** illustrates the trial design for Cohorts A and B.

- INO-5401 (3 mg each of hTERT, WT-1 and PSMA plasmids) combined with 1 mg INO-9012 (IL-12), for a total of 10 mg of DNA, administered via intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA® 2000 device, and delivered every three weeks for four doses, then every 9 weeks.
- Chemoradiation: Radiation (RT) given in a hypofractionated schedule (40 Gy over three weeks)
- Temozolomide (TMZ) concurrent with radiation (Cohorts A and B), followed by six

maintenance (adjuvant) cycles (Cohort B only)

[0188] Cemiplimab-rwlc (REGN2810) was administered IV at a dose of 350 mg every three weeks (Q3W) over approximately 30 minutes, starting at Day 0, and continued until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death.

[0189] INO-5401 is a mixture of three separate synthetic plasmids that target WT1, PSMA and hTERT proteins. Each plasmid was dosed at 3 mg DNA, for a total of 9 mg DNA per dose of INO-5401. INO-5401 was administered IM at Day 0, Week 3, Week 6, and Week 9, and then every 9 weeks thereafter, and continued until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. INO-9012 is a synthetic plasmid that expresses human IL-12, and is dosed at 1 mg DNA, and was administered IM together with INO-5401. The total dose of DNA in each dose of INO-5401 + INO-9012 when mixed and administered together was 10 mg. INO-5401 (3 mg each of hTERT, WT-1 and PSMA plasmids) combined with 1 mg INO-9012 (IL-12), for a total of 10 mg of DNA, was administered via intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA® 2000 device, and delivered every three weeks for four doses, then every 9 weeks.

[0190] All subjects received a total of 40 Gy in 15 fractions (three weeks).

[0191] Hypofractionated radiation therapy (hfRT) began no later than 42 days after surgery. Radiotherapy was given for three weeks.

[0192] All patients received TMZ, regardless of MGMT methylation status, unless clinically contraindicated, during radiotherapy. TMZ was administered at 75 mg/m^2 daily by mouth for 21 days concomitant (7 days a week for three weeks) with hfRT therapy.

[0193] Following radiation therapy, subjects with MGMT promoter methylation (Cohort B) continued TMZ maintenance therapy at a starting dose of 150 mg/m^2/day for 6 cycles on the first 5 days of a 28-day cycle (5 days "on," 23 days "off"), and increased each maintenance cycle by 50 mg/m^2/dose to a maximum of 200 mg/m^2/dose, in the absence of hematologic toxicity. Maintenance (adjuvant) TMZ started approximately four weeks after the last dose of RT (± 3 days) and following peripheral blood count recovery, per TMZ treatment guidelines. The dose was determined using actual body surface area (BSA) as calculated in square meters at the beginning of each treatment cycle.

[0194] The daily dose was rounded to the nearest 5 mg.

[0195] *Efficacy Evaluations/Endpoints ELISpot*

[0196] ELISpot was employed to give a qualitative measure of whether antigen specific T cells are present in a peripheral blood mononuclear cell (PBMC) sample. PBMCs were collected from subjects at study weeks 0, 3, 6, 9, 12, and 24 and assayed by IFN-g ELISpot. At the 12-month

data cut-off, antigen specific IFNg spot forming units (SFU) per million PBMCs are shown from before (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc from 8 subjects with sample to week 24. Each subject is represented by an open circle, bars represent the mean. The difference from pre to peak, delta, is shown for each antigen graph as well as together for 11 subjects assayed and for the 8 with sample available to week 24. At the 18-month data cut-off, antigen specific IFNg spot forming units (SFU) per million PBMCs are shown from before (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc from 39 subjects. Each subject is represented by an open circle, bars represent the mean. The difference from pre to peak, delta, is shown for each antigen graph as well as together for the 39 subjects. INO- 5401 is the sum of WT1, PSMA and hTERT. Box plots extend from the 25th to 75th percentile, with a horizontal line at the median, and "+" at the mean.

[0197] *Lytic Granule Loading*

[0198] A lytic granule loading assay was performed to explore the activation status and lytic potential of antigen-specific T cells present in PBMC samples collected from subjects at study weeks 0, 3, 6, 9, 12, and 24. PBMCs were stimulated with overlapping peptide libraries for INO-5401 antigens (hTERT, PSMA and WT1) or relevant controls in the absence of any exogenous cytokines. After 5 days, cells were stained with antibodies and assessed by flow cytometry. Frequencies of live, antigen-specific, activated (CD38+) CD3+CD8+ T cells with lytic potential (expressing Granzyme A, Perforin) from before treatment (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc from 8 subjects were determined at the 12-month data cut-off, and from 29 subjects at the 18-month data cut-off.

[0199] *Safety Assessment*

[0200] Adverse events (AE) graded per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03, classified by system organ class, preferred term, severity, and relationship to trial treatment; and clinically significant changes in safety laboratory parameters from baseline.

[0201] A safety run-in was performed using a modified Rolling 6 design, which enrolled up to six subjects to each Cohort (A and B up to 12 subjects total). Enrollment was staggered, with a waiting period of one week between enrollment of the first and second subject and again between the second and third subject in each cohort. Each subject was assessed up to Week 9. By Week 9 a subject had received three doses of REGN2810, three doses of INO-5401 + INO-9012, and had completed RT.

[0202] Once the first three subjects of these six in each cohort completed Week 9 assessments, in the absence of dose-limiting toxicity (DLT), following a review of all available safety

data from these patients by the Medical Monitors from the Sponsor and from Regeneron Pharmaceuticals, and the coordinating Principal Investigator, enrollment to that cohort began in full. However, if prior to the first three subjects in each cohort completing Week 9, a single subject from the first six in that cohort experienced a DLT then enrollment was to be limited to six subjects in that cohort until all six subjects reached Week 9 and were assessed for DLT.

[0203] If a second subject within the first 6 experienced a DLT in the same cohort within the first 9 weeks, enrollment to that cohort would have been stopped, and the Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) would have discussed the case, and decide whether to modify trial drug or concomitant drug (RT/TMZ) dose within that cohort, or to cease further enrollment to that cohort. If a change to the protocol was required, enrollment was only to be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB.

[0204] A DLT is defined as:

Non-Hematologic Toxicity

- Grade ≥2 uveitis.
- Grade ≥3 non-hematologic toxicity; with the exception of:
  - Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
  - Grade ≥3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
  - Grade 3 infusion-related reactions that respond to medical management.
  - Grade 3 Immune-Related Adverse Events (IRAE), other than uveitis, that improve within 14 days to Grade ≤2 with medical management (including treatment with steroids).

Hematologic Toxicity

- Grade 4 neutropenia >7 days.
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding.
- Grade ≥3 febrile neutropenia (fever ≥ 38.5°C with absolute neutrophil count [ANC] < 1000/mm3), or Grade ≥ 3 neutropenia with documented infection.

[0205] Events considered by the treating Investigator to be related to underlying tumor, concurrent medication or co-morbid event, and events considered unlikely related to trial therapy (INO-5401, INO-9012 or REGN 2810), but at least probably related to either temozolomide or RT were not to be considered a DLT. Patients who experienced DLT were to be discontinued from further trial

therapy and to enter the post-trial follow-up phase of the trial. Adverse events that meet DLT criteria but occur outside the DLT window were to be classified as unacceptable AEs and trial treatment was to be discontinued.

[0206] Following the safety run-in period, if at any point during the course of this clinical study, ≥30% of subjects in either cohort experienced a dose-limiting toxicity deemed related to investigational trial drug(s), enrollment to one or both cohorts was to be stopped, and the Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) were to discuss the safety profile of the trial drug(s), and a decision was to be made whether to modify trial drug or concomitant drug (RT/TMZ) dose within one or both cohorts, or to cease further enrollment to one or both cohorts. If a change to the protocol had been required, enrollment was only to be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB.

[0207] *Medical and Clinical Assessments*

[0208] Concomitant medications were collected from the time of signing the ICF and at all subsequent trial visits through trial discharge.

[0209] Assessment of all AEs were collected from the time of signing of ICF until 30 days post last dose of INO-5401 + INO-9012 or REGN2810, whichever was later, with the exception of AESIs, and SAE's as defined in this protocol, which were to be collected until 6 months post last dose of INO-5401 + INO-9012 or REGN2810, whichever is later. AEs were assessed using the NCI CTCAE v4.03.

[0210] *Physical Assessments*

[0211] A full examination including complete neurologic exam (cranial nerve assessment, deep tendon reflexes, muscle strength and sensation), and Karnofsky Performance Scale (KPS) were conducted every 3 weeks.

[0212] *Medical Post-Treatment Reaction Assessment*

[0213] On Day 0, vital signs were collected prior to both REGN2810 and INO-5401

+ INO-9012 treatment, at the end of the REGN2810 infusion, and every 30 minutes for the first 4 hours post-REGN2810 infusion, as well as 30 minutes after the INO-5401 + INO-9012 injection with EP. At all other visits, the Investigator assessed local and systemic reactions for 30 minutes post-each treatment (REGN2810 and/or INO-5401 + INO-9012) and at specified visits as per the Schedule of Events.

[0214] *Vital Signs*

[0215] Vital signs including body temperature, respiration rate, blood pressure and heart rate were measured at all the trial treatment visits.

[0216] *Weight, Height, and Body Mass Index*

[0217] Weight (kg) and height (cm) was collected at the screening visit. Weight was collected at each additional treatment visit from Day 0 through end of treatment.

[0218] Body Mass Index was assessed at Day 0, weeks 3, 6, 9, 18, and every 9 weeks after week 18 while the subject was receiving the EP procedure, secondary to the need to assess needle gauge.

[0219] *12-Lead ECG*

[0220] An ECG was performed at screening within 28 days prior to Day 0 for all subjects to determine subject eligibility. Abnormal ECGs were to be interpreted as clinically significant or not clinically significant. Abnormal ECGs at screening were to be discussed with the trial medical monitor to determine subject eligibility.

[0221] *Pregnancy Test*

[0222] For women of reproductive potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) was obtained at the screening visit and prior to each administration of INO-5401 + INO-9012 and REGN2810. If at any point, the β- HCG (pregnancy) test was positive, indicating that the subject is pregnant, no additional trial treatment was to be administered, but the subject was to be followed for the duration of the trial and beyond to determine the outcome of the pregnancy (with the subject's consent).

[0223] *Laboratory Evaluations*

[0224] Blood samples were collected as specified in the Trial Schedule of Events.

[0225] Screening labs may be used for Visit #1 (Day 0) if they were within 7 days of Day 0. Otherwise, all labs associated with any treatment visit (CBC and chemistry) were collected no more than 72 hours prior to treatment and reviewed/evaluated by the Investigator prior to treatment.

Complete blood count (CBC) should include:

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum chemistries should include:

- Glucose
- Albumin
- Total protein
- SGPT (serum glutamic-pyruvic transaminase; ALT)
- SGOT (serum glutamic-oxaloacetic transaminase; AST)
- Alkaline phosphatase
- Bilirubin (total)
- Direct bilirubin
- BUN (blood urea nitrogen)
- Calcium
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Lipase
- Amylase
- CPK

Assessments to be performed at screening only:

- HIV screening test (antibody immunoassay test); or documentation of these results in the medical record;
- Hepatitis B Serology: HBsAg (hepatitis B surface antigen); or documentation of these results in the medical record;
- Hepatitis C antibody immunoassay; or documentation of these results in the medical record;
- Urinalysis including specific gravity, glucose, blood and ketones;
- Activated partial thromboplastin time (aPTT), INR.

[0226] Peripheral Blood Immunogenicity Assessments

[0227] Whole blood and serum samples were obtained. Immunology samples were drawn at Screening, Day 0, Weeks 3, 6, 9, 12, and then every 12 weeks (Weeks 24, 36, 48, etc.).

[0228] T cell responses were assessed using antigen-specific IFN-γ ELISpot assay using overlapping peptide libraries covering the INO-5401 antigens (hTERT, WT-1, and PSMA). Additionally, PBMC responses against a pool of known antigenic epitopes combined from Cytomegalovirus, Epstein Barr Virus and Influenza (CEF) were evaluated in order to track general cellular immune competence during the trial.

[0229] T cell responses were assessed via flow cytometry overlapping peptide libraries covering the INO-5401 antigens. Flow cytometric assays may include an examination of the influence of immunotherapy on the ability of subject T cells to exhibit phenotypic markers

associated with cytolytic potential, activation or exhaustion after stimulation by peptides corresponding to INO-5401 antigens. Markers used for this purpose include CD3, CD4, CD8, CD137, CD69, CD38, PD-1, Granulysin, Granzyme A, Granzyme B and Perforin. These markers may change relative to new data becoming available that is informative for this assessment.

[0230] Assessment of the presence of cells that are known to play a role in immune suppression may occur via the application of flow cytometry. Flow cytometric assays may include an examination of the influence of these cells on the induction or expansion of an immune response after immunotherapy. Markers used for this purpose include CD3, CD16, CD19, CD20, CD56, CD11b, CD14, CD15, CD33 and HLA-DR. These markers may change relative to new data becoming available that is informative for this assessment.

[0231] TCR sequencing from PBMCs to assess diversity and putative antigen specificity were performed on whole PBMCs with or without prior *in vitro* stimulation.

[0232] Humoral responses were assessed via application of Enzyme Linked Immunosorbent Assay (ELISA) or other methods for the detection of antigen specific antibody secretion and/or employment of flow cytometry for B cell phenotyping. Analysis of TAA-specific T cells may occur via isolation of these cells based on expression of markers such as CD137 or others. Upon isolation, RNAseq may be performed in order to understand the unique transcriptome of these cells. Analysis of cytokine profiles from peripheral blood may be undertaken using an assessment platform such as Luminex.

[0233] Tissue Immunology

[0234] Immune infiltration and the presence of immunomodulatory factors in neoplastic tissue prior to and following INO-5401 dosing was examined via a number of assessments which may include:

- Expression of PD-L1 and tumor oncoproteins in tumor and infiltrating immune cells by IHC, immunofluorescence (IF) or genome sequencing
- Characterization of TIL infiltrate (CD3, CD8, CD4) by RNAScope
- Assessment of tumor Treg, myeloid immune suppressive populations and T cell immune checkpoint expression by RNAScope
- T cell receptor sequencing in resected tumor tissue to correlate any pre-existing clonal T cell populations with treatment related changes in T cell diversity in peripheral blood

[0235] Biomarkers

[0236] Biomarker assessments was performed from peripheral and tissue samples referenced above and collected per lab manual instructions. Immunohistochemical assessment of the

expression of the hTERT, WT1 and/or PSMA proteins within tissue samples from enrolled subjects occurred contingent on the presence of sufficient sample quantity and continued relevance as supported by available data. IDH-1 status was to be performed on tumor tissue if available. MicroRNA signatures in blood plasma and/or sera was to be assessed in order to determine disease and/or therapy specific signatures that predict disease course and/or response to treatment with INO-5401 as well as INO-5401 driven changes. RNAseq may be used for this method.

[0237] Assessment of circulating tumor cells, circulating endothelial cells and/or circulating cancer associated macrophage-like cells from peripheral blood may occur. Use of size exclusion based filters may be used for this purpose and markers may include GFAP, CD45, vimentin, PD-L1, CD146, TIE-2 and possibly others.

[0238] Clinical Assessments

[0239] Clinical evaluations for disease response was conducted at all of the trial visits (as assessed by clinical signs and symptoms of disease progression). MRI for disease progression was obtained for all subjects 9 weeks after Day 0 (± 3 days) and every 3 months thereafter, unless considered pseudo-progression by iRANO assessment. In that case, the repeat confirmatory MRI scan was to be performed at 3 months after the suspected pseudo-progression.

[0240] OVERALL SURVIVAL

[0241] All subjects were followed for survival. After completion of the End of Treatment visit, documentation of survival status was required every 6 months and at month 18 post day 0. The following methods were acceptable to document survival: phone call; personal contact; certified letter; or documentation of a visit confirmed in the medical record.

[0242] PROGRESSION

[0243] Progression was assessed by both RANO and iRANO. Patients that withdrew prior to progression were followed for progression and survival.

[0244] RANO AND IRANO: (IMMUNOTHERAPY) RESPONSE ASSESSMENT IN NEURO-ONCOLOGY

[0245] Both RANO and iRANO criteria were utilized in this trial. The Radiologic Assessment for Neuro-Oncology (RANO) criteria were proposed in 2010 to improve assessment of the evolving complexities of imaging for subjects with malignant glioma [Wen, et al., J Clin Oncol 2010,28:1963-1972.]. The RANO criteria provides guidance for the occurrence of pseudo-progression, which occurs in about 10-20 % of newly diagnosed subjects with GBM after radiotherapy and TMZ therapy. Clinical benefit, including long- term survival and tumor regression,

can still occur after initial disease progression or after the appearance of a new lesion. The iRANO criteria were developed by a multinational and multidisciplinary panel of neurooncology immunotherapy experts (RANO Working Group) who established a guidance for the determination of tumor progression in immunotherapy trials in neuro-oncology [Okada, et al. Lancet Oncol 2015,16:e534-542; Reardon, et al. Neuro Oncology 2014, 16 (Suppl 2)]. The iRANO working committee recommends that for subjects with early progressive findings (treatment with immunotherapy less than 6 months), including subjects who develop new lesions but who do not have substantial neurologic decline, confirmation of radiographic progression by follow-up imaging should be sought 3 months after initial radiographic evidence of progressive disease to decrease the likelihood of prematurely declaring progressive disease in subjects with pseudo-progression or delayed response. In such subjects, those with confirmation of further radiographic progression based comparison with the scan that first showed evidence of disease progression, or who develop substantial clinical decline at any time, were to be classified as having progressive disease with the date of disease progression back dated to the first date that the subjects met criteria for radiographic progression.

[0246] In this study, Investigators utilized iRANO criteria when making a decision as to whether to stop study drug in the face of suspected progression, however all subjects were to be assessed for progression by both RANO and iRANO criteria for progression.

[0247] NANO SCALE: NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY

[0248] The NANO scale is used only in conjunction with the iRANO and RANO criteria.

[0249] Although both the RANO and the iRANO scales specify that clinical status must be incorporated for overall assessment, neither scale provides specific parameters to do so. An international group of neuro-oncologists convened to draft the NANO criteria as an objective and quantifiable metric of neurologic function evaluable during a routine examination. The NANO scale involves evaluation of eight relevant neurologic domains based on direct observation/testing conducted during routine office visits. The score defines criteria for domain-specific and overall scores of response, progression, stable disease and "not assessed." These criteria provide a detailed and objective measure of neurologic function that can be assessed across clinical trials and therapeutic interventions [Nayak, et al., Neuro Oncol 2017,19:625-635]. This trial included clinical assessment utilizing the NANO scale when RANO and iRANO is assessed.

[0250] An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease

temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

[0251] In this study, AEs were monitored, classified, and summarized. Medical condition/diseases present before starting the investigational products were considered AEs only if they worsened after starting study treatment. An unexpected AE is one not identified in reference safety documents of the study drugs, or corresponding sections of the IBs. Throughout the course of the study, all AEs were monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to IP(s). AEs were followed until resolution or stable and the outcome documented on the appropriate CRF. All AEs were recorded in standard medical terminology rather than the subject's own words.

[0252] AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure.
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the trial drug phase of a human clinical trial.
- Complications of pregnancy. AEs do not include the following:
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure may be considered an AE.
- Diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose of study drug without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed is not an AE, unless it worsens. It is documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason (documented on a pregnancy CRF).

[0253] All AEs that occurred from the time of signing of consent onwards and throughout the duration of the trial, and 30 days (6 months for immune-related AEs; irAEs) post-last dose were recorded.

[0254] A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol (excluding death due to disease progression);
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred);
- Requires a subject's hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions);
- Results in congenital anomaly or birth defect;
- Is otherwise an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include:
  - Allergic bronchospasm requiring intensive treatment in an emergency room or at home;
  - Blood dyscrasias or convulsions that do not result in hospitalization;
  - The development of drug dependency or drug abuse. Note the following clarifications of SAEs:
- Death is an outcome of an AE, and not an AE in itself.
- The subject may not have been on IP when the event occurred.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time.

[0255] The Investigator was to attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis was to be documented as the AE and/or SAE and not the individual signs/symptoms.

[0256] STATISTICAL AND ANALYTICAL PLAN

[0257] This is a single-arm (INO-5401 + INO 9012 in combination with REGN2810), open-label, multi-center trial in subjects with newly-diagnosed GBM with a tumor with an unmethylated MGMT promoter (Cohort A) and with a tumor with a MGMT methylated promoter (Cohort B). The trial's primary analyses regard the safety and tolerability of INO-5401 and INO-9012 in combination with REGN2810. The trial's secondary analyses assessed the efficacy of INO-5401 and INO-9012 in combination with REGN2810 using OS18 and using immunogenicity biomarkers (ELISpot/flow cytometry/TCR sequencing/antigen-specific humoral responses).

[0258] Exploratory analyses concern the correlative association between clinical response and tumor genetics and biomarkers. Progression-Free Survival as assessed by RANO (Response Assessment in Neuro-oncology) criteria and Overall Survival were also assessed as exploratory endpoints.

[0259] STATISTICAL HYPOTHESES

[0260] Each cohort for this trial had a separate independent hypothesis to evaluate the secondary endpoint overall survival at 18 months (OS18). The true treatment effect for OS18 is defined as p, where p denotes the true population probability of OS18 in each cohort. Then, for the MGMT promoter unmethylated subjects (Cohort A), the hypothesis of superiority to the historical control is: H0: $p \leq 0.45$ vs. H1: $p > 0.45$, and for the MGMT promoter methylated subjects (Cohort B), the hypothesis of superiority to the historical control is: H0: $p \leq 0.60$ vs. H1: $p > 0.60$.

[0261] ANALYSIS POPULATIONS/DATASETS

[0262] Analysis populations were:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of the trial treatment. The mITT population will be used for analysis of the secondary endpoint of OS18 as well all of the exploratory efficacy endpoints, including OS and PFS.
- The per-protocol (PP) population is comprised of subjects who receive at least three of the first four doses of the trial treatment, and who have no protocol violations. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to locking the trial database.

- The safety analysis set includes all subjects who receive at least one dose of either INO-5401 or INO-9012 or REGN2810 trial treatment. Subjects will be analyzed as to the treatment they received.

[0263] DESCRIPTION OF STATISTICAL METHODS ANALYSIS OF PRIMARY SAFETY ENDPOINT

[0264] The primary analyses for this trial are safety analyses of Treatment Emergent Adverse Events (TEAE) and clinically significant changes in safety laboratory parameters from baseline.

[0265] TEAEs are defined for this trial as any AEs that occur on or after Day 0 up to 30 days after the last dose of trial treatment, with the exception of irAEs, AESIs and SAEs, which may occur up to 6 months after the last dose of trial treatment. All TEAEs will be summarized for the subjects in the safety analysis set by frequency, percentage and 95% Clopper-Pearson confidence intervals within each cohort and across both cohorts combined.

[0266] These frequencies will be presented overall and separately by dose number, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to trial treatment. Multiple occurrences of the same AE in a single subject will be counted only once following a worst-case approach with respect to severity and relationship to trial treatment. All serious TEAEs will also be summarized as above.

[0267] Any AEs with missing or partial onset/stop dates will be included in the overall AE summaries but excluded from the calculation of AE duration. AE duration will be calculated as AE Stop date - AE start date + 1 day. AEs, irAEs, AESIs and SAEs that are not TEAEs or serious TEAEs will be presented in listings.

[0268] Laboratory response variables will be descriptively summarized per time point and as changes from baseline including 95% confidence intervals. Shifts from baseline according to the CTCAE will also be presented. Laboratory values considered clinically significant will be presented in listings.

[0269] All of the safety analyses will be conducted on the subjects in the safety analysis set.

[0270] ANALYSIS OF SECONDARY EFFICACY ENDPOINT

[0271] The secondary endpoint of OS18 is summarized using frequency, percentage, 95% Clopper-Pearson confidence interval and p-value for each cohort. A subject is considered a survivor if they are determined to be alive after 18 months (548 days).

[0272] Superiority is concluded if the one-sided p-value is < 0.025. OS18 was analyzed on subjects in both the mITT and per protocol population and all mITT/PP subjects were included in the OS18 denominator.

[0273] Cellular and humoral immune responses will be presented using descriptive statistics at each time point and for changes from baseline.

[0274] ANALYSIS OF OTHER SAFETY DATA

[0275] The percentage of subjects with abnormal medical history findings will be summarized by body system and preferred term for each cohort for subjects in the safety population.

[0276] Prior medications are those that were used before the start of the trial (within 28 days prior to Day 0). Concomitant medications are those used during the course of trial (on or after day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages for each cohort for subjects in the safety population.

[0277] Measurements for vital signs as well as changes from baseline will be descriptively summarized by time point for each cohort for subjects in the safety analysis set. The percentage of subjects with abnormal physical examination findings at each time point will be descriptively summarized overall and within each cohort by body system for subjects in the safety analysis set.

[0278] ECG and viral serology at screening, and serum pregnancy at each time point will be descriptively summarized overall and within each cohort.

[0279] DISPOSITION

[0280] Subject disposition will be summarized by cohort and overall for all enrolled subjects and will include the number and percentage enrolled, the number and percentage who received each planned dose and the number who completed the trial. The number and percentage of subjects who discontinued treatment will be summarized overall and by reason. The number in each analysis population will also be presented.

[0281] DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

[0282] Demographic and baseline characteristic data were descriptively summarized by cohort for subjects in the safety analysis set.

[0283] EXPLORATORY ANALYSES

[0284] Progression-free survival as assessed by RANO (defined as the time from Day 0 until the date of death from any cause or progression whichever occurs first) and OS (defined as the time from Day 0 until the date of death from any cause) were summarized with Kaplan-Meier statistical methods within each cohort and overall. Subjects were censored for PFS at withdrawal of consent or the last progression assessment date where the subject was considered to have not progressed. Subjects who are not recorded as having died were censored for OS at withdrawal of consent or the last date the subject was known to be alive. Progression free survival and OS were analyzed in the mITT and Per Protocol populations.

[0285] Exploratory tumor genetics and/or biomarker responses were presented using descriptive statistics at each time point and as changes from baseline for the mITT population and per protocol population.

[0286] OS18, PFS, and OS were modeled using logistic regression models and Cox PH models against the exploratory responses to examine associations. Baseline variables such as patient demographics or patient disease characteristics were included in the models as potential confounders. Separately, cellular and humoral immune responses were used as explanatory variables.

[0287] RESULTS

[0288] Demographics of enrolled patients are shown in **Figure 2** (Demographics Table). Assessment of gene transcripts from tumors at diagnosis confirmed expression of antigens encoded by INO-5401 and a diverse immune gene profile. 5 of 47 subjects (811%) with available tissue for assessment exhibited transcript expression of one or more Tumor Associated Antigens encoded by INO-5401 (WT1, PSMA and hTERT). 43 of 47 subjects (89%) with available tissue for assessment exhibited transcript expression of two (2) or more Tumor Associated Antigens encoded by INO-5401 (WT1, PSMA and hTERT). 19 of 47 subjects (40%) exhibited transcript expression of all three Tumor Associated Antigens. No subject exhibited PD-1 expression without concomitant PD-L1 expression. 27 of 47 subjects (57%) exhibited PD-L1 expression with no concomitant PD-1 expression. 20 of 47 subjects (43%) showed co-expression of PD-1 and PD-L1. Normalized transcript read counts >1 were considered "positive."

[0289] *MRI Imaging*

[0290] Several patients have experienced pseudo-progression, with radiographic evidence of progression on MRI without evidence of tumor on repeat biopsy. Images from example patients demonstrate increase in MRI signal at timepoints following first dose of INO-5401 + INO-9012 and cemiplimab-rwlc, suggestive of edema or tumor. Biopsy on several patients shows treatment-related

changes with necrosis and mixed inflammation; absence of mitotic activity; and no evidence of viable tumor. Representative images from two patients are presented in **Figure 3**.

