CLAIMS

What is claimed is:

1. Use of a modulator of ICOS in the manufacture of a medicament for treating cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

2. Use of a modulator of ICOS in the manufacture of a medicament for treating cancer in a patient who has previously received treatment for the cancer, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor and the patient did not respond to the previous treatment or ceased responding to the previous treatment, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

3. The use of any preceding claim, wherein

   a) the level of PD-L1 expression in a tumour sample from the patient is determined, and if the tumour is PD-L1 negative or a PD-L1 low expression tumour, the ICOS modulator is to be administered to the patient; and/or

   b) the modulator of ICOS and an inhibitor of PD-L1 are to be administered to the patient, optionally wherein the modulator of ICOS and the inhibitor of PD-L1 are to be administered simultaneously, separately or sequentially.

4. The use according to any preceding claim, wherein

   a) the ICOS modulator is an ICOS agonist, optionally wherein the ICOS agonist is an agonistic anti-ICOS antibody, optionally wherein the anti-ICOS antibody is a bispecific antibody that specifically binds ICOS and PD-L1 or specifically binds ICOS and PD-1, optionally wherein the bispecific antibody is an ICOS agonist and a PD-L1 antagonist, or an ICOS agonist and a PD-1 antagonist;

   b) the PD-L1 inhibitor is an anti-PD-L1 binding molecule, optionally wherein the PD-L1 inhibitor is an anti-PD-L1 antibody or an anti-PD-1 antibody, optionally wherein the PD-L1 inhibitor inhibits the binding of PD-L1 to PD-1, optionally wherein the PD-L1 inhibitor is an antagonistic anti-PD-L1 antibody or an antagonistic anti-PD-1 antibody;

c) the tumour cells are PD-L1 negative or exhibit low PD-L1 expression;

d) the tumour comprises immune cells, and the immune cells are PD-L1 negative or exhibit low PD-L1 expression, optionally wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression and the immune cells are PD-L1 negative or exhibit low PD-L1 expression;

e) the cancer is associated with infectious agents, optionally wherein the cancer is a virally-induced cancer, optionally wherein the virus associated with the virally-induced cancer is selected from HPV (cervical cancer, oropharyngeal cancer), HBV, HCV, and EBV (Burkitts lymphomas, gastric cancer, Hodgkin's lymphoma, other EBV positive B cell lymphomas, nasopharyngeal carcinoma and post transplant lymphoproliferative disease), optionally wherein the cancer is selected from the group consisting of head and neck squamous cell carcinoma, cervical cancer, anogenital cancer and oropharyngeal cancer;

f) the tumour is HPV (Human papillomavirus) positive; and/or

g) the patient has undergone a test for HPV infection and/or wherein the patient has an HPV infection or has had an HPV infection.

5. The use according to any preceding claim, wherein the HPV status of the patient and/or the HPV status of the tumour are determined.

6. The use according to any preceding claim, wherein

a) the patient has previously

a. been administered a kinase inhibitor;
b. received surgical treatment for the cancer (for example complete or partial tumour resection) and/or radiotherapy and/or chemotherapy, optionally wherein the chemotherapy comprises docetaxel, fluorouracil, cisplatin, paclitaxel and/or nab-paclitaxel; and/or
c. received treatment for the cancer, optionally wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor (for example an anti-PD-L1 antibody or an anti-PD-1 antibody), optionally wherein the previous treatment for the cancer was PD-L1 inhibitor monotherapy or administration of a PD-L1 inhibitor as the sole immunotherapeutic agent;

b) the cancer is or has been characterised as refractory to:

a. PD-L1 inhibitor treatment (for example refractory to anti-PD-L1 antibody or anti-PD-1 antibody monotherapy);
b. PD-L1 inhibitor monotherapy treatment;
c. treatment with a PD-L1 inhibitor as the sole immunotherapy agent; and/or
d. treatment with nivolumab;

c) the tumour is a CD8+ tumour and/or a ICOS+ tumour; and/or

d) the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following treatment with another therapeutic agent, optionally wherein the method comprises administering a therapeutic agent to the patient, determining that the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following the treatment with said agent, and administering a modulator of ICOS (for example an anti-ICOS antibody such as an agonistic anti-ICOS antibody) to the patient to reduce the level of $ICOS^+$ regulatory T cells, optionally wherein the therapeutic agent is IL-2 or an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1 or anti-CTLA-4).

7. The use according to any preceding claim, wherein a single dose of the ICOS modulator optionally followed by multiple doses of the PD-L1 inhibitor are to be administered.

