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(57) Abstract: This disclosure relates to a monoclonal antibody directed against 0X40 or an antigen-binding fragment thereof, and the use of such antibody or antigen-binding fragment thereof in the treatment of tumors. The disclosure also relates to methods for the treatment of tumors comprising administering to a patient in need thereof an anti-OX40 antibody or antigenbinding fragment thereof in combination with a monoclonal antibody directed against programmed death-ligand l(PD-Ll), also known as B7 homolog 1 (B7-H1) or an antigenbinding fragment thereof or in combination with a monoclonal antibody directed against Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or an antigen-binding fragment thereof.

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# ANTI-OX40, ANTI-PD-L1 AND ANTI-CTLA-4 ANTIBODIES FOR TREATING TUMORS

## CROSS-REFERENCE TO RELATED APPLICATION

**[0001]** This application claims the priority of U.S. Provisional Application No. 62/747,424, filed October 18, 2018, which is incorporated herein by reference in its entirety.

## FIELD OF THE INVENTION

**[0002]** This disclosure relates to a monoclonal antibody directed against OX40 or an antigen-binding fragment thereof, and the use of such antibody or antigen-binding fragment thereof in the treatment of tumors. The disclosure also relates to methods for the treatment of tumors comprising administering to a patient in need thereof an anti-OX40 antibody or antigen-binding fragment thereof in combination with a monoclonal antibody directed against programmed death-ligand 1(PD-L1) also known as B7 homolog 1 (B7-H1), or an antigen-binding fragment thereof or in combination with a monoclonal antibody directed against Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or an antigen-binding fragment thereof.

## BACKGROUND

**[0003]** Cancer continues to be a major global health burden. Despite progress in the treatment of cancer, there continues to be an unmet medical need for more effective and less toxic therapies, especially for those patients with advanced disease or cancers that are resistant to existing therapeutics.

**[0004]** The role of the immune system, in particular T cell-mediated cytotoxicity, in tumor control is well recognized. There is mounting evidence that T cells control tumor growth and survival in cancer patients, both in early and late stages of the disease. However, tumor-specific T-cell responses are difficult to mount and sustain in cancer patients.

**[0005]** OX40 (CD134; TNFRSF4) is a tumor necrosis factor receptor found primarily on activated $CD4^+$ and $CD8^+$ T cells, regulatory T (Treg) cells and natural killer (NK) cells (Croft *et al.*, 2009, *Immunol. Rev.* 229: 173-91). OX40 has one known endogenous ligand, OX40 ligand (OX40L; CD152; TNFSF4), which exists in a trimeric form and can cluster OX40, resulting in potent cell signaling events within T cells. *Id.* Signaling through OX40 on activated $CD4^+$ and $CD8^+$ T cells leads to enhanced cytokine production, granzyme and perforin release, and expansion of effector and memory T cell pools (Jensen *et al.*, 2010, *Semin. Oncol.* 37: 524-32). In addition, OX40 signaling on Treg cells inhibits expansion of Tregs, shuts down the induction of Tregs and blocks Treg-suppressive function (Voo *et al.*,

2013, *J. Immunol.* 191: 3641-50; Vu *et al.*, 2007, *Blood* 110: 2501-10). MEDI0562 is a humanized monoclonal antibody directed against OX40, which selectively binds to and activates the OX40 receptor, inducing proliferation of memory and effector T-lymphocytes.

**[0006]** In a variety of nonclinical mouse tumor models, agonists of OX40, including antibodies and OX40 ligand fusion proteins, have been used successfully with promising results (Kjaergaard *et al.*, 2000, *Cancer Res.* 60: 5514-21; Ndhlovu *et al.*, 2001, *J. Immunol.* 167: 2991-99; Weinberg *et al.*, 2000, *J. Immunol.* 164: 2160-69). Co-stimulating T cells through OX40 promoted anti-tumor activity that in some cases was durable, providing long-lasting protection against subsequent tumor challenge (Weinberg *et al.*, 2000, *J. Immunol.* 164: 2160-69). Treg- cell inhibition and co-stimulation of effector T cells were shown to be necessary for tumor growth inhibition of OX40 agonists (Piconese *et al.*, 2008, *J. Exp. Med.* 205: 825-39). Many strategies and technologies have been explored to enhance the anti-tumor effect of OX40 agonist therapy through combinations with vaccines, chemotherapy, radiotherapy, and immunotherapy (Jensen *et al.*, 2010, *Semin. Oncol.* 37: 524-32; Melero *et al.*, 2013, *Clin. Cancer Res.* 19: 997-1008).