[0291] *ELISpot*

[0292] ELISpot is/was employed to give a qualitative measure of whether antigen specific T cells are present in a peripheral blood mononuclear cell (PBMC) sample. PBMCs are collected from subjects at study weeks 0, 3, 6, 9, 12, and 24 and assayed by IFN-g ELISpot. At the 12-month data cut-off, antigen specific IFNg spot forming units (SFU) per million PBMCs are shown from before (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc from 8 subjects with sample to week 24 (**Figure 4**). Each subject is represented by an open circle, bars represent the mean. The difference from pre to peak, delta, is shown for each antigen graph as well as together for 11 subjects assayed and for the 8 with sample available to week 24. INO- 5401 is the sum of WT1, PSMA and hTERT. Box plots extend from the 25th to 75th percentile, with a horizontal line at the median, and "+" at the mean. ELISpot results support the combination of INO-5401 and cemiplimab-rwlc are immunogenic- with IFN-g magnitudes above baseline to all 3 antigens in 5/11 subjects and to at least one antigen in 9 subjects as shown in **Figure 4**.

[0293] Assessment of post-INO-5401 peripheral immune responses by Cohort at the 18-month data cut-off revealed antigen-specific T cell responses by Interferon gamma ELISpot (cytokine production in response to each component of INO-5401). Results of assessment of post-INO-5401 peripheral immune responses by ELISpot at by Cohort are provided in **Figures 16A and 16B**. Baseline values from the peak timepoint following treatment are plotted. In Cohort A, 19/22 (86%) subjects tested to date had an IFN-g magnitude above baseline to one or more of the INO-5401 antigens (Figure 16A). In Cohort B, 16/17 (94%) subjects tested to date had an IFN-g magnitude above baseline to one or more of the INO-5401 antigens (Figure 16B).

[0294] *Lytic Granule Loading*

[0295] A lytic granule loading assay was performed to explore the activation status and lytic potential of antigen specific T cells present in PBMC samples collected from subjects at study weeks 0, 3, 6, 9, 12, and 24. PBMCs were stimulated with overlapping peptide libraries for INO-5401 antigens (hTERT, PSMA and WT1) or relevant controls in the absence of any exogenous cytokines. After 5 days, cells were stained with antibodies and assessed by flow cytometry. Frequencies of live, antigen-specific, activated (CD38+) CD3+CD8+ T cells with lytic potential (expressing Granzyme A, Perforin) are shown from before treatment at baseline (pre) and the highest magnitude (peak) after treatment with INO-5401 and cemiplimab-rwlc from 8 subjects for each antigen (**Figure 5A**). Each subject is represented by an open circle, bars represent the mean. The

difference from pre to peak, delta, is shown for each antigen as well as INO-5401 at the 12-month data cut-off for 8 subjects assayed (**Figure 5B**) and for the 5/8 subjects with sample available to week 12 (**Figure 5C**). INO-5401 is the sum of WT1, PSMA and hTERT. Box plots extend from the 25th to 75th percentile, with a horizontal line at the median, and "+" at the mean. Five subjects had a frequency of activated CD8+T cells with lytic potential (CD38+Prf+GrzA+) above baseline (pre) to more than one antigen; three subjects had a frequency of activated CD8+T cells with lytic potential (CD38+Prf+GrzA+) above baseline to all three antigens. Three subjects did not have a response above baseline to any antigen at any time.

[0296] Assessment of post-INO-5401 peripheral immune responses by Cohort at the 18-month data cut-off revealed antigen-specific T cell responses by flow cytometry (the expansion of antigen specific CD8+ T cells with lytic potential). In Cohort A, 13/19 (68%) subjects tested to date had a frequency of CD38+GrzA+Prf+ CD8+T cells above baseline to one or more of the INO-5401 antigens (**Figure 17A**). In Cohort B, 8/10 (80%) subjects tested to date had a frequency of CD38+GrzA+Prf+ CD8+T cells above baseline to one or more of the INO-5401 antigens (**Figure 17B**). Samples were collected Q3 weeks x 4 and then Q12 weeks. Baseline values from the peak timepoint following treatment are plotted.

[0297] *Progression-Free Survival*

[0298] **Figure 6** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A, patients with the O6-methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0299] **Figure 7** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort B, patients with the O6-methylguanine methyltransferase gene promoter methylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0300] **Figure 8** shows the visual representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A and Cohort B, patients with the O6-methylguanine methyltransferase gene promoter unmethylated or methylated in their tumor cells. The curve shows the probability of an event at a certain time interval. The probability of the event is

represented numerically on the y-axis, and the time interval on the x-axis. The event shown is progression-free survival. Progression-free survival is the absence of progression of disease at a given time point for a given subject.

[0301] **Figure 9** shows the tabular representation of the Kaplan-Meier estimator of the progression-free survival at six months (PFS6) for Cohort A, Cohort B, and both cohorts combined. The total number of subjects per cohort, number of events, estimation of the event (PFS6), and the 95% confidence interval (CI) in which the numerical estimate of the event (PFS6) exists are all provided.

[0302] Confirmed progressive disease (PD) is determined by confirmation by consecutive PD scan ≥4 weeks from original PD event, or progressed according to biopsy surgery. Subjects who terminated for any reason prior to 6 months other than PD included as confirmed progressive events, including two (2) subjects in Cohort B who came off-study at week three (3), and declined long-term follow-up.

[0303] *Overall Survival*

[0304] All efficacy analyses (OS12, OS18, & Kaplan-Meier) were analyzed on subjects in the modified intent-to-treat (mITT) population which is defined as all subjects who received at least one dose of planned treatment. Overall Survival at twelve months (OS12) was tabulated as the proportion of subjects alive at 12 months out of all subjects at risk of death at the start of the study. Subjects who dropped out were considered failures (that is deaths). All subjects in Cohort A who dropped out prior to 12 months also died before 12 months of follow-up. The 95% confidence intervals (CIs) are calculated using the Clopper-Pearson exact method. Overall Survival at eighteen months (OS18) was tabulated as the proportion of subjects alive at 18 months out of all subjects at risk of death at the start of the study. The 95% confidence intervals (CIs) are calculated using the Clopper-Pearson exact method.

[0305] **Figure 10A** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohort A, for patients with the O6-methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. **Figure 10B** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over eighteen months for Cohort A, for patients with the O6-methylguanine methyltransferase gene promoter unmethylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. Median follow-up in Cohort A is 17.8 months. mITT includes any subject who received ≥1 dose of study therapy. Shading represents confidence band on point estimate for survival at that timepoint.

[0306] **Figure 11A** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohort B, for patients with the O6-methylguanine methyltransferase gene promoter methylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. **Figure 11B** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over eighteen months for Cohort B, for patients with the O6-methylguanine methyltransferase gene promoter methylated in their tumor cells. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis. Median follow-up in Cohort B is 15.6 months. Censored; two subjects in Cohort B withdrew consent for follow-up at Week 3. mITT includes any subject who received ≥1 dose of study therapy. Shading represents confidence bands on point estimate for survival at that timepoint.

[0307] **Figure 12** shows the visual representation of the Kaplan-Meier estimator of the overall survival probability over twelve months for Cohorts A + B combined. The stepwise curve shows the probability of surviving up to and beyond a specific time point. The survival probability is represented numerically on the y-axis, and survival time in days on the x-axis.

[0308] **Figure 13** shows the efficacy data of the overall survival at 12 months and 18 months for Cohort A, for Cohort B, and combined. The figure shows the total number of subjects who were reported alive at 12 months and at 18 months. The total number of subjects, estimation of the event (OS12 or OS18), and the 95% confidence interval (CI) in which the numerical estimate of the event (OS12 or OS18) exists are all provided. The 95% CI were calculated using the exact Clopper-Pearson method.

[0309] *Safety Data*

[0310] Safety data was tabulated from subjects who were members of the safety analysis population, defined as having at least one dose of investigational product (IP).

[0311] All Adverse Events as defined by the Clinical Study Protocol ≥ NCI CTCAE Grade 3 are shown in **Figure 14**. Immune Related Adverse Events as defined by the Clinical Study Protocol are identified in **Figure 15**.

[0312] The most common Grade ≥3 adverse events reported in subjects were: platelet count decreased (11.5%), lymphocyte count decreased (11.5%), tumour inflammation (7.7%), seizure (7.7%), ALT increased (7.7%). One Grade 5 unrelated event of urosepsis was reported. There was only one SAE related to INO-5401 + INO-9012 reported, pyrexia. 48% of subjects reported irAEs, most frequently ALT increased (9.6%), AST increased (7.7%), diarrhea (7.7%), pyrexia (7.7%) and tumor inflammation (7.7%). 71% of the reported SAEs and irAEs occurred within the first 12 weeks of treatment.

[0313] Conclusions

[0314] In patients with newly diagnosed GBM, INO-5401 + INO-9012 in combination with cemiplimab-rwlc, given with radiation and temozolomide, has an acceptable safety profile, is immunogenic and is potentially efficacious in patients with newly diagnosed GBM. Common AEs included injection site administration events; ≥Grade 3 AEs were primarily due to TMZ or radiation, and immune-related AEs were consistent with the profile of cemiplimab-rwlc. SAEs were consistent with those seen in patients with GBM (seizure).

[0315] Antigen-specific T cell responses were seen to one or more of the antigens included in INO- 5401 in almost all patients tested to date. PFS6 exceeds that of historical controls in this study, in patients with and without MGMT promoter methylation, and OS12 exceeds that of historical controls in patients without MGMT promoter methylation [Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005, 352:987-996].

[0316] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents.

[0317] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of use of the invention, may be made without departing from the spirit and scope thereof.

SEQUENCE LISTING

SEQ ID NO: 1 R2810 HCVR

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30
Gly Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser
        115
```

SEQ ID NO: 2 R2810 LCVR

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Ser Ile Thr Ile Thr Cys Arg Ala Ser Leu Ser Ile Asn Thr Phe
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu His Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Thr Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn Thr Pro Phe
                85                  90                  95
Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg
            100                 105
```

SEQ ID NO: 3 R2810 HCDR1

```
Gly Phe Thr Phe Ser Asn Phe Gly
 1      5
```

SEQ ID NO: 4 R2810 HCDR2

```
Ile Ser Gly Gly Gly Arg Asp Thr
 1               5
```

SEQ ID NO: 5 R2810 HCDR3

```
Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr
 1               5                  10
```

SEQ ID NO: 6 R2810 LCDR1

```
Leu Ser Ile Asn Thr Phe
 1               5
```

SEQ ID NO: 7 R2810 LCDR2

```
Ala Ala Ser
 1
```

SEQ ID NO: 8 R2810 LCDR3

```
Gln Gln Ser Ser Asn Thr Pro Phe Thr
 1               5
```

SEQ ID NO: 9 R2810 HC

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30
Gly Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
        195                 200                 205
Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
    210                 215                 220
Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255
Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
            260                 265                 270
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285
Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300
```

```
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320
Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
                325                 330                 335
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
            340                 345                 350
Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385                 390                 395                 400
Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
                405                 410                 415
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            420                 425                 430
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440
```

SEQ ID NO: 10 R2810 LC

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1                5                  10                  15
Asp Ser Ile Thr Ile Thr Cys Arg Ala Ser Leu Ser Ile Asn Thr Phe
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu His Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Thr Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn Thr Pro Phe
                85                  90                  95
Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg Arg Thr Val Ala Ala
            100                 105                 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
Phe Asn Arg Gly Glu Cys
    210
```

SEQ ID NO: 11 PSMA with no IgE leader sequence and with HA tag

atgtggaacg cactgcatga gactgattct gctgtcgcac tgggacggag accccggtgg 60
ctgtgcgctg gagcactggt gctggccggc gggggattcc tgctgggatt cctgtttggc 120
tggtttatca aaagctccag cgaggctacc aatattaccc ctaagcacaa taagaaagca 180
ttcctggatg aactgaaagc cgagaacatc aagaaattcc tgtacaactt cacaagaatt 240
ccacatctgg ctggcactga gcagaacttc cagctggcaa aacagatcca gagtcagtgg 300
aaggaatttg ggctggactc agtggagctg acccactacg atgtcctgct gtcctatcca 360
aataagactc atcccaacta catctctatc attaacgaag acggaaatga gattttcaac 420
acctctctgt ttgaaccccc tccacccggc tatgagaatg tcagtgacgt ggtccctcca 480
ttctcagcct tcagccccca ggggatgcct gagggagatc tggtgtacgt caattatgct 540
agaacagaag acttctttaa gctggagagg gatatgaaaa tcaactgttc cggcaagatc 600
gtgattgccc ggtacgggaa ggtgttcaga ggaaataagg tcaaaaacgc tcagctggcc 660
ggagctaccg gcgtgatcct gtacagcgac cccgctgatt attttgcacc tggcgtgaag 720
tcctatccag acggatggaa tctgcccggc gggggagtgc agaggggaaa catcctgaac 780
ctgaatggag ccggcgatcc tctgactcca ggataccccg ccaacgaata cgcttatcgc 840
cggggaattg cagaggccgt gggcctgcct agcatcccag tccatcccat tggctattac 900
gatgcccaga agctgctgga gaaaatgggc gggagcgctc cccctgactc tagttggaag 960
ggctccctga aagtgcctta caatgtcggg ccaggattca ctgggaactt ttctacccag 1020
aaggtgaaaa tgcacatcca tagtaccagc gaggtgacac gaatctacaa cgtcattggc 1080
accctgagag gcgccgtgga gcctgatcgc tatgtcattc tgggaggcca cagagactca 1140
tgggtgttcg ggggaatcga tccacagagc ggagcagctg tggtccatga aattgtgcgc 1200
agctttggga ccctgaagaa agagggatgg cgacccaggc gcacaatcct gttcgcatcc 1260
tgggacgccg aggaatttgg gctgctgggc agcacagaat gggccgagga aaattctcgc 1320
ctgctgcagg agcgaggggt ggcttacatc aatgcagact caagcattga aggaaactat 1380
accctgcggg tggattgcac acccctgatg tacagtctgg tctataacct gacaaaggag 1440
ctgaaatcac ctgacgaggg cttcgaaggg aaaagcctgt acgaatcctg gactgagaag 1500
agcccatccc ccgaattcag cggcatgcct aggatctcta agctgggcag tgggaacgat 1560
tttgaggtgt tctttcagcg cctgggaatt gcctctggcc gagctcggta cacaaaaaat 1620
tgggagacta acaagttctc ctcttaccca ctgtatcaca gcgtgtacga gacttatgaa 1680
ctggtcgaga aattctacga ccccacttt aagtatcatc tgaccgtggc acaggtcagg 1740
ggcgggatgg tgttcgaact ggccaatagc atcgtcctgc catttgactg tcgagattac 1800
gctgtggtcc tgcggaagta cgcagacaag atctataaca tctccatgaa gcacccccag 1860
gagatgaagg cctattctgt gagtttcgat tccctgtttt ctgccgtcaa aaatttcacc 1920
gaaatcgcta gtaagttttc agagcgcctg caggacctgg ataagtccaa tcccatcctg 1980
ctgcggatta tgaacgatca gctgatgttc ctggaaagag cctttatcga ccctctgggc 2040
ctgcctgata gaccattcta caggcacgtg atctacgcac ctagttcaca taacaagtac 2100
gccggcgagt ctttcccagg gatctatgac gctctgtttg atattgaatc aaaggtggac 2160
cccagcaaag catggggcga ggtcaagaga cagatcagca ttgcagcctt tacagtgcag 2220
gccgccgccg aaaccctgtc cgaagtcgct tacccatacg atgtccccga ttacgcatga 2280
taa

SEQ ID NO: 12 PSMA with IgE leader sequence (underlined) and with HA tag

atggactgga catggattct gttcctggtc gccgccgcaa ctcgcgtgca ttcctggaac 60
gcactgcatg agactgattc tgctgtcgca ctgggacgga gaccccggtg gctgtgcgct 120
ggagcactgg tgctggccgg cgggggattc ctgctgggat tcctgtttgg ctggtttatc 180
aaaagctcca gcgaggctac caatattacc cctaagcaca ataagaaagc attcctggat 240
gaactgaaag ccgagaacat caagaaattc ctgtacaact tcacaagaat tccacatctg 300
gctggcactg agcagaactt ccagctggca aaacagatcc agagtcagtg gaaggaattt 360
gggctggact cagtggagct gacccactac gatgtcctgc tgtcctatcc aaataagact 420
catcccaact acatctctat cattaacgaa gacggaaatg agattttcaa cacctctctg 480
tttgaacccc ctccacccgg ctatgagaat gtcagtgacg tggtccctcc attctcagcc 540
ttcagccccc aggggatgcc tgagggagat ctggtgtacg tcaattatgc tagaacagaa 600
gacttcttta agctggagag ggatatgaaa atcaactgtt ccggcaagat cgtgattgcc 660
cggtacggga aggtgttcag aggaaataag gtcaaaaacg ctcagctggc cggagctacc 720
ggcgtgatcc tgtacagcga ccccgctgat tattttgcac ctggcgtgaa gtcctatcca 780
gacggatgga atctgcccgg cgggggagtg cagaggggaa acatcctgaa cctgaatgga 840
gccggcgatc ctctgactcc aggatacccc gccaacgaat acgcttatcg ccggggaatt 900
gcagaggccg tgggcctgcc tagcatccca gtccatccca ttggctatta cgatgcccag 960
aagctgctgg agaaaatggg cgggagcgct ccccctgact ctagttggaa gggctccctg 1020

aaagtgcctt acaatgtcgg gccaggattc actgggaact tttctaccca gaaggtgaaa 1080
atgcacatcc atagtaccag cgaggtgaca cgaatctaca acgtcattgg caccctgaga 1140
ggcgccgtgg agcctgatcg ctatgtcatt ctgggaggcc acagagactc atgggtgttc 1200
gggggaatcg atccacagag cggagcagct gtggtccatg aaattgtgcg cagctttggg 1260
accctgaaga aagagggatg gcgacccagg cgcacaatcc tgttcgcatc ctgggacgcc 1320
gaggaatttg ggctgctggg cagcacagaa tgggccgagg aaaattctcg cctgctgcag 1380
gagcgagggg tggcttacat caatgcagac tcaagcattg aaggaaacta taccctgcgg 1440
gtggattgca caccctgat gtacagtctg gtctataacc tgacaaagga gctgaaatca 1500
cctgacgagg gcttcgaagg gaaaagcctg tacgaatcct ggactgagaa gagcccatcc 1560
cccgaattca gcggcatgcc taggatctct aagctgggca gtgggaacga ttttgaggtg 1620
ttctttcagc gcctgggaat tgcctctggc cgagctcggt acacaaaaaa ttgggagact 1680
aacaagttct cctcttaccc actgtatcac agcgtgtacg agacttatga actggtcgag 1740
aaattctacg accccacttt taagtatcat ctgaccgtgg cacaggtcag gggcgggatg 1800
gtgttcgaac tggccaatag catcgtcctg ccatttgact gtcgagatta cgctgtggtc 1860
ctgcggaagt acgcagacaa gatctataac atctccatga agcaccccca ggagatgaag 1920
gcctattctg tgagtttcga ttccctgttt tctgccgtca aaaatttcac cgaaatcgct 1980
agtaagtttt cagagcgcct gcaggacctg gataagtcca atcccatcct gctgcggatt 2040
atgaacgatc agctgatgtt cctggaaaga gcctttatcg accctctggg cctgcctgat 2100
agaccattct acaggcacgt gatctacgca cctagttcac ataacaagta cgccggcgag 2160
tctttcccag ggatctatga cgctctgttt gatattgaat caaaggtgga ccccagcaaa 2220
gcatggggcg aggtcaagag acagatcagc attgcagcct ttacagtgca ggccgccgcc 2280
gaaaccctgt ccgaagtcgc ttacccatac gatgtccccg attacgcatg ataa

SEQ ID NO: 13 PSMA with no IgE leader sequence
Met Trp Asn Ala Leu His Glu Thr Asp Ser Ala Val Ala Leu Gly Arg
Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Gly
Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser Glu
Ala Thr Asn Ile Thr Pro Lys His Asn Lys Lys Ala Phe Leu Asp Glu
Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Arg Ile
Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr His
Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Val Val Pro Pro
Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr Gly
Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Lys
Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu Val
Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr
Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys Glu
Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser
Trp Thr Glu Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu
Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr Asn

Lys Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr Glu
Leu Val Glu Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu Thr Val
Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile Val
Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala
Asp Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys Ala
Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr
Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Leu Asp Lys Ser
Asn Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Phe Leu Glu
Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Ser Ile Ala Ala
Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala

SEQ ID NO: 14 PSMA with IgE leader sequence (underlined)
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
His Ser Trp Asn Ala Leu His Glu Thr Asp Ser Ala Val Ala Leu Gly
Arg Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly
Gly Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser
Glu Ala Thr Asn Ile Thr Pro Lys His Asn Lys Lys Ala Phe Leu Asp
Glu Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Arg
Ile Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln
Ile Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr
His Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr
Ile Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu
Phe Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Val Val Pro
Pro Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val
Tyr Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp
Met Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys
Val Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr
Gly Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val
Lys Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg
Gly Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly
Tyr Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val
Gly Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln
Lys Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp
Lys Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly
Asn Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu
Val Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu
Pro Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe
Gly Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val
Arg Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr
Ile Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser
Thr Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val
Ala Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg
Val Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys
Glu Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu
Ser Trp Thr Glu Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg
Ile Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg
Leu Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr
Asn Lys Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr
Glu Leu Val Glu Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu Thr
Val Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile
Val Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr
Ala Asp Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys
Ala Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe
Thr Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Leu Asp Lys
Ser Asn Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Phe Leu
Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr

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

SEQ ID NO: 15 Consensus WT1-L with modified Zinc Fingers nucleic acid sequence plus IgE leader

ggatccgcca ccatggactg gacctggatt ctgttcctgg tcgccgccgc aacacgggtg 60
catagtggga gtgatgtgag agacctgaac gccctgctgc cagcagtgcc atccctgcct 120
ggcgggggag gctgcgctct gccagtctct ggagcagctc agtgggctcc cgtgctggac 180
tttgcacccc ctgcagcccc ttacggaagt ctgggcggcc cacactcatt catcaaacag 240
gagccaagct ggggcggggc agatcctcat gaggaacagt gcctgtcagc cttcacagtc 300
cactttagcg ggcagttcac tggaaccgca ggagcttgta gatacggacc ctttggagca 360
ccacccctt cccaggcacc ttctggacag gcacgcatgt tcccaaacgc tccctatctg 420
cctaattgtc tggaaagcca gcccgctatt aggaaccagg gctactccac agtggcattt 480
gacgggactc ctagctatgg acatacccca tcccaccatg ctgcacagtt tcctaatcac 540
tccttcaagc atgaggaccc catgggacag caggggtccc tgggagaaca gcagtactct 600
gtgccccctc ccgtgtacgg atgccacaca ccaactgaca gttgtacagg ctcacaggcc 660
ctgctgctgc gaactccata caacagtgat aatctgtatc agatgacctc acagctggag 720
tgcatgacat ggaaccagat gaatctgggc agcacactga aaggccatgc cactgggtac 780
gaatctgaca accacaccac acctatgctg tacagttgtg gagcccagta tagaatccac 840
actcatggag tcttcagagg cattcaggat gtgcggagag tcccaggagt ggcaccaact 900
atcgtgcgga gcgcctccga gaccaacgaa aagcgcccct ttatgggcgc ctaccctgga 960
ggcaataagc ggtatttcaa actgtctcac ctgcagatgg ggagtagaaa ggggaccgga 1020
gagaaacctt atcagggcga ctttaaagat ggggaaaggc gcttctctcg cagtgaccag 1080
ctgaagcgag gacagcgacg aggaaccggg gtgaagccat ttcagtgcaa aacatgtcag 1140
agaaagttct caaggagcga tcacctgaag acccatacaa gaactcacac cggcaagacc 1200
agcgagaaac cattttcctg ccgatggccc tcttgtcaga agaaattcgc ccgctccgac 1260
gaactggtcc gacaccacaa tatgcatcag agaaatatga caaaactgca gctggctctg 1320
tgataactcg ag

SEQ ID NO: 16 Con WT1-L with modified Zinc Fingers protein sequence plus IgE leader (underlined)

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
His Ser Gly Ser Asp Val Arg Asp Leu Asn Ala Leu Leu Pro Ala Val
Pro Ser Leu Pro Gly Gly Gly Gly Cys Ala Leu Pro Val Ser Gly Ala
Ala Gln Trp Ala Pro Val Leu Asp Phe Ala Pro Pro Ala Ala Pro Tyr
Gly Ser Leu Gly Gly Pro His Ser Phe Ile Lys Gln Glu Pro Ser Trp
Gly Gly Ala Asp Pro His Glu Glu Gln Cys Leu Ser Ala Phe Thr Val
His Phe Ser Gly Gln Phe Thr Gly Thr Ala Gly Ala Cys Arg Tyr Gly
Pro Phe Gly Ala Pro Pro Pro Ser Gln Ala Pro Ser Gly Gln Ala Arg
Met Phe Pro Asn Ala Pro Tyr Leu Pro Asn Cys Leu Glu Ser Gln Pro
Ala Ile Arg Asn Gln Gly Tyr Ser Thr Val Ala Phe Asp Gly Thr Pro
Ser Tyr Gly His Thr Pro Ser His His Ala Ala Gln Phe Pro Asn His
Ser Phe Lys His Glu Asp Pro Met Gly Gln Gln Gly Ser Leu Gly Glu
Gln Gln Tyr Ser Val Pro Pro Pro Val Tyr Gly Cys His Thr Pro Thr
Asp Ser Cys Thr Gly Ser Gln Ala Leu Leu Leu Arg Thr Pro Tyr Asn
Ser Asp Asn Leu Tyr Gln Met Thr Ser Gln Leu Glu Cys Met Thr Trp
Asn Gln Met Asn Leu Gly Ser Thr Leu Lys Gly His Ala Thr Gly Tyr
Glu Ser Asp Asn His Thr Thr Pro Met Leu Tyr Ser Cys Gly Ala Gln
Tyr Arg Ile His Thr His Gly Val Phe Arg Gly Ile Gln Asp Val Arg
Arg Val Pro Gly Val Ala Pro Thr Ile Val Arg Ser Ala Ser Glu Thr
Asn Glu Lys Arg Pro Phe Met Gly Ala Tyr Pro Gly Gly Asn Lys Arg
Tyr Phe Lys Leu Ser His Leu Gln Met Gly Ser Arg Lys Gly Thr Gly
Glu Lys Pro Tyr Gln Gly Asp Phe Lys Asp Gly Glu Arg Arg Phe Ser
Arg Ser Asp Gln Leu Lys Arg Gly Gln Arg Arg Gly Thr Gly Val Lys
Pro Phe Gln Cys Lys Thr Cys Gln Arg Lys Phe Ser Arg Ser Asp His
Leu Lys Thr His Thr Arg Thr His Thr Gly Lys Thr Ser Glu Lys Pro
Phe Ser Cys Arg Trp Pro Ser Cys Gln Lys Lys Phe Ala Arg Ser Asp

