**Supplementary Materials and Methods**

**Recombinant protein expression**

Human CD137 extracellular domain (ECD) with C121S mutation was cloned into the GS vector under Flt-1 leader sequence with C-terminus FLAG tag or hexahistidine tag and a 3 Alanine (AAA) linker, and expressed in human 293-Freestyle cells (Invitrogen) using 293fectin (Thermo Fisher). CD137-FLAG protein was purified by passage over a gravity-flow column filled with Anti-FLAG M2 affinity gel (Sigma-Aldrich) and buffer exchange into 1xPBS. CD137-His protein was purified by passage over a Ni Sepharose Excel column attached to an AKTA Purifier followed by polishing on a preparative SEC column (GE Healthcare). Protein quality was evaluated by SDS-PAGE and analytical SEC.

**Binding ELISA**

Recombinant cynomolgus monkey and mouse extracellular CD137-Fc proteins (Eli Lilly and Company), were each immobilized onto 96-well plates (1g/mL and 0.5g/mL, respectively) and ELISA performed as outlined in Materials and Methods. Treatments included 7A5 antibody and anti-mouse CD137 antibody LOB12.3 (Bioxcell; BE0169) as indicated. To detect binding, HRP conjugated goat anti-human IgG or anti-rat IgG, F(ab’)2 fragment specific antibodies (Jackson ImmunoResearch Laboratories) were utilized. Data analysis for binding EC50 was performed with GraphPad Prism software.

**Biacore**

CD137-Fc proteins were prepared at 2.0g/mL and 2.5g/mL, respectively in 10mM sodium acetate (pH 4.0) and covalently immobilized to the CM5 sensor chip via amine coupling. Sample testing was performed at a flow rate of 30µL/min in HBS-EP+ buffer. 7A5 was injected at various concentrations and measurements obtained at 25°C. The surface was regenerated after each sample injection with 10mM Glycine-HCl pH2.0 at flow rate of 30L/min for 24 seconds and then stabilized with buffer for 10 seconds. Sensorgrams of concentrations ranging from 0.123 to 90nM were evaluated using Biacore T200 software. Calculation of association (Ka) and dissociation (Kd) rate constants was based on a 1:1 Langmuir binding model fit. The equilibrium dissociation constant (KD) or binding affinity constant was calculated from the ratio of kinetic rate constants Kd/Ka.

**Effector function assays**

Binding to FcγRI, FcγRIIa(H), FcγRIIb, FcγRIIIa(F), and FcγRIIIa(V) was determined using an MSD assay (Meso Scale Diagnostics). Briefly, Fcγ receptors were coated onto a Mesoscale plate overnight and serially diluted test antibodies were added to the plate and incubated for 2 hours. Signal was detected using an anti-human secondary antibody (MSD; D20TF-6) and the plate was developed with Read Buffer T (MSD; R92TC-1). Luminescence was measured on the Sector Imager 2400 (MSD) and data analyzed using GraphPad Prism. For binding to C1q, antibodies were serially diluted in PBS and coated onto an ELISA plate overnight at 4°C. Human C1q in casein buffer was added at a concentration of 10 mg/mL and incubated for 2 hours. Signal was detected by incubating the plates with anti-human C1q-HRP 1:200 dilution (AbD Serotec; 2221-5004P) for 1 hour and developed using TMB (KPL). Absorbance was measured at 450nm with Synergy Neo2 (BioTek).

For the ADCC effector function assay, CD137 positive or negative HEK-293 cells were plated in 96-well plate at 5x103 cells/well in 100 µL of cell growth medium. After an overnight incubation at 37C and 5% CO2, the medium was removed and 50µL ADCC assay buffer (RPMI 1640, with 0.5%BSA) added. 7A5 (IgG1 effector null and effector competent versions) was added to the target cells at indicated concentrations and incubated for 30 minutes. FcRIIIa-positive Jurkat cells containing NFAT luciferase reporter (Eli Lilly and Company) were added to target cells (1.5x105 cells/well) and incubated for 6 hours at 37C. Luminescence signal was measured using Bio-Glo reagent (Promega, G7940) and the EC50 calculated using GraphPad Prism software. The ADCC effector function assay with CD20-positive Wil2-s cells and anti-CD20 antibody rituximab (IgG1 effector competent) was performed as described above. Cells were plated at 1x104 cells/well in 50 µL of ADCC assay buffer and rituximab used at indicated concentrations as positive control.

For the CDC assay, human CD137-293 cells or CD20-positive Wil2-s cells were seeded in 96-well plates at 2.5x104 cells/well and 5.0x104 cells/well respectively in CDC assay buffer. Test and control antibodies were added in duplicate to the plates and incubated for 30 minutes. Human complement (50 µL of 1:5 dilution) (Sigma; S1764), was added for 1 hour. Following incubation, 16 µL of Alamar Blue reagent (Invitrogen; DAL1100) was added to each well and incubated for 23 hours. Fluorescence was read on Synergy Neo2 (excitation: 560nm) and the EC50 calculated with GraphPad Prism software.