**[0007]** Programmed death-ligand 1 (PD-L1) is also part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhematopoietic cells. Its normal function is to regulate the balance between T-cell activation and tolerance through interaction with its two receptors: programmed death 1 (also known as PD-1 or CD279) and CD80 (also known as B7-1 or B7.1). PD-L1 is also expressed by tumors and acts at multiple sites to help tumors evade detection and elimination by the host immune system. PD-L1 is expressed in a broad range of cancers with a high frequency. In some cancers, expression of PD-L1 has been associated with reduced survival and unfavorable prognosis. Antibodies that block the interaction between PD-L1 and its receptors are able to relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells in vitro. Durvalumab is a human monoclonal antibody directed against human PD-L1 that is capable of blocking the binding of PD-L1 to both the PD-1 and CD80 receptors.

**[0008]** Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is expressed on activated T cells and serves as a co-inhibitor to keep T cell responses in check following CD28-mediated T cell activation. CTLA-4 is believed to regulate the amplitude of the early activation of naive and memory T cells following TCR engagement and to be part of a central inhibitory pathway that affects both antitumor immunity and autoimmunity. CTLA-4 is

expressed exclusively on T cells, and the expression of its ligands CD80 (B7.1) and CD86 (B7.2) is largely restricted to antigen-presenting cells, T cells, and other immune mediating cells. Antagonistic anti-CTLA-4 antibodies that block the CTLA-4 signaling pathway have been reported to enhance T cell activation. One such antibody, ipilimumab, was approved by the FDA in 2011 for the treatment of metastatic melanoma. Another anti-CTLA-4 antibody, tremelimumab, is currently being investigated for the treatment of various cancer types.

## SUMMARY

**[0009]** The disclosure provides a method of treating a tumor in a human patient, comprising administering MEDI0562 to the patient. In particular embodiments, MEDI0562 is administered at a dose of 3 mg/kg. In other embodiments, MEDI0562 is administered at a dose of 10 mg/kg.

**[0010]** In particular embodiments, MEDI0562 is administered every 14 to 28 days. In other embodiments, MEDI0562 is administered every 14 days. In other embodiments, MEDI0562 is administered every 28 days.

**[0011]** In particular embodiments, the administration of MEDI0562 results in a partial response or a complete response. In other embodiments the administration of MEDI0562 results in disease stabilization.

**[0012]** The disclosure further provides a method of treating a tumor in a human patient, comprising administering MEDI0562 and an immune therapeutic agent to the patient. In particular embodiments, the immune therapeutic agent is durvalumab or tremelimumab.

**[0013]** In particular embodiments, MEDI0562 is administered at a dose of 2.25 mg, 7.5 mg, 22.5 mg, 75 mg, 225 mg, or 750 mg. In particular embodiments, durvalumab is administered at a dose of 750 mg or 1500 mg. In particular embodiments, tremelimumab is administered at a dose of 75 mg, 225 mg, or 750 mg.

**[0014]** In particular embodiments, MEDI0562 is administered every 14 days. In particular embodiments, durvalumab is administered every 28 days. In particular embodiments, tremelimumab is administered every 28 days. In particular embodiments, tremelimumab is administered four times. In certain embodiments, this treatment with tremelimumab (four times every 28 days) can be reinduced, i.e., repeated upon disease progression.

