

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, 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), and 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).

[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, 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), and 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).

[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);

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,

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), and

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).

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,

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), and

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.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).

~~3. The use according to any one of 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. The 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. The 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.~~

~~63.~~ The use according to ~~any one of claims 1 to or 52,~~ 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).

~~74.~~ The use according to any one of claims 1 to ~~63,~~ 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).

~~85.~~ The use according to any one of claims 1 to ~~74,~~ wherein said anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.

~~96.~~ The use according to any one of claims 1 to ~~85,~~ wherein said antibodies are to be administered simultaneously.

~~107.~~ The use according to any one of claims 1 to ~~96,~~ wherein said antibodies are to be administered sequentially.

~~118.~~ The use according to any one of claims 1 to ~~107,~~ wherein said cancer is selected from the group consisting of 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 or stomach cancer (including gastrointestinal cancer), esophageal cancer, melanoma, non-melanoma skin cancer (squamous and basal cell carcinoma), testicular germ cell tumors, MSI-high cancer, mesothelioma, merkel cell cancer, pancreatic cancer, glioma, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, larynx cancer, oral cavity cancer, urothelial cancer, KRAS mutant tumors, Myelodysplastic syndromes (MDS), as well as B-cell malignancies, B-cell lymphoma (NHL or HL) (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); Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, Hairy cell leukemia; chronic myeloblastic leukemia; adult T-cell leukemia/lymphoma; myeloma; multiple myeloma and post-transplant lymphoproliferative disorder (PTLD), lymphoid malignancies, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome, rectal cancer, renal cell cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, ovarian early or advanced (including metastatic) 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).

129. The use according to any one of claims 1 to 118, 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).