Glu Leu Val Arg His His Asn Met His Gln Arg Asn Met Thr Lys Leu
Gln Leu Ala Leu

SEQ ID NO: 17 Synthetic Consensus hTERT nucleic acid sequence operably linked to IgE (underlined)

atggattgga catggattct gttcctggtc gcagccgcca cacgagtgca tagccctaga 60
gccccacggt gtagagcagt ccgcagcctg ctgcgcagcc gataccggga agtgctgcct 120
ctggccacct ttgtccggag actgggacca cagggcaggc gcctggtgca gcgcggcgac 180
cccgcagctt tccgagcact ggtggcacag tgcctggtgt gcgtgccatg ggatgcacgg 240
ccccctccag cagcccctag ctttagacag gtgtcctgcc tgaaagaact ggtcgcaagg 300
gtggtccagc ggctgtgcga gagaggcgcc aggaacgtgc tggcattcgg ctttgcactg 360
ctggacggag ctaggggcgg gccccctgag gcattcacca caagcgtgcg ctcctacctg 420
ccaaatacag tcactgatac cctgcgaggc tccggagcat ggggactgct gctgcgacgg 480
gtgggggacg atgtgctggt ccacctgctg gctagatgcg cactgtatgt gctggtcgct 540
ccctcttgcg cataccaggt gtgcggacca cccctgtatg acctgggcgc tgcaacccag 600
gcaagacctc caccccacgc ctctggcact agaaggggac tgggcaccga acaggcatgg 660
aaccatagtg tcagggaggc aggagtgcca ctgggactgc cagcacctgg ggctcgccga 720
cggagaggga gtgccggacg gtcactgcca ctggctaaga gaccaaggcg cggagccgct 780
ccagaaccag agaggacacc tgtgggacag ggaagctggg cacaccctgg aagaactagg 840
gggccaagtg ataggggctt ctgcgtggtc tcaccagcac gaccagcaga ggaagctact 900
tctctggagg gagctctgag tggcacccgg cactctcatc ctagtgtggg aagacagcac 960
catgcaggcc ctccaagcac cagccggcct ccccggccat gggacactcc ttgtccaccc 1020
gtgtacgctg aaaccaaaca ctttctgtat agctccggag ataaggagca gctgcggccc 1080
tctttcctgc tgtctagtct gagacctagt ctgaccggag cacgacggct ggtggaaaca 1140
atctttctgg ggtcccgccc ttggatgcca ggaaccccca gaaggacacc tcgactgcca 1200
cagcggtact ggcagatgcg gccactgttc ctggagctgc tgggcaatca cgctcagtgc 1260
ccctatgggg cactgctgcg aacacattgt cctctgcggg cagccgtgac tccagctgca 1320
ggagtctgcg ccagggaaaa gccacagggc agcgtggcag ctcctgagga agaggacacc 1380
gatccacgcc gactggtgca gctgctgaga cagcactcaa gcccctggca ggtgtacgga 1440
tttctgaggg cctgtctgcg gagactggtg cctccaggac tgtgggggtc caggcacaac 1500
gaaaggcgct ttctgcgcaa tactaagaaa ttcatcagcc tgggcaagca tgctaaactg 1560
tccctgcagg agctgacctg gaaaatgagt gtgcgcgact gcgcatggct gcgacggtca 1620
ccaggagtcg ggtgcgtgcc tgcagccgag caccgcctgc gagaagagat tctggccaag 1680
tttctgcatt ggctgatgtc agtgtacgtg gtcgaactgc tgcggagctt cttttatgtg 1740
acagagacta ccttccagaa aaactacctg ttcttttatc gcaagtcagt gtggagcaaa 1800
ctgcagtcaa tcggcattcg gcagcacctg aagagagtgc agctgaggga actgagtgaa 1860
gccgaggtcc ggcagcatag agaggcaagg cctgccctgc tgacctcccg gctgagattc 1920
ctgcctaagc cagacgggct gagaccaatc gtgaacatgg attacgtggt cggagcacgg 1980
accttccgga gggaaaaacg cgctgagcga ctgacatccc gcgtgaagac tctgttctct 2040
gtcctgaatt atgagcgagc tcgccgaccc ggactgctgg gagcatctgt gctgggactg 2100
gacgatattc accgggcttg gagagcattt gtcctgaggg tgcgcgcaca ggaccctccc 2160
ccagaactgt acttcgtgaa agtcgccgtg accggggctt atgacacaat ccctcaggat 2220
cggctgactg aagtgatcgc ctccatcatt aagccacaga atacctactg cgtgcggaga 2280
tatgctgtgg tcaggcgcgc tgcacacggc catgtgagga agagcttcaa gcgccacgtc 2340
agcacactga ctgatctgca gccctacatg agacagttcg tggctcatct gcaggagacc 2400
agccctctga gggacgcagt ggtcatcgaa cagtcctcta gtctgaacga ggcatcaagc 2460
gggctgttcg atgtctttct gcggttcgtg tgccaccatg ccgtcagaat tggaggcaaa 2520
tcttacgtgc agtgtcaggg catcccccag ggcagcattc tgtctaccct gctgtgcagc 2580
ctgtgctatg gcgacatgga aaataagctg tttgccggaa tccgacggga tggcctgctg 2640
ctgagactgg tggccgcttt tctgctggtc actccacacc tgacccatgc caaagctttc 2700
ctgcgcacac tggtccgagg ggtgccagag tacggatgcg tggtcaacct gaggaagacc 2760
gtggtcaatt tcccagtgga agacgaggcc ctgggcggca cagcatttgt ccagctgcca 2820
gcacacggac tgttcccatg gtgtggactg ctgctggaca cccgcacact ggaggtgcag 2880
tccgattact cctcttatgc ccggacaagc atcagagctt ccctgacttt taacagaggc 2940
ttcaaggccg ggaggaatat gagaaggaaa ctgtttggcg tgctgcgcct gaagtgccat 3000
tccctgttcc tgtatctgca ggtgaactct ctgcagactg tctgtaccaa cgtgtacaaa 3060
atttttctgc tgcaggccta tcggttccac gcttgcgtgc tgcagctgcc attccatcag 3120
caggtcagga agaaccccac cttctttctg cgcgtgatct ctgatacagc tagtctgtgc 3180
tactcaattc tgaaggccaa aaatgctggc atgagcctgg gagcaaaagg agcagcagga 3240

ccatttcctt ccgaggctgc acagtggctg tgccaccagg cattcctgct gaagctggcc 3300
cgacatcggg tgacatatag gtgcctgctg ggcgcactgc gaacagcaca gactcagctg 3360
tgcagaaagc tgcccggggc cactctggct gccctggaag ccgctgccga ccctgccctg 3420
acctccgatt tcaagactat tctggac

SEQ ID NO: 18 Synthetic consensus hTERT amino acid sequence operably linked to IgE (underlined)

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
His Ser Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg
Ser Arg Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu
Gly Pro Gln Gly Arg Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe
Arg Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg
Pro Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu
Leu Val Ala Arg Val Val Gln Arg Leu Cys Glu Arg Gly Ala Arg Asn
Val Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro
Pro Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val
Thr Asp Thr Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg
Val Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Tyr
Val Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu
Tyr Asp Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser
Gly Thr Arg Arg Gly Leu Gly Thr Glu Gln Ala Trp Asn His Ser Val
Arg Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg
Arg Arg Gly Ser Ala Gly Arg Ser Leu Pro Leu Ala Lys Arg Pro Arg
Arg Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser
Trp Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys
Val Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly
Ala Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His
His Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr
Pro Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser
Gly Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg
Pro Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly
Ser Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Thr Pro Arg Leu Pro
Gln Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn
His Ala Gln Cys Pro Tyr Gly Ala Leu Leu Arg Thr His Cys Pro Leu
Arg Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro
Gln Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg
Leu Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly
Phe Leu Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly
Ser Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile
Ser Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys
Met Ser Val Arg Asp Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly
Cys Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys
Phe Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser
Phe Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Tyr Leu Phe Phe
Tyr Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln
His Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg
Gln His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe
Leu Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val
Val Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr
Ser Arg Val Lys Thr Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg
Arg Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His
Arg Ala Trp Arg Ala Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro
Pro Glu Leu Tyr Phe Val Lys Val Ala Val Thr Gly Ala Tyr Asp Thr
Ile Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro
Gln Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Arg Arg Ala Ala
His Gly His Val Arg Lys Ser Phe Lys Arg His Val Ser Thr Leu Thr
Asp Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr
Ser Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn
Glu Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Val Cys His

His Ala Val Arg Ile Gly Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile
Pro Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly
Asp Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu
Leu Arg Leu Val Ala Ala Phe Leu Leu Val Thr Pro His Leu Thr His
Ala Lys Ala Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly
Cys Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp
Glu Ala Leu Gly Gly Thr Ala Phe Val Gln Leu Pro Ala His Gly Leu
Phe Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln
Ser Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr
Phe Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe
Gly Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Tyr Leu Gln Val
Asn Ser Leu Gln Thr Val Cys Thr Asn Val Tyr Lys Ile Phe Leu Leu
Gln Ala Tyr Arg Phe His Ala Cys Val Leu Gln Leu Pro Phe His Gln
Gln Val Arg Lys Asn Pro Thr Phe Phe Leu Arg Val Ile Ser Asp Thr
Ala Ser Leu Cys Tyr Ser Ile Leu Lys Ala Lys Asn Ala Gly Met Ser
Leu Gly Ala Lys Gly Ala Ala Gly Pro Phe Pro Ser Glu Ala Ala Gln
Trp Leu Cys His Gln Ala Phe Leu Leu Lys Leu Ala Arg His Arg Val
Thr Tyr Arg Cys Leu Leu Gly Ala Leu Arg Thr Ala Gln Thr Gln Leu
Cys Arg Lys Leu Pro Gly Ala Thr Leu Ala Ala Leu Glu Ala Ala Ala
Asp Pro Ala Leu Thr Ser Asp Phe Lys Thr Ile Leu Asp

SEQ ID NO: 19 Synthetic Consensus hTERT nucleic acid sequence
CCTAGAGCCCCACGGTGTAGAGCAGTCCGCAGCCTGCTGCGCAGCCGATACCGGGAAGTGCTGCCTCTGGCCACC
TTTGTCCGGAGACTGGGACCACAGGGCAGGCGCCTGGTGCAGCGCGGCGACCCCGCAGCTTTCCGAGCACTGGTG
GCACAGTGCCTGGTGTGCGTGCCATGGGATGCACGGCCCCCTCCAGCAGCCCCTAGCTTTAGACAGGTGTCCTGC
CTGAAAGAACTGGTCGCAAGGGTGGTCCAGCGGCTGTGCGAGAGAGGCGCCAGGAACGTGCTGGCATTCGGCTTT
GCACTGCTGGACGGAGCTAGGGGCGGGCCCCCTGAGGCATTCACCACAAGCGTGCGCTCCTACCTGCCAAATACA
GTCACTGATACCCTGCGAGGCTCCGGAGCATGGGGACTGCTGCTGCGACGGGTGGGGGACGATGTGCTGGTCCAC
CTGCTGGCTAGATGCGCACTGTATGTGCTGGTCGCTCCCTCTTGCGCATACCAGGTGTGCGGACCACCCCTGTAT
GACCTGGGCGCTGCAACCCAGGCAAGACCTCCACCCCACGCCTCTGGCACTAGAAGGGGACTGGGCACCGAACAG
GCATGGAACCATAGTGTCAGGGAGGCAGGAGTGCCACTGGGACTGCCAGCACCTGGGGCTCGCCGACGGAGAGGG
AGTGCCGGACGGTCACTGCCACTGGCTAAGAGACCAAGGCGCGGAGCCGCTCCAGAACCAGAGAGGACACCTGTG
GGACAGGGAAGCTGGGCACACCCTGGAAGAACTAGGGGGCCAAGTGATAGGGGCTTCTGCGTGGTCTCACCAGCA
CGACCAGCAGAGGAAGCTACTTCTCTGGAGGGAGCTCTGAGTGGCACCCGGCACTCTCATCCTAGTGTGGGAAGA
CAGCACCATGCAGGCCCTCCAAGCACCAGCCGGCCTCCCCGGCCATGGGACACTCCTTGTCCACCCGTGTACGCT
GAAACCAAACACTTTCTGTATAGCTCCGGAGATAAGGAGCAGCTGCGGCCCTCTTTCCTGCTGTCTAGTCTGAGA
CCTAGTCTGACCGGAGCACGACGGCTGGTGGAAACAATCTTTCTGGGGTCCCGCCCTTGGATGCCAGGAACCCCC
AGAAGGACACCTCGACTGCCACAGCGGTACTGGCAGATGCGGCCACTGTTCCTGGAGCTGCTGGGCAATCACGCT
CAGTGCCCCTATGGGGCACTGCTGCGAACACATTGTCCTCTGCGGGCAGCCGTGACTCCAGCTGCAGGAGTCTGC
GCCAGGGAAAAGCCACAGGGCAGCGTGGCAGCTCCTGAGGAAGAGGACACCGATCCACGCCGACTGGTGCAGCTG
CTGAGACAGCACTCAAGCCCCTGGCAGGTGTACGGATTTCTGAGGGCCTGTCTGCGGAGACTGGTGCCTCCAGGA
CTGTGGGGGTCCAGGCACAACGAAAGGCGCTTTCTGCGCAATACTAAGAAATTCATCAGCCTGGGCAAGCATGCT
AAACTGTCCCTGCAGGAGCTGACCTGGAAAATGAGTGTGCGCGACTGCGCATGGCTGCGACGGTCACCAGGAGTC
GGGTGCGTGCCTGCAGCCGAGCACCGCCTGCGAGAAGAGATTCTGGCCAAGTTTCTGCATTGGCTGATGTCAGTG
TACGTGGTCGAACTGCTGCGGAGCTTCTTTTATGTGACAGAGACTACCTTCCAGAAAAACTACCTGTTCTTTTAT
CGCAAGTCAGTGTGGAGCAAACTGCAGTCAATCGGCATTCGGCAGCACCTGAAGAGAGTGCAGCTGAGGGAACTG
AGTGAAGCCGAGGTCCGGCAGCATAGAGAGGCAAGGCCTGCCCTGCTGACCTCCCGGCTGAGATTCCTGCCTAAG
CCAGACGGGCTGAGACCAATCGTGAACATGGATTACGTGGTCGGAGCACGGACCTTCCGGAGGGAAAAACGCGCT
GAGCGACTGACATCCCGCGTGAAGACTCTGTTCTCTGTCCTGAATTATGAGCGAGCTCGCCGACCCGGACTGCTG
GGAGCATCTGTGCTGGGACTGGACGATATTCACCGGGCTTGGAGAGCATTTGTCCTGAGGGTGCGCGCACAGGAC
CCTCCCCCAGAACTGTACTTCGTGAAAGTCGCCGTGACCGGGGCTTATGACACAATCCCTCAGGATCGGCTGACT
GAAGTGATCGCCTCCATCATTAAGCCACAGAATACCTACTGCGTGCGGAGATATGCTGTGGTCAGGCGCGCTGCA
CACGGCCATGTGAGGAAGAGCTTCAAGCGCCACGTCAGCACACTGACTGATCTGCAGCCCTACATGAGACAGTTC
GTGGCTCATCTGCAGGAGACCAGCCCTCTGAGGGACGCAGTGGTCATCGAACAGTCCTCTAGTCTGAACGAGGCA
TCAAGCGGGCTGTTCGATGTCTTTCTGCGGTTCGTGTGCCACCATGCCGTCAGAATTGGAGGCAAATCTTACGTG
CAGTGTCAGGGCATCCCCCAGGGCAGCATTCTGTCTACCCTGCTGTGCAGCCTGTGCTATGGCGACATGGAAAAT
AAGCTGTTTGCCGGAATCCGACGGGATGGCCTGCTGCTGAGACTGGTGGCCGCTTTTCTGCTGGTCACTCCACAC
CTGACCCATGCCAAAGCTTTCCTGCGCACACTGGTCCGAGGGGTGCCAGAGTACGGATGCGTGGTCAACCTGAGG
AAGACCGTGGTCAATTTCCCAGTGGAAGACGAGGCCCTGGGCGGCACAGCATTTGTCCAGCTGCCAGCACACGGA

CTGTTCCCATGGTGTGGACTGCTGCTGGACACCCGCACACTGGAGGTGCAGTCCGATTACTCCTCTTATGCCCGG
ACAAGCATCAGAGCTTCCCTGACTTTTAACAGAGGCTTCAAGGCCGGGAGGAATATGAGAAGGAAACTGTTTGGC
GTGCTGCGCCTGAAGTGCCATTCCCTGTTCCTGTATCTGCAGGTGAACTCTCTGCAGACTGTCTGTACCAACGTG
TACAAAATTTTTCTGCTGCAGGCCTATCGGTTCCACGCTTGCGTGCTGCAGCTGCCATTCCATCAGCAGGTCAGG
AAGAACCCCACCTTCTTTCTGCGCGTGATCTCTGATACAGCTAGTCTGTGCTACTCAATTCTGAAGGCCAAAAAT
GCTGGCATGAGCCTGGGAGCAAAAGGAGCAGCAGGACCATTTCCTTCCGAGGCTGCACAGTGGCTGTGCCACCAG
GCATTCCTGCTGAAGCTGGCCCGACATCGGGTGACATATAGGTGCCTGCTGGGCGCACTGCGAACAGCACAGACT
CAGCTGTGCAGAAAGCTGCCCGGGGCCACTCTGGCTGCCCTGGAAGCCGCTGCCGACCCTGCCCTGACCTCCGAT
TTCAAGACTATTCTGGACTGATAA

SEQ ID NO: 20 Synthetic Consensus hTERT amino acid sequence
PRAPRCRAVRSLLRSRYREVLPLATFVRRLGPQGRRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVVQRLCERGARNVLAFGFALLDGARGGPPEAFTTSVRSYLPNTVTDTLRGSGAWGLLLRRVGDDVLVH
LLARCALYVLVAPSCAYQVCGPPLYDLGAATQARPPPHASGTRRGLGTEQAWNHSVREAGVPLGLPAPGARRRRG
SAGRSLPLAKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCVVSPARPAEEATSLEGALSGTRHSHPSVGR
QHHAGPPSTSRPPRPWDTPCPPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRPWMPGTP
RRTPRLPQRYWQMRPLFLELLGNHAQCPYGALLRTHCPLRAAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQL
LRQHSSPWQVYGFLRACLRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRDCAWLRRSPGV
GCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNYLFFYRKSVWSKLQSIGIRQHLKRVQLREL
SEAEVRQHREARPALLTSRLRFLPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKTLFSVLNYERARRPGLL
GASVLGLDDIHRAWRAFVLRVRAQDPPPELYFVKVAVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVRRAA
HGHVRKSFKRHVSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLRFVCHHAVRIGGKSYV
QCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRDGLLLRLVAAFLLVTPHLTHAKAFLRTLVRGVPEYGCVVNLR
KTVVNFPVEDEALGGTAFVQLPAHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFG
VLRLKCHSLFLYLQVNSLQTVCTNVYKIFLLQAYRFHACVLQLPFHQQVRKNPTFFLRVISDTASLCYSILKAKN
AGMSLGAKGAAGPFPSEAAQWLCHQAFLLKLARHRVTYRCLLGALRTAQTQLCRKLPGATLAALEAAADPALTSD
FKTILD**

SEQ ID NO: 21 nucleic acid sequence encoding PSMA with IgE leader sequence
atggactggacatggattctgttcctggtcgccgccgcaactcgcgtgcattcctggaacgcactgcatgagact
gattctgctgtcgcactgggacggagaccccggtggctgtgcgctggagcactggtgctggccggcgggggattc
ctgctgggattcctgtttggctggtttatcaaaagctccagcgaggctaccaatattacccctaagcacaataag
aaagcattcctggatgaactgaaagccgagaacatcaagaaattcctgtacaacttcacaagaattccacatctg
gctggcactgagcagaacttccagctggcaaaacagatccagagtcagtggaaggaatttgggctggactcagtg
gagctgacccactacgatgtcctgctgtcctatccaaataagactcatcccaactacatctctatcattaacgaa
gacggaaatgagattttcaacacctctctgtttgaaccccctccacccggctatgagaatgtcagtgacgtggtc
cctccattctcagccttcagcccccaggggatgcctgagggagatctggtgtacgtcaattatgctagaacagaa
gacttctttaagctggagagggatatgaaaatcaactgttccggcaagatcgtgattgcccggtacgggaaggtg
ttcagaggaaataaggtcaaaaacgctcagctggccggagctaccggcgtgatcctgtacagcgaccccgctgat
tattttgcacctggcgtgaagtcctatccagacggatggaatctgcccggcgggggagtgcagaggggaaacatc
ctgaacctgaatggagccggcgatcctctgactccaggataccccgccaacgaatacgcttatcgccggggaatt
gcagaggccgtgggcctgcctagcatcccagtccatcccattggctattacgatgcccagaagctgctggagaaa
atgggcgggagcgctccccctgactctagttggaagggctccctgaaagtgccttacaatgtcgggccaggattc
actgggaacttttctacccagaaggtgaaaatgcacatccatagtaccagcgaggtgacacgaatctacaacgtc
attggcaccctgagaggcgccgtggagcctgatcgctatgtcattctgggaggccacagagactcatgggtgttc
gggggaatcgatccacagagcggagcagctgtggtccatgaaattgtgcgcagctttgggaccctgaagaaagag
ggatggcgacccaggcgcacaatcctgttcgcatcctgggacgccgaggaatttgggctgctgggcagcacagaa
tgggccgaggaaaattctcgcctgctgcaggagcgaggggtggcttacatcaatgcagactcaagcattgaagga
aactataccctgcgggtggattgcacacccctgatgtacagtctggtctataacctgacaaaggagctgaaatca
cctgacgagggcttcgaagggaaaagcctgtacgaatcctggactgagaagagcccatcccccgaattcagcggc
atgcctaggatctctaagctgggcagtgggaacgattttgaggtgttctttcagcgcctgggaattgcctctggc
cgagctcggtacacaaaaaattgggagactaacaagttctcctcttacccactgtatcacagcgtgtacgagact
tatgaactggtcgagaaattctacgacccccacttttaagtatcatctgaccgtggcacaggtcagggggcgggatg
gtgttcgaactggccaatagcatcgtcctgccatttgactgtcgagattacgctgtggtcctgcggaagtacgca
gacaagatctataacatctccatgaagcacccccaggagatgaaggcctattctgtgagtttcgattccctgttt
tctgccgtcaaaaatttcaccgaaatcgctagtaagttttcagagcgcctgcaggacctggataagtccaatccc
atcctgctgcggattatgaacgatcagctgatgttcctggaaagagcctttatcgaccctctgggcctgcctgat
agaccattctacaggcacgtgatctacgcacctagttcacataacaagtacgccggcgagtctttcccagggatc

tatgacgctctgtttgatattgaatcaaaggtggaccccagcaaagcatggggcgaggtcaagagacagatcagc
attgcagcctttacagtgcaggccgccgccgaaaccctgtccgaagtcgcttgataa

SEQ ID NO: 22 nucleic acid sequence encoding IL12 p35 (pGX6001)
atgtgtccagcgcgcagcctcctccttgtggctaccctggtcctcctggaccacctcagtttggccagaaaccctc
cccgtggccactccagacccaggaatgttcccatgccttcaccactcccaaaacctgctgagggccgtcagcaac
atgctccagaaggccagacaaactctagaatttaccccttgcacttctgaagagattgatcatgaagatatcaca
aaagataaaaccagcacagtggaggcctgtttaccattggaattaaccaagaatgagagttgcctaaattccaga
gagacctctttcataactaatgggagttgcctggcctccagaaagacctcttttatgatggccctgtgccttagt
agtatttatgaagacttgaagatgtaccaggtggagttcaagaccatgaatgcaaagcttctgatggatcctaag
aggcagatctttctagatcaaaacatgctggcagttattgatgagctgatgcaggccctgaatttcaacagtgag
actgtgccacaaaaatcctcccttgaagaaccggatttttataaaactaaaatcaagctctgcatacttcttcat
gctttcagaattcgggcagtgactattgatagagtgatgagctatctgaatgcttcctaa

SEQ ID NO: 23 IL12 p35 amino acid sequence(pGX6001)
MCPARSLLLVATLVLLDHLSLARNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDIT
KDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPK
RQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNAS

SEQ ID NO: 24 nucleic acid sequence encoding IL12 p40(pGX6001)
atgtgtcaccagcagttggtcatctcttggttttccctggtttttctggcatctcccctcgtggccatatgggaa
ctgaagaaagatgtttatgtcgtagaattggattggtatccggatgcccctggagaaatggtggtcctcacctgt
gacacccctgaagaagatggtatcacctggaccttggaccagagcagtgaggtcttaggctctggcaaaaccctg
accatccaagtcaaagagtttggagatgctggccagtacacctgtcacaaaggaggcgaggttctaagccattcg
ctcctgctgcttcacaaaaaggaagatggaatttggtccactgatattttaaaggaccagaaagaacccaaaaat
aagacctttctaagatgcgaggccaagaattattctggacgtttcacctgctggtggctgacgacaatcagtact
gatttgacattcagtgtcaaaagcagcagaggctcttctgacccccaaggggtgacgtgcggagctgctacactc
tctgcagagagagtcagaggggacaacaaggagtatgagtactcagtggagtgccaggaggacagtgcctgccca
gctgctgaggagagtctgcccattgaggtcatggtggatgccgttcacaagctcaagtatgaaaactacaccagc
agcttcttcatcagggacatcatcaaacctgacccacccaagaacttgcagctgaagccattaaagaattctcgg
caggtggaggtcagctgggagtaccctgacacctggagtactccacattcctacttctccctgacattctgcgtt
caggtccagggcaagagcaagagagaaaagaaagatagagtcttcacggacaagacctcagccacggtcatctgc
cgcaaaaatgccagcattagcgtgcgggcccaggaccgctactatagctcatcttggagcgaatgggcatctgtg
ccctgcagttag

SEQ ID NO: 25 IL12 p40 amino acid sequence(pGX6001)
MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTL
TIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTIST
DLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTS
SFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVIC
RKNASISVRAQDRYYSSSWSEWASVPCS

SEQ ID NO: 26 Con WT1-L with modified Zinc Fingers protein
GSDVRDLNALLPAVPSLPGGGGCALPVSGAAQWAPVLDFAPPAAPYGSLGGPHSFIKQEPSWGGADPHEEQCLSA
FTVHFSGQFTGTAGACRYGPFGAPPPSQAPSGQARMFPNAPYLPNCLESQPAIRNQGYSTVAFDGTPSYGHTPSH
HAAQFPNHSFKHEDPMGQQGSLGEQQYSVPPPVYGCHTPTDSCTGSQALLLRTPYNSDNLYQMTSQLECMTWNQM
NLGSTLKGHATGYESDNHTTPMLYSCGAQYRIHTHGVFRGIQDVRRVPGVAPTIVRSASETNEKRPFMGAYPGGN
KRYFKLSHLQMGSRKGTGEKPYQGDFKDGERRFSRSDQLKRGQRRGTGVKPFQCKTCQRKFSRSDHLKTHTRTHT
GKTSEKPFSCRWPSCQKKFARSDELVRHHNMHQRNMTKLQLAL**

SEQ ID NO: 27 Consensus WT1-L with modified Zinc Fingers nucleic acid
sequence
GGGAGTGATGTGAGAGACCTGAACGCCCTGCTGCCAGCAGTGCCATCCCTGCCTGGCGGGGGAGGCTGCGCTCTG
CCAGTCTCTGGAGCAGCTCAGTGGGCTCCCGTGCTGGACTTTGCACCCCCTGCAGCCCCTTACGGAAGTCTGGGC
GGCCCACACTCATTCATCAAACAGGAGCCAAGCTGGGGCGGGGCAGATCCTCATGAGGAACAGTGCCTGTCAGCC
TTCACAGTCCACTTTAGCGGGCAGTTCACTGGAACCGCAGGAGCTTGTAGATACGGACCCTTTGGAGCACCACCC
CCTTCCCAGGCACCTTCTGGACAGGCACGCATGTTCCCAAACGCTCCCTATCTGCCTAATTGTCTGGAAAGCCAG
CCCGCTATTAGGAACCAGGGCTACTCCACAGTGGCATTTGACGGGACTCCTAGCTATGGACATACCCCATCCCAC
CATGCTGCACAGTTTCCTAATCACTCCTTCAAGCATGAGGACCCCATGGGACAGCAGGGGTCCCTGGGAGAACAG

