

CLAIMS

1. An antibody that binds and neutralizes the inhibitory activity of NKG2A for use in the treatment of disease in an individual, the treatment comprising administering to the individual the antibody for at least one administration cycle in which the anti-NKG2A antibody is administered at least twice and in amounts effective to achieve, and/or to maintain between two successive administrations of the anti-NKG2A antibody, a blood concentration of anti-NKG2A antibody of at least 10 µg/ml.
2. The antibody of claim 1, wherein the anti-NKG2A antibody is administered at least twice and in amounts effective to maintain a continuous blood concentration of the anti-NKG2A antibody of at least 10 µg/ml throughout the administration cycle.
3. The antibody of any one of claims 1 or 2, wherein the antibody is administered to maintain a continuous blood concentration of anti-NKG2A antibody of at least 10 µg/ml, optionally between 10-100, 10-80 or 10-50 µg/ml, throughout the administration cycle.
4. The antibody of any one of claims 1-3 wherein the antibody is administered to achieve a peak blood concentration of anti-NKG2A antibody of at least 40 µg/ml, 50 µg/ml or 100 µg/ml upon administration.
5. The antibody of any one of claims 1-4 wherein the antibody is administered in an amount effective to provide a continuous (minimal) blood concentration of the anti-NKG2A antibody of at least about 40 µg/ml, 50 µg/ml or 100 µg/ml for at least one week, optionally two weeks, following administration of the anti-NKG2A antibody.
6. The antibody of any one of claims 1-5 wherein the antibody is administered to maintain a continuous (minimal) blood concentration of the anti-NKG2A antibody of at least about 100 µg/ml between two successive administrations of the anti-NKG2A antibody.
7. The antibody of any one of claim 1-6, wherein the antibody is administered to maintain a continuous blood concentration of the anti-NKG2A antibody of at least 100 µg/ml, optionally between 100-200 µg/ml, between two successive administrations of the anti-NKG2A antibody, optionally throughout the administration cycle.

8. The antibody of any of the above claims, wherein the antibody is administered in amounts effective to maintain a continuous blood concentration of anti-NKG2A antibody of at least 40 µg/ml between two successive administrations of the anti-NKG2A antibody.
9. The antibody of any of the above claims, wherein the antibody is administered 2 times per month.
10. The antibody of any of the above claims, wherein the antibody is administered intravenously two times per month and the amount of anti-NKG2A antibody of at least 10 µg/ml between at least two successive administrations of the anti-NKG2A antibody administered is between 2-10 mg/kg, optionally 2-6 mg/kg, optionally 2-8 mg/kg, or optionally 2-4 mg/kg body weight.
11. The antibody of any of the above claims, wherein the antibody is administered intravenously two times per month and the amount of anti-NKG2A antibody of at least 100 µg/ml between at least two successive administrations of the anti-NKG2A antibody administered is between 4-10 mg/kg, optionally 4-6 mg/kg, optionally 4-8 mg/kg, optionally about 4 mg/kg, optionally about 6 mg/kg, optionally about 8 mg/kg, or optionally about 10 mg/kg body weight.
12. The antibody of any of the above claims, wherein the treatment comprises a loading period in which the antibody is administered at least once at an initial dose effective to maintain a blood concentration of at least 100 µg/ml until the next successive administration of the anti-NKG2A antibody, followed by a maintenance period in which the antibody is administered at least twice in a second dose and at a frequency effective to maintain a continuous blood concentration of the anti-NKG2A antibody of at least 100 µg/ml between successive administrations of the anti-NKG2A antibody.
13. The antibody of claim 12, wherein the antibody is administered intravenously, and wherein the loading period comprises administering the antibody once at a dose of between 8-10 mg/kg, optionally about 10 mg/kg, and the maintenance period comprises administering the antibody at least twice, at an interval of about two weeks at dose of between 2-6 mg/kg, optionally between 2-5 mg/kg, optionally between 2-4 mg/kg, optionally about 2 mg/kg, optionally about 3 mg/kg, optionally about 4 mg/kg, or optionally about 6 mg/kg body weight.

