

CLAIMS:

1. An agent that specifically binds to Herpesvirus entry mediator (HVEM) on a cell,
 - a. inhibits interaction between said HVEM and B- and T-lymphocyte attenuator (BTLA); and
 - b. activates downstream signaling through said HVEM within said cell.
2. The agent of claim 1, wherein said agent does not substantially inhibit interaction between said HVEM and tumor necrosis factor superfamily member 14 (TNFSF14).
3. The agent of claim 1 or 2, wherein at least one of:
 - a. said agent inhibits interaction between said HVEM and CD160, lymphotoxin alpha (LT α) or both;
 - b. said agent does not directly induce apoptosis of a cell expressing HVEM upon binding to said HVEM expressed by said cell;
 - c. said agent is an antibody or antigen binding fragment thereof;
 - d. said agent is an antibody or antigen binding fragment thereof comprising an IgG2, IgG4 or a modified IgG1 or IgG3 that is not cytotoxic to said cell;
 - e. said agent is a single chain antibody (scFv); and
 - f. said cell is a cancer cell and said signaling comprises an anti-tumor effect.
4. The agent of any one of claims 1 to 3, wherein at least one of:
 - a. said downstream signaling through HVEM comprises nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) mediated transcription;
 - b. said downstream signaling through HVEM comprises increased cytotoxicity of an immune cell expressing said HVEM, optionally wherein said increased cytotoxicity comprises increased secretion of a proinflammatory cytokine; and
 - c. said cell is an immune cell, and said signaling induces immune activation, optionally wherein said immune cell is a tumor infiltrating lymphocyte (TIL) or a peripheral blood mononuclear cell (PBMC).

5. The agent of any one of claims 1 to 4, wherein said agent is an antibody or antigen binding fragment thereof comprises three heavy chain CDRs (CDR-H) and three light chain CDRs (CDR-L), wherein: CDR-H1 comprises the amino acid sequence set forth in SEQ ID NO: 1 (SYAMS), CDR-H2 comprises the amino acid sequence as set forth in SEQ ID NO: 2 (AISGSGGSTYYADSVKG), CDR-H3 comprises the amino acid sequence as set forth in SEQ ID NO: 3 (APGDYTAYFDY), CDR-L1 comprises the amino acid sequence as set forth in SEQ ID NO: 4 (RASQSVSSYLA), CDR-L2 comprises the amino acid sequence as set forth in SEQ ID NO: 5 (GASSRAT), and CDR-L3 comprises the amino acid sequence as set forth in SEQ ID NO: 6 (QQYGSSPPYT).
6. The agent of claim 5, comprising a heavy chain comprising the sequence
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWV
SAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAK
APGDYTAYFDYWGQGTLVTVSS (SEQ ID NO: 7) and a light chain comprising the
sequence
ELVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYG
ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPYTFGQG
TKVEIK (SEQ ID NO: 8), optionally comprising a heavy chain comprising the
sequence
MGWSCII LFLVATATGVHSQVQLVQSGGGLVQPGGSLRLSCAASGFTFSS
YAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLY
LQMNSLRAEDTAVYYCAKAPGDYTAYFDYWGQGTLVTVSSASTKGPSV
FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCP
APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL
PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH
EALHNHYTQKSLSLGLK (SEQ ID NO: 9) and a light chain comprising the
sequence
MGWSCII LFLVATATGVHSELVLTQSPATLSLSPGERATLSCRASQSVSSY

LAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDF
AVYYCQQYGSSPPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 10).

7. An antibody or antigen binding fragment thereof comprises three heavy chain CDRs (CDR-H) and three light chain CDRs (CDR-L), wherein: CDR-H1 comprises the amino acid sequence set forth in SEQ ID NO: 1 (SYAMS), CDR-H2 comprises the amino acid sequence as set forth in SEQ ID NO: 2 (AISGSGGSTYYADSVKG), CDR-H3 comprises the amino acid sequence as set forth in SEQ ID NO: 3 (APGDYTAYFDY), CDR-L1 comprises the amino acid sequence as set forth in SEQ ID NO: 4 (RASQSVSSYLA), CDR-L2 comprises the amino acid sequence as set forth in SEQ ID NO: 5 (GASSRAT), and CDR-L3 comprises the amino acid sequence as set forth in SEQ ID NO: 6 (QQYGSSPPYT), optionally comprising a heavy chain comprising the sequence
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWV
SAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAK
APGDYTAYFDYWGQGTLVTVSS (SEQ ID NO: 7) and a light chain comprising the
sequence
ELVLTQSPATLSLSPGERATLSCRASQSVSSYLA
WYQQKPGQAPRLLIYG
ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPYTFGQG
TKVEIK (SEQ ID NO: 8).
8. The antibody or antigen binding fragment thereof of claim 7, comprising a heavy chain comprising the sequence
MGWSCILFLVATATGVHSQVQLVQSGGGLVQPGGSLRLSCAASGFTFSS
YAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLY
LQMNSLRAEDTAVYYCAKAPGDYTAYFDYWGQGTLVTVSSASTKGPSV
FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSVVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCP
APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL
PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE

WESNGQPENNYKTTTPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMH
EALHNHYTQKSLSLGLGK (SEQ ID NO: 9) and a light chain comprising the
sequence

MGWSCILFLVATATGVHSELVLTQSPATLSLSPGERATLSCRASQSVSSY
LAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDF
AVYYCQQYGSSPPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTYSLSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 10).

9. A pharmaceutical composition comprising an agent of any one of claims 1 to 6, or an antibody or antigen binding fragment thereof of claim 7 or 8 and a pharmaceutically acceptable carrier, excipient or adjuvant.
10. The pharmaceutical composition of claim 9, for use in treating a disease or condition characterized by HVEM positive disease cells, wherein said disease is selected from:
 - a. an HVEM positive cancer or precancerous lesion;
 - b. an HVEM positive cancer selected from melanoma, renal cancer, cervical cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, breast cancer and head and neck cancer; and
 - c. an infectious disease wherein said infected cells comprise HVEM expression.
11. The pharmaceutical composition of claim 10, for use in combination with at least one of: an anti-PD-1/PD-L1 based immunotherapy and adoptive cell therapy, optionally wherein said adoptive cell therapy is selected from adoptive tumor infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor (CAR) expressing immune cell therapy, wherein said CAR targets a non-HVEM protein on a surface of said HVEM expressing cells.
12. The pharmaceutical composition of claim 10 or 11, wherein said disease is an HVEM positive cancer selected from melanoma and renal cell carcinoma.
13. A method of determining suitability of a subject to be treated with a pharmaceutical composition of any one of claims 9 to 12, comprising obtaining a disease sample from said subject and determining HVEM levels in said sample, wherein positive

- expression of HVEM indicates the subject is suitable for treatment with a pharmaceutical composition of any one of claims 9 to 12, optionally wherein positive expression of HVEM comprises an elevated HVEM level as compared to a healthy sample or predetermined threshold.
14. A method of detecting HVEM in a sample, the method comprising contacting said sample with an agent of any one of claims 1 to 6, or an antibody or antigen binding fragment thereof of claim 7 or 8, thereby detecting HVEM.
 15. A kit comprising, the pharmaceutical composition of claim 9 and at least one of:
 - a. an anti-PD-1/PD-L1 based immunotherapy;
 - b. a label stating the pharmaceutical composition of the invention is for use with an anti-PD-1/PD-L1 based immunotherapy; and
 - c. a secondary detection molecule for detecting said at least one agent of any one of claims 1 to 6 or said at least one antibody or antigen binding fragment thereof of claim 7 or 8.