CAGTACTCTGTGCCCCCTCCCGTGTACGGATGCCACACACCAACTGACAGTTGTACAGGCTCACAGGCCCTGCTG
CTGCGAACTCCATACAACAGTGATAATCTGTATCAGATGACCTCACAGCTGGAGTGCATGACATGGAACCAGATG
AATCTGGGCAGCACACTGAAAGGCCATGCCACTGGGTACGAATCTGACAACCACACCACACCTATGCTGTACAGT
TGTGGAGCCCAGTATAGAATCCACACTCATGGAGTCTTCAGAGGCATTCAGGATGTGCGGAGAGTCCCAGGAGTG
GCACCAACTATCGTGCGGAGCGCCTCCGAGACCAACGAAAAGCGCCCCTTTATGGGCGCCTACCCTGGAGGCAAT
AAGCGGTATTTCAAACTGTCTCACCTGCAGATGGGGAGTAGAAAGGGGACCGGAGAGAAACCTTATCAGGGCGAC
TTTAAAGATGGGGAAAGGCGCTTCTCTCGCAGTGACCAGCTGAAGCGAGGACAGCGACGAGGAACCGGGGTGAAG
CCATTTCAGTGCAAAACATGTCAGAGAAAGTTCTCAAGGAGCGATCACCTGAAGACCCATACAAGAACTCACACC
GGCAAGACCAGCGAGAAACCATTTTCCTGCCGATGGCCCTCTTGTCAGAAGAAATTCGCCCGCTCCGACGAACTG
GTCCGACACCACAATATGCATCAGAGAAATATGACAAAACTGCAGCTGGCTCTGTGATAA

SEQ ID NO: 28 PSMA
WNALHETDSAVALGRRPRWLCAGALVLAGGGFLLGFLFGWFIKSSSEATNITPKHNKKAFLDELKAENIKKFLYN
FTRIPHLAGTEQNFQLAKQIQSQWKEFGLDSVELTHYDVLLSYPNKTHPNYISIINEDGNEIFNTSLFEPPPPGY
ENVSDVVPPFSAFSPQGMPEGDLVYVNYARTEDFFKLERDMKINCSGKIVIARYGKVFRGNKVKNAQLAGATGVI
LYSDPADYFAPGVKSYPDGWNLPGGGVQRGNILNLNGAGDPLTPGYPANEYAYRRGIAEAVGLPSIPVHPIGYYD
AQKLLEKMGGSAPPDSSWKGSLKVPYNVGPGFTGNFSTQKVKMHIHSTSEVTRIYNVIGTLRGAVEPDRYVILGG
HRDSWVFGGIDPQSGAAVVHEIVRSFGTLKKEGWRPRRTILFASWDAEEFGLLGSTEWAEENSRLLQERGVAYIN
ADSSIEGNYTLRVDCTPLMYSLVYNLTKELKSPDEGFEGKSLYESWTEKSPSPEFSGMPRISKLGSGNDFEVFFQ
RLGIASGRARYTKNWETNKFSSYPLYHSVYETYELVEKFYDPTFKYHLTVAQVRGGMVFELANSIVLPFDCRDYA
VVLRKYADKIYNISMKHPQEMKAYSVSFDSLFSAVKNFTEIASKFSERLQDLDKSNPILLRIMNDQLMFLERAFI
DPLGLPDRPFYRHVIYAPSSHNKYAGESFPGIYDALFDIESKVDPSKAWGEVKRQISIAAFTVQAAAETLSEVA*
*

SEQ ID NO: 29 nucleic acid sequence encoding PSMA
TGGAACGCACTGCATGAGACTGATTCTGCTGTCGCACTGGGACGGAGACCCCGGTGGCTGTGCGCTGGAGCACTG
GTGCTGGCCGGCGGGGGATTCCTGCTGGGATTCCTGTTTGGCTGGTTTATCAAAAGCTCCAGCGAGGCTACCAAT
ATTACCCCTAAGCACAATAAGAAAGCATTCCTGGATGAACTGAAAGCCGAGAACATCAAGAAATTCCTGTACAAC
TTCACAAGAATTCCACATCTGGCTGGCACTGAGCAGAACTTCCAGCTGGCAAAACAGATCCAGAGTCAGTGGAAG
GAATTTGGGCTGGACTCAGTGGAGCTGACCCACTACGATGTCCTGCTGTCCTATCCAAATAAGACTCATCCCAAC
TACATCTCTATCATTAACGAAGACGGAAATGAGATTTTCAACACCTCTCTGTTTGAACCCCCTCCACCCGGCTAT
GAGAATGTCAGTGACGTGGTCCCTCCATTCTCAGCCTTCAGCCCCCAGGGGATGCCTGAGGGAGATCTGGTGTAC
GTCAATTATGCTAGAACAGAAGACTTCTTTAAGCTGGAGAGGGATATGAAAATCAACTGTTCCGGCAAGATCGTG
ATTGCCCGGTACGGGAAGGTGTTCAGAGGAAATAAGGTCAAAAACGCTCAGCTGGCCGGAGCTACCGGCGTGATC
CTGTACAGCGACCCCGCTGATTATTTTGCACCTGGCGTGAAGTCCTATCCAGACGGATGGAATCTGCCCGGCGGG
GGAGTGCAGAGGGGAAACATCCTGAACCTGAATGGAGCCGGCGATCCTCTGACTCCAGGATACCCCGCCAACGAA
TACGCTTATCGCCGGGGAATTGCAGAGGCCGTGGGCCTGCCTAGCATCCCAGTCCATCCCATTGGCTATTACGAT
GCCCAGAAGCTGCTGGAGAAAATGGGCGGGAGCGCTCCCCCTGACTCTAGTTGGAAGGGCTCCCTGAAAGTGCCT
TACAATGTCGGGCCAGGATTCACTGGGAACTTTTCTACCCAGAAGGTGAAAATGCACATCCATAGTACCAGCGAG
GTGACACGAATCTACAACGTCATTGGCACCCTGAGAGGCGCCGTGGAGCCTGATCGCTATGTCATTCTGGGAGGC
CACAGAGACTCATGGGTGTTCGGGGGAATCGATCCACAGAGCGGAGCAGCTGTGGTCCATGAAATTGTGCGCAGC
TTTGGGACCCTGAAGAAAGAGGGATGGCGACCCAGGCGCACAATCCTGTTCGCATCCTGGGACGCCGAGGAATTT
GGGCTGCTGGGCAGCACAGAATGGGCCGAGGAAAATTCTCGCCTGCTGCAGGAGCGAGGGGTGGCTTACATCAAT
GCAGACTCAAGCATTGAAGGAAACTATACCCTGCGGGTGGATTGCACACCCCTGATGTACAGTCTGGTCTATAAC
CTGACAAAGGAGCTGAAATCACCTGACGAGGGCTTCGAAGGGAAAAGCCTGTACGAATCCTGGACTGAGAAGAGC
CCATCCCCCGAATTCAGCGGCATGCCTAGGATCTCTAAGCTGGGCAGTGGGAACGATTTTGAGGTGTTCTTTCAG
CGCCTGGGAATTGCCTCTGGCCGAGCTCGGTACACAAAAAATTGGGAGACTAACAAGTTCTCCTCTTACCCACTG
TATCACAGCGTGTACGAGACTTATGAACTGGTCGAGAAATTCTACGACCCCACTTTTAAGTATCATCTGACCGTG
GCACAGGTCAGGGGCGGGATGGTGTTCGAACTGGCCAATAGCATCGTCCTGCCATTTGACTGTCGAGATTACGCT
GTGGTCCTGCGGAAGTACGCAGACAAGATCTATAACATCTCCATGAAGCACCCCCAGGAGATGAAGGCCTATTCT
GTGAGTTTCGATTCCCTGTTTTCTGCCGTCAAAAATTTCACCGAAATCGCTAGTAAGTTTTCAGAGCGCCTGCAG
GACCTGGATAAGTCCAATCCCATCCTGCTGCGGATTATGAACGATCAGCTGATGTTCCTGGAAAGAGCCTTTATC
GACCCTCTGGGCCTGCCTGATAGACCATTCTACAGGCACGTGATCTACGCACCTAGTTCACATAACAAGTACGCC
GGCGAGTCTTTCCCAGGGATCTATGACGCTCTGTTTGATATTGAATCAAAGGTGGACCCCAGCAAAGCATGGGGC
GAGGTCAAGAGACAGATCAGCATTGCAGCCTTTACAGTGCAGGCCGCCGCCGAAACCCTGTCCGAAGTCGCTTGA
TAA

What is claimed:

1. A method of treating brain cancer in a subject in need thereof, the method comprising administering to the subject:

an immunogenic composition comprising a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28; and

an anti-programmed cell death receptor 1 (PD-1) antibody.

2. The method of claim 1, further comprising administering to the subject interleukin-12 (IL12), IL12 p35 subunit, IL12 p40 subunit, IL12 p35 subunit and IL12 p40 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or a DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit.

3. A vaccine comprising:

immunogenic composition comprising a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleic acid sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28;

when used in combination with an anti-programmed cell death receptor 1 (PD-1) antibody to treat brain cancer in a subject.

4. The vaccine of claim 3, further comprising interleukin-12 (IL12), IL12 p35 subunit, IL12 p40 subunit, IL12 p35 subunit and IL12 p40 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or a DNA

plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit.

5. Use of a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleotide sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28 in the manufacture of a medicament to treat brain cancer in a subject, wherein the medicament is provided for administration in combination with an anti-programmed cell death receptor 1 (PD-1) antibody.

6. Use of a DNA plasmid comprising a nucleic acid sequence encoding a human telomerase reverse transcriptase (hTERT) antigen comprising the amino acid sequence of SEQ ID NO: 20, a DNA plasmid comprising a nucleic acid sequence encoding a Wilms Tumor-1 (WT-1) antigen comprising the amino acid sequence of SEQ ID NO: 26, and a DNA plasmid comprising a nucleic acid sequence encoding a prostate specific membrane antigen (PSMA) comprising the amino acid sequence of SEQ ID NO: 28; and an anti-programmed cell death receptor 1 (PD-1) antibody, in the manufacture of a medicament to treat brain cancer in a subject.

7. The use of claim 5 or claim 6, further comprising in combination with interleukin-12 (IL12), IL12 p35 subunit, IL12 p40 subunit, IL12 p35 subunit and IL12 p40 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, a DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or a DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit.

8. The method of claim 1 or 2, the vaccine of claim 3 or 4, or the use of any one of claims 5-7, wherein:

the hTERT antigen, the WT-1 antigen, and the PSMA antigen are encoded by the same DNA plasmid;

two of the hTERT antigen, the WT-1 antigen, and the PSMA antigen are encoded by the same DNA plasmid; or

the hTERT antigen, the WT-1 antigen, and the PSMA antigen are each encoded by a different DNA plasmid.

9. The method of any one of claims 1, 2 and 8, the vaccine of any one of claims 3, 4 and 8, or the use of any one of claims 5-8, wherein the anti-PD-1 antibody:

comprises the heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2;

comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3, HCDR2 comprises the amino acid sequence of SEQ ID NO: 4, HCDR3 comprises the amino acid sequence of SEQ ID NO: 5, LCDR1 comprises the amino acid sequence of SEQ ID NO: 6, LCDR2 comprises the amino acid sequence of SEQ ID NO: 7, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8;

comprises (i) a HCVR having a sequence with 90% sequence identity to SEQ ID NO: 1, provided that the HCVR comprises the heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) of the HCVR sequence set forth in SEQ ID NO: 1, and (ii) a LCVR having a sequence with 90% sequence identity to SEQ ID NO: 2, provided that the LCVR comprises the light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) of the LCVR sequence set forth in SEQ ID NO: 2;

comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1 and a LCVR comprising the amino acid sequence of SEQ ID NO: 2;

comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and a light chain comprising the amino acid sequence of SEQ ID NO: 10;

is an IgG4 antibody; or

is REGN2810 or a biosimilar or bioequivalent thereof.

10. The method of any one of claims 1, 2, 8 and 9 or the vaccine of any one of claims 3, 4, 8 and 9, wherein the anti-PD-1 antibody is administered intravenously or subcutaneously, or the use of any one of claims 5-9, wherein the anti-PD-1 antibody is provided for intravenous or subcutaneous administration.

11. The method of any one of claims 1, 2 and 8-10 or the vaccine of any one of claims 3, 4 and 8-10, wherein 350 mg of the anti-PD-1 antibody is administered every three weeks, or the use of any one of claims 5-10, wherein the anti-PD-1 antibody is provided for administration every three weeks.

12. The method of any one of claims 1, 2 and 8-11, the vaccine of any one of claims 3, 4 and 8-11, or the use of any one of claims 5-11, wherein:

the IL12 p35 subunit comprises the amino acid sequence of SEQ ID NO: 23;

the IL12 p40 subunit comprises the amino acid sequence of SEQ ID NO: 25;

the IL12 p35 subunit comprises the amino acid sequence of SEQ ID NO: 23 and the IL12 p40 subunit comprises the amino acid sequence of SEQ ID NO: 25;

the nucleic acid sequence encoding the IL12 p35 subunit comprises the nucleic acid sequence of SEQ ID NO: 22;

the nucleic acid sequence encoding the IL12 p40 subunit comprises the nucleic acid sequence of SEQ ID NO: 24; or

the nucleic acid sequence encoding the IL12 p35 subunit comprises the nucleic acid sequence of SEQ ID NO: 22 and the nucleic acid sequence encoding the IL12 p40 subunit comprises the nucleic acid sequence of SEQ ID NO: 24.

13. The method of any one of claims 1, 2 and 8-12, the vaccine of any one of claims 3, 4 and 8-13, or the use of any one of claims 5-13, wherein:

the nucleic acid sequence encoding the hTERT antigen comprises the nucleic acid sequence of SEQ ID NO: 19;

the nucleic acid sequence encoding the WT-1 antigen comprises the nucleic acid sequence of SEQ ID NO: 27; and/or

the nucleic acid sequence encoding the PSMA antigen comprises the nucleic acid sequence of SEQ ID NO: 29.

14. The method of any one of claims 1, 2 and 8-13, wherein the method comprises administering to the subject 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the hTERT antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the PSMA antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the WT-1 antigen, and 1 mg of the DNA plasmid comprising the nucleic acid sequence encoding IL-12, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or the DNA plasmid comprising a

nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit,

the vaccine of any one of claims 3, 4 and 8-14, comprising 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the hTERT antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the PSMA antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the WT-1 antigen, and 1 mg of the DNA plasmid comprising the nucleic acid sequence encoding IL-12, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit, or

the use of any one of claims 5-14, wherein the medicament comprises 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the hTERT antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the PSMA antigen, 3 mg of the DNA plasmid comprising the nucleic acid sequence encoding the WT-1 antigen, and 1 mg of the DNA plasmid comprising the nucleic acid sequence encoding IL-12, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit.

15. The method of any one of claims 2 and 8-14 or the vaccine of any one of claims 4 and 8-14, wherein the immunogenic composition is co-administered by intramuscular injection every three weeks for four doses and then every nine weeks with the IL12, the IL12 p35 subunit, the IL12 p40 subunit, the IL12 p35 subunit and the IL12 p40 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit, or the use of any one of claims 7-14, wherein the medicament is provided for co-administration by intramuscular injection every three weeks for four doses and then every nine weeks with the IL12, the IL12 p35 subunit, the IL12 p40 subunit, the IL12 p35 subunit and the IL12 p40 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit, the DNA plasmid comprising a nucleic acid sequence encoding IL12 p40 subunit, or the DNA plasmid comprising a nucleic acid sequence encoding IL12 p35 subunit and a nucleic acid sequence encoding IL12 p40 subunit.

16. The method, the vaccine or the use of claim 15, further comprising electroporation following each intramuscular injection.

17. The method of any one of claims 1, 2 and 8-16, wherein the method further comprises administering to the subject one or more doses of radiation therapy; the vaccine of any one of claims 3, 4 and 8-16, wherein the vaccine is administered in combination with one or more doses of radiation therapy; or the use of any one of claims 5-16, wherein the medicament is provided for administration in combination with one or more doses of radiation therapy.

18. The method, the vaccine, or the use of claim 17, wherein each dose of radiation therapy comprises 20- 50 Gy.

19. The method, the vaccine, or the use of claim 18, wherein the radiation therapy is fractionated radiation therapy.

20. The method, the vaccine, or the use of claim 19, wherein the fractionated radiation therapy comprises 2-20 fractions.

21. The method, the vaccine, or the use of claim 19 or claim 20, wherein the fractionated radiation therapy comprises 40 Gy in 15 fractions.

22. The method, the vaccine, or the use of any one of claims 19-21, wherein the fractionated radiotherapy is given over 21 consecutive days.

23. The method of any one of claims 1, 2 and 8-22, wherein the method further comprises administering to the subject one or more doses of a chemotherapeutic agent; the vaccine of any one of claims 3, 4 and 8-22, wherein the vaccine is administered to the subject in combination with one or more doses of a chemotherapeutic agent; or the use of any one of claims 5-22, wherein the medicament is provided for administration in combination with one or more doses of a chemotherapeutic agent; and optionally wherein the chemotherapeutic agent is temozolomide.

24. The method or the vaccine of claim 23, wherein 75 mg/m^2 temozolomide is administered to the subject daily for 21 consecutive days with the fractionated radiotherapy, or the use of claim 23,

wherein 75 mg/m^2 temozolomide is provided for daily administration to the subject for 21 consecutive days with the fractionated radiotherapy.

25. The method, the vaccine, or the use of claim 23 or claim 24, further comprising temozolomide maintenance therapy if the brain cancer is characterized by a methylated MGMT promoter.

26. The method of any one of claims 1, 2 and 8-25, the vaccine of any one of claims 3, 4 and 8-25, or the use of any one of claims 5-25, wherein the brain cancer is glioblastoma.

27. The method, the vaccine or the use of claim 26, wherein the brain cancer is glioblastoma characterized by a methylated MGMT promoter.

28. The method, the vaccine, or the use of claim 26, wherein the brain cancer is glioblastoma characterized by an unmethylated MGMT promoter.

Figure 1

STUDY SCHEMA

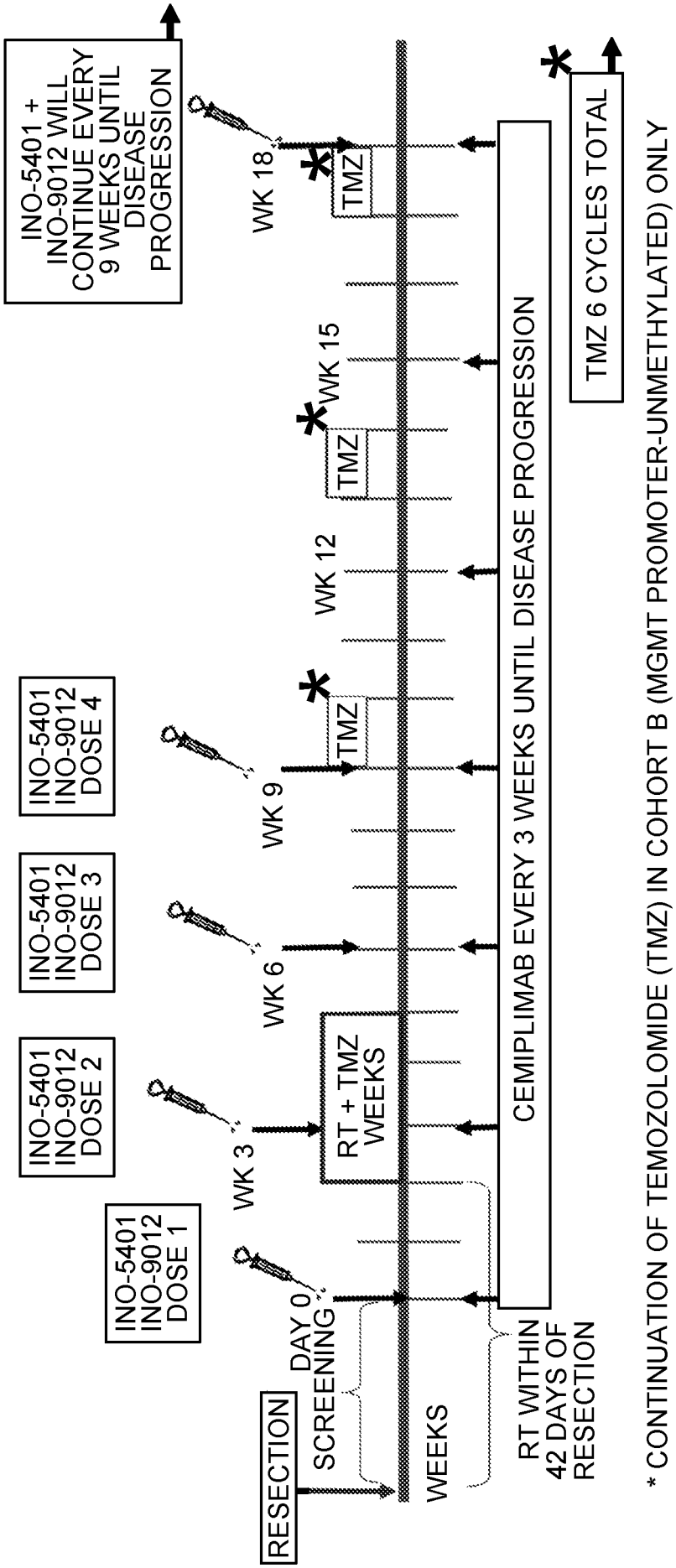


Figure 2
Study Population Demographics

	Cohort A (n=32)	Cohort B (n=20)
Age ≤65 years (%)	25 (78)	13 (65)
Age ≥65 years (%)	7 (22)	7 (35)
Median Age in Years (range)	59 (19-71)	63 (33-78)
Female Sex (%)	11 (34)	7 (35)
Male Sex (%)	21 (66)	13 (65)
Karnofsky Performance Score 90-100 (%)	23 (72)	17 (85)
Karnofsky Performance Score 70-80 (%)	9 (28)	3 (15)
Median Time on Study from First Dose (Days; range)	541 (113-722)	557 (40-750)
Median Exposure* (Dosing cycles; range) of INO-5401	6 (1-14)	7.5 (1-13)
Median Exposure* (Dosing cycles; range) of cemiplimab	10 (1-34)	17 (1-29)
Subjects of dexamethasone at Day 0 (N, %)	14 (44)	5 (25)
Discontinued Therapy to Date (N)**	28	13

* INO-5401 is given Q3 weeks x 4 and then Q9 weeks; cemiplimab is given Q3 weeks
** The majority of subjects who discontinued have discontinued therapy for progressive disease. 11 subjects continue therapy as of date of analysis.