**[0015]** In particular embodiments, the methods disclosed herein can be used to treat a solid tumor such as squamous cell carcinoma of the head and neck, cervical cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, or urothelial bladder

cancer. In particular embodiments, the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

**[0016]** In further embodiments, any of the foregoing treatment methods can be combined with chemotherapy.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** Figures 1A-1I show that concurrent checkpoint blockade and OX40 costimulation enhances antitumor activity as compared to monotherapy, i.e., these protocols were utilized for both combination and monotherapy studies. Ten BALB/c mice in each group were inoculated subcutaneously (SC) on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 17 and administered intraperitoneally an isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 20 mg/kg anti-CTLA-4 mAb 9D9 mouse IgG2b, 20 mg/kg anti-PD-1 mAb RMP1-14 rat IgG2a, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. All antibodies were administered as indicated twice a week for 2 weeks, except OX86 which was administered twice a week for only the first week. Individual values of tumor volumes over time are shown for untreated mice (Fig 1A), isotype control mice (Fig. 1B), and mice administered a monotherapy of anti-CTLA-4 mAb 9D9 mouse IgG2b (Fig. 1C), anti-PD-1 mAb RMP1-14 rat IgG2a (Fig. 1D), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 1E), and anti-OX40 mAb OX86 mouse IgG2a (Fig. 1F). Individual values of tumor volumes over time are shown for dual immunotherapy for CTLA-4 + OX40 (Fig. 1G), PD-1 + OX40 (Fig. 1H) and PD-L1 + OX40 (Fig. 1I). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0018]** Figures 2A and 2B show that concurrent checkpoint blockade and OX40 costimulation enhances survival as compared to monotherapy or dual immunotherapy. Twelve C57BL/6 mice in each group were inoculated SC on day 1 with MCA205 cells. Tumor-bearing mice were randomized on day 14 and control article (isotype control) and test articles (20 mg/kg mouse OX40 ligand mouse IgG1 fusion protein, 20 mg/kg anti-CTLA-4 mAb 9D9 mouse IgG2b and/or 20 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b) were administered as indicated by arrows twice a week for 2 weeks, except for the OX40 ligand fusion protein which was administered twice a week for only the first week. Figure 2A displays effects of control and single agents on survival over time. Figure 2B displays effects of control and combination treatment on survival over time.

**[0019]** Figures 3A-3I show that triple combination of immunotherapy agents improves antitumor activity in mice bearing MCA205 sarcoma as compared to monotherapy or dual

immunotherapy. Twelve C57BL/6 mice in each group were inoculated SC on day 1 with MCA205 cells. Tumor-bearing mice were randomized on day 14 and control article (isotype control) and test articles (20 mg/kg mouse OX40 ligand mouse IgG1 fusion protein, 20 mg/kg anti-CTLA-4 mAb 9D9 mouse IgG2b and/or 20 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b) were administered as indicated by arrows twice a week for 2 weeks, except for the OX40 ligand fusion protein which was administered twice a week for only the first week. Individual values of tumor volumes over time are shown for untreated mice (Fig 3A), isotype control mice (Fig. 3B), and mice administered a monotherapy of anti-CTLA-4 mAb 9D9 mouse IgG2b (Fig. 3C), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 3D), and mouse OX40 ligand mouse IgG1 fusion protein (Fig. 3E). Individual values of tumor volumes over time are shown for dual immunotherapy for CTLA-4 + PD-L1 (Fig. 3F), PD-L1 + OX40 (Fig. 3G), CTLA-4 + OX40 (Fig. 3H) and for triple combination therapy of CTLA-4 + PD-L1 +OX40 (Fig. 3I). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0020]** Figures 4A-4F show that concurrent checkpoint blockade and OX40 costimulation enhances antitumor activity as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and on study days 15 and 19 administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Individual values of tumor volumes over time are shown for mice administered a monotherapy of anti-OX40 mAb OX86 mouse IgG2a (Fig. 4A), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 4B), and anti-PD-L1 mAb clone 80 mouse IgG1 (Fig 4C). Individual values of tumor volumes over time are shown for concurrent dual immunotherapy for OX40 + isotype mix (Fig. 4D), OX40 + PD-L1 clone 80 (Fig. 4E) and OX40 + PD-L1 clone 10F.9G2 (Fig. 4F). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0021]** Figure 5 shows that concurrent checkpoint blockade and OX40 costimulation inhibits tumor growth as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and on study days 15 and 19 were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Mean values of tumor volumes over time are shown. Error bars represent standard error of the mean.

