Claims

1. An anti-PVRIG (Poliovirus Receptor Related Immunoglobulin Domain Containing Protein) antibody for use in the treatment of cancer, wherein the antibody activates T cells and/or NK cells.

2. An anti-PVRIG antibody for use according to claim 1, wherein said anti-PVRIG antibody comprises: the vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3 sequences selected from the group consisting of:

    - the vhCDR1 as set out in SEQ ID NO:877, vhCDR2 as set out in SEQ ID NO:878, vhCDR3 as set out in SEQ ID NO:879, vlCDR1 as set out in SEQ ID NO:881, vlCDR2 as set out in SEQ ID NO:882 and vlCDR3 as set out in SEQ ID NO:883,
    - the vhCDR1 as set out in SEQ ID NO:885, vhCDR2 as set out in SEQ ID NO:886, vhCDR3 as set out in SEQ ID NO:887, vlCDR1 as set out in SEQ ID NO:889, vlCDR2 as set out in SEQ ID NO:890 and vlCDR3 as set out in SEQ ID NO:891,
    - the vhCDR1 as set out in SEQ ID NO:917, vhCDR2 as set out in SEQ ID NO:918, vhCDR3 as set out in SEQ ID NO:919, vlCDR1 as set out in SEQ ID NO:921, vlCDR2 as set out in SEQ ID NO:922 and vlCDR3 as set out in SEQ ID NO:923,
    - the vhCDR1 as set out in SEQ ID NO:941, vhCDR2 as set out in SEQ ID NO:942, vhCDR3 as set out in SEQ ID NO:943, vlCDR1 as set out in SEQ ID NO:945, vlCDR2 as set out in SEQ ID NO:946 and vlCDR3 as set out in SEQ ID NO:947,
    - the vhCDR1 as set out in SEQ ID NO:949, vhCDR2 as set out in SEQ ID NO:950, vhCDR3 as set out in SEQ ID NO:951, vlCDR1 as set out in SEQ ID NO:953, vlCDR2 as set out in SEQ ID NO:954 and vlCDR3 as set out in SEQ ID NO:955,
    - the vhCDR1 as set out in SEQ ID NO:973, vhCDR2 as set out in SEQ ID NO:974, vhCDR3 as set out in SEQ ID NO:975, vlCDR1 as set out in SEQ ID NO:977, vlCDR2 as set out in SEQ ID NO:978 and vlCDR3 as set out in SEQ ID NO:979,
    - the vhCDR1 as set out in SEQ ID NO:981, vhCDR2 as set out in SEQ ID NO:982, vhCDR3 as set out in SEQ ID NO:983, vlCDR1 as set out in SEQ ID NO:985, vlCDR2 as set out in SEQ ID NO:986 and vlCDR3 as set out in SEQ ID NO:987,

- the vhCDR1 as set out in SEQ ID NO:997, vhCDR2 as set out in SEQ ID NO:998, vhCDR3 as set out in SEQ ID NO:999, vlCDR1 as set out in SEQ ID NO:1001, vlCDR2 as set out in SEQ ID NO:1002 and vlCDR3 as set out in SEQ ID NO:1003,
- the vhCDR1 as set out in SEQ ID NO:1037, vhCDR2 as set out in SEQ ID NO:1038, vhCDR3 as set out in SEQ ID NO:1039, vlCDR1 as set out in SEQ ID NO:1041, vlCDR2 as set out in SEQ ID NO:1042 and vlCDR3 as set out in SEQ ID NO:1043.

3. An anti-PVRIG antibody for use according to any of claims 1 to 2, wherein said antibody comprises the variable heavy domain as set out in SEQ ID NO:884 and the variable light domain as set out in SEQ ID NO:888.

4. An anti-PVRIG antibody for use according to any of claims 1 to 3, wherein said antibody comprises the variable heavy domain as set out in SEQ ID NO:980 and the variable light domain as set out in SEQ ID NO:984.

5. An anti-PVRIG antibody for use according to any one of claims 1 to 4, wherein the anti-PVRIG antibody is for use in combination with an immunostimulatory antibody, a cytokine therapy, or an immunomodulatory drug.

6. An anti-PVRIG antibody comprising
i) the heavy chain variable domain of SEQ ID NO:1434 and
ii) the light chain variable domain of SEQ ID NO:1453, for use in treatment of cancer by activating T-cells and/or NK cells in a patient.