Figure 3
REPRESENTATIVE MRI IMAGES FROM TWO PATIENTS

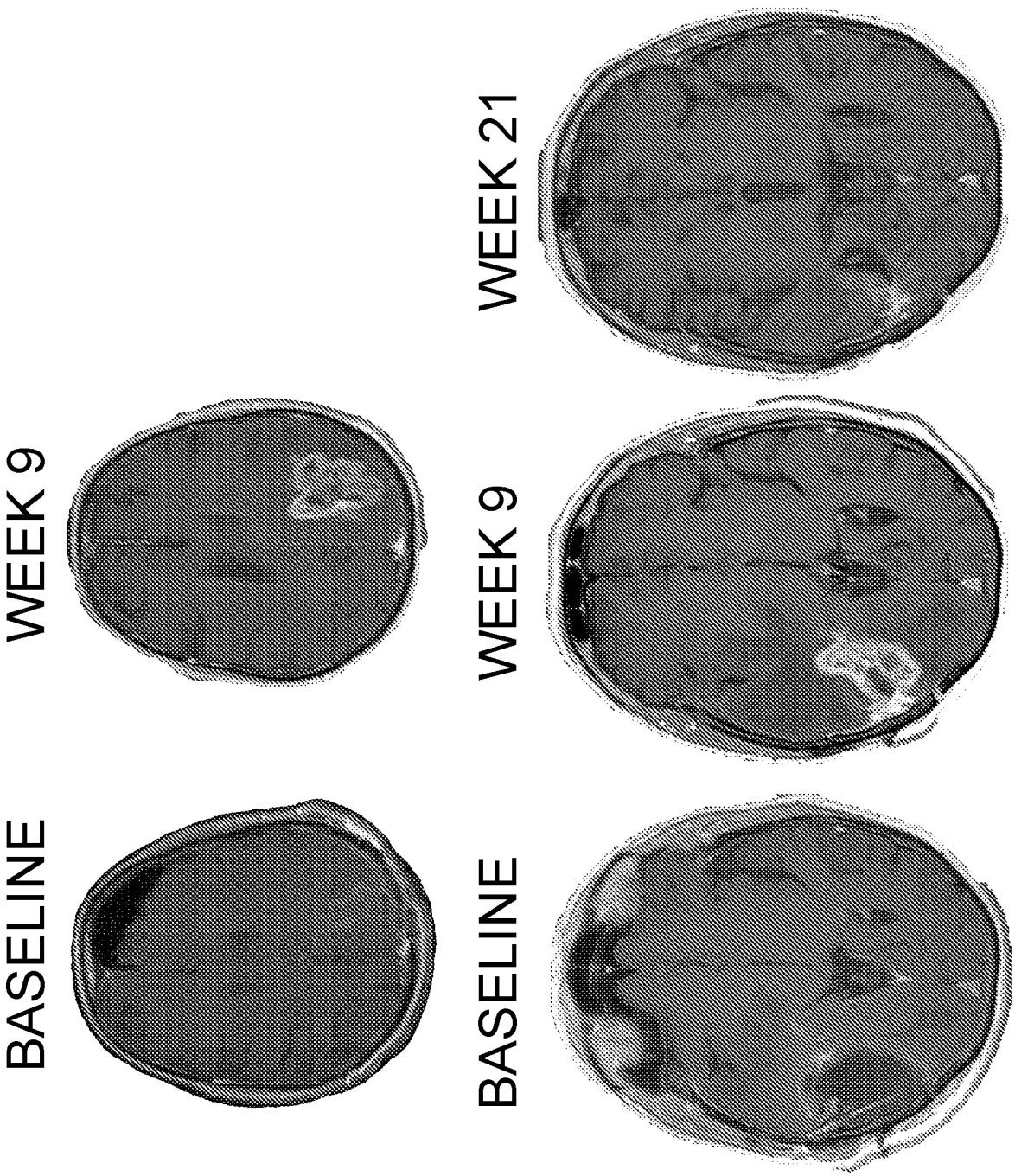


Figure 4

Immunogenicity by ELISpot

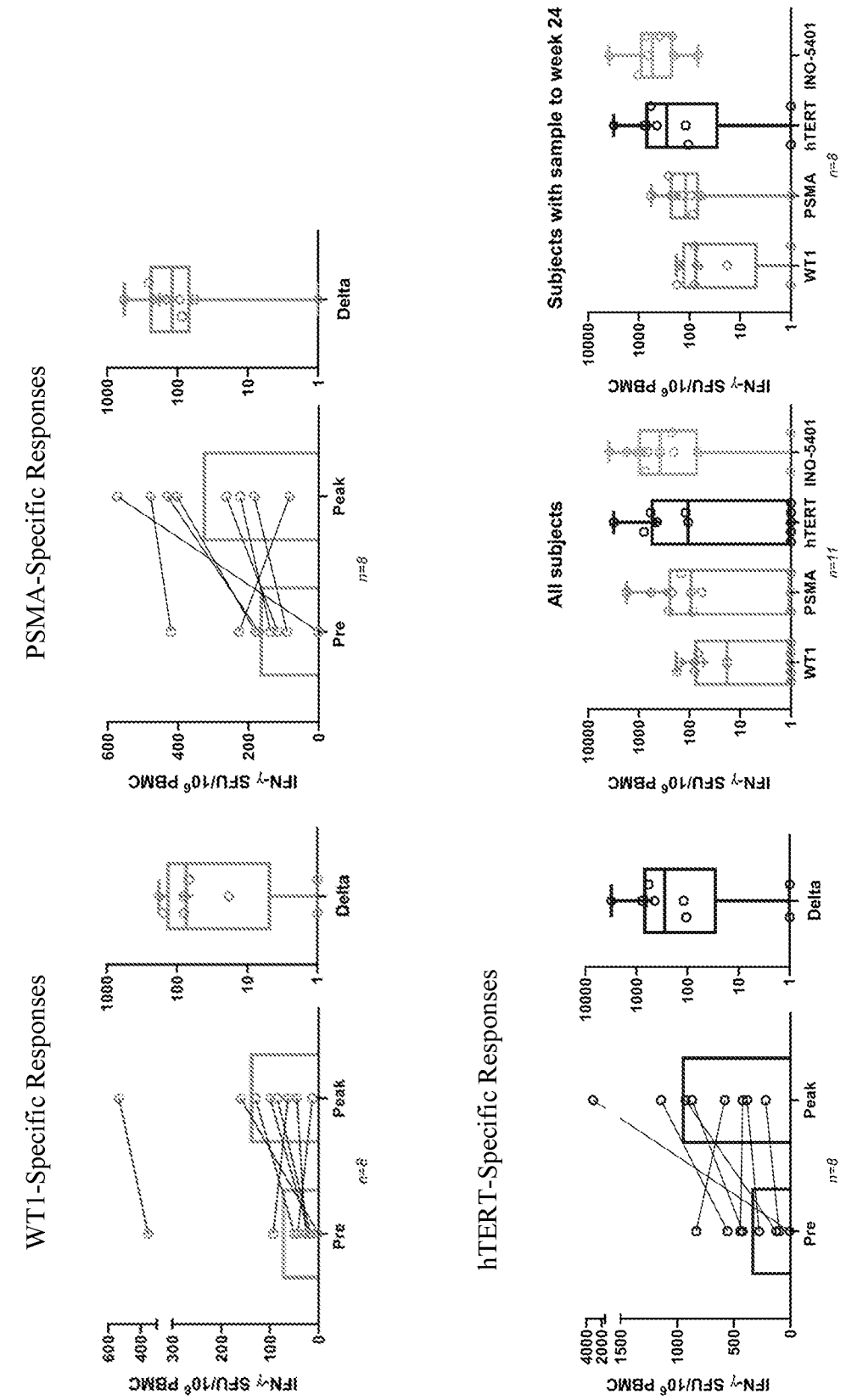


Figure 5A

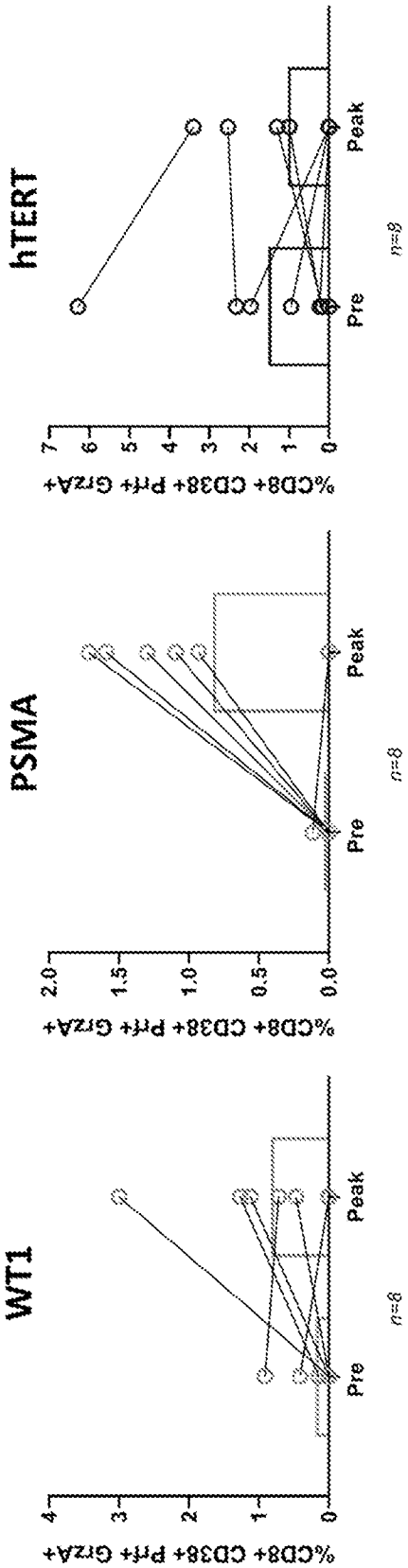


Figure 5B

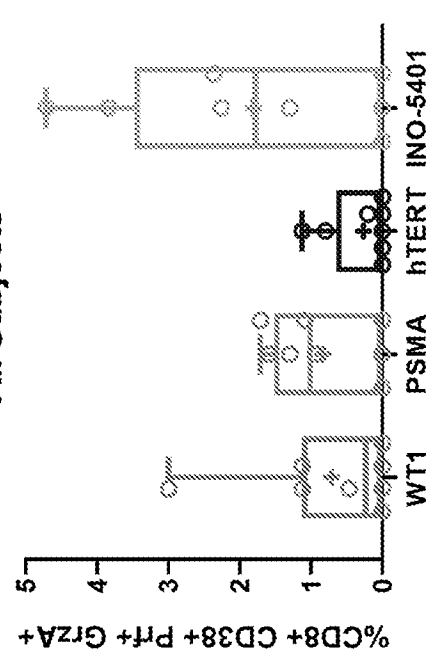


Figure 5C

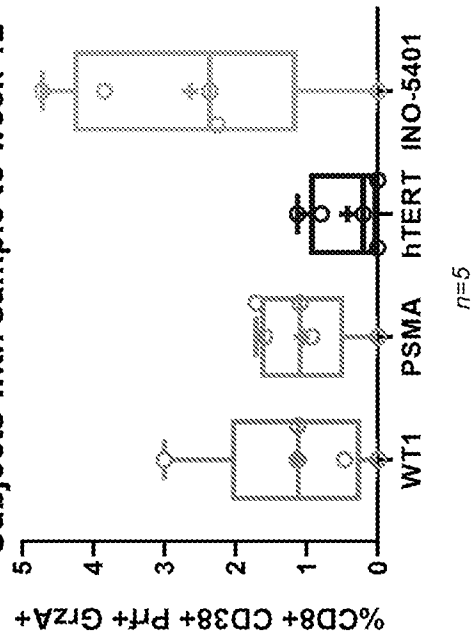


Figure 6 - Confirmed PFS (Cohort A)

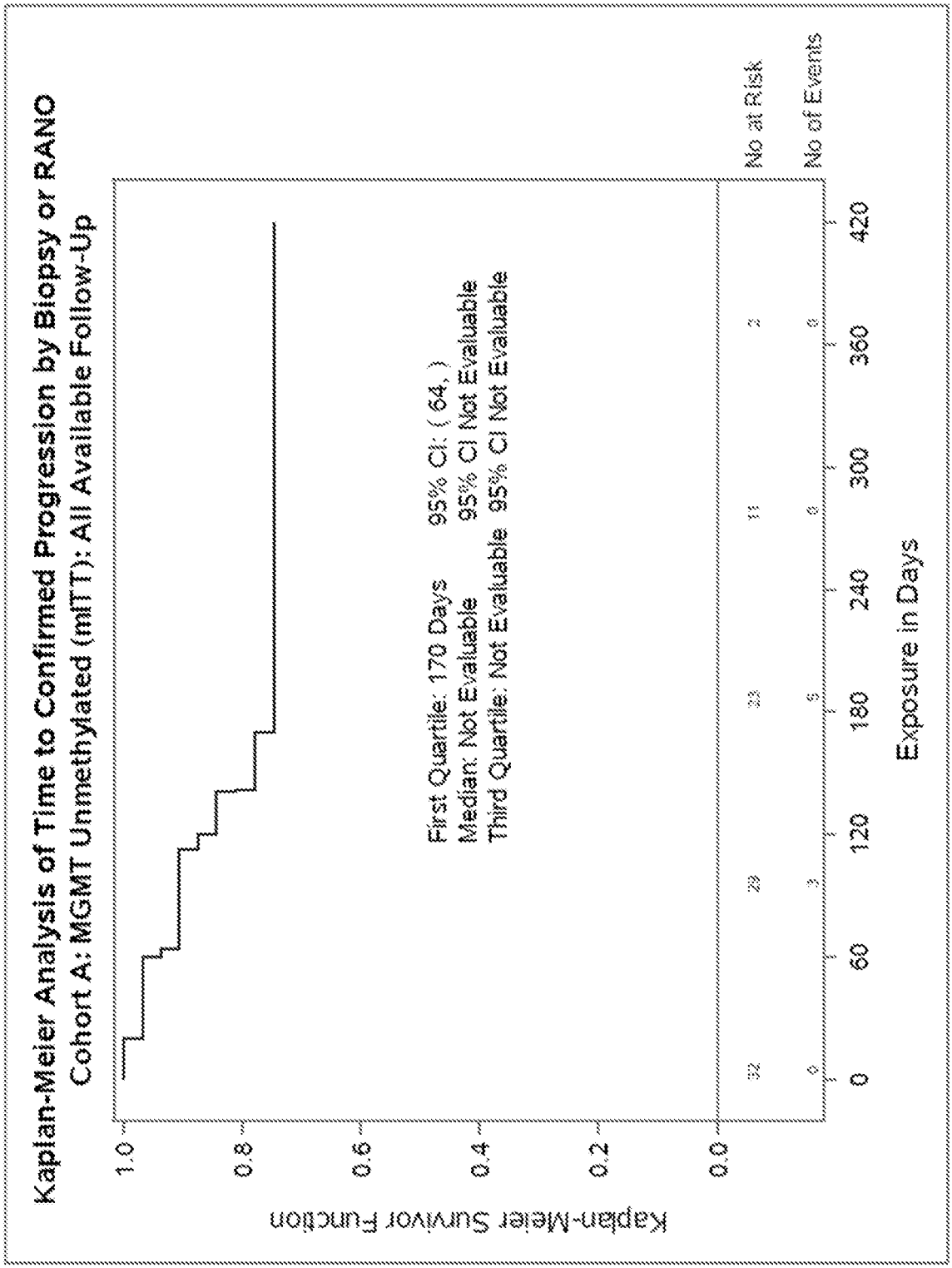


Figure 7 – Confirmed PFS (Cohort B)

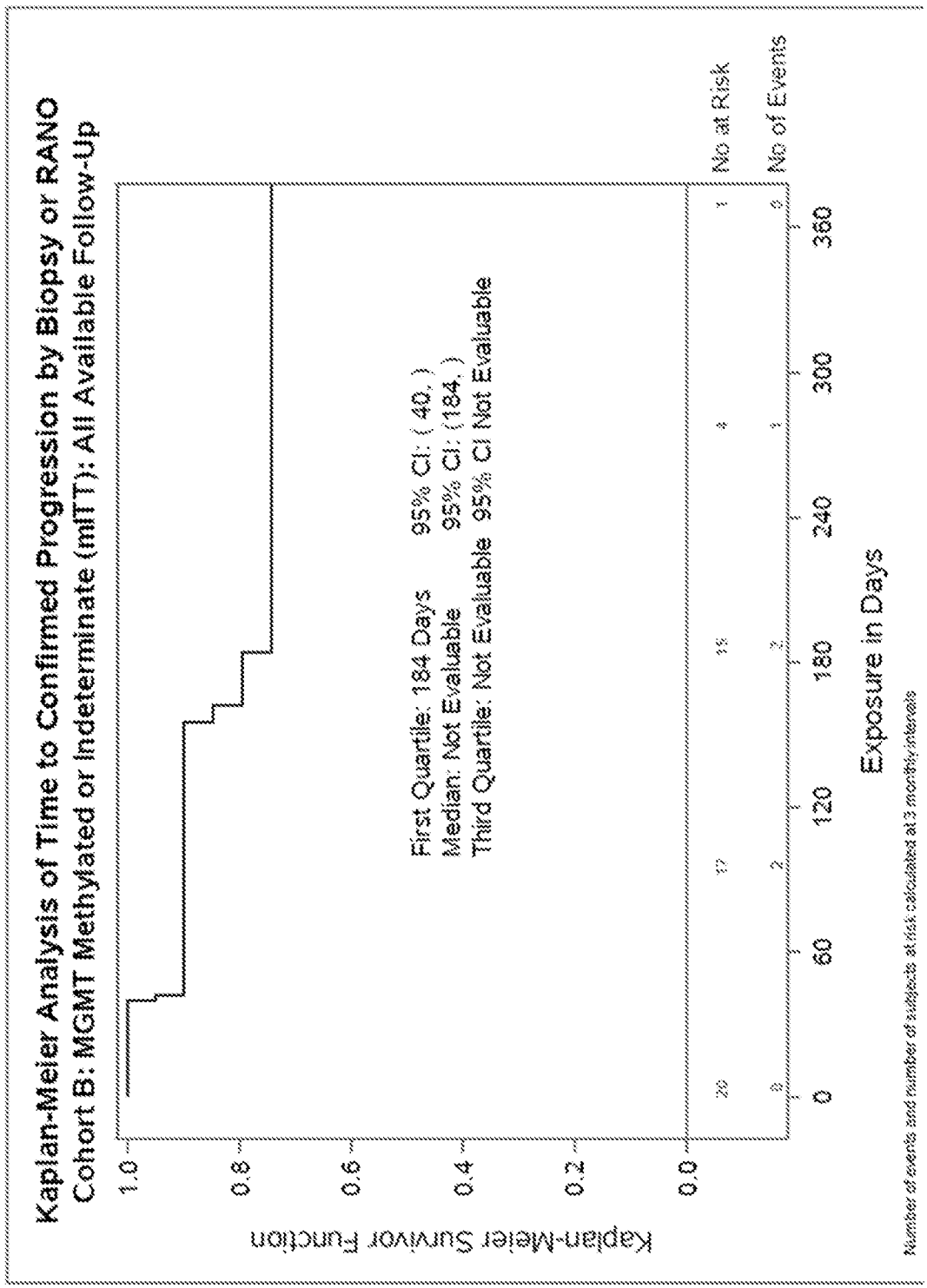


Figure 8 – Confirmed PFS (Cohort A + B)

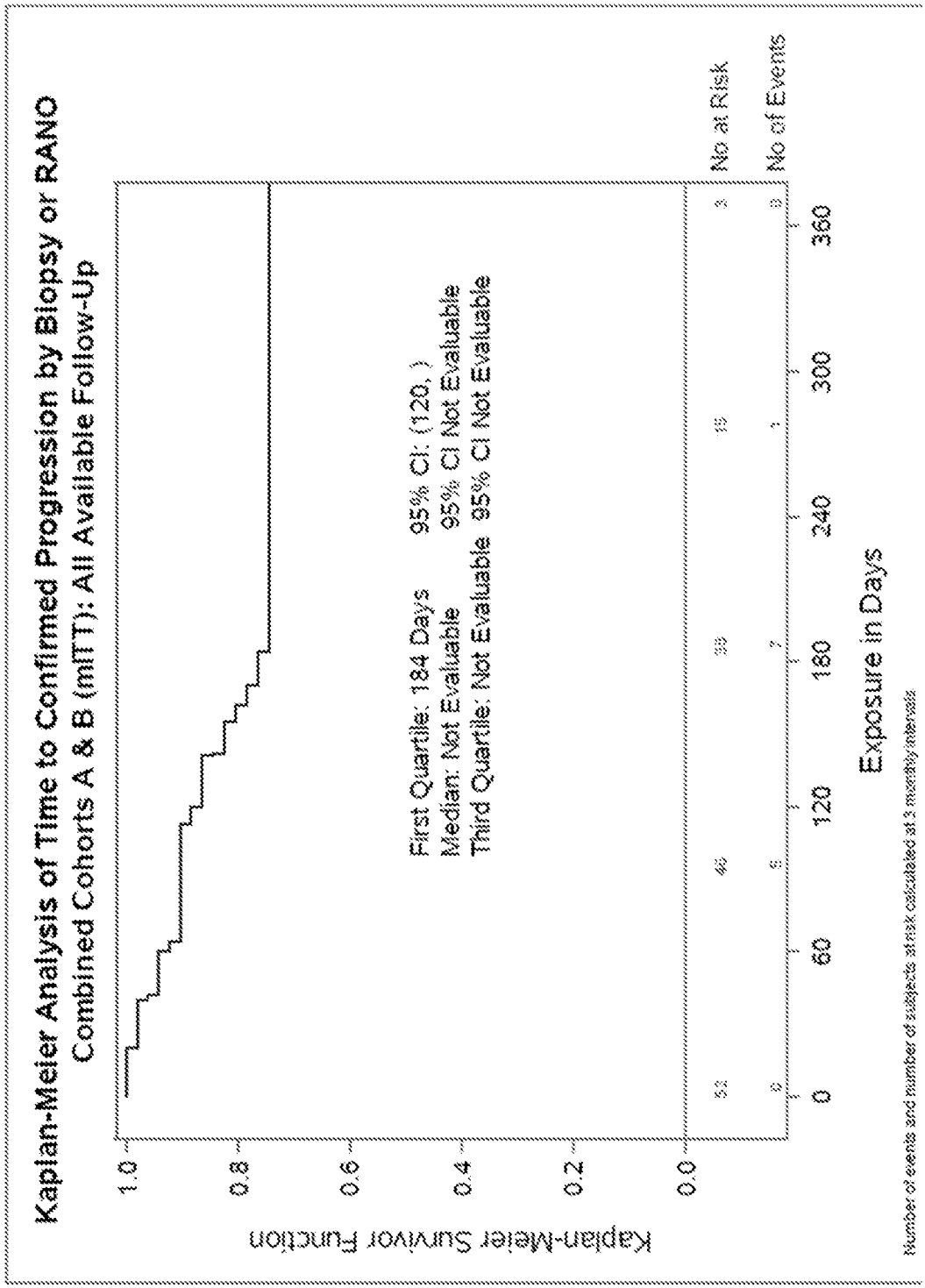


Figure 9

Cohort	N Total Subjects	N Event-free Subjects	PFS6 (%)	95% CI Lower Bound	95% CI Upper Bound
Cohort A (MGMT Unmethylated)	32	24	75.00	56.60	88.54
Cohort B (MGMT Methylated)	20	16	80.00	56.34	94.27
Both Cohorts Combined	52	40	76.92	63.16	87.47

Figure 10A

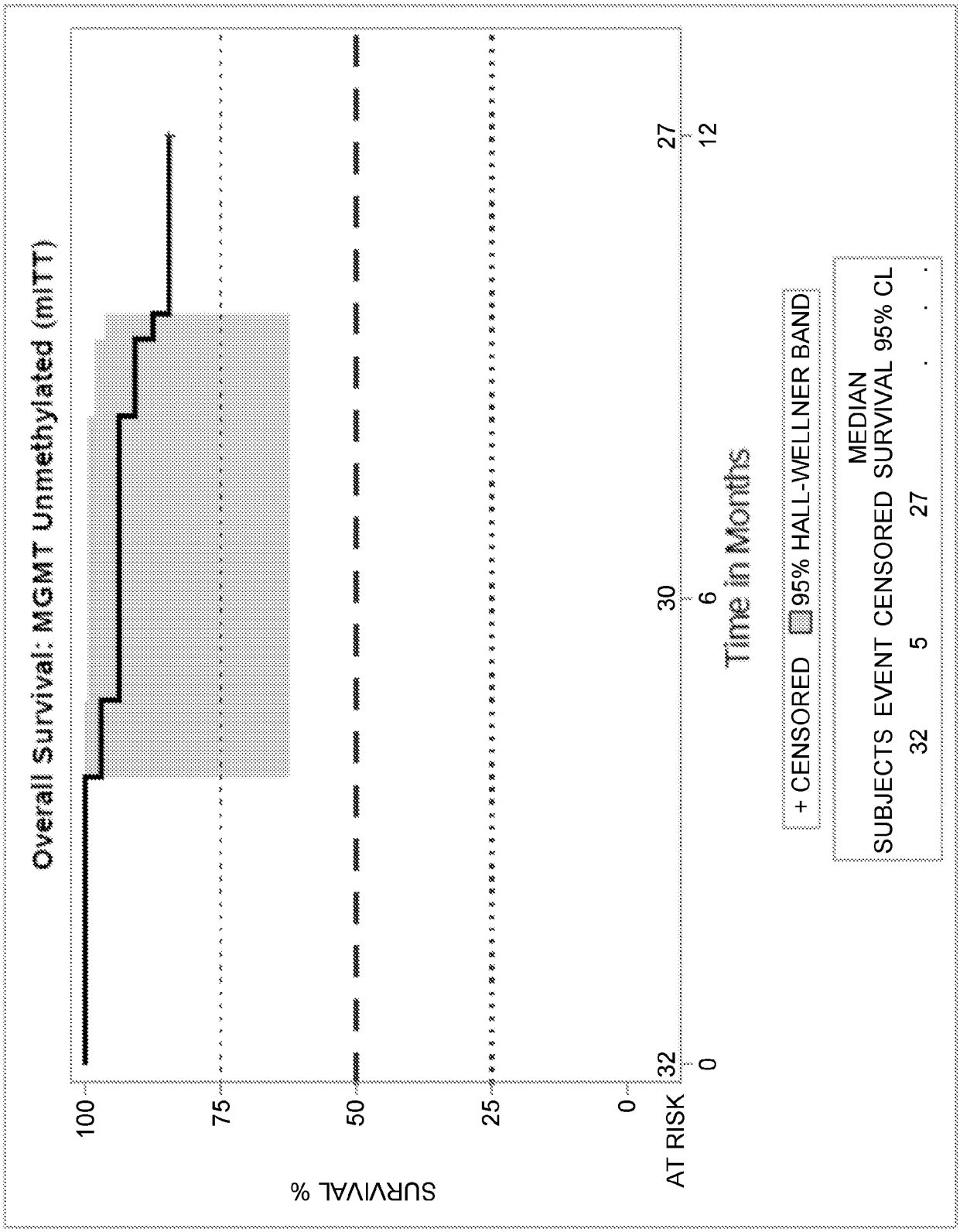

Overall Survival: MGMT Unmethylated (mITT)
SURVIVAL %
100
75
50
25
0
AT RISK
32
30
27
12
0
6
Time in Months
+ CENSORED
95% HALL-WELLNER BAND
MEDIAN
SUBJECTS EVENT CENSORED SURVIVAL 95% CL
32 5 27 . . .

Figure 10B

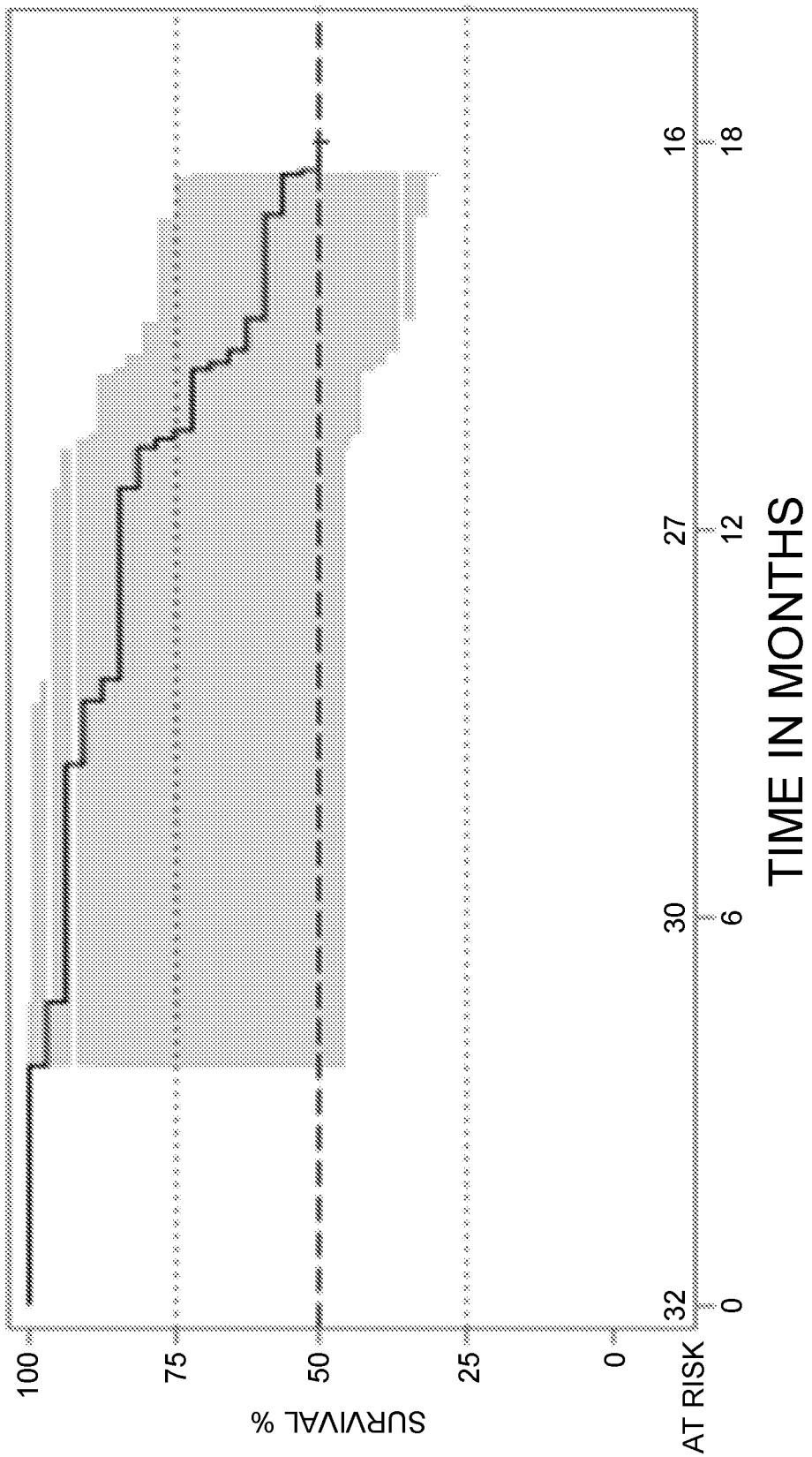

MGMT UNMETHYLATED (mITT)
SURVIVAL %
100
75
50
25
0
AT RISK
32
30
27
16
0
6
12
18
TIME IN MONTHS

Figure 11A

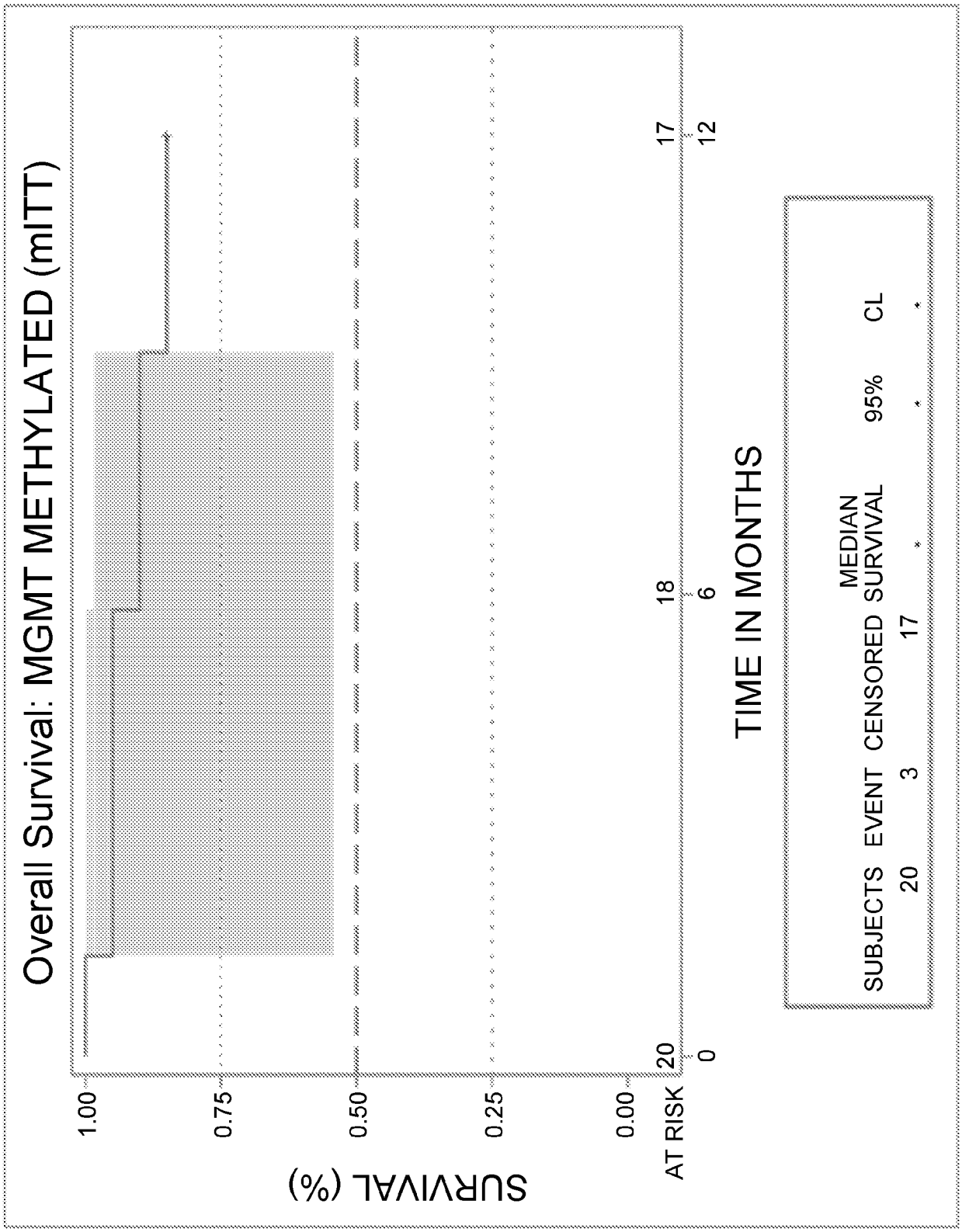

Overall Survival: MGMT METHYLATED (mITT)
SURVIVAL (%)
1.00
0.75
0.50
0.25
0.00
AT RISK
20
18
17
12
0
6
TIME IN MONTHS
SUBJECTS EVENT CENSORED MEDIAN SURVIVAL 95% CL
20 3 17 * * *

