CLAIMS

1. An agent that neutralizes the inhibitory activity of human NKG2A for use in treating a cancer in a human patient, the treatment comprising administering to the patient an effective amount of each of: (a) an agent, optionally an antibody, that neutralizes the inhibitory activity of human NKG2A, and (b) an agent, optionally an antibody, that neutralizes the inhibitory activity of human PD-1.

2. A method of activating NKG2A+/PD1+ CD8+ T cells in an individual comprising co-administering to the individual an anti-NKG2A antibody and an anti-PD1, anti-PDL1 antibody, and/or anti-PDL2 antibody.

3. The compound for use of claim 1 or the method of claim 2, wherein at least two doses of the antibody that neutralizes the inhibitory activity of human NKG2A are administered in an amount effective to achieve a continuous blood concentration of anti-NKG2A antibody of at least 10 μg/ml for at least one week following administration thereof.

4. The compound for use or the method of any one of claims 1-3, wherein the treatment comprises at least one administration cycle, optionally wherein the cycle is a period of eight weeks, wherein for each cycle, two, three or four doses of the antibody that neutralizes the inhibitory activity of human NKG2A are administered and two, three or four doses of the antibody that neutralizes the inhibitory activity of PD-1 antibody are administered.

5. The compound for use or the method of any one of claims 1-4, wherein the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are formulated for separate administration and are administered concurrently or sequentially.

6. The compound for use or the method of any one of claims 1-5, wherein the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are formulated simultaneously administered in a single formulation.

7. The compound for use or the method of any one of claims 1-6, wherein the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are formulated simultaneously administered on the same day.

8. The compound for use or the method of any of the above claims, wherein the cancer is a solid tumor.

9. The compound for use or the method of claim 8, wherein the cancer is hematological tumor.

10. The compound for use or the method of claim 8, wherein the cancer is selected from the group consisting of lung cancer, renal cell carcinoma (RCC), melanoma, colorectal cancer, and ovarian cancer.

11. The compound for use or the method of any one of claims 8-10, wherein the cancer is an HLA-E-expressing cancer.

12. The compound for use or the method of any of the above claims, wherein an antibody that neutralizes the inhibitory activity of NKG2A comprises the CDR1, CDR2 and CDR3 domains of a heavy chain having the sequence set forth in any one of SEQ ID NOS: 4-8, and the CDR1, CDR2 and CDR3 domains of a light chain having the sequence set forth in SEQ ID NO: 9.

13. The compound for use or the method of any of the above claims, wherein an antibody that neutralizes the inhibitory activity of PD-1 is an antibody that binds a PD-1 polypeptide.

14. The compound for use or the method of any of the above claims, wherein an antibody that neutralizes the inhibitory activity of PD-1 is an antibody that binds a PD-L1 polypeptide.

15. The compound for use or the method of any of the above claims, wherein said antibody is a chimeric, human or humanized antibody.

16. The compound for use or the method of any of the above claims, wherein said antibody that neutralizes the inhibitory activity of NKG2A is a non-depleting antibody.

17. The compound for use or the method of any of the above claims, wherein said antibody that neutralizes the inhibitory activity of PD-1 is a non-depleting antibody.

18. The compound for use or the method of any of the above claims, wherein said antibody is IgG4 antibody.

19. The compound for use or the method of any of the above claims, wherein said antibody lacks an Fc domain or comprises an Fc domain that is modified to reduce binding between the Fc domain and an Fcγ receptor.

20. The compound for use or the method of any of the above claims, wherein said antibody is an antibody fragment.

21. The compound for use or the method of claim 20, wherein said antibody fragment is selected from Fab, Fab', Fab'-SH, F(ab') 2, Fv, a diabody, a single-chain antibody fragment, or a multispecific antibody comprising multiple different antibody fragments.

22. A pharmaceutical composition comprising an agent, optionally an antibody, that neutralizes the inhibitory activity of NKG2A, an agent, optionally an antibody, that neutralizes the inhibitory activity of PD-1, and a pharmaceutically acceptable carrier.

23. A kit comprising: (a) a dose of an agent, optionally an antibody, that neutralizes the inhibitory activity of NKG2A, and (b) a dose of an agent, optionally an antibody, that neutralizes the inhibitory activity of PD-1.

24. A kit comprising: (a) multiple packages of single-dose pharmaceutical compositions containing an effective amount of an antibody that neutralizes the inhibitory activity of NKG2A, and (b) multiple packages of single-dose pharmaceutical compositions containing an effective amount of an antibody that neutralizes the inhibitory activity of PD-1.

25. An antibody that neutralizes the inhibitory activity of NKG2A, for use in the modulation of NKGA+ PD-1+ lymphocytes, optionally CD8+ T cells in an individual the method comprising administering to said individual an effective amount of an agent, optionally an antibody, that neutralizes the inhibitory activity of NKG2A and an agent, optionally an antibody, that neutralizes the inhibitory activity of PD-1.

