mechanisms that tumor cells employ to escape and/or diminish these treatments. For example, in order to escape a patient's specific immune system, many tumor cells utilize immune checkpoint molecules and/or lower specific Major Histocompatibility Complex (MHC) expression so as to suppress and/or evade detection by the specific CD8 T cells of the immune system. Scott et al. (2012). Tumor cells have additionally been shown to evade a patient's innate immune response by modifying or decreasing tumor antigen expression on the tumor cell surface which can decrease both antibody binding, and tumor killing by the NK cells. *Id.*

[014] More recently it has been discovered that tumor cells can evade the immune system and cancer therapies by entering an equilibrium phase with a cancer patient's immune system. *See* Bhatia et al., Cancer Microenvrionment vol. 4: 209-217 (2011). In at least one aspect of the equilibrium phase, tumor cells can remain in the body below the threshold of conventional morphologic recognition or cytogenetic recognition. *Id.* For example, expression of tumor antigen receptors on tumor cells will fluctuate and, in many cases, decrease to a point that is below the threshold at which the immune system can recognize the tumor cell. *Id.*

[015] Given the ability of cancers and tumor cells to actively evade cancer therapies and a patient's immune system, there exists a substantial need for developing cancer treatments that effectively target and kill those tumor cells that actively evade the immune system. Additionally, there exists a need for cancer treatments that can attack and kill tumors and tumor cells that utilize an equilibrium phase to evade therapies and immune systems. At least in one aspect, the various embodiments of the present invention successfully overcome difficulties involving treating tumor cells that actively evade the immune system.

BRIEF SUMMARY OF THE INVENTION

[016] In a first aspect the present invention provides a use of a pharmaceutical combination in the manufacture of a medicament for use in reducing tumor size and/or increasing survival in a cancer patient, as defined in claim 1. Further features of the invention are provided in the dependent claims. It was determined in the various embodiments of the present invention that a recombinant MVA when administered intravenously to a patient in

combination with antibody against a tumor surface antigen enhances treatment of the cancer patient, more particularly increases reduction in tumor volume and/or increases survival of the cancer patient.

We claim:

1. Use of a pharmaceutical combination in the manufacture of a medicament for reducing tumor size and/or increasing survival in a cancer patient, the combination comprising:

(a) a recombinant modified vaccinia virus Ankara (MVA), wherein the recombinant MVA is to be administered via intravenous administration to said patient, and wherein the recombinant MVA comprises:

(i) a first nucleic acid encoding a first heterologous tumor-associated antigen (TAA); and

(ii) a second nucleic acid encoding CD40L; and

(b) an antibody, wherein the antibody comprises an Fc domain and is specific to an antigen that is expressed on the cell membrane of a tumor cell;

wherein administration of (a) and (b) to the cancer patient reduces tumor size and/or increases the survival rate of the cancer patient as compared to a non-intravenous administration of (a) or an administration of (b) alone.

2. Use of claim 1, wherein the recombinant MVA further comprises a third nucleic acid encoding a second heterologous TAA.

3. Use of any one of claims 1- 2, wherein the first and/or second TAA is selected from the group consisting of: 5-α-reductase, α-fetoprotein ("AFP"), AM-1, APC, April, B melanoma antigen gene ("BAGE"), β-catenin, Bcl12, bcr-abl, Brachyury, CA-125, caspase-8 ("CASP-8", also known as "FLICE"), Cathepsins, CD19, CD20, CD21/complement receptor 2 ("CR2"), CD22/BL-CAM, CD23/FcεRII, CD33, CD35/complement receptor 1 ("CR1"), CD44/PGP-1, CD45/leucocyte common antigen ("LCA"), CD46/membrane cofactor protein ("MCP"), CD52/CAMPATH-1, CD55/decay accelerating factor ("DAF"), CD59/protectin, CDC27, CDK4, carcinoembryonic antigen ("CEA"), c-myc, cyclooxygenase-2 ("cox-2"), deleted in colorectal cancer gene ("DCC"), DcR3, E6/E7, CGFR, EMBP, Dna78, farnesyl transferase, fibroblast growth factor-8a ("FGF8a"), fibroblast growth factor-8b ("FGF8b"), FLK-1/KDR, folic acid receptor, G250, G melanoma antigen gene family ("GAGE-family"), gastrin 17, gastrin-releasing hormone, ganglioside 2 ("GD2")/ganglioside 3 ("GD3")/ganglioside-monosialic acid-2 ("GM2"), gonadotropin releasing hormone ("GnRH"), UDP-GlcNAc:R1Man(α1-6)R2 [GlcNAc to