Figure 11B

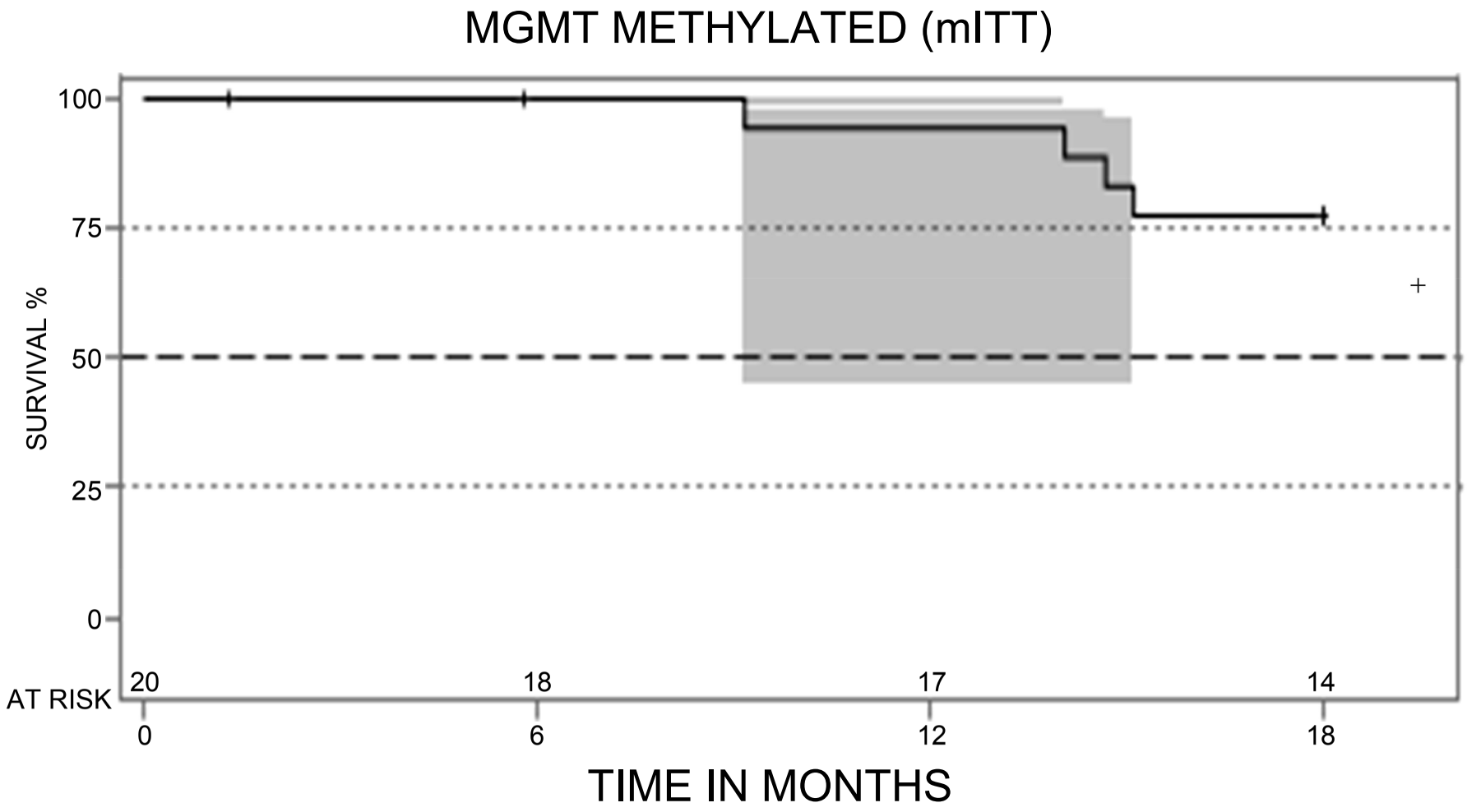

MGMT METHYLATED (mITT)
100
75
50
25
0
SURVIVAL %
AT RISK
20
18
17
14
0
6
12
18
TIME IN MONTHS

Figure 12

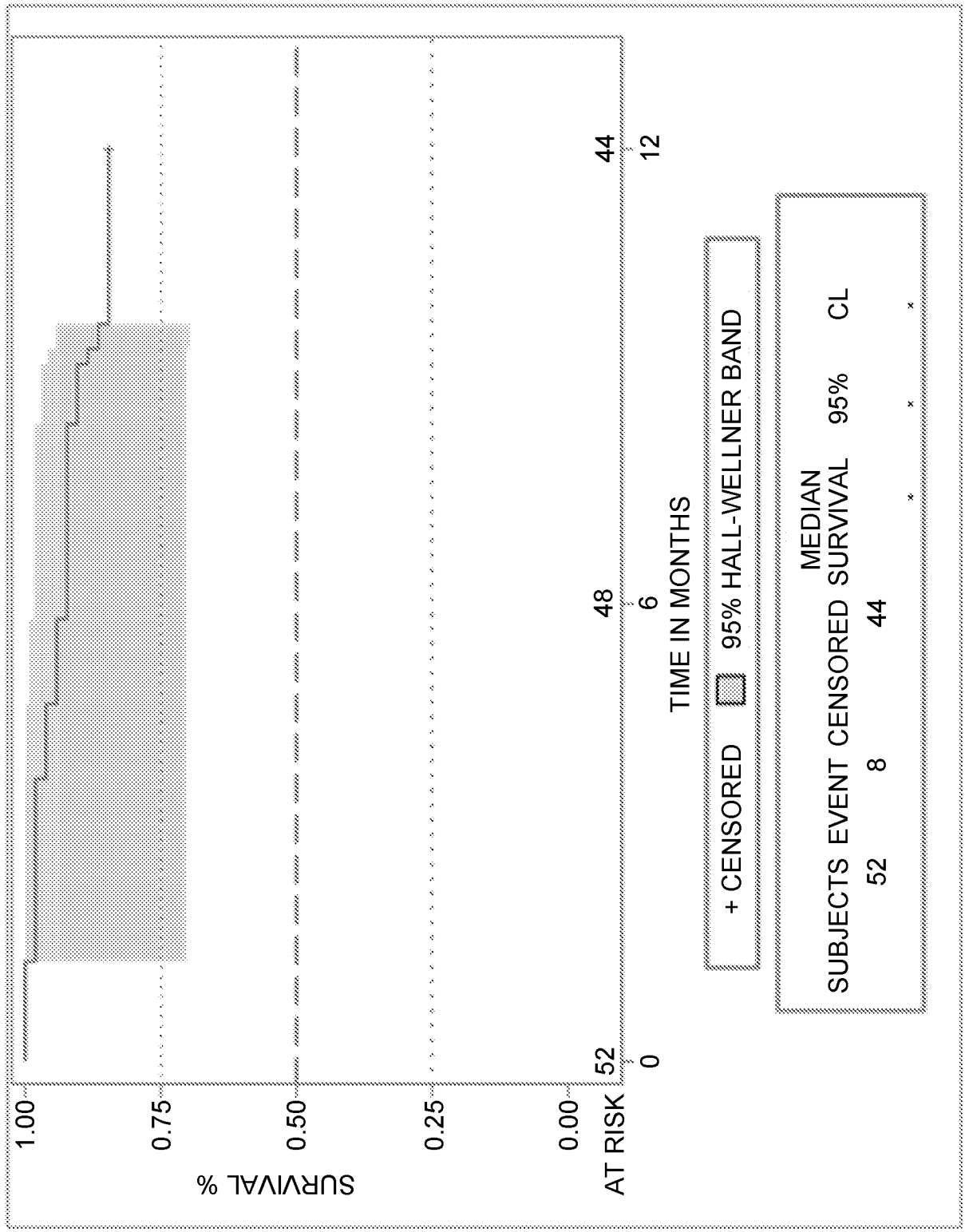

OVERALL SURVIVAL: MGMT UNMETHYLATED & METHYLATED (mITT)
SURVIVAL %
1.00
0.75
0.50
0.25
0.00
AT RISK
52
48
44
0
6
12
TIME IN MONTHS
+ CENSORED
95% HALL-WELLNER BAND
MEDIAN
SUBJECTS EVENT CENSORED SURVIVAL 95% CL
52 8 44

Figure 13 Interim Overall Survival at 18 Months

Median OS; unmethylated (Cohort A)	**17.9 mo (14.5-NR)**	
Median OS; methylated (Cohort B)	**NR (18.4-NR)**	
Overall Survival at 12 Months	**n Alive/N Total**	**OS12 (95% CI)**
MGMT Unmethylated (Cohort A)	**27/32**	**84.4 (67.2-94.7)**
MGMT Methylated (Cohort B)	**17*/20**	**85.0 (62.1-96.8)**
Combined	**44/52**	**84.6 (71.9-93.1)**
Overall Survival at 18 Months	**n Alive/N Total**	**OS18 (95% CI)**
MGMT Unmethylated (Cohort A)	**16/32**	**50 (31.9-68.1)**
MGMT Methylated (Cohort B)	**14/20***	**70 (45.7-88.1)**
Combined	**30/52**	**57.7 (14.5-71.3)**

* Two patients in Cohort B withdrew consent for additional follow-up at Week 3 and are included in the denominator

NR: not reached

Figure 14 NCI CTCAE ≥3 Adverse Events Reported in More than One Subject

System Organ Class Preferred Term	Unmethylated MGMT (Cohort A) (N=32) n(%)	Methylated MGMT (Cohort B) (N=20) n(%)	Combined Unmethylated/ Methylated MGMT (N=52) n(%)
Blood and lymphatic system disorders			
Anaemia	1 (3.1)	1 (5.0)	2 (3.8)
Gastrointestinal disorders			
Diarrhoea	2 (6.3)	0 (0.0)	2 (3.8)
Infections and infestations			
Pneumonia	2 (6.3)	0 (0.0)	2 (3.8)
Investigations			
Amylase increased	1 (3.1)	1 (5.0)	2 (3.8)
Alanine aminotransferase increased	2 (6.3)	2 (10.0)	4 (7.7)
Lipase increased	1 (3.1)	2 (10.0)	3 (5.8)
Lymphocyte count decreased	4 (12.5)	2 (10.0)	6 (11.5)
Neutrophil count decreased	0 (0.0)	3 (15.0)	3 (5.8)
Platelet count decreased	2 (6.3)	4 (20.0)	6 (11.5)
White blood cell count decreased	0 (0.0)	3 (15.0)	3 (5.8)
Metabolism and nutrition disorders			
Hyponatraemia	2 (6.3)	0 (0.0)	2 (3.8)
Musculoskeletal and connective tissue disorders			
Muscular weakness	2 (6.3)	0	2 (3.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour inflammation	3 (9.4)	1 (5.0)	4 (7.7)
Nervous system disorders			
Hemiparesis	1 (3.1)	1 (5.0)	2 (3.8)
Seizure	4 (12.5)	0 (0.0)	4 (7.7)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	2 (6.3)	0 (0.0)	2 (3.8)
Pulmonary embolism	2 (6.3)	1 (5.0)	3 (5.8)
Skin and subcutaneous tissue disorders			
Rash maculo-papular	2 (6.3)	0 (0.0)	2 (3.8)

Note: MGMT = O6-methylguanine methyltransferase. TEAE = Treatment-emergent adverse event. Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22. If a subject experienced more than one event in a given system organ class, that subject is counted once for that system organ class. If a subject experienced more than one event with a given preferred term, that subject is counted only once for that preferred term by highest severity grade.

Figure 15 Immune-Related Adverse Events

System Organ Class Preferred Term	Unmethylated MGMT (Cohort A) (N=32)	Methylated MGMT (Cohort B) (N=20)	Combined Unmethylated/ Methylated MGMT (N=52)
Cardiac disorders			
Myocarditis		1	1
Endocrine disorders			
Diabetes insipidus	0	1	1
Immune-related hypothyroidism	2	0	2
Gastrointestinal disorders			
Diarrhoea	3	1	4
Immune-mediated enterocolitis	1	0	1
Pancreatitis	0	1	1
General disorders and administration site conditions			
Fatigue		1	1
Influenza like illness	1	1	2
Night sweats	0	1	1
Pyrexia	2	2	4
Hepatobiliary disorders			
Immune-mediated hepatitis*	3	0	3
Immune system disorders			
Hypersensitivity	1	0	1
Myasthenia gravis	0	1	1
Investigations			
Alanine aminotransferase increased	4	1	5
Amylase increased	1	0	1
Aspartate aminotransferase increased	4	0	1
Increased alkaline phosphatase	1	0	1
Lipase increased	0	1	1
Transaminitis	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia*	4	0	4
Eosinophilic fasciitis	0	1	1
Muscular weakness	0	1	1
Myositis	0	1	1
Nervous system disorders			
Brain Oedema	2	0	2
Encephalitis autoimmune	0	1	1
Headache	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Figure 15 Immune-Related Adverse Events - continued

Tumour inflammation	4	1	5
Renal and urinary disorders			
Acute kidney injury	1	1	2
Autoimmune nephritis*	3	0	3
Haematuria	0	1	1
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	3	0	3
Skin and subcutaneous tissue disorders			
Pruritus	1	1	2
Rash	0	1	1
Rash erythematous	1	0	1
Rash maculo-papular	2	0	2
Rash papular	1	0	1
Urticaria	1	0	1

*Subject experienced same event more than one time.
Arthralgia: 2 events reported for one subject
Autoimmune nephritis: 3 events reported for one subject
Immune-mediated hepatitis: 2 events reported for one subject

Figure 16A

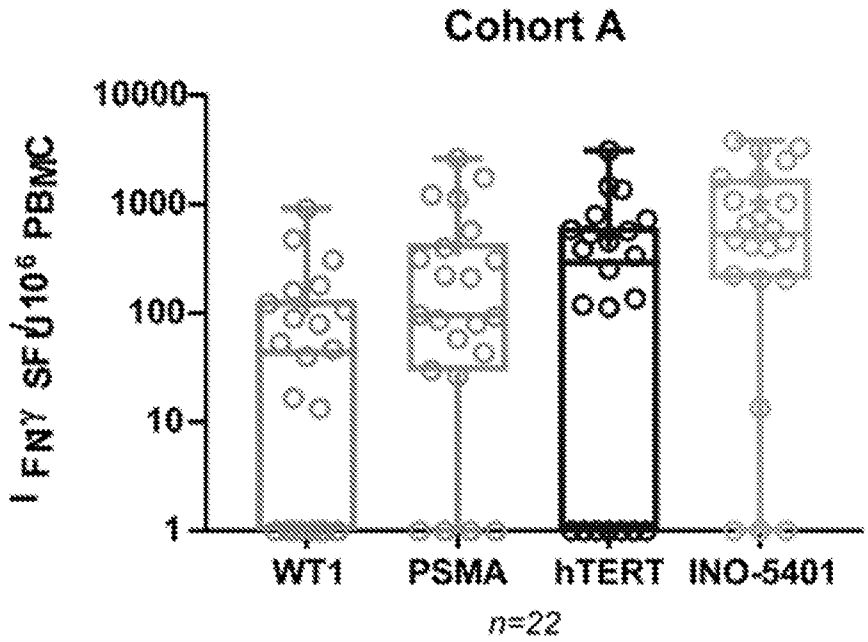


Figure 16B

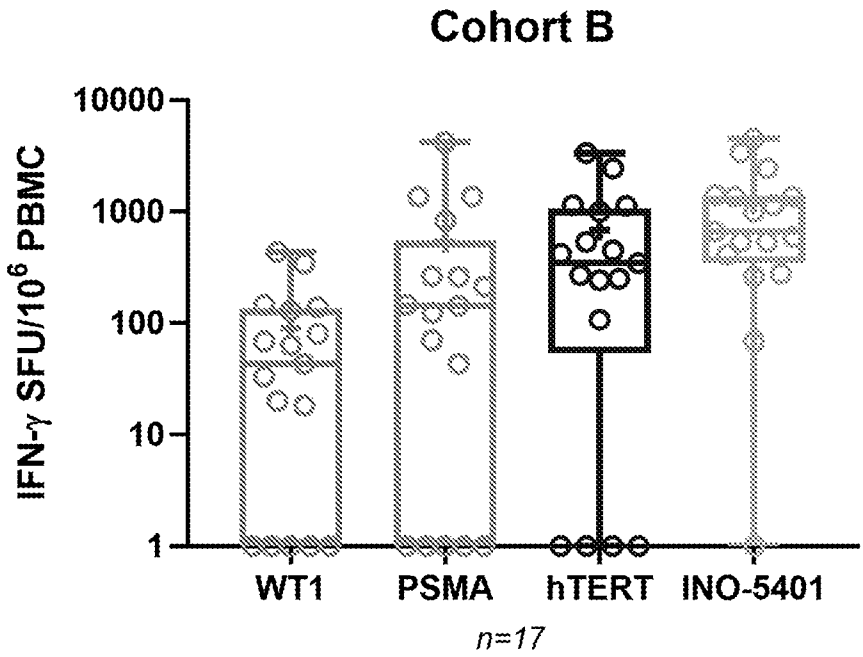


Figure 17A

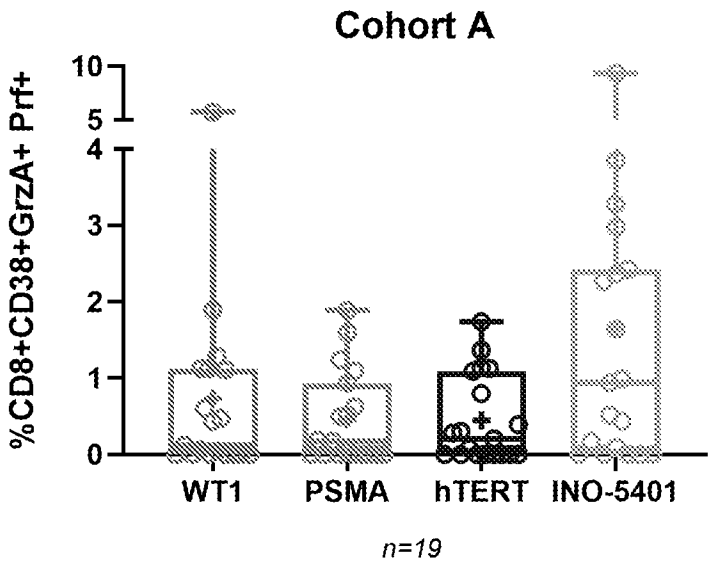
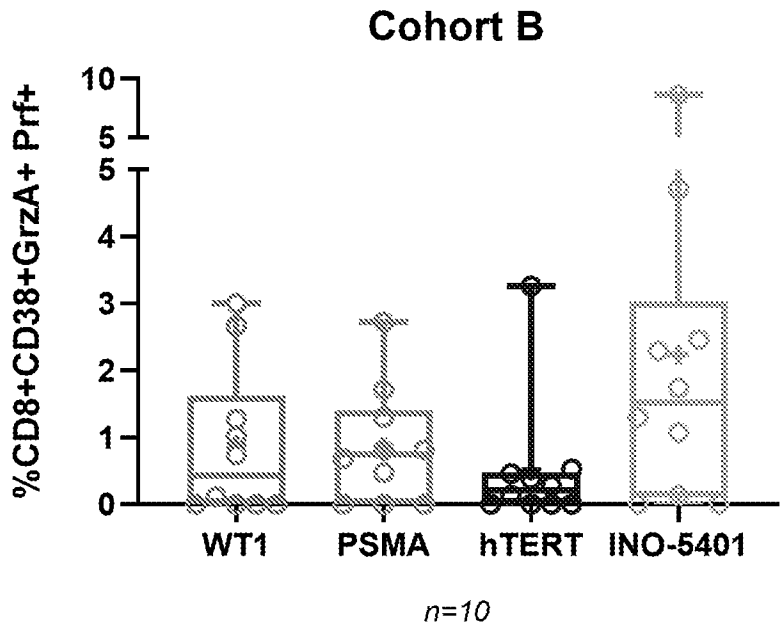


Figure 17B



SEQUENCE LISTING

<110> INOVIO PHARMACEUTICALS, INC.
REGENERON PHARMACEUTICALS, INC.
YAN, JIAN
FERRARO, BERNADETTE
WALTERS, JEWELL

<120> COMBINATION THERAPY TO TREAT BRAIN CANCER

<130> 104409.000581

<140>
<141>

<150> 63/070,987
<151> 2020-08-27

<150> 63/018,060
<151> 2020-04-30

<150> 62/988,102
<151> 2020-03-11

<150> 62/930,417
<151> 2019-11-04

<160> 29

<170> PatentIn version 3.5

<210> 1
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 1
Glu Val Gln Leu Leu Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
20 25 30

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

Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
        115

<210> 2
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 2
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Ser Ile Thr Ile Thr Cys Arg Ala Ser Leu Ser Ile Asn Thr Phe
            20   25   30

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

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

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

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

Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg
            100   105

<210> 3
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 3
Gly Phe Thr Phe Ser Asn Phe Gly
1   5

<210> 4
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 4
Ile Ser Gly Gly Gly Arg Asp Thr
1   5

<210> 5
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 5
Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr
1 5 10

<210> 6
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 6
Leu Ser Ile Asn Thr Phe
1 5

<210> 7
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 7
Ala Ala Ser
1

<210> 8
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 8
Gln Gln Ser Ser Asn Thr Pro Phe Thr
1 5

<210> 9
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 9
Glu Val Gln Leu Leu Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly

```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30

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

Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe Ala Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140

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

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
    210                 215                 220

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
            260                 265                 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285
```

```
Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
                325                 330                 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
            340                 345                 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385                 390                 395                 400

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
                405                 410                 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            420                 425                 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440
```

<210> 10
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 10

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

Asp Ser Ile Thr Ile Thr Cys Arg Ala Ser Leu Ser Ile Asn Thr Phe
            20                  25                  30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Thr Leu Gln Pro
```

65 70 75 80

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

Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 11
<211> 2283
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 11
atgtggaacg cactgcatga gactgattct gctgtcgcac tgggacggag accccggtgg 60

ctgtgcgctg gagcactggt gctggccggc gggggattcc tgctgggatt cctgtttggc 120

tggtttatca aaagctccag cgaggctacc aatattaccc ctaagcacaa taagaaagca 180

ttcctggatg aactgaaagc cgagaacatc aagaaattcc tgtacaactt cacaagaatt 240

ccacatctgg ctggcactga gcagaacttc cagctggcaa aacagatcca gagtcagtgg 300

aaggaatttg ggctggactc agtggagctg acccactacg atgtcctgct gtcctatcca 360

aataagactc atcccaacta catctctatc attaacgaag acggaaatga gattttcaac 420

acctctctgt ttgaaccccc tccacccggc tatgagaatg tcagtgacgt ggtccctcca 480

ttctcagcct tcagccccca ggggatgcct gagggagatc tggtgtacgt caattatgct 540

agaacagaag acttctttaa gctggagagg gatatgaaaa tcaactgttc cggcaagatc 600

gtgattgccc ggtacgggaa ggtgttcaga ggaaataagg tcaaaaacgc tcagctggcc 660

ggagctaccg gcgtgatcct gtacagcgac cccgctgatt attttgcacc tggcgtgaag 720

tcctatccag acggatggaa tctgcccggc gggggagtgc agaggggaaa catcctgaac 780

ctgaatggag ccggcgatcc tctgactcca ggataccccg ccaacgaata cgcttatcgc 840

cggggaattg cagaggccgt gggcctgcct agcatcccag tccatcccat tggctattac 900

gatgcccaga agctgctgga gaaaatgggc gggagcgctc cccctgactc tagttggaag 960

ggctccctga aagtgcctta caatgtcggg ccaggattca ctgggaactt ttctacccag 1020

aaggtgaaaa tgcacatcca tagtaccagc gaggtgacac gaatctacaa cgtcattggc 1080

accctgagag gcgccgtgga gcctgatcgc tatgtcattc tgggaggcca cagagactca 1140

tgggtgttcg ggggaatcga tccacagagc ggagcagctg tggtccatga aattgtgcgc 1200

agctttggga ccctgaagaa agagggatgg cgacccaggc gcacaatcct gttcgcatcc 1260

tgggacgccg aggaatttgg gctgctgggc agcacagaat gggccgagga aaattctcgc 1320

ctgctgcagg agcgaggggt ggcttacatc aatgcagact caagcattga aggaaactat 1380

accctgcggg tggattgcac acccctgatg tacagtctgg tctataacct gacaaaggag 1440

ctgaaatcac ctgacgaggg cttcgaaggg aaaagcctgt acgaatcctg gactgagaag 1500

agcccatccc ccgaattcag cggcatgcct aggatctcta agctgggcag tgggaacgat 1560

tttgaggtgt tctttcagcg cctgggaatt gcctctggcc gagctcggta cacaaaaaat 1620

tgggagacta acaagttctc ctcttaccca ctgtatcaca gcgtgtacga gacttatgaa 1680

ctggtcgaga aattctacga ccccactttt aagtatcatc tgaccgtggc acaggtcagg 1740

ggcgggatgg tgttcgaact ggccaatagc atcgtcctgc catttgactg tcgagattac 1800

gctgtggtcc tgcggaagta cgcagacaag atctataaca tctccatgaa gcacccccag 1860

gagatgaagg cctattctgt gagtttcgat tccctgtttt ctgccgtcaa aaatttcacc 1920

gaaatcgcta gtaagttttc agagcgcctg caggacctgg ataagtccaa tcccatcctg 1980

ctgcggatta tgaacgatca gctgatgttc ctggaaagag cctttatcga ccctctgggc 2040

ctgcctgata gaccattcta caggcacgtg atctacgcac ctagttcaca taacaagtac 2100

gccggcgagt ctttcccagg gatctatgac gctctgtttg atattgaatc aaaggtggac 2160

cccagcaaag catggggcga ggtcaagaga cagatcagca ttgcagcctt tacagtgcag 2220

gccgccgccg aaaccctgtc cgaagtcgct tacccatacg atgtccccga ttacgcatga 2280

taa 2283

<210> 12
<211> 2334
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 12

atggactgga catggattct gttcctggtc gccgccgcaa ctcgcgtgca ttcctggaac 60

gcactgcatg agactgattc tgctgtcgca ctgggacgga gaccccggtg gctgtgcgct 120

ggagcactgg tgctggccgg cgggggattc ctgctgggat tcctgtttgg ctggtttatc 180

aaaagctcca gcgaggctac caatattacc cctaagcaca ataagaaagc attcctggat 240

gaactgaaag ccgagaacat caagaaattc ctgtacaact tcacaagaat tccacatctg 300

gctggcactg agcagaactt ccagctggca aaacagatcc agagtcagtg gaaggaattt 360

gggctggact cagtggagct gacccactac gatgtcctgc tgtcctatcc aaataagact 420

catcccaact acatctctat cattaacgaa gacggaaatg agattttcaa cacctctctg 480

tttgaacccc ctccacccgg ctatgagaat gtcagtgacg tggtccctcc attctcagcc 540

ttcagccccc aggggatgcc tgagggagat ctggtgtacg tcaattatgc tagaacagaa 600

gacttcttta agctggagag ggatatgaaa atcaactgtt ccggcaagat cgtgattgcc 660

cggtacggga aggtgttcag aggaaataag gtcaaaaacg ctcagctggc cggagctacc 720

ggcgtgatcc tgtacagcga ccccgctgat tattttgcac ctggcgtgaa gtcctatcca 780

gacggatgga atctgcccgg cgggggagtg cagaggggaa acatcctgaa cctgaatgga 840

gccggcgatc ctctgactcc aggatacccc gccaacgaat acgcttatcg ccggggaatt 900

gcagaggccg tgggcctgcc tagcatccca gtccatccca ttggctatta cgatgcccag 960

aagctgctgg agaaaatggg cgggagcgct ccccctgact ctagttggaa gggctccctg 1020

aaagtgcctt acaatgtcgg gccaggattc actgggaact tttctaccca gaaggtgaaa 1080

atgcacatcc atagtaccag cgaggtgaca cgaatctaca acgtcattgg caccctgaga 1140

ggcgccgtgg agcctgatcg ctatgtcatt ctgggaggcc acagagactc atgggtgttc 1200

gggggaatcg atccacagag cggagcagct gtggtccatg aaattgtgcg cagctttggg 1260

accctgaaga aagagggatg gcgacccagg cgcacaatcc tgttcgcatc ctgggacgcc 1320

gaggaatttg ggctgctggg cagcacagaa tgggccgagg aaaattctcg cctgctgcag 1380

gagcgagggg tggcttacat caatgcagac tcaagcattg aaggaaacta taccctgcgg 1440

gtggattgca cacccctgat gtacagtctg gtctataacc tgacaaagga gctgaaatca 1500

cctgacgagg gcttcgaagg gaaaagcctg tacgaatcct ggactgagaa gagcccatcc 1560

cccgaattca gcggcatgcc taggatctct aagctgggca gtgggaacga ttttgaggtg 1620

ttctttcagc gcctgggaat tgcctctggc cgagctcggt acacaaaaaa ttgggagact 1680

aacaagttct cctcttaccc actgtatcac agcgtgtacg agacttatga actggtcgag 1740

aaattctacg accccacttt taagtatcat ctgaccgtgg cacaggtcag gggcgggatg 1800

gtgttcgaac tggccaatag catcgtcctg ccatttgact gtcgagatta cgctgtggtc 1860

ctgcggaagt acgcagacaa gatctataac atctccatga agcaccccca ggagatgaag 1920

gcctattctg tgagtttcga ttccctgttt tctgccgtca aaaatttcac cgaaatcgct 1980

agtaagtttt cagagcgcct gcaggacctg gataagtcca atcccatcct gctgcggatt 2040

atgaacgatc agctgatgtt cctggaaaga gcctttatcg accctctggg cctgcctgat 2100

agaccattct acaggcacgt gatctacgca cctagttcac ataacaagta cgccggcgag 2160

tctttcccag ggatctatga cgctctgttt gatattgaat caaaggtgga ccccagcaaa 2220

gcatggggcg aggtcaagag acagatcagc attgcagcct ttacagtgca ggccgccgcc 2280

gaaaccctgt ccgaagtcgc ttacccatac gatgtccccg attacgcatg ataa 2334

<210> 13
<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 13
Met Trp Asn Ala Leu His Glu Thr Asp Ser Ala Val Ala Leu Gly Arg
1 5 10 15

Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Gly
20 25 30

Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser Glu
35 40 45

Ala Thr Asn Ile Thr Pro Lys His Asn Lys Lys Ala Phe Leu Asp Glu
50 55 60

Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Arg Ile
65 70 75 80

Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
85 90 95

Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr His
100 105 110

Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
115 120 125

Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
130 135 140

Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Val Val Pro Pro
145 150 155 160

Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
165 170 175

Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
180 185 190

Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val