**[0022]** Figures 6A-6F show that concurrent checkpoint blockade and OX40 costimulation enhances antitumor activity as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and on study days 15, 19, 22, and 25 were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Individual values of tumor volumes over time are shown for mice administered a monotherapy of anti-OX40 mAb OX86 mouse IgG2a (Fig. 6A), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 6B), and anti-PD-L1 mAb clone 80 mouse IgG1 (Fig 6C). Individual values of tumor volumes over time are shown for concurrent dual immunotherapy for OX40 + isotype mix (Fig. 6D), OX40 + PD-L1 clone 80 (Fig. 6E) and OX40 + PD-L1 clone 10F.9G2 (Fig. 6F). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0023]** Figure 7 shows that concurrent checkpoint blockade and OX40 costimulation inhibits tumor growth as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and on study days 15, 19, 22, and 25 were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Mean values of tumor volumes over time are shown. Error bars represent standard error of the mean.

**[0024]** Figures 8A-8F show that sequential OX40 costimulation followed by checkpoint blockade enhances antitumor activity as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Control and test articles were administered on the indicated study days for each group. Individual values of tumor volumes over time are shown for mice administered a monotherapy of anti-OX40 mAb OX86 mouse IgG2a (Fig. 8A), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 8B), and anti-PD-L1 mAb clone 80 mouse IgG1 (Fig 8C). Individual values of tumor volumes over time are shown for sequential dual immunotherapy for OX40 + isotype mix (Fig. 8D), OX40 + PD-L1 clone 80 (Fig. 8E) and OX40 + PD-L1 clone 10F.9G2 (Fig. 8F). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0025]** Figure 9 shows that sequential OX40 costimulation followed by checkpoint blockade inhibits tumor growth as compared to monotherapy. Twelve BALB/c mice in each

group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Control and test articles were administered on the indicated study days for each group. Mean values of tumor volumes over time are shown. Error bars represent standard error of the mean.

**[0026]** Figures 10A-10F show that sequential checkpoint blockade followed by OX40 costimulation enhances antitumor activity as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Control and test articles were administered on the indicated study days for each group. Individual values of tumor volumes over time are shown for mice administered a monotherapy of anti-PD-L1 mAb clone 80 mouse IgG1 (Fig 10A), anti-PD-L1 mAb 10F.9G2 rat IgG2b (Fig. 10B), and anti-OX40 mAb OX86 mouse IgG2a (Fig. 10C). Individual values of tumor volumes over time are shown for sequential dual immunotherapy for OX40 + isotype mix (Fig. 10D), PD-L1 clone 80 + OX40 (Fig. 10E) and PD-L1 clone 10F.9G2 + OX40 (Fig. 10F). The number of complete responses (CR; no measurable tumor) are listed for each group.

**[0027]** Figure 11 shows that sequential OX40 costimulation followed by checkpoint blockade does not inhibit tumor growth as compared to monotherapy. Twelve BALB/c mice in each group were inoculated SC on day 1 with CT26 cells. Tumor-bearing mice were randomized on day 14 and were administered intraperitoneally isotype control, 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and/or 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. Control and test articles were administered on the indicated study days for each group. Mean values of tumor volumes over time are shown. Error bars represent standard error of the mean.

**[0028]** Figures 12A and 12B show that OX40 agonist antibody OX86 mIgG2a induces transient upregulation of Ki67 and cell surface CD25 on live peripheral blood CD45+CD4+FoxP3- and CD45+CD4+FoxP3+ cells in C57BL/6 mice. C57BL/6 mice (n=5) were administered 30 mg/kg isotype control antibody or 2.5 mg/kg OX86 mIgG2a intraperitoneally on study day 0 and/or day 21. At the indicated intervals, peripheral blood cells were tested for cell surface expression of CD45, CD4, and CD25, and intracellular FoxP3 and Ki67. Figure 12A represents the percentage of CD45+CD4+FoxP3- cells that

were Ki67 positive over time. Figure 12B represents the percentage of CD45+CD4+FoxP3+ cells that also expressed CD25 over time.