26. An in vitro method for detecting a NKG2A+ PD-1+ lymphocyte, optionally an NK or CD8+ T cell, comprising providing a biological sample comprising tumor infiltrating lymphocytes and determining whether the lymphocytes express NKG2A and PD-1.

27. An in vitro method for modulating the activity of NKG2A+ PD-1+ lymphocytes, optionally CD8+ T cells, comprising bringing lymphocytes expressing at their surface NKG2A and PD-1 into contact with an antibody that neutralizes the inhibitory activity of NKG2A and an antibody that neutralizes the inhibitory activity of PD-1.

28. An antibody that neutralizes the inhibitory activity of NKG2A, for use in the treatment or prevention of a cancer in an individual, the treatment comprising:

a) determining the HLA-E polypeptide status of malignant cells within the individual having a cancer, and

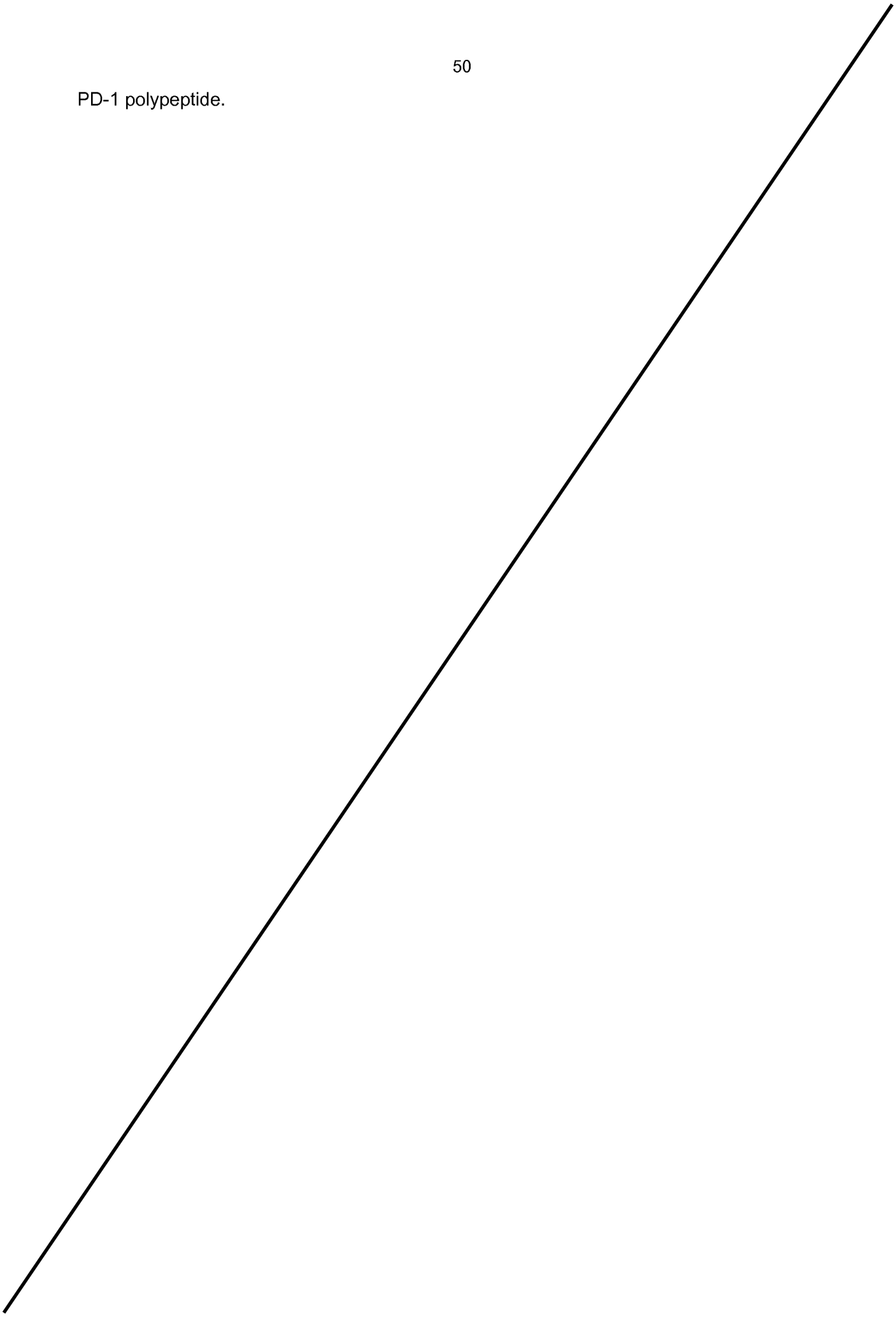
b) upon a determination that HLA-E polypeptides are prominently expressed by (e.g. on the surface of) malignant cells (e.g. tumor cells), administering to the individual a compound that neutralizes the inhibitory activity of a human NKG2A polypeptide and an agent that inhibits a human PD-1 polypeptide.

