

PD1 inhibition of T cell responses does not involve competition for ligand binding with a costimulatory receptor.

[0004] The immune checkpoint, poliovirus receptor related immunoglobulin domain containing (PVRIG, also known as CD112R) represents a new inhibitory receptor within the TIGIT family of receptors. PVRIG binds with high affinity to its cognate ligand, poliovirus receptor-related 2 (PVRL2, also known as CD112 or nectin-2) to deliver an inhibitory signal through its ITIM motif within T and NK cells. The affinity of TIGIT to PVR and of PVRIG to PVRL2 is higher than the affinity of CD226 to either PVR or PVRL2, suggesting TIGIT and PVRIG can outcompete PVR and PVRL2 from CD226 and providing an indirect mechanism by which TIGIT and PVRIG can reduce lymphocyte function. Thus, two receptors with the same family, TIGIT and PVRIG, deliver inhibitory signals to dampen T and NK cell responses.

[0005] Accordingly, TIGIT and PVRIG are attractive for triple therapy combinations with checkpoint inhibitors, including anti-PD-1 antibodies.

II. BRIEF SUMMARY OF THE DISCLOSURE

[0006] The present disclosure provides methods and compositions comprising combinations of the TIGIT antibodies as disclosed herein and as provided in the claims with PVRIG antibodies and checkpoint inhibitors, including anti-PD-1 antibodies. The present disclosure also provides for nucleic acids encoding said antibodies and compositions thereof.

[0007] The present disclosure provides a method of treating cancer said patient comprising: a) providing a biopsy from said patient comprising tumor cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with

a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0007a] In one aspect, the present disclosure refers to use of an anti-TIGIT antibody in the manufacture of a medicament for treating cancer in a patient, wherein the use comprises:

- a) providing a biopsy from said patient comprising tumor cells;
- b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;
- c) wherein if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a triple combination therapy with an anti-PVRIG antibody and an anti-PD-1 antibody; and
- d) wherein if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a double combination therapy with an anti-PVRIG antibody.

[0007b] In one aspect, the present disclosure refers to use of an anti-PVRIG antibody in the manufacture of a medicament for treating cancer in a patient, wherein the use comprises:

- a) providing a biopsy from said patient comprising tumor cells;
- b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;
- c) wherein if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a triple combination therapy with an anti-TIGIT antibody and an anti-PD-1 antibody; and
- d) wherein if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody

for the antibodies used, the medicament is to be administered as a double combination therapy with an anti-TIGIT antibody.

[0008] In some examples of the method, anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P) and CHA.9.547.13.H4(S241P).

[0009] In some examples of the method, anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0010] In some examples of the method, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.

[0011] In some examples of the method, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0012] In some examples of the method, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P);

CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0013] In some examples of the method, the antibodies are administered simultaneously.

[0014] In some examples of the method, the antibodies are administered sequentially.

[0015] In some examples of the method, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS). In some examples of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS). In some examples of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, and MSI-high cancer.

[0016] The present disclosure also provides a method of treating cancer said patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-1 antibody.

[0017] In some examples of the method, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0018] In some examples of the method, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0019] In some examples of the method, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab and nivolumab.

[0020] In some examples of the method, the triple combination therapy comprises the administration of an anti-PD-1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0021] In some examples of the method, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P),

nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0022] In some examples of the method, the antibodies are administered simultaneously.

[0023] In some examples of the method, the antibodies are administered sequentially.

[0024] In some examples of the method, the cancer for the triple combination therapy is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).. In some examples of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0025] The present disclosure also provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; and b) a container comprising a unit dosage of an anti- PVRIG antibody.

[0026] The present disclosure also provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; b) a container comprising a unit dosage of an anti- PVRIG antibody; and c) a container comprising an anti-PD-1 antibody.

[0027] In a further example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein; v) PD-L1 protein; vi) PVRL2; and vii) a relevant isotype control for the antibodies in i)-vi); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1, PVRL2 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $> 1\%$ for either TIGIT or PVR, and for either PVRIG or PVRL2, and for either PD-1 or PD-L1, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[0028] In a further example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVR protein; iii) PD-1 protein; iv) PD-L1 protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVR, PD-1, and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq 1\%$ for all 4 receptors, e) administering antibodies to TIGIT and PD-1 to said patient.

[0029] In an additional example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) PD-1 protein; iv) PD-L1 protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, PD-1 and PD-L1,

determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq 1\%$ for all 4 receptors, e) administering antibodies to PVRIG and PD-1 to said patient.

[0030] In a further example, the disclosure provides methods comprising a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) TIGIT protein; iv) PVR protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq 1\%$ for all 4 receptors, e) administering antibodies to PVRIG and TIGIT to said patient.

[0031] In an additional example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) TIGIT protein; iii) PVRL2 protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, TIGIT, PVRL2, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq 1\%$ for all 5 receptors, e) administering antibodies to PVRIG, TIGIT, and PD-1 to said patient.

[0032] In a further example, the disclosure provides methods comprising a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) TIGIT protein; iv) PVR protein; v) PD-1; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq 1\%$ for all 4 receptors, e) administering antibodies to PVRIG, TIGIT, and PD-1 to said patient.

[0033] In some examples, the present disclosure provides a method of treating cancer in a patient comprising: a) providing a biopsy from said patient comprising tumor

cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0034] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0035] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0036] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0037] In some examples, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0038] In some examples, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0039] In some examples, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, Cemiplimab and nivolumab.

[0040] In some examples, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P);

CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0041] In some examples, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), and CHA.9.547.13.H4(S241P), and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0042] In some examples, the antibodies are administered simultaneously.

[0043] In some examples, the antibodies are administered sequentially.

[0044] In some examples, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer,

cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0045] In some examples, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0046] In some examples, the present disclosure provides a method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-1 antibody.