**[0029]** Figures 13A and 13B show that OX40 agonist mAb OX86 mIgG2a alters the levels of free and total OX40 on live peripheral blood CD45+CD4+FoxP3+ cells in C57BL/6 mice. C57BL/6 mice (n=5) were administered 30 mg/kg isotype control antibody or 2.5 mg/kg OX86 mIgG2a intraperitoneally on study day 0 and/or day 21. At the indicated intervals, peripheral blood cells were tested for cell surface expression of free OX40 (as determined by staining with OX86 mAb) and total OX40 (as determined by staining with mouse OX40 ligand mouse IgG1 fusion protein; non-competitive to OX86 binding to mouse OX40) on CD45+CD4+FoxP3+ cells. Figure 13A represents the percentage of free OX40 positive CD45+CD4+FoxP3- cells over time. Figure 13B represents the percentage of total OX40 positive CD45+CD4+FoxP3+ cells over time.

**[0030]** Figure 14 shows the study flow diagram for a dose-escalation study administering MEDI0562 as a monotherapy to human patients with advanced solid tumors.

**[0031]** Figure 15 shows the dosing schema for the screening, treatment, and follow-up periods of the study administering MEDI0562 as a monotherapy to human patients with advanced solid tumors.

**[0032]** Figure 16 illustrates tumor burden change in human patients with solid tumors measured by irRECIST at varying doses of MEDI0562 monotherapy administered Q2W.

**[0033]** Figure 17A shows mean (standard deviation) percentage Ki67+CD4+ memory T cells in subjects with advanced solid tumors following multiple IV doses of MEDI0562 (as-treated population). Figure 17B shows mean (standard deviation) percentage Ki67+CD8+ memory T cells in subjects with advanced solid tumors following multiple IV doses of MEDI0562 (as-treated population). CD = cluster of differentiation; IV = intravenous; Q2W = every 2 weeks. Screening visit is labelled as Day -14.

**[0034]** Figure 18A shows programmed death ligand 1 positive (PD-L1+) cell densities in tumor biopsy samples. Figure 18B shows CD8+ tumor infiltrating lymphocyte (TIL) densities in tumor biopsy samples.

**[0035]** Figure 19A shows mean (standard deviation) concentration-time profiles of MEDI0562 in subjects with advanced solid tumors following the first IV doses of MEDI0562 (as-treated population). Figure 19B shows mean (standard deviation) concentration-time profiles of MEDI0562 in subjects with advanced solid tumors following multiple IV doses of MEDI0562 Q2W (as-treated population). IV = intravenous; LLOQ = lower limit of

quantification; Q2W = every 2 weeks. Data below the LLOQ (0.025 μg/mL; as shown by the dotted horizontal line) are plotted at 1/2 LLOQ for illustrative purposes.

**[0036]** Figure 20 shows individual concentration-time profiles of MEDI0562 by ADA status for each dose cohort in subjects with advanced solid tumors following multiple IV doses of MEDI0562 Q2W (as-treated population). ADA = anti-drug antibody; IV = intravenous; LLOQ = lower limit of quantification; Q2W = every 2 weeks. Data below the LLOQ (0.025 μg/mL; as shown by the dotted horizontal line) are plotted at 1/2 LLOQ for illustrative purposes. ADA status is positive if any post-baseline sample is positive, negative if all post-baseline samples are negative, unknown if there is no post-baseline ADA sample.

**[0037]** Figures 21A-21B are graphs illustrating that OX40+FOXP3+ T cells measured by immunohistochemistry (IHC) decreased in tumors administered MEDI0562 in a dose dependent manner indicating a decrease in Tregs. Figure 101C is an image of a tumor sample showing OX40+FOXP3+ T cells pre- (day 0 or D0) and post-treatment (day 29 or D29) with MEDI0562.

**[0038]** Figures 22A-22C illustrate that T effector:T regulatory cell gene signature ratio increased in tumors at high doses of MEDI0562 monotherapy. Figure 22A is a graph showing T effector cell gene signature in tumors following MEDI0562 treatment. Figure 22B is a graph showing T regulatory cell gene signature in tumors following MEDI0562 treatment. Figure 22C is a graph showing the T effector:T regulatory cell gene signature ratio in tumors following MEDI0562 treatment.