7. An anti-PVRIG antibody comprising:
i) the heavy chain variable domain of SEQ ID NO:1447 and
ii) the light chain variable domain of SEQ ID NO:1462,
for use in treatment of cancer by activating T-cells and/or NK cells in a patient.

8. The anti-PVRIG antibody for use according to claim 6 or 7 wherein said T-cells are cytotoxic T-cells (CTLs).

9. The anti-PVRIG antibody for use according to any of claims 6 to 8 wherein said T-cells are selected from the group consisting of $CD4^+$ T-cells and $CD8^+$ T-cells.

10. The anti-PVRIG antibody for use according to any of claims 6 to 9 wherein said activation is measured as an increase in interferon-γ production and/or an increase in pro-inflammatory cytokine secretion.

11. The anti-PVRIG antibody for use according to any of claims 6 to 10 wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, pancreatic cancer, stomach cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, melanoma, non-melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, carcinoma, blastoma, sarcoma, leukemia, squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric cancer (including gastrointestinal cancer), glioblastoma, bladder cancer, hepatoma, colon cancer, uterine carcinoma, salivary gland carcinoma, kidney cancer, vulval cancer, hepatic carcinoma, B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/follicular NHL, intermediate grade diffuse NHL, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, mantle cell lymphoma, AIDS-related lymphoma, and Waldenström's Macroglobulinemia), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), Hairy cell leukemia, chronic myeloblastic leukemia, multiple myeloma, post-transplant lymphoproliferative disorder (PTLD), lymphoid malignancies, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), Meigs' syndrome, rectal cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, and multiple myeloma.

12. A nucleic acid composition comprising:
a) a first nucleic acid encoding the heavy chain variable domain of SEQ ID NO:1434; and
b) a second nucleic acid encoding the light chain variable domain of SEQ ID NO:1453.

13. An expression vector composition comprising:
a) a first expression vector comprising said first nucleic acid of claim 12; and
b) a second expression vector comprising said second nucleic acid of claim 12.

14. An expression vector composition comprising an expression vector comprising said first nucleic acid of claim 12 and said second nucleic acid of claim 12.

15. A host cell comprising the expression vector composition of claim 13 or 14.

16. A method of making an anti-PVRIG antibody comprising:
a) culturing the host cell of claim 15 under conditions wherein said antibody is expressed; and
b) recovering said antibody.

17. A nucleic acid composition comprising:
a) a first nucleic acid encoding the heavy chain variable domain of SEQ ID NO:1447; and
b) a second nucleic acid encoding the light chain variable domain of SEQ ID NO:1462.

18. An expression vector composition comprising:
a) a first expression vector comprising said first nucleic acid of claim 17; and
b) a second expression vector comprising said second nucleic acid of claim 17.

19. An expression vector composition comprising an expression vector comprising said first nucleic acid of claim 17 and said second nucleic acid of claim 17.

20. A host cell comprising the expression vector composition of claim 18 or 19.

21. A method of making an anti-PVRIG antibody comprising:
a) culturing the host cell of claim 20 under conditions wherein said antibody is expressed; and
b) recovering said antibody.

22. An anti-PVRIG (Poliovirus Receptor Related lmmunoglobulin Domain Containing Protein) antibody, wherein said anti-PVRIG antibody comprises: the following vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3 sequences or sequences that differ from those CDR amino acid sequences by 1 or 2 amino acid substitutions, wherein vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3 are selected from the group consisting of:

- the vhCDR1 as set out in SEQ ID NO:885, vhCDR2 as set out in SEQ ID NO:886, vhCDR3 as set out in SEQ ID NO:887, vlCDR1 as set out in SEQ ID NO:889, vlCDR2 as set out in SEQ ID NO:890 and vlCDR3 as set out in SEQ ID NO:891; and
- the vhCDR1 as set out in SEQ ID NO:981, vhCDR2 as set out in SEQ ID NO:982, vhCDR3 as set out in SEQ ID NO:983, vlCDR1 as set out in SEQ ID NO:985, vlCDR2 as set out in SEQ ID NO:986 and vlCDR3 as set out in SEQ ID NO:987.

