

What is claimed:

1. A combination therapy for the treatment of brain cancer comprising:

~~1. an immunogenic composition comprising human telomerase reverse transcriptase (hTERT), Wilms Tumor-1 (WT-1), and prostate specific membrane antigen (PSMA)-;~~

~~IL12; and~~

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

2. The ~~immunogenic composition~~combination therapy of claim 1 wherein hTERT is encoded by a DNA plasmid, WT-1 is encoded by a DNA plasmid, and/or PSMA is encoded by a DNA plasmid.

3. The ~~immunogenic composition~~combination therapy of claim 2, wherein hTERT, WT-1, and PSMA are encoded by the same DNA plasmid; wherein two of hTERT, WT-1, and PSMA are encoded by the same DNA plasmid; or wherein hTERT, WT-1, and PSMA are encoded by different DNA plasmids.

4. The ~~immunogenic composition~~combination therapy of any preceding claim wherein:

the hTERT comprises the amino acid sequence of SEQ ID NO: 20 or is encoded by the nucleic acid sequence of SEQ ID NO: 19;

the WT-1 comprises the amino acid sequence of SEQ ID NO: 26 or is encoded by the nucleic acid sequence of SEQ ID NO: 27; and/or

the PSMA comprises the amino acid sequence of SEQ ID NO: 28 or is encoded by the nucleic acid sequence of SEQ ID NO: 29.

~~5. A vaccine comprising:~~

~~the immunogenic composition~~The combination therapy of any preceding claim;

~~IL12; and~~

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

~~6.5. The vaccine of claim 5, 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 a HCVR with 90% sequence identity to SEQ ID NO: 1; comprises a LCVR with 90% sequence identity to SEQ ID NO: 2;

comprises a HCVR with 90% sequence identity to SEQ ID NO: 1 and a LCVR with 90% sequence identity to 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.

~~7.6. The vaccine combination therapy of any preceding claim 5 or claim 6, wherein the IL-12 is encoded by a DNA plasmid.~~

~~8.7. The vaccine combination therapy of any preceding claim 5, claim 6, or claim 7, 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 IL12 p35 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 22; the IL12 p40 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 24; or

the IL12 p35 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 22 and the IL12 p40 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 24.

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, or both.

~~9. A method of treating brain cancer in a subject, comprising administering to the subject: interleukin-12 (IL-12);~~

~~an~~ 8. An immunogenic composition of human telomerase reverse transcriptase (hTERT),
Wilms Tumor-1 (WT-1), and prostate specific membrane antigen
(PSMA); and), and interleukin-12 (IL-12) in combination with an anti-
programmed cell death receptor 1 (PD-1) antibody;

~~10.8. A vaccine for use in treating the treatment of brain cancer in a subject, wherein the vaccine comprises:~~

~~an~~

An immunogenic composition of a DNA plasmid encoding human telomerase reverse transcriptase (hTERT),

9. a DNA plasmid encoding Wilms Tumor-1 (WT-1), and a DNA plasmid encoding
prostate specific membrane antigen (PSMA); and an) and a DNA plasmid encoding
interleukin-12 (IL-12) in combination with an anti-programmed cell death receptor 1
(PD-1) antibody for use in the treatment of brain cancer.

10. Use of an anti-programmed cell death receptor 1 (PD-1) antibody and an immunogenic
composition of human telomerase reverse transcriptase (hTERT), Wilms Tumor-1 (WT-
1), prostate specific membrane antigen (PSMA), and interleukin-12 (IL-12) in
preparation of a medicament for use in the treatment of brain cancer.

11. The use according to claim 10 wherein the subject has brain cancer is characterized by an unmethylated O6- methylguanine methyltransferase (MGMT) gene promoter.
12. The method of claim 9 or vaccine for use of according to claim 10 wherein the subject has brain cancer is characterized by a methylated O6- methylguanine methyltransferase (MGMT) gene promoter.
13. The method or vaccine for use of according to any one of claims 9 to 10-12, wherein IL-12 is encoded by a DNA plasmid.
14. The method or vaccine for use of according to any one of claims 9 to 13, wherein hTERT is encoded by a DNA plasmid, WT-1 is encoded by a DNA plasmid, and/or PSMA is encoded by a DNA plasmid.
15. The method or vaccine for use of according to claim 14, wherein hTERT, WT-1, and PSMA are encoded by the same DNA plasmid; two of hTERT, WT-1, and PSMA are encoded by the same DNA plasmid; or wherein hTERT, WT-1, and PSMA are each encoded by a different DNA plasmid.
16. The method or vaccine for use of according to any one of claims 9 to 15, 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 a HCVR with 90% sequence identity to SEQ ID NO: 1; comprises a LCVR with 90% sequence identity to SEQ ID NO: 2;
 comprises a HCVR with 90% sequence identity to SEQ ID NO: 1 and a LCVR with 90% sequence identity to 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.