```
        195                 200                 205

Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr Gly
    210                 215                 220

Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
225                 230                 235                 240

Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
                245                 250                 255

Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
            260                 265                 270

Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
        275                 280                 285

Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
    290                 295                 300

Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Lys
305                 310                 315                 320

Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
                325                 330                 335

Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu Val
            340                 345                 350

Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
        355                 360                 365

Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
    370                 375                 380

Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
385                 390                 395                 400

Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
                405                 410                 415

Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr
            420                 425                 430

Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
        435                 440                 445

Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
    450                 455                 460

Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys Glu
465                 470                 475                 480
```

```
Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser
                485                 490                 495

Trp Thr Glu Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
            500                 505                 510

Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu
        515                 520                 525

Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr Asn
    530                 535                 540

Lys Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr Glu
545                 550                 555                 560

Leu Val Glu Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu Thr Val
                565                 570                 575

Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile Val
            580                 585                 590

Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala
        595                 600                 605

Asp Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys Ala
    610                 615                 620

Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr
625                 630                 635                 640

Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Leu Asp Lys Ser
                645                 650                 655

Asn Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Phe Leu Glu
            660                 665                 670

Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
        675                 680                 685

His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
    690                 695                 700

Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
705                 710                 715                 720

Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Ser Ile Ala Ala
                725                 730                 735

Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
            740                 745                 750
```

<210> 14
<211> 767
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 14
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Trp Asn Ala Leu His Glu Thr Asp Ser Ala Val Ala Leu Gly
20 25 30

Arg Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly
35 40 45

Gly Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser
50 55 60

Glu Ala Thr Asn Ile Thr Pro Lys His Asn Lys Lys Ala Phe Leu Asp
65 70 75 80

Glu Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Arg
85 90 95

Ile Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln
100 105 110

Ile Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr
115 120 125

His Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr
130 135 140

Ile Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu
145 150 155 160

Phe Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Val Val Pro
165 170 175

Pro Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val
180 185 190

Tyr Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp
195 200 205

Met Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys
210 215 220

Val Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr
225 230 235 240

```
Gly Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val
                245                 250                 255

Lys Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg
            260                 265                 270

Gly Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly
        275                 280                 285

Tyr Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val
    290                 295                 300

Gly Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln
305                 310                 315                 320

Lys Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp
                325                 330                 335

Lys Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly
            340                 345                 350

Asn Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu
        355                 360                 365

Val Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu
    370                 375                 380

Pro Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe
385                 390                 395                 400

Gly Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val
                405                 410                 415

Arg Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr
            420                 425                 430

Ile Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser
        435                 440                 445

Thr Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val
    450                 455                 460

Ala Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg
465                 470                 475                 480

Val Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys
                485                 490                 495

Glu Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu
            500                 505                 510
```

```
Ser Trp Thr Glu Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg
        515                 520                 525

Ile Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg
    530                 535                 540

Leu Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr
545                 550                 555                 560

Asn Lys Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr
                565                 570                 575

Glu Leu Val Glu Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu Thr
            580                 585                 590

Val Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile
        595                 600                 605

Val Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr
    610                 615                 620

Ala Asp Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys
625                 630                 635                 640

Ala Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe
                645                 650                 655

Thr Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Leu Asp Lys
            660                 665                 670

Ser Asn Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Phe Leu
        675                 680                 685

Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr
    690                 695                 700

Arg His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu
705                 710                 715                 720

Ser Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val
                725                 730                 735

Asp Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Ser Ile Ala
            740                 745                 750

Ala Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
        755                 760                 765
```

<210> 15
<211> 1332
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 15
ggatccgcca ccatggactg gacctggatt ctgttcctgg tcgccgccgc aacacgggtg 60

catagtggga gtgatgtgag agacctgaac gccctgctgc cagcagtgcc atccctgcct 120

ggcgggggag gctgcgctct gccagtctct ggagcagctc agtgggctcc cgtgctggac 180

tttgcacccc ctgcagcccc ttacggaagt ctgggcggcc cacactcatt catcaaacag 240

gagccaagct ggggcggggc agatcctcat gaggaacagt gcctgtcagc cttcacagtc 300

cactttagcg ggcagttcac tggaaccgca ggagcttgta gatacggacc ctttggagca 360

ccacccccct cccaggcacc ttctggacag gcacgcatgt tcccaaacgc tccctatctg 420

cctaattgtc tggaaagcca gcccgctatt aggaaccagg gctactccac agtggcattt 480

gacgggactc ctagctatgg acatacccca tcccaccatg ctgcacagtt tcctaatcac 540

tccttcaagc atgaggaccc catgggacag caggggtccc tgggagaaca gcagtactct 600

gtgccccctc ccgtgtacgg atgccacaca ccaactgaca gttgtacagg ctcacaggcc 660

ctgctgctgc gaactccata caacagtgat aatctgtatc agatgacctc acagctggag 720

tgcatgacat ggaaccagat gaatctgggc agcacactga aaggccatgc cactgggtac 780

gaatctgaca accacaccac acctatgctg tacagttgtg gagcccagta tagaatccac 840

actcatggag tcttcagagg cattcaggat gtgcggagag tcccaggagt ggcaccaact 900

atcgtgcgga gcgcctccga gaccaacgaa aagcgcccct ttatgggcgc ctaccctgga 960

ggcaataagc ggtatttcaa actgtctcac ctgcagatgg ggagtagaaa ggggaccgga 1020

gagaaacctt atcagggcga ctttaaagat ggggaaaggc gcttctctcg cagtgaccag 1080

ctgaagcgag gacagcgacg aggaaccggg gtgaagccat ttcagtgcaa aacatgtcag 1140

agaaagttct caaggagcga tcacctgaag acccatacaa gaactcacac cggcaagacc 1200

agcgagaaac cattttcctg ccgatggccc tcttgtcaga agaaattcgc ccgctccgac 1260

gaactggtcc gacaccacaa tatgcatcag agaaatatga caaaactgca gctggctctg 1320

tgataactcg ag 1332

<210> 16
<211> 436
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 16
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Gly Ser Asp Val Arg Asp Leu Asn Ala Leu Leu Pro Ala Val
20 25 30

```
Pro Ser Leu Pro Gly Gly Gly Gly Cys Ala Leu Pro Val Ser Gly Ala
        35                  40                  45

Ala Gln Trp Ala Pro Val Leu Asp Phe Ala Pro Pro Ala Ala Pro Tyr
    50                  55                  60

Gly Ser Leu Gly Gly Pro His Ser Phe Ile Lys Gln Glu Pro Ser Trp
65                  70                  75                  80

Gly Gly Ala Asp Pro His Glu Glu Gln Cys Leu Ser Ala Phe Thr Val
                85                  90                  95

His Phe Ser Gly Gln Phe Thr Gly Thr Ala Gly Ala Cys Arg Tyr Gly
            100                 105                 110

Pro Phe Gly Ala Pro Pro Pro Ser Gln Ala Pro Ser Gly Gln Ala Arg
        115                 120                 125

Met Phe Pro Asn Ala Pro Tyr Leu Pro Asn Cys Leu Glu Ser Gln Pro
    130                 135                 140

Ala Ile Arg Asn Gln Gly Tyr Ser Thr Val Ala Phe Asp Gly Thr Pro
145                 150                 155                 160

Ser Tyr Gly His Thr Pro Ser His His Ala Ala Gln Phe Pro Asn His
                165                 170                 175

Ser Phe Lys His Glu Asp Pro Met Gly Gln Gln Gly Ser Leu Gly Glu
            180                 185                 190

Gln Gln Tyr Ser Val Pro Pro Pro Val Tyr Gly Cys His Thr Pro Thr
        195                 200                 205

Asp Ser Cys Thr Gly Ser Gln Ala Leu Leu Leu Arg Thr Pro Tyr Asn
    210                 215                 220

Ser Asp Asn Leu Tyr Gln Met Thr Ser Gln Leu Glu Cys Met Thr Trp
225                 230                 235                 240

Asn Gln Met Asn Leu Gly Ser Thr Leu Lys Gly His Ala Thr Gly Tyr
                245                 250                 255

Glu Ser Asp Asn His Thr Thr Pro Met Leu Tyr Ser Cys Gly Ala Gln
            260                 265                 270

Tyr Arg Ile His Thr His Gly Val Phe Arg Gly Ile Gln Asp Val Arg
        275                 280                 285

Arg Val Pro Gly Val Ala Pro Thr Ile Val Arg Ser Ala Ser Glu Thr
    290                 295                 300
```

```
Asn Glu Lys Arg Pro Phe Met Gly Ala Tyr Pro Gly Gly Asn Lys Arg
305                 310                 315                 320

Tyr Phe Lys Leu Ser His Leu Gln Met Gly Ser Arg Lys Gly Thr Gly
                325                 330                 335

Glu Lys Pro Tyr Gln Gly Asp Phe Lys Asp Gly Glu Arg Arg Phe Ser
            340                 345                 350

Arg Ser Asp Gln Leu Lys Arg Gly Gln Arg Arg Gly Thr Gly Val Lys
        355                 360                 365

Pro Phe Gln Cys Lys Thr Cys Gln Arg Lys Phe Ser Arg Ser Asp His
    370                 375                 380

Leu Lys Thr His Thr Arg Thr His Thr Gly Lys Thr Ser Glu Lys Pro
385                 390                 395                 400

Phe Ser Cys Arg Trp Pro Ser Cys Gln Lys Lys Phe Ala Arg Ser Asp
                405                 410                 415

Glu Leu Val Arg His His Asn Met His Gln Arg Asn Met Thr Lys Leu
            420                 425                 430

Gln Leu Ala Leu
        435
```

<210> 17
<211> 3447
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 17

```
atggattgga catggattct gttcctggtc gcagccgcca cacgagtgca tagccctaga       60

gccccacggt gtagagcagt ccgcagcctg ctgcgcagcc gataccggga agtgctgcct      120

ctggccacct ttgtccggag actgggacca cagggcaggc gcctggtgca gcgcggcgac      180

cccgcagctt tccgagcact ggtggcacag tgcctggtgt gcgtgccatg ggatgcacgg      240

ccccctccag cagcccctag ctttagacag gtgtcctgcc tgaaagaact ggtcgcaagg      300

gtggtccagc ggctgtgcga gagaggcgcc aggaacgtgc tggcattcgg ctttgcactg      360

ctggacggag ctaggggcgg gccccctgag gcattcacca caagcgtgcg ctcctacctg      420

ccaaatacag tcactgatac cctgcgaggc tccggagcat ggggactgct gctgcgacgg      480

gtgggggacg atgtgctggt ccacctgctg gctagatgcg cactgtatgt gctggtcgct      540

ccctcttgcg cataccaggt gtgcggacca cccctgtatg acctgggcgc tgcaacccag      600

gcaagacctc caccccacgc ctctggcact agaaggggac tgggcaccga acaggcatgg      660
```

aaccatagtg tcagggaggc aggagtgcca ctgggactgc cagcacctgg ggctcgccga 720

cggagaggga gtgccggacg gtcactgcca ctggctaaga gaccaaggcg cggagccgct 780

ccagaaccag agaggacacc tgtgggacag ggaagctggg cacaccctgg aagaactagg 840

gggccaagtg ataggggctt ctgcgtggtc tcaccagcac gaccagcaga ggaagctact 900

tctctggagg gagctctgag tggcacccgg cactctcatc ctagtgtggg aagacagcac 960

catgcaggcc ctccaagcac cagccggcct ccccggccat gggacactcc ttgtccaccc 1020

gtgtacgctg aaaccaaaca ctttctgtat agctccggag ataaggagca gctgcggccc 1080

tctttcctgc tgtctagtct gagacctagt ctgaccggag cacgacggct ggtggaaaca 1140

atctttctgg ggtcccgccc ttggatgcca ggaaccccca gaaggacacc tcgactgcca 1200

cagcggtact ggcagatgcg gccactgttc ctggagctgc tgggcaatca cgctcagtgc 1260

ccctatgggg cactgctgcg aacacattgt cctctgcggg cagccgtgac tccagctgca 1320

ggagtctgcg ccagggaaaa gccacagggc agcgtggcag ctcctgagga agaggacacc 1380

gatccacgcc gactggtgca gctgctgaga cagcactcaa gcccctggca ggtgtacgga 1440

tttctgaggg cctgtctgcg gagactggtg cctccaggac tgtgggggtc caggcacaac 1500

gaaaggcgct ttctgcgcaa tactaagaaa ttcatcagcc tgggcaagca tgctaaactg 1560

tccctgcagg agctgacctg gaaaatgagt gtgcgcgact gcgcatggct gcgacggtca 1620

ccaggagtcg ggtgcgtgcc tgcagccgag caccgcctgc gagaagagat tctggccaag 1680

tttctgcatt ggctgatgtc agtgtacgtg gtcgaactgc tgcggagctt cttttatgtg 1740

acagagacta ccttccagaa aaactacctg ttcttttatc gcaagtcagt gtggagcaaa 1800

ctgcagtcaa tcggcattcg gcagcacctg aagagagtgc agctgaggga actgagtgaa 1860

gccgaggtcc ggcagcatag agaggcaagg cctgccctgc tgacctcccg gctgagattc 1920

ctgcctaagc cagacgggct gagaccaatc gtgaacatgg attacgtggt cggagcacgg 1980

accttccgga gggaaaaacg cgctgagcga ctgacatccc gcgtgaagac tctgttctct 2040

gtcctgaatt atgagcgagc tcgccgaccc ggactgctgg gagcatctgt gctgggactg 2100

gacgatattc accgggcttg gagagcattt gtcctgaggg tgcgcgcaca ggaccctccc 2160

ccagaactgt acttcgtgaa agtcgccgtg accggggctt atgacacaat ccctcaggat 2220

cggctgactg aagtgatcgc ctccatcatt aagccacaga atacctactg cgtgcggaga 2280

tatgctgtgg tcaggcgcgc tgcacacggc catgtgagga agagcttcaa gcgccacgtc 2340

agcacactga ctgatctgca gccctacatg agacagttcg tggctcatct gcaggagacc 2400

agccctctga gggacgcagt ggtcatcgaa cagtcctcta gtctgaacga ggcatcaagc 2460

gggctgttcg atgtctttct gcggttcgtg tgccaccatg ccgtcagaat tggaggcaaa 2520

tcttacgtgc agtgtcaggg catcccccag ggcagcattc tgtctaccct gctgtgcagc 2580

ctgtgctatg gcgacatgga aaataagctg tttgccggaa tccgacggga tggcctgctg 2640

ctgagactgg tggccgcttt tctgctggtc actccacacc tgacccatgc caaagctttc 2700

ctgcgcacac tggtccgagg ggtgccagag tacggatgcg tggtcaacct gaggaagacc 2760

gtggtcaatt tcccagtgga agacgaggcc ctgggcggca cagcatttgt ccagctgcca 2820

gcacacggac tgttcccatg gtgtggactg ctgctggaca cccgcacact ggaggtgcag 2880

tccgattact cctcttatgc ccggacaagc atcagagctt ccctgacttt taacagaggc 2940

ttcaaggccg ggaggaatat gagaaggaaa ctgtttggcg tgctgcgcct gaagtgccat 3000

tccctgttcc tgtatctgca ggtgaactct ctgcagactg tctgtaccaa cgtgtacaaa 3060

atttttctgc tgcaggccta tcggttccac gcttgcgtgc tgcagctgcc attccatcag 3120

caggtcagga agaaccccac cttctttctg cgcgtgatct ctgatacagc tagtctgtgc 3180

tactcaattc tgaaggccaa aaatgctggc atgagcctgg gagcaaaagg agcagcagga 3240

ccatttcctt ccgaggctgc acagtggctg tgccaccagg cattcctgct gaagctggcc 3300

cgacatcggg tgacatatag gtgcctgctg ggcgcactgc gaacagcaca gactcagctg 3360

tgcagaaagc tgcccggggc cactctggct gccctggaag ccgctgccga ccctgccctg 3420

acctccgatt tcaagactat tctggac 3447

<210> 18
<211> 1149
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 18
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg
20 25 30

Ser Arg Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu
35 40 45

Gly Pro Gln Gly Arg Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe
50 55 60

Arg Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg
65 70 75 80

Pro Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu
85 90 95

Leu Val Ala Arg Val Val Gln Arg Leu Cys Glu Arg Gly Ala Arg Asn
100 105 110

Val Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro
115 120 125

Pro Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val

```
    130                 135                 140

Thr Asp Thr Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg
145                 150                 155                 160

Val Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Tyr
                165                 170                 175

Val Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu
            180                 185                 190

Tyr Asp Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser
        195                 200                 205

Gly Thr Arg Arg Gly Leu Gly Thr Glu Gln Ala Trp Asn His Ser Val
    210                 215                 220

Arg Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg
225                 230                 235                 240

Arg Arg Gly Ser Ala Gly Arg Ser Leu Pro Leu Ala Lys Arg Pro Arg
                245                 250                 255

Arg Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser
            260                 265                 270

Trp Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys
        275                 280                 285

Val Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly
    290                 295                 300

Ala Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His
305                 310                 315                 320

His Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr
                325                 330                 335

Pro Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser
            340                 345                 350

Gly Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg
        355                 360                 365

Pro Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly
    370                 375                 380

Ser Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Thr Pro Arg Leu Pro
385                 390                 395                 400

Gln Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn
                405                 410                 415
```

```
His Ala Gln Cys Pro Tyr Gly Ala Leu Leu Arg Thr His Cys Pro Leu
            420                 425                 430

Arg Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro
        435                 440                 445

Gln Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg
    450                 455                 460

Leu Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly
465                 470                 475                 480

Phe Leu Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly
                485                 490                 495

Ser Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile
            500                 505                 510

Ser Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys
        515                 520                 525

Met Ser Val Arg Asp Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly
    530                 535                 540

Cys Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys
545                 550                 555                 560

Phe Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser
                565                 570                 575

Phe Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Tyr Leu Phe Phe
            580                 585                 590

Tyr Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln
        595                 600                 605

His Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg
    610                 615                 620

Gln His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe
625                 630                 635                 640

Leu Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val
                645                 650                 655

Val Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr
            660                 665                 670

Ser Arg Val Lys Thr Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg
        675                 680                 685
```

```
Arg Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His
    690                 695                 700

Arg Ala Trp Arg Ala Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro
705                 710                 715                 720

Pro Glu Leu Tyr Phe Val Lys Val Ala Val Thr Gly Ala Tyr Asp Thr
                725                 730                 735

Ile Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro
            740                 745                 750

Gln Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Arg Arg Ala Ala
        755                 760                 765

His Gly His Val Arg Lys Ser Phe Lys Arg His Val Ser Thr Leu Thr
    770                 775                 780

Asp Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr
785                 790                 795                 800

Ser Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn
                805                 810                 815

Glu Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Val Cys His
            820                 825                 830

His Ala Val Arg Ile Gly Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile
        835                 840                 845

Pro Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly
    850                 855                 860

Asp Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu
865                 870                 875                 880

Leu Arg Leu Val Ala Ala Phe Leu Leu Val Thr Pro His Leu Thr His
                885                 890                 895

Ala Lys Ala Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly
            900                 905                 910

Cys Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp
        915                 920                 925

Glu Ala Leu Gly Gly Thr Ala Phe Val Gln Leu Pro Ala His Gly Leu
    930                 935                 940

Phe Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln
945                 950                 955                 960
```

```
Ser Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr
                965                 970                 975


Phe Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe
            980                 985                 990


Gly Val Leu Arg Leu Lys Cys His  Ser Leu Phe Leu Tyr  Leu Gln Val
        995                1000                1005


Asn Ser  Leu Gln Thr Val Cys  Thr Asn Val Tyr Lys  Ile Phe Leu
    1010                1015                1020


Leu Gln  Ala Tyr Arg Phe His  Ala Cys Val Leu Gln  Leu Pro Phe
    1025                1030                1035


His Gln  Gln Val Arg Lys Asn  Pro Thr Phe Phe Leu  Arg Val Ile
    1040                1045                1050


Ser Asp  Thr Ala Ser Leu Cys  Tyr Ser Ile Leu Lys  Ala Lys Asn
    1055                1060                1065


Ala Gly  Met Ser Leu Gly Ala  Lys Gly Ala Ala Gly  Pro Phe Pro
    1070                1075                1080


Ser Glu  Ala Ala Gln Trp Leu  Cys His Gln Ala Phe  Leu Leu Lys
    1085                1090                1095


Leu Ala  Arg His Arg Val Thr  Tyr Arg Cys Leu Leu  Gly Ala Leu
    1100                1105                1110


Arg Thr  Ala Gln Thr Gln Leu  Cys Arg Lys Leu Pro  Gly Ala Thr
    1115                1120                1125


Leu Ala  Ala Leu Glu Ala Ala  Ala Asp Pro Ala Leu  Thr Ser Asp
    1130                1135                1140


Phe Lys  Thr Ile Leu Asp
    1145


<210> 19
<211> 3399
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polynucleotide

<400> 19
cctagagccc cacggtgtag agcagtccgc agcctgctgc gcagccgata ccgggaagtg       60

ctgcctctgg ccacctttgt ccggagactg ggaccacagg gcaggcgcct ggtgcagcgc      120

ggcgaccccg cagctttccg agcactggtg gcacagtgcc tggtgtgcgt gccatgggat      180

gcacggcccc ctccagcagc ccctagcttt agacaggtgt cctgcctgaa agaactggtc      240
```

gcaagggtgg tccagcggct gtgcgagaga ggcgccagga acgtgctggc attcggcttt 300

gcactgctgg acggagctag gggcgggccc cctgaggcat tcaccacaag cgtgcgctcc 360

tacctgccaa atacagtcac tgataccctg cgaggctccg gagcatgggg actgctgctg 420

cgacgggtgg gggacgatgt gctggtccac ctgctggcta gatgcgcact gtatgtgctg 480

gtcgctccct cttgcgcata ccaggtgtgc ggaccacccc tgtatgacct gggcgctgca 540

acccaggcaa gacctccacc ccacgcctct ggcactagaa ggggactggg caccgaacag 600

gcatggaacc atagtgtcag ggaggcagga gtgccactgg gactgccagc acctggggct 660

cgccgacgga gagggagtgc cggacggtca ctgccactgg ctaagagacc aaggcgcgga 720

gccgctccag aaccagagag gacacctgtg ggacagggaa gctgggcaca ccctggaaga 780

actaggggggc caagtgatag gggcttctgc gtggtctcac cagcacgacc agcagaggaa 840

gctacttctc tggagggagc tctgagtggc acccggcact ctcatcctag tgtgggaaga 900

cagcaccatg caggccctcc aagcaccagc cggcctcccc ggccatggga cactccttgt 960

ccacccgtgt acgctgaaac caaacacttt ctgtatagct ccggagataa ggagcagctg 1020

cggccctctt tcctgctgtc tagtctgaga cctagtctga ccggagcacg acggctggtg 1080

gaaacaatct ttctggggtc ccgcccttgg atgccaggaa cccccagaag gacacctcga 1140

ctgccacagc ggtactggca gatgcggcca ctgttcctgg agctgctggg caatcacgct 1200

cagtgcccct atggggcact gctgcgaaca cattgtcctc tgcgggcagc cgtgactcca 1260

gctgcaggag tctgcgccag ggaaaagcca cagggcagcg tggcagctcc tgaggaagag 1320

gacaccgatc cacgccgact ggtgcagctg ctgagacagc actcaagccc ctggcaggtg 1380

tacggatttc tgagggcctg tctgcggaga ctggtgcctc caggactgtg ggggtccagg 1440

cacaacgaaa ggcgctttct gcgcaatact aagaaattca tcagcctggg caagcatgct 1500

aaactgtccc tgcaggagct gacctggaaa atgagtgtgc gcgactgcgc atggctgcga 1560

cggtcaccag gagtcgggtg cgtgcctgca gccgagcacc gcctgcgaga agagattctg 1620

gccaagtttc tgcattggct gatgtcagtg tacgtggtcg aactgctgcg gagcttcttt 1680

tatgtgacag agactacctt ccagaaaaac tacctgttct tttatcgcaa gtcagtgtgg 1740

agcaaactgc agtcaatcgg cattcggcag cacctgaaga gagtgcagct gagggaactg 1800

agtgaagccg aggtccggca gcatagagag gcaaggcctg ccctgctgac ctcccggctg 1860

agattcctgc ctaagccaga cgggctgaga ccaatcgtga acatggatta cgtggtcgga 1920

gcacggacct tccggaggga aaaacgcgct gagcgactga catcccgcgt gaagactctg 1980

ttctctgtcc tgaattatga gcgagctcgc cgacccggac tgctgggagc atctgtgctg 2040

ggactggacg atattcaccg ggcttggaga gcatttgtcc tgagggtgcg cgcacaggac 2100

cctcccccag aactgtactt cgtgaaagtc gccgtgaccg gggcttatga cacaatccct 2160

caggatcggc tgactgaagt gatcgcctcc atcattaagc cacagaatac ctactgcgtg 2220

cggagatatg ctgtggtcag gcgcgctgca cacggccatg tgaggaagag cttcaagcgc 2280

cacgtcagca cactgactga tctgcagccc tacatgagac agttcgtggc tcatctgcag 2340

gagaccagcc ctctgaggga cgcagtggtc atcgaacagt cctctagtct gaacgaggca 2400

tcaagcgggc tgttcgatgt ctttctgcgg ttcgtgtgcc accatgccgt cagaattgga 2460

ggcaaatctt acgtgcagtg tcagggcatc ccccagggca gcattctgtc taccctgctg 2520

tgcagcctgt gctatggcga catggaaaat aagctgtttg ccggaatccg acgggatggc 2580

ctgctgctga gactggtggc cgcttttctg ctggtcactc cacacctgac ccatgccaaa 2640

gctttcctgc gcacactggt ccgaggggtg ccagagtacg gatgcgtggt caacctgagg 2700

aagaccgtgg tcaatttccc agtggaagac gaggccctgg gcggcacagc atttgtccag 2760

ctgccagcac acggactgtt cccatggtgt ggactgctgc tggacacccg cacactggag 2820

gtgcagtccg attactcctc ttatgcccgg acaagcatca gagcttccct gacttttaac 2880

agaggcttca aggccgggag gaatatgaga aggaaactgt ttggcgtgct gcgcctgaag 2940

tgccattccc tgttcctgta tctgcaggtg aactctctgc agactgtctg taccaacgtg 3000

tacaaaattt ttctgctgca ggcctatcgg ttccacgctt gcgtgctgca gctgccattc 3060

catcagcagg tcaggaagaa ccccaccttc tttctgcgcg tgatctctga tacagctagt 3120

ctgtgctact caattctgaa ggccaaaaat gctggcatga gcctgggagc aaaaggagca 3180

gcaggaccat ttccttccga ggctgcacag tggctgtgcc accaggcatt cctgctgaag 3240

ctggcccgac atcgggtgac atataggtgc ctgctgggcg cactgcgaac agcacagact 3300

cagctgtgca gaaagctgcc cggggccact ctggctgccc tggaagccgc tgccgaccct 3360

gccctgacct ccgatttcaa gactattctg gactgataa 3399

<210> 20
<211> 1131
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 20
Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg Ser Arg
1 5 10 15

Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu Gly Pro
20 25 30

Gln Gly Arg Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe Arg Ala
35 40 45

Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg Pro Pro
50 55 60

Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu Leu Val
65 70 75 80