**[0039]** Figures 23A-23C illustrate that human patients with high exposure to MEDI0562 and/or high baseline of OX40 levels exhibit dual mechanisms of action on T cells. Figure 23A is a graph showing T effector cell gene signature in tumors following MEDI0562 treatment. Figure 23B is a graph showing OX40 gene signature in tumors following MEDI0562 treatment. Figure 23C is a graph showing T regulatory cell gene signature reduction in tumors following MEDI0562 treatment.

**[0040]** Figures 24A-24F illustrate changes in peripheral gene expression following administration of varying doses of MEDI0562 monotherapy. Figure 24A is a graph showing the change in T effector / T regulatory cell gene signature ratio. Figure 24B is graph showing the change in IFNγ gene signature. Figure 24C is a graph showing the change in CXCL9 gene expression. Figure 24D is a graph showing the change in T effector cell gene signature. Figure 24E is a graph showing the change in PD-L1 gene expression. Figure 104F is a graph showing the change in OX40 gene expression.

**[0041]** Figures 25A-25B are graphs illustrating the exposure relationship of peak %OX40+ response in the peripheral blood following varying doses of MEDI0562. Figure 25A shows a box plot of the maximum % decrease in % OX40+CD4+ memory T cells in peripheral blood from baseline during the first dosing cycle (0-14 days post first dose) by dose level. Circles represent individual data. Figure 25B shows a scatter plot of individual maximum % decrease in %OX40+CD4+ memory T cells in peripheral blood from baseline during the first dosing cycle vs. $AUC_{0\text{-}14d}$ stratified by ADA status at day 15. The peak OX40+ response saturated at 0.3 mg/kg of MEDI0562 with a trend of greater peak OX40+ response with increased exposure. Solid line represents the loess smooth line, and the grey area represents the standard error of the smooth line.

**[0042]** Figure 26 shows the study flow diagram for the dose-expansion and dose-escalation portions of the study administering MEDI0562 as a combination therapy with durvalumab to human patients with advanced solid tumors.

**[0043]** Figure 27 shows the study flow diagram for the dose-expansion and dose-escalation portions of the study administering MEDI0562 as a combination therapy with tremelimumab to human patients with advanced solid tumors.

**[0044]** Figure 28 shows the dosing schema for the screening, treatment, and follow-up periods of the study administering MEDI0562 as a combination therapy with durvalumab or tremelimumab to human patients with advanced solid tumors. PD = progressive disease; Q2W = every 2 weeks; Q4W = every 4 weeks; Treme = tremelimumab; tox = toxicity.

**[0045]** Figure 29 is a graph that shows the mean (SD) MEDI0562 concentration-time profiles in serum following intravenous infusion of 2.25-22.5 mg MEDI0562 Q2W in combination with Durvalumab/Tremelimumab Q4W in subjects with solid tumors.

**[0046]** Figure 30A is a graph that shows the mean (SD) %Ki67+ CD4+ memory T cell-time profiles following intravenous infusion of 2.25-22.5 mg MEDI0562 Q2W in combination with Durvalumab/Tremelimumab Q4W in subjects with solid tumors. Figure 30 B is a graph that shows the mean (SD) %Ki67+ CD8+ memory T cell-time profiles following intravenous infusion of 2.25-22.5 mg MEDI0562 Q2W in combination with Durvalumab/Tremelimumab Q4W in subjects with solid tumors. Figure 30C is a graph that shows the mean (SD) %OX40+ CD4+ memory T Cell-time profiles following intravenous infusion of 2.25-22.5 mg MEDI0562 Q2W in combination with Durvalumab/Tremelimumab Q4W in subjects with solid tumors.

## DETAILED DESCRIPTION

**[0047]** This disclosure relates to a monoclonal antibody directed against OX40, such as MEDI0562, or an antigen-binding fragment thereof, and the use of such antibody or antigen-binding fragment thereof in the treatment of tumors. The disclosure also relates to methods for the treatment of a tumor comprising administering to a patient in need thereof an anti-OX40 antibody, such as MEDI0562, or antigen-binding fragment thereof in combination with a monoclonal antibody directed against programmed death-ligand 1(PD-L1), also known as B7 homolog 1 (B7-H1), such as durvalumab, or an antigen-binding fragment thereof or in combination with a monoclonal antibody directed against Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as tremelimumab, or an antigen-binding fragment thereof.

