CLAIMS

1. An oncolytic herpes simplex virus (HSV) encoding a CTLA-4 inhibitor.

2. The virus of claim 1, wherein the CTLA-4 inhibitor is an anti-CTLA-4 antibody, or an antigen binding fragment thereof.

3. The virus of claim 2, wherein the fragment comprises a scFv molecule, or is a scFv molecule linked to one or more IgG1 constant regions.

4. The virus of claim 2 or 3, wherein the antibody or fragment comprises a light chain variable region sequence linked to an IgG heavy chain.

5. The virus of any one of claims 2 to 4, wherein the antibody or fragment comprises (a) the light chain variable region sequence shown in SEQ ID NO: 1 and the heavy chain variable region sequence shown in SEQ ID NOs: 3; or (b) the light chain variable region sequence shown in SEQ ID NO: 11 and the heavy chain variable region sequence shown in SEQ ID NO: 12; optionally, wherein the antibody or fragment: (a) comprises the amino acid sequence of SEQ ID NO: 9 or 14, and/or (b) is encoded by the nucleotide sequence of SEQ ID NO: 10 or 15.

6. The virus of any one of the preceding claims, wherein the virus further comprises: (a) a GM-CSF-encoding gene; (b) an immune co-stimulatory pathway activating molecule-encoding gene; and/or (c) a fusogenic protein-encoding gene.

7. The virus of claim 6, wherein the immune co-stimulatory pathway activating molecule-encoding gene encodes: (a) CD40 ligand (CD40L), ICOS ligand, GITR ligand, 4-1-BB ligand, OX40 ligand, TL1A, CD30 ligand, CD27 or flt3 ligand; or (b) CD40 ligand, GITR ligand, 4-1-BB ligand, OX40 ligand, or ICOS ligand.

8. The virus of claim 6 where the fusogenic protein is:

(a) selected from the group consisting of vesicular stomatitis virus (VSV) G-protein, syncitin-1, syncitin-2, simian virus 5 (SV5) F-protein, measles virus (MV) H-protein, MV F-protein, respiratory syncytial virus (RSV) F-protein and a

glycoprotein from gibbon ape leukemia virus (GALV), murine leukemia virus (MLV), Mason-Pfizer monkey virus (MPMV) or equine infectious anaemia virus (EIAV) from which the R peptide has been deleted; or

(b) the glycoprotein from gibbon ape leukemia virus (GALV) and has the R transmembrane peptide mutated or removed (GALV-R-).

9. The virus of any one of the preceding claims, which:

(a) encodes more than one immune co-stimulatory pathway activating molecule; and/or

(b) is a modified HSV clinical isolate.

10. The virus of any one of the preceding claims, which is:

(a) a HSV1; and/or

(b) a HSV which

(i) does not express functional ICP34.5;

(ii) does not express functional ICP47; and/or

(iii) expresses the US11 gene as an immediate early gene.

11. The virus of any one of the preceding claims, which is a HSV or HSV1, wherein an anti-CTLA-4 inhibiting protein encoding gene has been inserted into the ICP34.5 encoding locus by insertion, partial deletion or complete deletion;

optionally wherein the anti-CTLA-4 inhibiting protein encoding gene is included in a cassette also including one or more immune stimulating gene(s) such as GM-CSF and/or an immune co-stimulatory pathway activating molecule encoding gene and/or a fusogenic protein encoding gene.

12. The virus of any one of the preceding claims, wherein the sequence encoding the CTLA-4 inhibitor, the sequence encoding GM-CSF, the sequence encoding an immune co-stimulatory pathway activating molecule and/or the sequence encoding the fusogenic protein is codon optimized so as to increase expression levels in target cells.

13. A virus according to any one of the preceding claims, which expresses:

(a) three heterologous genes, wherein each of the three heterologous genes is driven by a different promoter selected from the CMV promoter, the RSV promoter, the SV40 promoter and a retroviral long term repeat (LTR) promoter, such as from moloney murine leukemia virus (MMLV), and/or terminated by a different poly adenylation sequence selected from the bovine growth hormone (BGH), SV40, human growth hormone (HGH) and rabbit beta-globin gene (RBG) poly adenylation sequences; or

(b) four heterologous genes driven by each of the CMV promoter, the RSV promoter, the SV40 promoter and a retroviral long term repeat (LTR) promoter, such as from moloney murine leukemia virus (MMLV), respectively; and/or terminated by each of the bovine growth hormone (BGH), SV40, human growth hormone (HGH) and rabbit beta-globin gene (RBG) poly adenylation sequences, respectively.

14. A pharmaceutical composition comprising a virus according to any one of claims 1 to 13 and a pharmaceutically acceptable carrier or diluent.

15. The virus of any one of claims 1 to 13 for use in therapy.

16. Use of the virus of any one of claims 1 to 13 in the manufacture of a medicament for treating cancer.

17. Use of the virus of any one of claims 1 to 13 in the manufacture of a medicament for treating tumors that have metastasized from the site of the original tumor.

18. The use according to claim 16 or 17, wherein the medicament comprises that a further anti-cancer agent is to be administered.

19. The use according to claim 18, wherein the further anti-cancer agent is selected from an agent targeting an immune co-inhibitory or immune co-stimulatory pathway, radiation and/or chemotherapy, an agent that targets a specific genetic mutation which occurs in tumors, an agent intended to induce an immune response to one or more tumor antigen(s) or neoantigen(s), a cellular product derived from T cells or NK cells, an agent intended to stimulate the STING, cGAS, TLR or other innate immune response and/or

inflammatory pathway, a second virus optionally an oncolytic virus, and combinations thereof;

optionally wherein the agent targeting an immune co-inhibitory pathway is a PD-1 inhibitor, a PD-L1 inhibitor, a LAG-3 inhibitor, a TIM-3 inhibitor, a VISTA inhibitor, aCSF1R inhibitor, an IDO inhibitor, a KIR inhibitor, a SLAMF7 inhibitor, a CEACAM1 inhibitor or a CD47 inhibitor, and/or the agent targeting an immune co-stimulatory pathway is a GITR agonist, a 4-1-BB agonist, an OX40 agonist, a CD40 agonist or an ICOS agonist.

20. The use according to claim 18 or 19, wherein:

(a) the further anti-cancer agent is an antibody;

(b) the medicament comprises that an inhibitor of the indoleamine 2,3-dioxygenase (IDO) pathway and a further antagonist of an immune co-inhibitory pathway, or an agonist of an immune co-stimulatory pathway is to be administered;

(c) the virus and the further anti-cancer agent(s) are to be administered separately or concurrently; and/or

(d) the cancer is a solid tumor.