8. The use according to any preceding claim, wherein treatment

a. results in reducing the size of the tumour;
b. inhibits tumour growth;
c. results in stable disease;
d. extends the survival of the patient and/or delays disease progression;
e. depletes ICOS+ immune cells (such as $ICOS^+$ regulatory T cells) in the tumour microenvironment; and/or
f. increases the CD8+ to ICOS+ immune cell ratio (for example the CD8+ to ICOS+ regulatory T cell ration) in the tumour microenvironment.

9. The use according to any preceding claim, wherein the ICOS modulator is an anti-ICOS antibody, optionally wherein the anti-ICOS antibody is any of the following antibodies, may comprise the VH and VL domains of any of the following antibodies or may comprise the HCDRs and/or LCDRs of any of the following antibodies:

a. KY1044;

b. anti-ICOS antibodies described in PCT/GB2017/052352 WO2018/029474 or US9957323, the contents of which are incorporated herein by reference (e.g., STIM001, STIM002, STIM002B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009);
c. anti-ICOS antibodies described in PCT/GB2018/053701 WO2019/122884 the contents of which are incorporated herein by reference (e.g., STIM017, STIM020, STIM021, STIM022, STIM023, STIM039, STIM040, STIM041, STIM042, STIM043, STIM044, STIM050, STIM051, STIM052, STIM053, STIM054, STIM055, STIM056, STIM057, STIM058, STIM059, STIM060, STIM061, STIM062, STIM063, STIM064, STIM065 or STIM066);
d. anti-ICOS/PD-L1 mAb2 bispecific antibodies described in PCT/GB2018/053698 WO2019/122882;
e. vopratelimab;
f. anti-ICOS antibodies described in WO2016/154177 or US2016/0304610 (e.g., 37A10S713, 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710 or 35A9S89);
g. anti-ICOS antibodies described in WO2016/120789 or US2016/0215059 (e.g., 422.2 H2L5);
h. antibody C398.4 or a humanised antibody thereof as described in WO2018/187613 or US2018/0289790, e.g., ICOS.33 IgG1f S267E, ICOS.4, ICOS34 G1f, ICOS35 G1f, 17C4, 9D5, 3E8, 1D7a, 1D7b or 2644 (for sequences see WO2018187613 Table 35), e.g., the antibody BMS-986226 in NCT03251924;
i. antibody JMAb 136, “136”, or any other antibody described in WO2010/056804;
j. antibody 314-8, the antibody produced from hybridoma CNCM I-4180, or any other anti-ICOS antibody described in WO2012/131004, WO2014/033327 or US2015/0239978;
k. antibody Icos145-1, the antibody produced by hybridoma CNCM I-4179, or any other antibody described in WO2012/131004, US9,376,493 or US2016/0264666;
l. antibody MIC-944 (from hybridoma DSMZ 2645), 9F3 (DSMZ 2646) or any other anti-ICOS antibody described in WO99/15553, US7,259,247, US7,132,099, US7,125,551, US7,306,800, US7,722,872, WO05/103086, US8,318.905 or US8,916,155;
m. anti-ICOS antibodies described in WO98/3821, US7,932,358B2, US2002/156242, US7,030,225, US7,045,615, US7,279,560, US7,226,909, US7,196,175, US7,932,358, US8,389,690, WO02/070010, US7,438,905, US7,438,905, WO01/87981, US6,803,039, US7,166,283, US7,988,965, WO01/15732,

US7,465,445 or US7,998,478 (e.g., JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140 or JMAb-141, e.g., JMAb136);

n. anti-ICOS antibodies described in WO2014/08911;
o. anti-ICOS antibodies described in WO2012/174338;
p. anti-ICOS antibodies described in US2016/0145344;
q. anti-ICOS antibodies described in WO2011/020024, US2016/002336, US2016/024211 or US8,840,889;
r. anti-ICOS antibodies described in US8,497,244; or
s. antibody clone ISA-3 (eBioscience), clone SP98 (Novus Biologicals), clone 1 G1, clone 3G4 (Abnova Corporation), clone 669222 (R&D Systems), clone TQ09 (Creative Diagnostics), clone 2C7 (Deng et al. Hybridoma Hybridomics 2004), clone ISA-3 (eBioscience) or clone 17G9 (McAdam et al. J Immunol 2000).

10. The use according to claim 9, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, wherein the antibody comprises a VH domain comprising an amino acid sequence having at least 95 % sequence identity to the STIM003 VH domain SEQ ID NO: 408 and a VL domain comprising an amino acid sequence having at least 95 % sequence identity to the STIM003 VL domain SEQ ID NO: 415, optionally wherein

a) the VH domain comprises a set of heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, wherein

a. HCDR1 is the STIM003 HCDR1 having amino acid sequence SEQ ID NO: 405,
b. HCDR2 is the STIM003 HCDR2 having amino acid sequence SEQ ID NO: 406,
c. HCDR3 is the STIM003 HCDR3 having amino acid sequence SEQ ID NO: 407; and/or