**[0048]** As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

**[0049]** The term "antibody" as used herein refers to a protein that is capable of recognizing and specifically binding to an antigen. Ordinary or conventional mammalian antibodies comprise a tetramer, which is typically composed of two identical pairs of polypeptide chains, each pair consisting of one "light" chain (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). The terms "heavy chain" and "light chain," as used herein, refer to any immunoglobulin polypeptide having sufficient variable domain sequence to confer specificity for a target antigen. The amino-terminal portion of each light and heavy chain typically includes a variable domain of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant domain responsible for effector function. Thus, in a naturally occurring antibody, a full-length heavy chain immunoglobulin polypeptide includes a variable domain ($V_H$) and three constant domains ($C_{H1}$, $C_{H2}$, and $C_{H3}$) and a hinge region between $C_{H1}$ and $C_{H2}$, wherein the $V_H$ domain is at the amino-terminus of the polypeptide and the $C_{H3}$ domain is at the carboxyl-terminus, and a full-length light chain immunoglobulin polypeptide includes a variable domain ($V_L$) and a constant domain ($C_L$), wherein the $V_L$ domain is at the amino-terminus of the polypeptide and the $C_L$ domain is at the carboxyl-terminus.

**[0050]** Within full-length light and heavy chains, the variable and constant domains typically are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. The variable regions of each

light/heavy chain pair typically form an antigen-binding site. The variable domains of naturally occurring antibodies typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From the amino-terminus to the carboxyl-terminus, both light and heavy chain variable domains typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

**[0051]** The term "antigen-binding fragment" refers to a portion of an intact antibody and/or refers to the antigenic determining variable domains of an intact antibody. It is known that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of antibody fragments include, but are not limited to, Fab, Fab′, F(ab′)2, and Fv fragments, linear antibodies, single chain antibodies, diabodies, and multispecific antibodies formed from antibody fragments.

**[0052]** The term "patient" as used herein includes human subjects.

**[0053]** A "disorder" is any condition that would benefit from treatment using the antibodies of the disclosure. "Disorder" and "condition" are used interchangeably herein and include chronic and acute disorders or diseases, including those pathological conditions that predispose a patient to the disorder in question.

**[0054]** The term "solid tumor" as used herein refers to an abnormal mass of tissue that normally does not contain cysts or liquid areas. Examples of solid tumors include squamous cell carcinoma of the head and neck, cervical cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, and urothelial bladder cancer.

**[0055]** The terms "treatment" or "treat" as used herein refer to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include patients having a tumor as well as those prone to have a tumor or those in which a tumor is to be prevented. In particular embodiments, the antibodies disclosed herein can be used to treat tumors such as solid tumors. In particular embodiments, treatment of a tumor includes inhibiting tumor growth, promoting tumor reduction, or both.

**[0056]** The terms "pharmaceutical composition" or "therapeutic composition" as used herein refer to a compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient. One embodiment of the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one antibody of the disclosure.

**[0057]** The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of one or more antibodies of the disclosure.

**[0058]** The term "MEDI0562" as used herein refers to a humanized immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that specifically binds to and triggers signaling by human OX40 (CD134; TNFRSF4), a member of the tumor necrosis factor receptor superfamily, as disclosed in U.S. Patent No. 9,738,723 (referred to as "OX40mAb24"), which is incorporated by reference herein in its entirety.

**[0059]** In particular embodiments, MEDI0562 or an antigen binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain. In particular embodiments, MEDI0562 comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 2. In other embodiments, MEDI0562 or an antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 3-5, and wherein the light chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 6-8.

**[0060]** In particular embodiments, a tumor in a human patient is treated by administering MEDI0562 or an antigen-binding fragment thereof to the patient.