14. An antibody that binds and neutralizes the inhibitory activity of NKG2A for use in treating an individual, the treatment comprising administering to the individual the antibody for at least one administration cycle in which the anti-NKG2A antibody is administered at a dose of between 4-10 mg/kg, optionally 4-6 mg/kg, optionally 4-8 mg/kg, optionally about 4 mg/kg, optionally about 6 mg/kg, optionally about 8 mg/kg, or optionally about 10 mg/kg body weight.
15. An antibody that binds and neutralizes the inhibitory activity of NKG2A for use in treating an individual, the treatment comprising administering to the individual the antibody for at least one administration cycle, wherein the method comprises:
 - a. a loading period in which antibody is administered intravenously at least once at an initial dose of between 8-10 mg/kg, optionally about 10 mg/kg, and,
 - b. a maintenance period in which the antibody is administered intravenously every two weeks at least twice in a dose of between 2-6 mg/kg, optionally between 2-5 mg/kg, optionally between 2-4 mg/kg, optionally about 2 mg/kg, optionally about 3 mg/kg, optionally about 4 mg/kg, or optionally about 6 mg/kg body weight, optionally wherein the first administration within the maintenance period occurs no more than two weeks after the initial dose.
16. The antibody of claim 15 wherein the antibody is administered at a frequency and an amount effective to maintain a continuous blood concentration of the anti-NKG2A antibody of at least 10 µg/ml, optionally at least 40 µg/ml, 50 µg/ml or 100 µg/ml, throughout the administration cycle.
17. The antibody of any of the above claims, wherein the administration cycle is 8 weeks or at least 8 weeks.
18. The antibody of any of the above claims, wherein the administration cycle comprises at least 4 administrations of the anti-NKG2A antibody.
19. The antibody of any of the above claims, wherein the individual has a cancer.
20. The antibody of claim 19, wherein the individual has a hematological tumor.
21. The antibody of any of claims 1-2 or 4-19, wherein the individual has a solid tumor.
22. The antibody of claim 21, wherein the individual has a HNSCC.

23. The antibody of any of the above claims, wherein the individual has a solid tumor and is treated with the anti-NKG2A antibody prior to surgery to remove the tumor.
24. The antibody of claim 23, wherein the individual is treated with a complete administration cycle of the anti-NKG2A antibody prior to surgery to remove the tumor.
25. The antibody of any of the above claims, wherein antibody competes with HLA-E for binding to NKG2A.
26. The antibody of any of the above claims, wherein antibody has an EC_{50} for binding to NKG2A-expressing cells of between 1-10 ng/ml.
27. The antibody of any of the above claims, wherein antibody has K_D of between 10^{-10} M and 10^{-12} M for binding to a recombinant soluble NKG2A polypeptide.
28. The antibody of any of the above claims, wherein the antibody comprises a human IgG4 constant region.
29. The antibody of any of the above claims, wherein the antibody comprises an Fc-engineered constant region comprising an amino acid modification that reduces binding to a human Fcγ receptor.
30. The antibody of any of the above claims, wherein the antibody is an antibody fragment.
31. The antibody of claim 30, wherein the antibody fragment lacks an Fc domain.
32. The antibody of claims 30 or 31, wherein the antibody fragment is from the group consisting of a Fab fragment, a Fab' fragment, a Fab'-SH fragment, a $F(ab)^2$ fragment, a $F(ab')^2$ fragment, an Fv fragment, a heavy chain Ig (a llama or camel Ig), a V_{HH} fragment, a single domain Fv, and a single-chain antibody fragment.
33. The antibody of any of the above claims, wherein the antibody competes for binding to human NKG2A with an antibody having a heavy chain comprising the amino acid sequence of any of SEQ ID NOS: 2-6 and the light chain sequence of SEQ ID NO: 7.

34. The antibody of any of the above claims, wherein the antibody comprises the CDR1, CDR2 and CDR3 domains of a heavy chain having the sequence set forth in SEQ ID NO: 2, and the CDR1, CDR2 and CDR3 domains of a light chain having the sequence set forth in SEQ ID NO: 3.

35. The antibody of any of the above claims, wherein the antibody comprises the VH CDRs of the heavy chain comprising an amino acid sequence of any one of SEQ ID NO: 2-6 and the VL CDRs of the light chain comprising the amino acid sequence of SEQ ID NO: 7 respectively.

36. The antibody of any of the above claims, wherein the anti-NKG2A antibody is administered as a pharmaceutically acceptable composition comprising a therapeutically effective amount of the anti-NKG2A antibody.

37. The antibody of claim 36, wherein the composition is free of any other pharmaceutically active agents.

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

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

b) upon a determination that the patient has HLA-E polypeptides prominently expressed on the surface of malignant cells, administering to the individual the in an amount effective to achieve a blood (serum) concentration of anti-NKG2A antibody that corresponds to at least the EC_{50} , optionally the EC_{100} , for NKG2A+ NK cell response.

39. The method of claim 38, wherein determining the HLA-E polypeptide status in step (a) comprises determining the level of expression of a HLA-E nucleic acid or polypeptide of malignant cells in a biological sample and comparing the level to a reference level.