23. The anti-PVRIG antibody of claim 22, wherein the anti-PVRIG antibody comprises:
(i) a heavy chain variable domain at least 90% identical to SEQ ID NO:1434 and
(ii) a light chain variable domain at least 90% identical to SEQ ID NO:1453.

24. The anti-PVRIG antibody of claim 22 or claim 23, wherein the anti-PVRIG antibody

comprises:

(i) a heavy chain variable domain at least 95% identical to SEQ ID NO:1434 and

(ii) a light chain variable domain at least 95% identical to SEQ ID NO:1453.

25. The anti-PVRIG antibody of claim 22, wherein the anti-PVRIG antibody comprises:

(i) a heavy chain variable domain at least 90% identical to SEQ ID NO:1447 and

(ii) a light chain variable domain at least 90% identical to SEQ ID NO:1462.

26. The anti-PVRIG antibody of any one of claims 22 to 25, wherein the anti-PVRIG antibody comprises:

(i) a heavy chain variable domain at least 95% identical to SEQ ID NO:1447 and

(ii) a light chain variable domain at least 95% identical to SEQ ID NO:1462.

27. An anti-PVRIG antibody competing with an antibody of any one of claims 22 to 26 to specifically bind to the PVRIG molecule.

28. The anti-PVRIG antibody of any one of claims 22 to 27 for use in the treatment of cancer, wherein the antibody activates T cells and/or NK cells.

29. The anti-PVRIG antibody for use in the treatment of cancer of claim 28, wherein the anti-PVRIG antibody is used in combination with antibodies targeting additional immune checkpoints.

30. The anti-PVRIG antibody for use in the treatment of cancer of claim 29, wherein the antagonistic antibodies targeting additional immune checkpoints include anti-TIGIT antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-LAG-3 antibodies, anti-TIM-3 antibodies, anti-BTLA antibodies, anti-B7-H4 antibodies, anti-B7-H3 antibodies and anti-VISTA antibodies.

31. The anti-PVRIG antibody for use in the treatment of cancer of claim 30, wherein anti-CTLA4 antibodies include ipilimumab and tremelimumab.

32. The anti-PVRIG antibody for use in the treatment of cancer of claim 30, wherein anti-PD-1 antibodies include nivolumab BMS-936558/MDX-1106/ONO-4538, AMP224, CT-011 and MK-3475.

33. The anti-PVRIG antibody for use in the treatment of cancer of claim 30, wherein anti-PDL-1 antibodies include BMS-936559/MDX-1105, MEDl4736 and RG-7446/ MPDL3280A.

34. The anti-PVRIG antibody for use in the treatment of cancer of claim 30, wherein anti-LAG-3 antibodies include IMP-321.

35. The anti-PVRIG antibody for use in the treatment of cancer of claim 28, wherein the anti-PVRIG antibody is used in combination with an anti-TIGIT antibody.

36. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein the anti-PVRIG antibody comprises:

a) the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1434 and

b) the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1453,

wherein said CDRs comprise from 1 to 6 substitutions and wherein no individual CDR comprises more than 1 substitution, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

37. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein the anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising a sequence exhibiting at least 90% identity to SEQ ID NO:1434, wherein each individual vhCDR from SEQ ID NO:1447 comprises no more than 1 substitution, and

ii) a light chain variable domain comprising a sequence exhibiting at least 90% identity to SEQ ID NO:1453, wherein each individual vlCDR from SEQ ID NO:1462 comprises no more than 1 substitution, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

38. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:1434 and wherein said heavy chain variable domain comprises a sequence exhibiting at least 90% identity to SEQ ID NO:1434, wherein each individual vhCDR from SEQ ID NO:1434 comprises no more than 1 substitution, and

ii) a light chain variable domain comprising the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:1453 and wherein said light chain variable domain comprises a sequence exhibiting at least 90% identity to SEQ ID NO:1453, wherein each individual vlCDR from SEQ ID NO:1453 comprises no more than 1 substitution, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

39. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1447 and

b) the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1462,

wherein said CDRs comprise from 1 to 6 substitutions, and no said CDR comprises more than 1 substitution, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

40. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising a sequence exhibiting at least 90% identity to SEQ ID NO:1447, wherein each individual vhCDR from SEQ ID NO:1447 comprises no more than 1 substitution, and

ii) a light chain variable domain comprising a sequence exhibiting at least 90% identity to SEQ ID NO:1462, wherein each individual vlCDR from SEQ ID NO:1462 comprises no more than 1 substitution, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

41. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:1447 and wherein said heavy chain variable domain comprises a sequence exhibiting at least 90% identity to SEQ ID NO:1447, and

ii) a light chain variable domain comprising the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:1462 and wherein said light chain variable domain comprises a sequence exhibiting at least 90% identity to SEQ ID NO:1462, and

wherein a subset of said T-cells and/or NK cells of said patient are activated.

42. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain variable domain comprising:

i) a vhCDR1 selected from the group consisting of SEQ ID NO:885 or a SEQ ID NO:885 variant comprising 1 amino acid substitution;

ii) a vhCDR2 selected from the group consisting of SEQ ID NO:886 or a SEQ ID NO:886 variant comprising 1 amino acid substitution;

iii) a vhCDR3 selected from the group consisting of SEQ ID NO:887 or a SEQ ID NO:887 variant comprising 1 amino acid substitution; and

b) a light chain variable domain comprising:

i) a vlCDR1 selected from the group consisting of SEQ ID NO:889 or a SEQ ID NO:889 variant comprising 1 amino acid substitution;

ii) a vlCDR2 selected from the group consisting of SEQ ID NO:890 or a SEQ ID NO:890 variant comprising 1 amino acid substitution;

iii) a vlCDR3 selected from the group consisting of SEQ ID NO:891 or a SEQ ID NO:891 variant comprising 1 amino acid substitution, and

wherein said CDRs comprise from 1 to 6 amino acid substitutions, and wherein a subset of said T-cells and/or NK cells of said patient are activated.

43. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1434 and

ii) a light chain variable domain comprising the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1453,

wherein a subset of said T-cells and/or NK cells of said patient are activated; and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-L1 antibody.

44. The use according to claim 43, wherein said anti-PVRIG antibody comprises the heavy chain variable domain of SEQ ID NO:1434 and the light chain variable domain of SEQ ID NO:1453.

45. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1447 and

ii) a light chain variable domain comprising the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1462,

wherein a subset of said T-cells and/or NK cells of said patient are activated; and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-L1 antibody.

46. The use according to claim 45, wherein said anti-PVRIG antibody comprises the heavy chain variable domain of SEQ ID NO:1447 and the light chain variable domain of SEQ ID NO:1462.

47. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain variable domain comprising:

i) a vhCDRl comprising SEQ ID NO:885;

ii) a vhCDR2 comprising SEQ ID NO:886;

iii) a vhCDR3 comprising SEQ ID NO:887; and

b) a light chain variable domain comprising:

i) a vlCDRl comprising SEQ ID NO:889;

ii) a vlCDR2 comprising SEQ ID NO:890;

iii) a vlCDR3 comprising SEQ ID NO:891,

wherein a subset of said T-cells and/or NK cells of said patient are activated; and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-L1 antibody.

48. The use according to any one of claims 36-47, wherein said anti-PVRIG antibody comprises the CH1-hinge-CH2-CH3 region from IgGl, IgG2, IgG3, or IgG4, wherein said hinge region optionally comprises mutations.

49. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1434 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1453 and wherein the CL region is from human kappa 2 light chain;

and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-L1 antibody.

50. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1447 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1462 and wherein the CL region is from

human kappa 2 light chain;

and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-L1 antibody.

51. The use according to claim 49 or claim 50, wherein said hinge region optionally comprises mutations.

52. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:1434 and

ii) a light chain variable domain comprising the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:1453,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-1 protein.

53. The use according to claim 52 wherein said anti-PVRIG antibody comprises the heavy chain variable domain of SEQ ID NO:1434 and the light chain variable domain of SEQ ID NO:1453.

54. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:1447 and

ii) a light chain variable domain comprising the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:1462,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-1 protein.

55. The use according to claim 54 wherein said antibody comprises the heavy chain variable domain of SEQ ID NO:1447 and the light chain variable domain of SEQ ID NO:1462.

56. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain variable domain comprising:

i) a vhCDR1 comprising SEQ ID NO:885;

ii) a vhCDR2 comprising SEQ ID NO:886;

iii) a vhCDR3 comprising SEQ ID NO:887; and

b) a light chain variable domain comprising:

i) a vlCDR1 comprising SEQ ID NO:889;

ii) a vlCDR2 comprising SEQ ID NO:890;

iii) a vlCDR3 comprising SEQ ID NO:891,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-1 protein.

57. The use according to any one of claims 54-56 wherein said anti-PVRIG antibody comprises the CH1-hinge-CH2-CH3 region from IgG1, IgG2, IgG3, or IgG4, wherein said hinge region optionally comprises mutations.

58. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1434 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1453 and wherein the CL region is from human kappa 2 light chain

and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-1 protein.

59. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1447 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1462 and wherein the CL region is from human kappa 2 light chain

and wherein said anti-PVRIG antibody is formulated for administration with an anti-PD-1 protein.

60. The use according to claim 58 or claim 59 wherein said hinge region optionally comprises mutations.

61. The use according to any one of claims 52-60 wherein said anti-PD-1 protein is an anti-PD-1 antibody.

62. The use according to claim 61 wherein said anti-PD-1 antibody is Keytruda® (pembrolizumab).

63. The use according to claim 61 wherein said anti-PD-1 antibody is Opdivo® (nivolumab).

64. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1434 and

ii) a light chain variable domain comprising the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1453,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-TIGIT antibody.

65. The use according to claim 64, wherein said anti-PVRIG antibody comprises the heavy chain variable domain of SEQ ID NO:1434 and the light chain variable domain of SEQ ID NO:1453.

66. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

i) a heavy chain variable domain comprising the vhCDRl, vhCDR2, and vhCDR3 from SEQ ID NO:1447 and

ii) a light chain variable domain comprising the vlCDRl, vlCDR2, and vlCDR3 from SEQ ID NO:1462,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-TIGIT antibody.

67. The use according to claim 66, wherein said anti-PVRIG antibody comprises the heavy chain variable domain of SEQ ID NO:1447 and the light chain variable domain of SEQ ID NO:1462.

68. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain variable domain comprising:

i) a vhCDRl comprising SEQ ID NO:885;

ii) a vhCDR2 comprising SEQ ID NO:886;

iii) a vhCDR3 comprising SEQ ID NO:887; and

b) a light chain variable domain comprising:

i) a vlCDRl comprising SEQ ID NO:889;

ii) a vlCDR2 comprising SEQ ID NO:890;

iii) a vlCDR3 comprising SEQ ID NO:891,

wherein a subset of said T-cells and/or NK cells of said patient are activated and wherein said anti-PVRIG antibody is formulated for administration with an anti-TIGIT antibody.

69. The use according to any one of claims 64-68, wherein said anti-PVRIG antibody comprises the CH1-hinge-CH2-CH3 region from IgGl, IgG2, IgG3, or IgG4, wherein said hinge region optionally comprises mutations.

70. The use according to any one of claims 64-68, wherein said anti-PVRIG antibody comprises the CL region of human kappa 2 light chain.

71. The use according to any one of claims 64-68, wherein said T-cells are cytotoxic T-cells (CTLs).

72. The use according to any one of claims 64-68, wherein said T-cells are selected from the group consisting of $CD4^+$ T-cells and $CD8^+$ T-cells.

73. The use according to any one of claims 64-68, wherein said activation is measured as an increase in interferon-y production and/or an increase in cytokine secretion.

74. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1434 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1453 and wherein the CL region is from human kappa 2 light chain

and wherein said anti-PVRIG antibody is formulated for administration with an anti-TIGIT antibody.

75. Use of an anti-PVRIG antibody in the manufacture of a medicament for activating T-cells and/or NK cells of a patient with cancer, wherein said anti-PVRIG antibody comprises:

a) a heavy chain comprising:

i) a VH-CH1-hinge-CH2-CH3, wherein the VH is SEQ ID NO:1447 and wherein the CH1-hinge-CH2-CH3 region is from IgG4; and

b) a light chain comprising:

i) a VL-CL, wherein the VL is SEQ ID NO:1462 and wherein the CL region is from human kappa 2 light chain

and wherein said anti-PVRIG antibody is formulated for administration with an anti-TIGIT antibody.

76. The use according to claim 74 or claim 75, wherein said hinge region optionally comprises mutations.