wherein the VL domain comprises a set of light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein:

d. LCDR1 is the STIM003 LCDR1 having amino acid sequence SEQ ID NO: 412,
e. LCDR2 is the STIM003 LCDR2 having amino acid sequence SEQ ID NO: 413,
f. LCDR3 is the STIM003 LCDR3 having amino acid sequence SEQ ID NO: 414;

b) the VH domain amino acid sequence is SEQ ID NO: 408 and/or wherein the VL domain amino acid sequence is SEQ ID NO: 415; or

c) the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, comprising

an antibody VH domain comprising complementarity determining regions (CDRs) HCDR1, HCDR2 and HCDR3, and

an antibody VL domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein

HCDR1 is the HCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

HCDR2 is the HCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

HCDR3 is the HCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that HCDR3 with 1, 2, 3, 4 or 5 amino acid alterations; and/or

wherein LCDR1 is the LCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004 STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

LCDR2 is the LCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

LCDR3 is the LCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that LCDR3 with 1, 2, 3, 4 or 5 amino acid alterations, optionally wherein

i) the antibody heavy chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 heavy chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations; and/or wherein the antibody light chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 light chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations, optionally wherein the antibody VH domain has the heavy chain CDRs of STIM003 and/or wherein the antibody VL domain has the light chain CDRs of STIM003;

ii) the antibody comprises VH and/or VL domain framework regions of human germline gene segment sequences; and/or

iii) the antibody comprises an antibody VH domain which is the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009; and/or wherein the antibody comprises an antibody VL domain which is the VL domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, optionally wherein the antibody comprises the STIM003 VH domain and the STIM003 VL domain, optionally wherein the anti-ICOS antibody is STIM0003.

11. The use according to any one of claims 9 to 10, wherein

a) the antibody comprises an antibody constant region, optionally wherein the constant region comprises a human heavy and/or light chain constant region, optionally wherein the constant region is Fc effector positive; and/or

b) the antibody is a multispecific antibody.

12. The use according to claim 9, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 50 nM as determined by surface plasmon resonance, or less than 5 nM as determined by surface plasmon resonance.

13. The use according to any preceding claim, wherein

a) the PD-L1 inhibitor is
   i. an anti-PD-L1 antibody selected from the group consisting of atezoliumab (Roche), avelumab (Merck), durvalumab/Medi4736 (Medimmune), KN035, CK-301, AUNP12, CA-170, BMS-936559/MDX-1105 (BMS), FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/220990, WO2017/034916,

WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874; or

ii) the an anti-PD-1 antibody selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, JTX-401, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), dostarlimab (TSR-042, WBP-285), INCMGA00012 (MGA012), AMP-224 and AMP-514, MEDI-0680/AMP514, PDR001, Lambrolizumab, BMS-936558, REGN2810, BGB-A317, BGB-108, PDR-001, SHR-1210, JS-001, JNJ-63723283, AGEN-2034, PF-06801591, genolimzumab, MGA-012 (INCMGA00012), IBI-308, BCD-100, TSR-042 ANA011, AUNP-12, KD033, MCLA-134, mDX400, muDX400, STI-A1110, AB011, 244C8, 388D4, XCE853, or pidilizumab/CT-011, or from any one of the anti-PD-1 antibodies described in WO2015/112800 & US2015/0203579 (including the antibodies in Tables 1 to 3), US9,394,365, US5,897,862 and US7,488,802, WO2017/087599 (including antibody SSI-361 and SHB-617), WO2017/079112, WO2017/071625 (including deposit C2015132, hybridoma LT004, and antibodies 6F5/6 F5 (Re), 6F5H1 L1 and 6F5 H2L2), WO2017/058859 (including PD1AB-1 to PD1AB-6), WO2017/058115 (including 67D9, c67D9, and hu67D9), WO2017/055547 (including 12819.15384, 12748.15381, 12748.16124, 12865.15377, 12892.15378, 12796.15376, 12777.15382, 12760.15375 and 13112.15380), WO2017/040790 (including AGEN2033w, AGEN2034w, AGEN2046w, AGEN2047w, AGEN2001w and AGEN2002w), WO2017/025051 & WO2017/024515 (including 1.7.3 hAb, 1.49.9 hAb, 1.103.11 hAb, 1.103.11-v2 hAb, 1.139.15 hAb and 1.153.7 hAb), WO2017/025016 & WO2017/024465 (including antibody A to antibody I), WO2017/020858 & WO2017/020291 (including 1.4.1, 1.14.4, 1.20.15 and 1.46.11), WO2017/019896 & WO2015/112900 & US2015/0210769 (including BAP049-hum01 to BAP049-hum16 and BAP049-Clone-A to BAP049-Clone-E), WO2017/019846 (including PD-1 mAb 1 to PD-1 mAb 15), WO2017/016497 (including MHC723, MHC724, MHC725, MHC728, MHC729, m136-M13, m136-M19, m245-M3, m245-M5 and