17. The ~~method or vaccine for use of~~according to any one of claims 9 to 10-16, wherein the anti-PD-1 antibody is ~~administered intravenously or subcutaneously~~prepared for intravenous or subcutaneous administration.

18. The ~~method or vaccine for use of~~according to any one of claims 9 to 10-17 wherein, comprising 350 mg of the anti-PD-1 antibody~~is administered every three weeks.~~

19. The ~~method or vaccine for use of~~according to any one of claims 9 to 10-18, 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 IL12 p35 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 22; the IL12 p40 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 24; or
 the IL12 p35 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 22 and the IL12 p40 subunit is encoded by the nucleic acid sequence of SEQ ID NO: 24.

20. The ~~method or vaccine for use of~~according to any one of claims 9 to ~~10-19~~₁, wherein the hTERT comprises the amino acid sequence of SEQ ID NO: 20 or is encoded by the nucleic acid sequence of SEQ ID NO: 19; the WT-1 comprises the amino acid sequence of SEQ ID NO: 26 or is encoded by the nucleic acid sequence of SEQ ID NO: 27; and/or the PSMA comprises the amino acid sequence of SEQ ID NO: 28 or is encoded by the nucleic acid sequence of SEQ ID NO: 29.

21. The ~~method or vaccine for use of~~according to claim 20, ~~comprising the method comprises administering to the subject, or wherein the vaccine~~immunogenic composition comprises, 3 mg of the DNA plasmid encoding hTERT, 3 mg of the DNA plasmid encoding PSMA, 3 mg of the DNA plasmid encoding WT-1, and 1 mg of the plasmid encoding IL-12.

22. The ~~method or vaccine for use of~~according to any one of claims ~~9~~₁₀ to 21, wherein the ~~IL-12 and the immunogenic composition are co-~~is to be administered by electroporation and intramuscular injection every three weeks for four doses and then every nine weeks.

~~23.—The method or vaccine for use of claim 22 further comprising electroporation following each intramuscular injection.~~
use according to

~~24.23. —The method or vaccine for use of any one of claims 9~~₁₀ to ~~23~~₂₂ wherein the treatment further ~~comprising administering to the subject one or more doses of~~comprises radiation therapy.

~~25.24. —The method or vaccine for use of~~according to claim ~~24~~₂₃, wherein each dose ~~of the~~ radiation therapy comprises 20- 50 Gy.

~~26.25. —The method or vaccine for use of~~according to claim ~~25~~₂₄, wherein the radiation therapy is fractionated radiation therapy.

26. The use according to claim 25, wherein the fractionated radiation therapy comprises 2-20 fractions.

~~27. The method or vaccine for use of~~according to claim 26, wherein the fractionated radiation therapy comprises 2-20 fractions.

~~28.27. The method or vaccine for use of claim 27, wherein the fractionated radiation therapy comprises~~40 Gy in 15 fractions.

~~29. The method or vaccine for use of claim 28, wherein the fractionated radiotherapy is given over 21 consecutive days.~~

~~30.28. The method or vaccine for use of~~The use according to any one of claims 910 to 29,27, wherein the treatment further comprising administering to the subject one or more doses ofcomprises a chemotherapeutic agent; optionally wherein the chemotherapeutic agent is temozolomide.

~~31.29. The method or vaccine for use of~~according to claim ~~30~~28, comprising administering 75 mg/m² temozolomide to the subject daily for 21 consecutive days with the fractionated radiotherapy.

~~32.30. The method or vaccine for use of~~according to claim ~~30~~28 or claim 31, further29, comprising administering temozolomide maintenance therapy to the subject if the subject has a tumor havingbrain cancer is characterized by a methylated MGMT promoter.

~~33.31. The method or vaccine for use of~~according to any one of claims 910 to ~~32~~30, wherein the brain cancer is glioblastoma.

~~34.32.~~ The method or vaccine for use according to claim ~~3331~~, wherein the brain cancer is MGMT-methylated glioblastoma.

~~35.33.~~ The method or vaccine for use according to claim ~~3331~~, wherein the brain cancer is MGMT-unmethylated glioblastoma.

~~36.~~ The method or vaccine for use of any one of claims ~~9 to 35~~, wherein the method is clinically proven safe, clinically proven effective, or both.

~~37.~~ The immunologic composition according to any one of claims ~~1 to 4~~ for use in the manufacture of a medicament for treating a brain cancer.

~~38.~~ The immunologic composition for use according to claim ~~37~~, wherein the brain cancer is glioblastoma.

~~39.~~ The immunologic composition for use according to claim ~~38~~, wherein the brain cancer is MGMT-methylated glioblastoma.

~~40.~~ The immunologic composition for use according to claim ~~38~~, wherein the brain cancer is MGMT-unmethylated glioblastoma.