[0047] In some examples, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0048] In some examples, the said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0049] In some examples, the anti-PD-1 antibody is an antibody selected from the group consisting of pembrolizumab, cemiplimab, and nivolumab.

[0050] In some examples, the triple combination therapy comprises the administration of an anti-PD-1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0051] In some examples, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0052] In some examples, the antibodies are administered simultaneously.

[0053] In some examples, the antibodies are administered sequentially.

[0054] In some examples, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0055] In some examples, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0056] In some examples, the present disclosure provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; and b) a container comprising a unit dosage of an anti-PVRIG antibody.

[0057] In some examples, the present disclosure provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; b) a container comprising a unit dosage of an anti-PVRIG antibody; and c) a container comprising an anti-PD-1 antibody.

[0058] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0059] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0060] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0061] In some examples, the present disclosure provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the

percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[0062] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0063] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0064] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0065] In some examples, the TIGIT antibody is CPA.9.086.

[0066] In some examples, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0067] In some examples, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0068] In some examples, the present disclosure provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) TIGIT protein; iii) PVRL2 protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, TIGIT, PVRL2, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to PVRIG and PD-1 to said patient.

[0069] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0070] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0071] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0072] In some examples, the anti-PD-L1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0073] In some examples, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0074] In some examples, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0075] In some examples, the TIGIT antibody is CPA.9.086.

[0076] In some examples, the present disclosure provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PD-1 protein; iii) PVRL2 protein; iv) TIGIT protein; v) PVR protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to PVRIG and TIGIT to said patient.

[0077] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0078] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0079] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0080] In some examples, the anti-PD-L1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0081] In some examples, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0082] In some examples, the TIGIT antibody is CPA9.086.

[0083] In some examples, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0084] In some examples, the present disclosure provides a method of treating cancer in a patient comprising: a) providing a biopsy from said patient comprising tumor cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-L1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0085] In some examples, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0086] In some examples, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0087] In some examples, the anti-PD-1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0088] In some examples, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0089] In some examples, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0090] 58. A method according to any one of claims 52 to 57, wherein said anti-PD-L1 antibody is an antibody chosen from at least one of atezolizumab, avelumab, and durvalumab.

[0091] In some examples, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0092] In some examples, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

[0093] In some examples, the antibodies are administered simultaneously.

[0094] In some examples, the antibodies are administered sequentially.

[0095] In some examples, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0096] In some examples, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0097] In some examples, the present disclosure provides a method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-L1 antibody.

[0098] In some examples, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0099] In some examples, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[00100] In some examples, the anti-PD-L1 antibody is an antibody selected from the group consisting of atezolizumab, avelumab, and durvalumab.

[00101] In some examples, the triple combination therapy comprises the administration of an anti-PD-L1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and

CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[00102] In some examples, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

[00103] In some examples, the antibodies are administered simultaneously.

[00104] In some examples, the antibodies are administered sequentially.

[00105] In some examples, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[00106] In some examples, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

III. BRIEF DESCRIPTION OF THE DRAWINGS

[00107] Figure 1A-1B depicts the amino acid sequences of the constant domains of human IgG1 (with some useful amino acid substitutions), IgG2, IgG3, IgG4, IgG4 with a hinge variant that finds particular use in the present invention, and the constant domains of the kappa and lambda light chains.

[00108] Figure 2 depicts the sequence of human and cynomolgus macaque (referred to as cyno) TIGIT, PVRIG and PD-1 proteins.

[00109] Figure 3A-3SSSS depicts the sequences of four anti-TIGIT antibodies that block the interaction of TIGIT and PVR, CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P) and CHA.9.547.13.H4(S241P), as well as benchmark antibodies, BM26 and BM29, and numerous other anti-TIGIT antibodies.

[00110] Figure 4A-4C shows the FACS K_D results of anti-TIGIT antibodies (CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P), as well as benchmark antibodies, BM26 and BM29, binding to human (A), cynomolgus (B), and mouse (C) TIGIT over-expressing Expi293 HEK cells.

[00111] Figure 5A-5F depicts the sequences of two anti-PVRIG antibodies, CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P). Other PVRIG antibodies are provided in Figure 63.

WHAT IS CLAIMED IS:

1. Use of an anti-TIGIT antibody in the manufacture of a medicament for treating cancer in a patient, wherein the use comprises:

- a) providing a biopsy from said patient comprising tumor cells;
- b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;
- c) wherein if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a triple combination therapy with an anti-PVRIG antibody and an anti-PD-1 antibody; and
- d) wherein if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a double combination therapy with an anti-PVRIG antibody.

2. Use of an anti-PVRIG antibody in the manufacture of a medicament for treating cancer in a patient, wherein the use comprises:

- a) providing a biopsy from said patient comprising tumor cells;
- b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;
- c) wherein if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a triple combination therapy with an anti-TIGIT antibody and an anti-PD-1 antibody; and
- d) wherein if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, the medicament is to be administered as a double combination therapy with an anti-TIGIT antibody.

3. A use according to claim 1 or 2, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.
4. A use according to claim 1 or 2, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.
5. A use according to claim 1 or 2, wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.
6. A use according to claims 1 to 5, wherein said anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).
7. A use according to claims 1 to 6, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).
8. A use according to claims 1 to 7, wherein said anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.
9. A use according to any one of claims 1 to 8, wherein said double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).
10. A use according to any one of claims 1 to 9, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and

CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

11. A use according to any one of claims 1 to 10, wherein said antibodies are to be administered simultaneously.

12. A use according to any one of claims 1 to 11, wherein said antibodies are to be administered sequentially.

13. A use according to any one of claims 1 to 12, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), 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, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

14. A use according to any one of claims 1 to 13, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small

cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).