m136-M14), WO2016/201051 (including antibody EH12.2H7, antibody hPD-1 mAb2, antibody hPD-1 mAb7, antibody hPD-1 mAb9, antibody hPD-1 mAb15, or an anti-PD-1 antibody selected from Table 1), WO2016/197497 (including DFPD1-1 to DFPD1-13), WO2016/197367 (including 2.74.15 and 2.74.15.hAb4 to 2.74.15.hAb8), WO2016/196173 (including the antibodies in Table 5, and Figures 1-5), WO2016/127179 (including R3A1, R3A2, R4B3, and R3D6), WO2016/077397 (including the antibodies described in Table 1 of Example 9), WO2016/106159 (including the murine antibodies in Table 3 of Example 2 and the humanised antibodies in Tables 7, 8 and 9 of Example 3), WO2016/092419 (including C1, C2, C3, EH12.1, mAb7-G4, mAb15-G4, mAb-AAA, mAb15-AAA), WO2016/068801 (including clone A3 and its variants and the other antibodies described in Figures 1 to 4), WO2016/014688 (including 10D1, 4C10, 7D3, 13F1, 15H5, 14A6, 22A5, 6E1, 5A8, 7A4, and 7A4D and the humanised antibodies of Examples 9/10), WO2016/015685 (including 10F8, BA08-1, BA-08-2 and 15H6), WO2015/091911 & WO2015/091910 (including the anti-canine PD-1 antibodies in Examples 2, 3 and 4) , WO2015/091914 (including the anti-canine PD-1 antibodies in Table 3), WO2015/085847 (including mAb005, H005-1 to H005-4), WO2015/058573 (including cAB7), WO2015/036394 (including LOPD180), WO2015/035606 (including the antibodies in Table 1 of Example 2, in Tables 14, 15 and 16 of Example 7 and in tables 20, 21 and 22 of Example 11), WO2014/194302 (including GA2, RG1B3, RG1H10, RG2A7, RG2H10, SH-A4, RG4A6, GA1, GB1, GB6, GH1, A2, C7, H7, SH-A4, SH-A9, RG1H11, and RG6B), WO2014/179664 (including 9A2, 10B11, 6E9, APE1922, APE1923, APE1924, APE1950, APE1963 and APE2058), WO2014/206107 (including clone 1, 10, 11, 55, 64, 38, 39, 41 and 48), WO2012/135408 (including h409A11, h409A16, and h409A17), WO2012/145493 (including antibodies 1E3, 1E8, 1H3 and h1H3 Var 1 to h1H3 Var 14), WO2011/110621 (including antibody 949 and the modified versions disclosed in Figures 1 to 11), WO2011/110604 (including antibody 948 and the modified versions disclosed in Figures 3 to 11), WO2010/089411 (including CNCM deposit number 1-4122, 1-4080 or 1-4081), WO2010/036959 (including the antibodies in Table 1 of Example 1), WO2010/029435 & WO2010/029434 (including clones 2, 10 and 19), WO2008/156712 (including hPD-1.08A, hPD-1.09A, h409A11, h409A16 and h409A17 and the antibodies described in Example 2, Table H, Example 4 and table IV), WO2006/121168 (including clones 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, and 2D3), WO2004/004771 and WO2004/056875 (including PD1-17, PD1-28, PD1-33, PD1-35, PD1-F2 and the Abs described in Table 1);

b) the ICOS modulator is an IgG1 anti-ICOS antibody and/or the PD-L1 inhibitor is an IgG1 anti-PD-L1 antibody or an IgG1 anti-PD-1 antibody, optionally wherein the IgG1 anti-ICOS antibody and/or the IgG1 anti-PD-L1 antibody or anti-PD-1 antibody comprises a human IgG1 constant region comprising amino acid sequence SEQ ID NO: 340; and/or

d) the cancer is liver cancer (e.g. hepatocellular carcinoma), renal cell cancer, head and neck cancer (e.g. metastatic squamous cell carcinoma), melanoma, non small cell lung cancer, diffuse large B-cell lymphoma, breast cancer (e.g. triple negative breast cancer), penile cancer, pancreatic cancer or oesophageal cancer.

14. Use of an ICOS modulator in the manufacture of a medicament for treating cancer in a patient, wherein
    a. the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression; or
    b. the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor.

15. The use as claimed in claim 14, wherein

a) the ICOS modulator is for use in combination with a PD-L1 inhibitor, optionally wherein the ICOS modulator is an agonistic anti-ICOS antibody, optionally wherein the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist; and/or

b) the use is the use of any one of claims 1 to 13.