

CLAIMS

What is claimed is:

1. Use of an immune checkpoint inhibitor, an expanded population of isolated
5 cytotoxic immune cells, and a chemotherapeutic agent for the manufacture of a medicament for the treatment of cancer, wherein:
 - i. the immune checkpoint inhibitor targets PD-1, PDL1, or CTLA-4;
 - ii. the expanded population of isolated cytotoxic immune cells comprises $\gamma\delta$ T-cells, wherein greater than about 50% of the $\gamma\delta$ T-cells have been
10 genetically modified to express a polypeptide that confers resistance to a chemotherapeutic agent; and
 - iii. the chemotherapeutic agent is a chemotherapeutic agent to which the genetically modified $\gamma\delta$ T-cells are resistant.
- 15 2. The use of claim 1, wherein the cancer is selected from glioma, glioblastoma, lymphoma, melanoma, neuroblastoma, non-small cell lung cancer, renal cell carcinoma, and small cell lung cancer.
- 20 3. The use of claim 2, wherein the cancer is glioma, glioblastoma, or neuroblastoma.
4. The use of claim 1, wherein the polypeptide that confers resistance to the chemotherapeutic agent is alkyl guanine transferase (AGT), P140KMGMT, O⁶
25 methylguanine DNA methyltransferase (MGMT), L22Y-DHFR, thymidylate synthase, dihydrofolate reductase, or multiple drug resistance-1 protein (MDR1).
5. The use of claim 4, wherein the polypeptide that confers resistance to the chemotherapeutic agent is P140KMGMT.
- 30 6. The use of claim 1, wherein the immune checkpoint inhibitor targets CTLA-4.
7. The use of claim 1, wherein the checkpoint inhibitor targets PD-1 or PDL1.

8. The use of claim 1, wherein the immune checkpoint inhibitor is selected from Tremelimumab, PD-L1 monoclonal Antibody, MK-3475, Nivolumab, CT-011, AMP224, BMS-936559, MPLDL3280A, MSB0010718C, ipilimumab, and pembrolizumab.
- 5 9. The use of claim 1, wherein the chemotherapeutic agent is selected from an alkylating agent; a metabolic antagonist; a DNA demethylating agent; a substituted nucleotide; a substituted nucleoside; an antitumor antibiotic; a plant-derived antitumor agent; cisplatin; carboplatin; etoposide; methotrexate (MTX);
10 trimethotrexate (TMTX); temozolomide; raltitrexed; S-(4-Nitrobenzyl)-6-thioinosine (NBMPR); 6-benzyguanidine (6-BG); a nitrosourea; cytarabine; camptothecin; and a therapeutic derivative of any thereof.
- 15 10. The use of claim 1, wherein $\gamma\delta$ T-cells have been genetically modified to be resistant to two chemotherapeutic agents selected from an alkylating agent; a metabolic antagonist; a DNA demethylating agent; a substituted nucleotide; a substituted nucleoside; an antitumor antibiotic; a plant-derived antitumor agent; cisplatin; carboplatin; etoposide; methotrexate (MTX); trimethotrexate (TMTX); temozolomide; raltitrexed; S-(4-Nitrobenzyl)-6-thioinosine (NBMPR); 6-
20 benzyguanidine (6-BG); a nitrosourea; cytarabine; camptothecin; and a therapeutic derivative of any thereof.
- 25 11. The use of claim 10, wherein the two chemotherapeutic agents are temozolomide and methotrexate.
12. The use of claim 10, wherein the $\gamma\delta$ T-cells have been genetically modified with the polypeptides that confer resistance to alkyl guanine transferase (AGT) and dihydrofolate reductase.
- 30 13. The use of claim 1, wherein administration of the genetically modified immune cells and the administration of the checkpoint inhibitors occurs substantially simultaneously or sequentially.

14. A composition comprising at least one checkpoint inhibitor, and an expanded population of isolated cytotoxic immune cells comprising $\gamma\delta$ T-cells, wherein greater than about 50% of the population of cytotoxic immune cells express a polypeptide that confers resistance to a chemotherapeutic agent, wherein the checkpoint inhibitor targets PD-1, PDL1, or CTLA-4.
15. The composition of claim 14, wherein the isolated population of cytotoxic immune cells comprises about 50% to about 95% $\gamma\delta$ T-cells and comprises about 5% to about 25% NK cells.
16. The composition of claim 14, wherein the polypeptide that confers resistance to the chemotherapeutic agent is alkyl guanine transferase (AGT), P140KMGMT, O⁶ methylguanine DNA methyltransferase (MGMT), L22Y-DHFR, thymidylate synthase, dihydrofolate reductase, or multiple drug resistance-1 protein (MDR1).
17. The use of claim 1, wherein the isolated cytotoxic immune cells are derived from human induced pluripotent stem cells (hiPSCs).
18. The use of claim 1, wherein the chemotherapeutic agent is temozolomide and the isolated cytotoxic immune cells express MGMT.
19. The use of claim 1, wherein administration of the genetically modified immune cells, administration of the checkpoint inhibitor, and administration of the chemotherapeutic agent occurs substantially simultaneously or sequentially.
20. Use of an immune checkpoint inhibitor agent for the manufacture of a medicament for the treatment of cancer, wherein the treatment comprises combined administration of the immune checkpoint inhibitor, an expanded population of isolated cytotoxic immune cells, and a chemotherapeutic agent, wherein:
- i. the immune checkpoint inhibitor targets PD-1, PDL1, or CTLA-4;
 - ii. the expanded population of isolated cytotoxic immune cells comprises $\gamma\delta$ T-cells, wherein greater than about 50% of the $\gamma\delta$ T-cells have been

genetically modified to express a polypeptide that confers resistance to a chemotherapeutic agent; and

- iii. the chemotherapeutic agent is a chemotherapeutic agent to which the genetically modified $\gamma\delta$ T-cells are resistant.