```
Ala Arg Val Val Gln Arg Leu Cys Glu Arg Gly Ala Arg Asn Val Leu
                85                  90                  95

Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro Pro Glu
            100                 105                 110

Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val Thr Asp
        115                 120                 125

Thr Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg Val Gly
    130                 135                 140

Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Tyr Val Leu
145                 150                 155                 160

Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu Tyr Asp
                165                 170                 175

Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser Gly Thr
            180                 185                 190

Arg Arg Gly Leu Gly Thr Glu Gln Ala Trp Asn His Ser Val Arg Glu
        195                 200                 205

Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg Arg Arg
    210                 215                 220

Gly Ser Ala Gly Arg Ser Leu Pro Leu Ala Lys Arg Pro Arg Arg Gly
225                 230                 235                 240

Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser Trp Ala
                245                 250                 255

His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys Val Val
            260                 265                 270

Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly Ala Leu
        275                 280                 285

Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His His Ala
    290                 295                 300

Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro Cys
305                 310                 315                 320

Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly Asp
                325                 330                 335

Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro Ser
            340                 345                 350

Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser Arg
```

```
        355                 360                 365

Pro Trp Met Pro Gly Thr Pro Arg Arg Thr Pro Arg Leu Pro Gln Arg
    370                 375                 380

Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His Ala
385                 390                 395                 400

Gln Cys Pro Tyr Gly Ala Leu Leu Arg Thr His Cys Pro Leu Arg Ala
                405                 410                 415

Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln Gly
            420                 425                 430

Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg Leu Val
        435                 440                 445

Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe Leu
    450                 455                 460

Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser Arg
465                 470                 475                 480

His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser Leu
                485                 490                 495

Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met Ser
            500                 505                 510

Val Arg Asp Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys Val
        515                 520                 525

Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe Leu
    530                 535                 540

His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe Phe
545                 550                 555                 560

Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Tyr Leu Phe Phe Tyr Arg
                565                 570                 575

Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His Leu
            580                 585                 590

Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Gln His
        595                 600                 605

Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe Leu Pro
    610                 615                 620

Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val Val Gly
625                 630                 635                 640
```

```
Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr Ser Arg
                645                 650                 655

Val Lys Thr Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg Arg Pro
            660                 665                 670

Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg Ala
        675                 680                 685

Trp Arg Ala Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro Pro Glu
    690                 695                 700

Leu Tyr Phe Val Lys Val Ala Val Thr Gly Ala Tyr Asp Thr Ile Pro
705                 710                 715                 720

Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro Gln Asn
                725                 730                 735

Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Arg Arg Ala Ala His Gly
            740                 745                 750

His Val Arg Lys Ser Phe Lys Arg His Val Ser Thr Leu Thr Asp Leu
        755                 760                 765

Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr Ser Pro
    770                 775                 780

Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn Glu Ala
785                 790                 795                 800

Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Val Cys His His Ala
                805                 810                 815

Val Arg Ile Gly Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro Gln
            820                 825                 830

Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp Met
        835                 840                 845

Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu Arg
    850                 855                 860

Leu Val Ala Ala Phe Leu Leu Val Thr Pro His Leu Thr His Ala Lys
865                 870                 875                 880

Ala Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys Val
                885                 890                 895

Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu Ala
            900                 905                 910
```

```
Leu Gly Gly Thr Ala Phe Val Gln Leu Pro Ala His Gly Leu Phe Pro
        915                 920                 925

Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser Asp
    930                 935                 940

Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe Asn
945                 950                 955                 960

Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly Val
                965                 970                 975

Leu Arg Leu Lys Cys His Ser Leu Phe Leu Tyr Leu Gln Val Asn Ser
            980                 985                 990

Leu Gln Thr Val Cys Thr Asn Val  Tyr Lys Ile Phe Leu  Leu Gln Ala
        995                 1000                1005

Tyr Arg  Phe His Ala Cys Val  Leu Gln Leu Pro Phe  His Gln Gln
    1010                1015                1020

Val Arg  Lys Asn Pro Thr Phe  Phe Leu Arg Val Ile  Ser Asp Thr
    1025                1030                1035

Ala Ser  Leu Cys Tyr Ser Ile  Leu Lys Ala Lys Asn  Ala Gly Met
    1040                1045                1050

Ser Leu  Gly Ala Lys Gly Ala  Ala Gly Pro Phe Pro  Ser Glu Ala
    1055                1060                1065

Ala Gln  Trp Leu Cys His Gln  Ala Phe Leu Leu Lys  Leu Ala Arg
    1070                1075                1080

His Arg  Val Thr Tyr Arg Cys  Leu Leu Gly Ala Leu  Arg Thr Ala
    1085                1090                1095

Gln Thr  Gln Leu Cys Arg Lys  Leu Pro Gly Ala Thr  Leu Ala Ala
    1100                1105                1110

Leu Glu  Ala Ala Ala Asp Pro  Ala Leu Thr Ser Asp  Phe Lys Thr
    1115                1120                1125

Ile Leu  Asp
    1130
```

<210> 21
<211> 2307
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 21
atggactgga catggattct gttcctggtc gccgccgcaa ctcgcgtgca ttcctggaac 60

gcactgcatg agactgattc tgctgtcgca ctgggacgga gaccccggtg gctgtgcgct 120

ggagcactgg tgctggccgg cgggggattc ctgctgggat tcctgtttgg ctggtttatc 180

aaaagctcca gcgaggctac caatattacc cctaagcaca ataagaaagc attcctggat 240

gaactgaaag ccgagaacat caagaaattc ctgtacaact tcacaagaat tccacatctg 300

gctggcactg agcagaactt ccagctggca aaacagatcc agagtcagtg gaaggaattt 360

gggctggact cagtggagct gacccactac gatgtcctgc tgtcctatcc aaataagact 420

catcccaact acatctctat cattaacgaa gacggaaatg agattttcaa cacctctctg 480

tttgaacccc ctccacccgg ctatgagaat gtcagtgacg tggtccctcc attctcagcc 540

ttcagccccc aggggatgcc tgagggagat ctggtgtacg tcaattatgc tagaacagaa 600

gacttcttta agctggagag ggatatgaaa atcaactgtt ccggcaagat cgtgattgcc 660

cggtacggga aggtgttcag aggaaataag gtcaaaaacg ctcagctggc cggagctacc 720

ggcgtgatcc tgtacagcga ccccgctgat tattttgcac ctggcgtgaa gtcctatcca 780

gacggatgga atctgcccgg cgggggagtg cagaggggaa acatcctgaa cctgaatgga 840

gccggcgatc ctctgactcc aggatacccc gccaacgaat acgcttatcg ccggggaatt 900

gcagaggccg tgggcctgcc tagcatccca gtccatccca ttggctatta cgatgcccag 960

aagctgctgg agaaaatggg cgggagcgct ccccctgact ctagttggaa gggctccctg 1020

aaagtgcctt acaatgtcgg gccaggattc actgggaact tttctaccca gaaggtgaaa 1080

atgcacatcc atagtaccag cgaggtgaca cgaatctaca acgtcattgg caccctgaga 1140

ggcgccgtgg agcctgatcg ctatgtcatt ctgggaggcc acagagactc atgggtgttc 1200

gggggaatcg atccacagag cggagcagct gtggtccatg aaattgtgcg cagctttggg 1260

accctgaaga aagagggatg gcgacccagg cgcacaatcc tgttcgcatc ctgggacgcc 1320

gaggaatttg ggctgctggg cagcacagaa tgggccgagg aaaattctcg cctgctgcag 1380

gagcgagggg tggcttacat caatgcagac tcaagcattg aaggaaacta taccctgcgg 1440

gtggattgca cacccctgat gtacagtctg gtctataacc tgacaaagga gctgaaatca 1500

cctgacgagg gcttcgaagg gaaaagcctg tacgaatcct ggactgagaa gagcccatcc 1560

cccgaattca gcggcatgcc taggatctct aagctgggca gtgggaacga ttttgaggtg 1620

ttctttcagc gcctgggaat tgcctctggc cgagctcggt acacaaaaaa ttgggagact 1680

aacaagttct cctcttaccc actgtatcac agcgtgtacg agacttatga actggtcgag 1740

aaattctacg accccacttt taagtatcat ctgaccgtgg cacaggtcag gggcgggatg 1800

gtgttcgaac tggccaatag catcgtcctg ccatttgact gtcgagatta cgctgtggtc 1860

ctgcggaagt acgcagacaa gatctataac atctccatga agcaccccca ggagatgaag 1920

gcctattctg tgagtttcga ttccctgttt tctgccgtca aaaatttcac cgaaatcgct 1980

agtaagtttt cagagcgcct gcaggacctg gataagtcca atcccatcct gctgcggatt 2040

atgaacgatc agctgatgtt cctggaaaga gcctttatcg accctctggg cctgcctgat 2100

agaccattct acaggcacgt gatctacgca cctagttcac ataacaagta cgccggcgag 2160

tctttcccag ggatctatga cgctctgttt gatattgaat caaaggtgga ccccagcaaa 2220

gcatggggcg aggtcaagag acagatcagc attgcagcct ttacagtgca ggccgccgcc 2280

gaaaccctgt ccgaagtcgc ttgataa 2307

<210> 22
<211> 660
<212> DNA
<213> Homo sapiens

<400> 22
atgtgtccag cgcgcagcct cctccttgtg gctaccctgg tcctcctgga ccacctcagt 60

ttggccagaa acctccccgt ggccactcca gacccaggaa tgttcccatg ccttcaccac 120

tcccaaaacc tgctgagggc cgtcagcaac atgctccaga aggccagaca aactctagaa 180

ttttaccctt gcacttctga agagattgat catgaagata tcacaaaaga taaaaccagc 240

acagtggagg cctgtttacc attggaatta accaagaatg agagttgcct aaattccaga 300

gagacctctt tcataactaa tgggagttgc ctggcctcca gaaagacctc ttttatgatg 360

gccctgtgcc ttagtagtat ttatgaagac ttgaagatgt accaggtgga gttcaagacc 420

atgaatgcaa agcttctgat ggatcctaag aggcagatct ttctagatca aaacatgctg 480

gcagttattg atgagctgat gcaggccctg aatttcaaca gtgagactgt gccacaaaaa 540

tcctcccttg aagaaccgga tttttataaa actaaaatca agctctgcat acttcttcat 600

gctttcagaa ttcgggcagt gactattgat agagtgatga gctatctgaa tgcttcctaa 660

<210> 23
<211> 219
<212> PRT
<213> Homo sapiens

<400> 23
Met Cys Pro Ala Arg Ser Leu Leu Leu Val Ala Thr Leu Val Leu Leu
1 5 10 15

Asp His Leu Ser Leu Ala Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
20 25 30

Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala Val
35 40 45

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

Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr Ser
65 70 75 80

Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser Cys
85 90 95

```
Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu Ala
            100                 105                 110

Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile Tyr
        115                 120                 125

Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala Lys
    130                 135                 140

Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met Leu
145                 150                 155                 160

Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu Thr
                165                 170                 175

Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
            180                 185                 190

Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val Thr
        195                 200                 205

Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
    210                 215
```

<210> 24
<211> 987
<212> DNA
<213> Homo sapiens

<400> 24

```
atgtgtcacc agcagttggt catctcttgg ttttccctgg tttttctggc atctcccctc       60

gtggccatat gggaactgaa gaaagatgtt tatgtcgtag aattggattg gtatccggat      120

gcccctggag aaatggtggt cctcacctgt gacacccctg aagaagatgg tatcacctgg      180

accttggacc agagcagtga ggtcttaggc tctggcaaaa ccctgaccat ccaagtcaaa      240

gagtttggag atgctggcca gtacacctgt cacaaaggag gcgaggttct aagccattcg      300

ctcctgctgc ttcacaaaaa ggaagatgga atttggtcca ctgatatttt aaaggaccag      360

aaagaaccca aaaataagac ctttctaaga tgcgaggcca agaattattc tggacgtttc      420

acctgctggt ggctgacgac aatcagtact gatttgacat tcagtgtcaa aagcagcaga      480

ggctcttctg acccccaagg ggtgacgtgc ggagctgcta cactctctgc agagagagtc      540

agaggggaca acaaggagta tgagtactca gtggagtgcc aggaggacag tgcctgccca      600

gctgctgagg agagtctgcc cattgaggtc atggtggatg ccgttcacaa gctcaagtat      660

gaaaactaca ccagcagctt cttcatcagg gacatcatca aacctgaccc acccaagaac      720

ttgcagctga agccattaaa gaattctcgg caggtggagg tcagctggga gtaccctgac      780

acctggagta ctccacattc ctacttctcc ctgacattct gcgttcaggt ccagggcaag      840

agcaagagag aaaagaaaga tagagtcttc acggacaaga cctcagccac ggtcatctgc      900
```

cgcaaaaatg ccagcattag cgtgcgggcc caggaccgct actatagctc atcttggagc 960

gaatgggcat ctgtgccctg cagttag 987

<210> 25
<211> 328
<212> PRT
<213> Homo sapiens

<400> 25
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
165 170 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn

225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser
325

<210> 26
<211> 418
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 26
Gly Ser Asp Val Arg Asp Leu Asn Ala Leu Leu Pro Ala Val Pro Ser
1 5 10 15

Leu Pro Gly Gly Gly Gly Cys Ala Leu Pro Val Ser Gly Ala Ala Gln
20 25 30

Trp Ala Pro Val Leu Asp Phe Ala Pro Pro Ala Ala Pro Tyr Gly Ser
35 40 45

Leu Gly Gly Pro His Ser Phe Ile Lys Gln Glu Pro Ser Trp Gly Gly
50 55 60

Ala Asp Pro His Glu Glu Gln Cys Leu Ser Ala Phe Thr Val His Phe
65 70 75 80

Ser Gly Gln Phe Thr Gly Thr Ala Gly Ala Cys Arg Tyr Gly Pro Phe
85 90 95

Gly Ala Pro Pro Pro Ser Gln Ala Pro Ser Gly Gln Ala Arg Met Phe
100 105 110

Pro Asn Ala Pro Tyr Leu Pro Asn Cys Leu Glu Ser Gln Pro Ala Ile
115 120 125

```
Arg Asn Gln Gly Tyr Ser Thr Val Ala Phe Asp Gly Thr Pro Ser Tyr
    130                 135                 140

Gly His Thr Pro Ser His His Ala Ala Gln Phe Pro Asn His Ser Phe
145                 150                 155                 160

Lys His Glu Asp Pro Met Gly Gln Gln Gly Ser Leu Gly Glu Gln Gln
                165                 170                 175

Tyr Ser Val Pro Pro Pro Val Tyr Gly Cys His Thr Pro Thr Asp Ser
            180                 185                 190

Cys Thr Gly Ser Gln Ala Leu Leu Leu Arg Thr Pro Tyr Asn Ser Asp
        195                 200                 205

Asn Leu Tyr Gln Met Thr Ser Gln Leu Glu Cys Met Thr Trp Asn Gln
    210                 215                 220

Met Asn Leu Gly Ser Thr Leu Lys Gly His Ala Thr Gly Tyr Glu Ser
225                 230                 235                 240

Asp Asn His Thr Thr Pro Met Leu Tyr Ser Cys Gly Ala Gln Tyr Arg
                245                 250                 255

Ile His Thr His Gly Val Phe Arg Gly Ile Gln Asp Val Arg Arg Val
            260                 265                 270

Pro Gly Val Ala Pro Thr Ile Val Arg Ser Ala Ser Glu Thr Asn Glu
        275                 280                 285

Lys Arg Pro Phe Met Gly Ala Tyr Pro Gly Gly Asn Lys Arg Tyr Phe
    290                 295                 300

Lys Leu Ser His Leu Gln Met Gly Ser Arg Lys Gly Thr Gly Glu Lys
305                 310                 315                 320

Pro Tyr Gln Gly Asp Phe Lys Asp Gly Glu Arg Arg Phe Ser Arg Ser
                325                 330                 335

Asp Gln Leu Lys Arg Gly Gln Arg Arg Gly Thr Gly Val Lys Pro Phe
            340                 345                 350

Gln Cys Lys Thr Cys Gln Arg Lys Phe Ser Arg Ser Asp His Leu Lys
        355                 360                 365

Thr His Thr Arg Thr His Thr Gly Lys Thr Ser Glu Lys Pro Phe Ser
    370                 375                 380

Cys Arg Trp Pro Ser Cys Gln Lys Lys Phe Ala Arg Ser Asp Glu Leu
385                 390                 395                 400

Val Arg His His Asn Met His Gln Arg Asn Met Thr Lys Leu Gln Leu
```

405 410 415

Ala Leu

<210> 27
<211> 1260
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 27
gggagtgatg tgagagacct gaacgccctg ctgccagcag tgccatccct gcctggcggg 60

ggaggctgcg ctctgccagt ctctggagca gctcagtggg ctcccgtgct ggactttgca 120

ccccctgcag ccccttacgg aagtctgggc ggcccacact cattcatcaa acaggagcca 180

agctgggggcg gggcagatcc tcatgaggaa cagtgcctgt cagccttcac agtccacttt 240

agcgggcagt tcactggaac cgcaggagct tgtagatacg gacccttttgg agcaccaccc 300

ccttcccagg caccttctgg acaggcacgc atgttcccaa acgctcccta tctgcctaat 360

tgtctggaaa gccagcccgc tattaggaac cagggctact ccacagtggc atttgacggg 420

actcctagct atggacatac cccatcccac catgctgcac agtttcctaa tcactccttc 480

aagcatgagg accccatggg acagcagggg tccctgggag aacagcagta ctctgtgccc 540

cctcccgtgt acggatgcca cacaccaact gacagttgta caggctcaca ggccctgctg 600

ctgcgaactc catacaacag tgataatctg tatcagatga cctcacagct ggagtgcatg 660

acatggaacc agatgaatct gggcagcaca ctgaaaggcc atgccactgg gtacgaatct 720

gacaaccaca ccacacctat gctgtacagt tgtggagccc agtatagaat ccacactcat 780

ggagtcttca gaggcattca ggatgtgcgg agagtcccag gagtggcacc aactatcgtg 840

cggagcgcct ccgagaccaa cgaaaagcgc ccctttatgg gcgcctaccc tggaggcaat 900

aagcggtatt tcaaactgtc tcacctgcag atggggagta gaaaggggac cggagagaaa 960

ccttatcagg gcgactttaa agatggggaa aggcgcttct ctcgcagtga ccagctgaag 1020

cgaggacagc gacgaggaac cggggtgaag ccatttcagt gcaaaacatg tcagagaaag 1080

ttctcaagga gcgatcacct gaagacccat acaagaactc acaccggcaa gaccagcgag 1140

aaaccatttt cctgccgatg gccctcttgt cagaagaaat tcgcccgctc cgacgaactg 1200

gtccgacacc acaatatgca tcagagaaat atgacaaaac tgcagctggc tctgtgataa 1260

<210> 28
<211> 749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 28
Trp Asn Ala Leu His Glu Thr Asp Ser Ala Val Ala Leu Gly Arg Arg
1   5   10   15

Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Gly Phe
            20   25   30

Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser Glu Ala
        35   40   45

Thr Asn Ile Thr Pro Lys His Asn Lys Lys Ala Phe Leu Asp Glu Leu
    50   55   60

Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Arg Ile Pro
65   70   75   80

His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile Gln
                85   90   95

Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr His Tyr
            100   105   110

Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile Ser
        115   120   125

Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe Glu
    130   135   140

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

Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr Val
                165   170   175

Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met Lys
            180   185   190

Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val Phe
        195   200   205

Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr Gly Val
    210   215   220

Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys Ser
225   230   235   240

Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly Asn
                245   250   255

Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr Pro
            260   265   270

```
Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly Leu
        275                 280                 285

Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys Leu
    290                 295                 300

Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Lys Gly
305                 310                 315                 320

Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn Phe
                325                 330                 335

Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu Val Thr
            340                 345                 350

Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro Asp
        355                 360                 365

Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly Gly
    370                 375                 380

Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg Ser
385                 390                 395                 400

Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile Leu
                405                 410                 415

Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr Glu
            420                 425                 430

Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala Tyr
        435                 440                 445

Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val Asp
    450                 455                 460

Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys Glu Leu
465                 470                 475                 480

Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser Trp
                485                 490                 495

Thr Glu Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile Ser
            500                 505                 510

Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu Gly
        515                 520                 525

Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr Asn Lys
    530                 535                 540

Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr Glu Leu
```

545 550 555 560

Val Glu Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu Thr Val Ala
565 570 575

Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile Val Leu
580 585 590

Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala Asp
595 600 605

Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys Ala Tyr
610 615 620

Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr Glu
625 630 635 640

Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Leu Asp Lys Ser Asn
645 650 655

Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Phe Leu Glu Arg
660 665 670

Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg His
675 680 685

Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser Phe
690 695 700

Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp Pro
705 710 715 720

Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Ser Ile Ala Ala Phe
725 730 735

Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
740 745

<210> 29
<211> 2253
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 29
tggaacgcac tgcatgagac tgattctgct gtcgcactgg gacggagacc ccggtggctg 60

tgcgctggag cactggtgct ggccggcggg ggattcctgc tgggattcct gtttggctgg 120

tttatcaaaa gctccagcga ggctaccaat attaccccta agcacaataa gaaagcattc 180

ctggatgaac tgaaagccga gaacatcaag aaattcctgt acaacttcac aagaattcca 240

catctggctg gcactgagca gaacttccag ctggcaaaac agatccagag tcagtggaag 300

gaatttgggc tggactcagt ggagctgacc cactacgatg tcctgctgtc ctatccaaat 360

aagactcatc ccaactacat ctctatcatt aacgaagacg gaaatgagat tttcaacacc 420

tctctgtttg aacccccctcc acccggctat gagaatgtca gtgacgtggt ccctccattc 480

tcagccttca gcccccaggg gatgcctgag ggagatctgg tgtacgtcaa ttatgctaga 540

acagaagact tctttaagct ggagagggat atgaaaatca actgttccgg caagatcgtg 600

attgcccggt acgggaaggt gttcagagga aataaggtca aaaacgctca gctggccgga 660

gctaccggcg tgatcctgta cagcgacccc gctgattatt ttgcacctgg cgtgaagtcc 720

tatccagacg gatggaatct gcccggcggg ggagtgcaga ggggaaacat cctgaacctg 780

aatggagccg gcgatcctct gactccagga taccccgcca acgaatacgc ttatcgccgg 840

ggaattgcag aggccgtggg cctgcctagc atcccagtcc atcccattgg ctattacgat 900

gcccagaagc tgctggagaa aatgggcggg agcgctcccc ctgactctag ttggaagggc 960

tccctgaaag tgccttacaa tgtcgggcca ggattcactg ggaacttttc tacccagaag 1020

gtgaaaatgc acatccatag taccagcgag gtgacacgaa tctacaacgt cattggcacc 1080

ctgagaggcg ccgtggagcc tgatcgctat gtcattctgg gaggccacag agactcatgg 1140

gtgttcgggg gaatcgatcc acagagcgga gcagctgtgg tccatgaaat tgtgcgcagc 1200

tttgggaccc tgaagaaaga gggatggcga cccaggcgca caatcctgtt cgcatcctgg 1260

gacgccgagg aatttgggct gctgggcagc acagaatggg ccgaggaaaa ttctcgcctg 1320

ctgcaggagc gaggggtggc ttacatcaat gcagactcaa gcattgaagg aaactatacc 1380

ctgcgggtgg attgcacacc cctgatgtac agtctggtct ataacctgac aaaggagctg 1440

aaatcacctg acgagggctt cgaagggaaa agcctgtacg aatcctggac tgagaagagc 1500

ccatcccccg aattcagcgg catgcctagg atctctaagc tgggcagtgg gaacgatttt 1560

gaggtgttct ttcagcgcct gggaattgcc tctggccgag ctcggtacac aaaaaattgg 1620

gagactaaca agttctcctc ttacccactg tatcacagcg tgtacgagac ttatgaactg 1680

gtcgagaaat tctacgaccc cacttttaag tatcatctga ccgtggcaca ggtcaggggc 1740

gggatggtgt tcgaactggc caatagcatc gtcctgccat ttgactgtcg agattacgct 1800

gtggtcctgc ggaagtacgc agacaagatc tataacatct ccatgaagca cccccaggag 1860

atgaaggcct attctgtgag tttcgattcc ctgttttctg ccgtcaaaaa tttcaccgaa 1920

atcgctagta agttttcaga gcgcctgcag gacctggata agtccaatcc catcctgctg 1980

cggattatga acgatcagct gatgttcctg gaaagagcct ttatcgaccc tctgggcctg 2040

cctgatagac cattctacag gcacgtgatc tacgcaccta gttcacataa caagtacgcc 2100

ggcgagtctt tcccagggat ctatgacgct ctgtttgata ttgaatcaaa ggtggacccc 2160

agcaaagcat ggggcgaggt caagagacag atcagcattg cagcctttac agtgcaggcc 2220

gccgccgaaa ccctgtccga agtcgcttga taa 2253