Man(α1-6)] β1,6-N¬-acetylglucosaminyltransferase V ("GnT V"), GP1, gp100/Pme117, gp-100-in4, gp15, gp75/tyrosine-related protein-1 ("gp75/TRP-1"), human chorionic gonadotropin ("hCG"), heparanase, HER2, human mammary tumor virus ("HMTV"), 70 kiloDalton heat-shock protein ("HSP70"), human telomerase reverse transcriptase ("hTERT"), insulin-like growth factor receptor-1 ("IGFR-1"), interleukin-13 receptor ("IL-13R"), inducible nitric oxide synthase ("iNOS"), Ki67, KIAA0205, K-ras, H-ras, N-ras, KSA, LKLR-FUT, melanoma antigen-encoding gene 1 ("MAGE-1"), melanoma antigen-encoding gene 2 ("MAGE-2"), melanoma antigen-encoding gene 3 ("MAGE-3"), melanoma antigen-encoding gene 4 ("MAGE-4"), mammaglobin, MAP17, Melan-A/melanoma antigen recognized by T-cells-1 ("MART-1"), mesothelin, MIC A/B, MT-MMPs, mucin, testes-specific antigen NY-ESO-1, osteonectin, p15, P170/MDR1, p53, p97/melanotransferrin, PAI-1, platelet-derived growth factor ("PDGF"), μPA, PRAME, probasin, progenipoietin, prostate-specific antigen ("PSA"), prostate-specific membrane antigen ("PSMA"), RAGE-1, Rb, RCAS1, SART-1, SSX-family, STAT3, STn, TAG-72, transforming growth factor-alpha ("TGF-α"), transforming growth factor-beta ("TGF-β"), Thymosin-beta-15, tumor necrosis factor-alpha ("TNF-α"), TP1, TRP-2, tyrosinase, vascular endothelial growth factor ("VEGF"), ZAG, p16INK4, and glutathione-S-transferase ("GST").

4. Use of any one of claims 1- 3, wherein the first and/or second TAA comprise one or more mutations to prevent the antibody from binding to the first and/or second TAA.

5 Use of any one of claims 1- 4, wherein the first TAA is HER2.

6. Use of claim 5, wherein the HER2 antigen comprises at least one mutation to: (a) prevent a HER2 antibody binding to the HER2 antigen; (b) prevent extracellular dimerization of the HER2 antigen; (c) prevent tyrosine kinase activity of the HER2 antigen; and/or (d) prevent phosphorylation of the HER2 antigen.

7. Use of claim 6, wherein the HER2 antigen comprises at least one mutation selected from the group consisting of: E580, D582, P594, F595, K615, and Q624.

8. Use of claim 6, wherein the HER2 antigen comprises at least one mutation selected from the group consisting of: H267, Y274, F279, V308, S310, L317, H318, K333, and P337.

9. Use of claim 5 or 6, wherein the HER2 antigen comprises at least one mutation selected from the group consisting of:

(a) a mutation that prevents extracellular dimerization of HER2 that is D277R or E280K;

(b) a mutation that prevents tyrosine kinase activity of HER2 that is K753M; and

(c) a mutation that interferes with phosphorylation of HER2 that is Y1023A or is the deletion of residues 1139-1248.

10. Use of claim 1, wherein the first nucleic acid encodes a HER2 antigen having the amino acid sequence set forth in SEQ ID NO:1 or SEQ ID NO: 13.

11. Use of claim 1, wherein the first nucleic acid encodes a HER2 antigen and the antibody is an anti-HER2 antibody.

12. Use of any of claims 1-2, wherein the first nucleic acid encodes a HER2 antigen that comprises the sequence set forth in SEQ ID NO: 2 or SEQ ID NO:14.

13. Use of any of claims 2-12, wherein the second TAA is Brachyury.

14. Use of claim 13, wherein the Brachyury antigen comprises one or more mutations to the nuclear localization domain.

15. Use of claim 14, wherein the second nucleic acid encodes a Brachyury antigen comprising the amino acid sequence set forth in SEQ ID NO:3.

16. Use of any one of claims 1-15, wherein the antibody is selected from the group consisting of: Anti-CD20 (e.g., rituximab; ofatumumab; tositumomab), Anti-CD52 (e.g., alemtuzumab Campath®), Anti-EGFR (e.g., cetuximab Erbitux®¸ panitumumab), Anti-CD2 (e.g.,Siplizumab), Anti-CD37 (e.g., BI836826), Anti-CD123 (e.g., JNJ-56022473), Anti-CD30 (e.g., XmAb2513), Anti-CD38 (e.g., daratumumab Darzalex®), Anti-PDL1 (e.g., avelumab, atezolilzumab, durvalumab), Anti-GD2 (e.g., 3F8, ch14.18, KW-2871, dinutuximab), anti-CTLA-4, Anti-CEA, Anti-MUC1, Anti-FLT3, Anti-CD19, Anti-CD40, Anti-SLAMF7, Anti-CCR4, Anti-B7-H3, Anti-ICAM1, Anti-CSF1R, anti-CA125 (e.g. Oregovomab), anti-FRα (e.g. MOv18-IgG1, Mirvetuximab soravtansine (IMGN853), MORAb-202), anti-mesothelin (e.g. MORAb-009), anti-Trp1, and Anti-HER2.

17. Use of claim 11, wherein the antibody is selected from Pertuzumab, Trastuzumab, Herzuma, ABP 980, and Ado-trastuzumab emtansine.

18. Use of any one of claims 1-17, wherein the MVA is MVA-BN.

19. Use of any one of claims 1-18, wherein (a) is to be administered at the same time as or after (b).

20. Use of any one of claims 1-19, wherein (a) and (b) are to be administered to the cancer patient in a priming administration followed by one or more boosting administrations of (a) and (b) to be administered to the cancer patient.

21. Use of any one of claims 1-20, wherein the cancer patient is suffering from and/or is diagnosed with a cancer selected from the group consisting of: breast cancer, lung cancer, head and neck cancer, thyroid, melanoma, gastric cancer, bladder cancer, kidney cancer, liver cancer, melanoma, pancreatic cancer, prostate cancer, ovarian cancer, or colorectal cancer.

22. Use of claim 21, wherein the cancer patient is suffering from and/or is diagnosed with breast cancer that is HER2 positive.