**Receptor modulation**

Human CD137-293 cells were incubated with human IgG1 or CD137 antibodies across a range of concentrations (highest at 300nM). After 24 hours, cells were dissociated with non-enzymatic reagent and stained for 2 hours with the same antibodies at 300nM in cold buffer containing 0.09% sodium azide (to prevent receptor internalization). Cells were washed and stained with Alexa Fluor 647 labeled anti-human IgG detection antibody (Jackson ImmunoResearch) for 30 minutes. Dead cells were differentially labeled with Zombie Green (BioLegend). All samples were analyzed on Fortessa X-20 and the MFI calibrated to an Alexa Fluor 647 MESF (molecules of equivalent soluble fluorochrome) standard curve (calibration beads were from Bangs Labs) and normalized to untreated stained controls (100%) and untreated isotype stained controls (0%).

**CD8 Memory T cells**

CD8+ T cells were purified from human PBMCs using a CD8+ T Cell isolation kit (Miltenyi Biotec) and plated onto 96-well plates (8.5x104/well) coated with anti-human CD3 antibody HIT3a (BD Biosciences) at 100ng/well. Cells were treated with human IgG1 (50g/ml), 7A5 (0.5-50g/mL) or BMS20H4.9 (50g/mL) antibodies. After 8 days of culture, cells were stained with a panel of fluorescently labeled antibodies including CD45RA PE/Cy7 (clone HI100, 304126), CCR7 BV421 (clone G043H7, 353208), and Zombie Red fixable viability dye (all from BioLegend). Cells were acquired using the Fortessa X-20 and analyzed using FlowJo software. Quantification of memory populations was evaluated as percent of viable single cells gated as CD45RA-CCR7+, CD45RA-CCR7-, or CD45RA+CCR7- cells. Data was analyzed using GraphPad Prism software, and one-way ANOVA. Each condition was tested and analyzed in triplicate.

**In vivo efficacy studies**

The %T/C was calculated by the formula 100  T / C if T > 0 of the geometric mean values. T = mean tumor volume of the drug-treated group on the observation day of the study – mean tumor volume of the drug-treated group on initial day of dosing; C = mean tumor volume of the control group on the observation day of the study – mean tumor volume of the control group on initial day of dosing. Additionally, Regression was calculated using the formula = 100 x ∆T / Tinitial, if  < 0. The % change in body weight (BW) was calculated by the formula (BW on observation day - BW on initial day) / BW initial day x 100%.

**CD3 T cell immunohistochemistry**

Human L55 NSCLC cells(University of Pennsylvania) were injected subcutaneously into NSG mice (5x106 cells). When tumor xenografts were established (day 37), mice were randomized into groups and human PBMCs injected (8x106 cells). Human IgG1 and 7A5 antibody were dosed at 10mg/kg IP weekly for 4 weeks. Tumors were collected at end of study in formalin, processed into paraffin, sectioned and stained for CD3+ T cells. Images were acquired at 200x magnification by Aperio XT Scanscope and semiquantitatively analyzed by pathologist. The percentage CD3+ T cell infiltrates per 20x field was scored: no T cells (-), 10-20 cells (+), 30-70 cells (++), >100 cells (+++).

**Mechanism of action study in NCI-H292 human tumor xenograft mouse model**

NSG mice were injected subcutaneously on the right flank with 0.2 ml mixture of 2x106 NCI-H292 cells and 0.5x106 PBMCs. Mice implanted with NCI-H292 cells only served as a control group and received human IgG1 antibody, while mice injected with the mixture of NCI-H292 and PBMCs were randomly assigned to antibody treatment groups (n=5/group) receiving human IgG1, 7A5 or anti-PD-L1 antibody LY3300054. Antibodies were dosed at 10mg/kg (except LY3300054 at 1mg/kg) and given on day 0 or 1, 7 and 14 by IP administration. Tumors were collected on day 15 and snap frozen in liquid N2.

**Quantigene Plex gene expression assay**

List of targets: *ARG1, C10ORF54, CCL2, CCL22, CCL3, CCL4, CCL5, CCR6, CD14, CD19, CD200R1, CD226, CD27, CD274, CD28, CD3E, CD4, CD40LG, CD68, CD8b, CSF1, CSF2, CTLA4, CXCL10, CXCL9, DPP4, EOMES, FAS, FOXP3, GATA3, GUSB, GZMB, HAVCR2, HLA-DRA, HPRT1, ICAM1, ICOS, IDO1, IFNA2, IFNB1, IFNG, IL10, IL15, IL17A, IL1B, IL2, IL21, IL23A, IL2RA, IL3RA, IL6, IL7, IL7R, IL8, ITGAL, ITGAM, ITGAX, LAG3, NCAM1, NOS2, PAF1, PDCD1, PDCD1LG2, PPIB, PRF1, PTPRC, RORC, RPS18, TBX21, TDO2, TGFB1, TGFB2, TGFB3, TIGIT, TNF, TNFRSF18, TNFRSF4, TNFRSF9, TNFSF18, TNFSF9*.