40. The method of claims 38-39, wherein the antibody is administered in an amount effective to achieve an extravascular tissue concentration of anti-NKG2A antibody that corresponds to at least the EC_{50} , optionally the EC_{100} , for NKG2A+ NK cell response.

41. The method of claims 38-40, wherein the EC_{50} for NKG2A+ NK cell response is

about 4 µg/ml.

42. The method of claims 38-40, wherein the EC₁₀₀ for NKG2A+ NK cell response is about 10 µg/ml.

43. The method of claims 38-42, wherein antibody competes with HLA-E for binding to NKG2A.

44. An antibody that binds and neutralizes the inhibitory activity of NKG2A for use in a treatment of disease in an individual, the treatment comprising administering to the individual the antibody in an amount effective to achieve a blood concentration that corresponds to at least the EC₅₀, optionally the EC₁₀₀, for NKG2A+ NK cell response.

45. The method of claim 44, wherein the EC₅₀ for NKG2A+ NK cell response is about 4 µg/ml.

46. The method of claim 44, wherein the EC₁₀₀ for NKG2A+ NK cell response is about 10 µg/ml.

47. The method of claims 44-46, wherein antibody competes with HLA-E for binding to NKG2A.

48. The method of any of the above claims, wherein NKG2A+ NK cell response is the NKG2A+ NK cell response to an HLA-E expressing target cell.

CLAIMS

1. Use of an antibody that binds and neutralizes the inhibitory activity of NKG2A (anti-NKG2A) in the preparation of a medicament for the treatment of cancer in an individual, in which the antibody is to be administered to the individual for at least one administration cycle, in which the anti-NKG2A antibody is to be administered twice per month intravenously at a dose of between 4-10 mg/kg or of about 10 mg/kg body weight.
2. Use according to Claim 1, in which the anti-NKG2A antibody is to be administered at a at least first loading dose of about 10 mg/kg body weight followed by at least two maintenance doses of about 4 mg/kg body weight.
3. Use according to Claim 1 or 2, in which the administration cycle is 8 weeks or at least 8 weeks.
4. Use according to Claim 1, 2 or 3, in which the administration cycle comprises at least 4 administrations of the anti-NKG2A antibody.
5. Use according to any preceding claim, in which the individual has a hematological tumor.
6. Use according to Claim 5, in which the hematological tumor is selected from the group consisting of leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkitt lymphoma, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, promyelocytic leukemia and myelodysplastic syndrome.
7. Use according to any one of Claims 1 to 4, in which the individual has a solid tumor.
8. Use according to Claim 7, in which the individual has a HNSCC.
9. Use according to Claim 7, in which the individual has lung cancer.
10. Use according to any preceding claim, in which the antibody competes with HLA-E for binding to NKG2A.

11. Use according to any preceding claim, in which the antibody has a K_D of between 10^{-10} M and 10^{-12} M for binding to a recombinant soluble NKG2A polypeptide, as assessed by surface plasmon resonance.
12. Use according to any preceding claim, in which the antibody comprises a human IgG4 constant region, in which the antibody comprises an Fc- engineered constant region comprising an amino acid modification that reduces binding to a human Fc γ receptor or in which the antibody is an antibody fragment lacking an Fc domain.
13. Use according to Claim 12, in which the antibody fragment is from the group consisting of a Fab fragment, a Fab' fragment, a Fab'-SH fragment, a F(ab)² fragment, a F(ab')² fragment, an Fv fragment, a heavy chain Ig (a llama or camel Ig), a V_{HH} fragment, a single domain FV and a single-chain antibody fragment.
14. Use according to any preceding claim, in which the antibody comprises the VH CDRs of a heavy chain comprising an amino acid sequence of any one of SEQ ID NO: 2-6 and the VL CDRs of the light chain comprising the amino acid sequence of SEQ ID NO: 7 respectively.
15. Use according to any preceding claim, in which the antibody comprises a heavy chain comprising an amino acid sequence of any one of SEQ ID NO: 2-6 and a light chain comprising the amino acid sequence of SEQ ID NO: 7.
16. Use according to any preceding claim, in which the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 3 and a light chain comprising the amino acid sequence of SEQ ID NO: 7.
17. Use according to any preceding claim, in which the antibody is to be administered at a dose of about 4 mg/kg body weight.
18. Use according to any preceding claim, in which the antibody is to be administered at a dose of between 6-10 mg/kg body weight.
19. Use according to any preceding claim, in which the anti-NKG2A antibody is to be administered as a pharmaceutically acceptable composition comprising a therapeutically effective amount of the anti-NKG2A antibody.

20. Use according to Claim 19, in which the composition is free of any other pharmaceutically active agents.