29. An antibody that neutralizes the inhibitory activity of NKG2A, for use in the treatment or prevention of a cancer in an individual, the treatment comprising:

a) determining the NKG2A and PD-1 polypeptide status of tumor infiltrating lymphocytes from the individual, and

b) upon a determination that NKG2A and PD-1 polypeptides are expressed on the surface of a significant proportion of tumor infiltrating lymphocytes from the individual, administering to the individual a therapeutic regimen that comprises (i) a compound that neutralizes the inhibitory activity of a human NKG2A polypeptide and (ii) an agent that inhibits a human

PD-1 polypeptide.



CLAIMS

1. Use of an antibody that neutralizes the inhibitory activity of human NKG2A in the preparation of a medicament for the treatment of non-small cell lung cancer in a human patient, in which an effective amount of each of: (a) an antibody that neutralizes the inhibitory activity of human NKG2A, and (b) an antibody that neutralizes the inhibitory activity of human PD-1 are to be administered to the patient.

2. Use according to Claim 1, in which the antibody that neutralizes the inhibitory activity of human NKG2A comprises the CDR1, CDR2 and CDR3 domains of a heavy chain having the sequence set forth in any one of SEQ ID NOS: 4-8, and the CDR1, CDR2 and CDR3 domains of a light chain having the sequence set forth in SEQ ID NO: 9.

3. Use according to Claim 1 or 2, in which the antibody that neutralizes the inhibitory activity of human NKG2A comprises the CDR1, CDR2 and CDR3 domains of a heavy chain having the sequence set forth in SEQ ID NO: 5 and the CDR1, CDR2 and CDR3 domains of a light chain having the sequence set forth in SEQ ID NO: 9.

4. Use according to Claim 1, 2 or 3, in which the antibody that neutralizes the inhibitory activity of human NKG2A comprises a heavy chain having the sequence set forth in SEQ ID NO: 5 and a light chain having the sequence set forth in SEQ ID NO: 9.

5. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of human PD-1 is selected from the group consisting of pembrolizumab, nivolumab, AMP-514, MEDI-4736, CT-011 and MPDL3280A.

6. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of human PD-1 is MEDI-4736.

7. Use according to any of Claims 1 to 4, in which the antibody that neutralizes the inhibitory activity of human PD-1 is an anti-PD-L1 antibody that inhibits the binding of PD-L1 to PD-1.

8. Use according to Claim 7, in which the anti-PD-L1 antibody is MEDI-4736.

9. Use according to any preceding claim, in which at least two doses of the antibody that neutralizes the inhibitory activity of human NKG2A are to be administered in an amount

effective to achieve a continuous blood concentration of anti-NKG2A antibody of at least 10 µg/ml for at least one week following administration thereof.

10. Use according to any preceding claim, in which the treatment comprises at least one administration cycle, in which for each cycle, two, three or four doses of the antibody that neutralizes the inhibitory activity of human NKG2A are to be administered and two, three or four doses of the antibody that neutralizes the inhibitory activity of PD-1 antibody are to be administered.

11. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are formulated for separate administration and are to be administered concurrently or sequentially.

12. Use according to any of Claims 1 to 10, in which the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are to be administered in a single formulation.

13. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of human NKG2A and the antibody that neutralizes the inhibitory activity of PD-1 are to be administered on the same day.

14. Use according to any preceding claim, in which the non-small cell lung cancer is an HLA-E-expressing cancer.

15. Use according to any preceding claim, in which the non-small cell lung cancer is an advanced cancer.

16. Use according to any preceding claim, in which the non-small cell lung cancer is a refractory cancer.

17. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of NKG2A is a non-depleting antibody.

18. Use according to any preceding claim, in which the antibody that neutralizes the inhibitory activity of NKG2A is an IgG4 antibody, in which the antibody that neutralizes the inhibitory activity of human NKG2A lacks an Fc domain or in which the antibody that

neutralizes the inhibitory activity of human NKG2A comprises an Fc domain that is modified to reduce binding between the Fc domain and an Fcγ receptor.

19. Use according to Claim 10, in which the at least one administration cycle comprises a period of eight weeks.

20. Use of an antibody that neutralizes the inhibitory activity of human NKG2A in the preparation of a medicament for the treatment of non-small cell lung cancer in a human patient, in which an effective amount of each of: (a) an antibody that neutralizes the inhibitory activity of human NKG2A comprising a heavy chain having the sequence set forth in SEQ ID NO: 5 and a light chain having the sequence set forth in SEQ ID NO: 9, and (b) an antibody that neutralizes the inhibitory activity of human PD-1, in which the antibody that neutralizes the inhibitory activity of human PD-1 is MEDI-4736, are to be administered to the patient.