**[0061]** The monotherapy dose of MEDI0562 or an antigen-binding fragment thereof to be administered to the patient will vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient.

**[0062]** In particular embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy, wherein the dose is 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg. In some embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy wherein the dose is 0.1 mg/kg. In other embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy wherein the dose is 0.3 mg/kg. In still other embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy wherein the dose is 1.0 mg/kg. In other embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy wherein the dose is 3.0 mg/kg. In other

embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a monotherapy wherein the dose is 10 mg/kg.

**[0063]** In particular embodiments, a patient presenting with a tumor is administered MEDI0562 or an antigen-binding fragment thereof only once or infrequently while still providing benefit to the patient. In further embodiments, the patient is administered additional follow-on doses. Follow-on doses can be administered at various time intervals depending on the patient's age, weight, clinical assessment, tumor burden, and/or other factors, including the judgment of the attending physician.

**[0064]** In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered over a two-week treatment period, over a four-week treatment period, over a six-week treatment period, over an eight-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered over a three-week treatment period, over a six-week treatment period, over a nine-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered over a two-month treatment period, over a four-month treatment period, or over a six-month or more treatment period (e.g., during a maintenance phase).

**[0065]** In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered every two weeks, every four weeks, every six weeks, every eight weeks, every ten weeks, or every twelve weeks.

**[0066]** In particular embodiments, the administration of MEDI0562 is repeated every 14 to 28 days. In other embodiments, the administration is repeated every 14 days. In further embodiments, the administration is repeated every 28 days.

**[0067]** Also provided herein are methods for treating a solid tumor in a human patient, comprising administering 3 mg/kg of MEDI0562 or an antigen-binding fragment thereof to the patient.

**[0068]** In particular embodiments, the patient receiving treatment using the antibodies disclosed herein has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

**[0069]** In particular embodiments, the patient receiving treatment has a solid tumor such as squamous cell carcinoma of the head and neck, cervical cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, or urothelial bladder cancer.

**[0070]** In other embodiments, MEDI0562 or an antigen-binding fragment thereof can be administered in a combination therapy with an immune therapeutic agent for treatment of a tumor.

**[0071]** The term "durvalumab" as used herein refers to an antibody that selectively binds PD-L1 and blocks the binding of PD-L1 to the PD-1 and CD80 receptors, as disclosed in U.S. Patent No. 9,493,565 (referred to as "2.14H9OPT"), which is incorporated by reference herein in its entirety. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC). Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation in vitro and inhibits tumor growth in a xenograft model via a T-cell dependent mechanism.

**[0072]** In particular embodiments, the immune therapeutic agent is durvalumab or an antigen-binding fragment thereof. In particular embodiments, durvalumab or an antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain. In particular embodiments, durvalumab comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 10. In other embodiments, durvalumab or an antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 11-13, and wherein the light chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 14-16.

**[0073]** The term "tremelimumab" as used herein refers to an antibody that selectively binds a CTLA-4 polypeptide, as disclosed in U.S. Patent No. 8,491,895 (referred to as clone 11.2.1), which is incorporated by reference herein in its entirety. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) antibody-dependent cell-mediated cytotoxicity (ADCC) activity, and does not deliver inhibitory signals following plate-bound aggregation.

**[0074]** In another embodiment, the immune therapeutic agent is tremelimumab or an antigen-binding fragment thereof. In particular embodiments, tremelimumab or an antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain. In particular embodiments, tremelimumab comprises a light chain variable domain

comprising the amino acid sequence of SEQ ID NO: 17 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18. In particular embodiments, tremelimumab or an antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 19-21, and wherein the light chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 22-24.

**[0075]** In particular embodiments, a patient presenting with a tumor is administered MEDI0562 or an antigen-binding fragment thereof in combination with durvalumab or tremelimumab only once or infrequently while still providing benefit to the patient. In further embodiments, the patient is administered additional follow-on doses. Follow-on doses can be administered at various time intervals depending on the patient's age, weight, clinical assessment, tumor burden, and/or other factors, including the judgment of the attending physician.

**[0076]** In particular embodiments, MEDI0562 or an antigen-binding fragment thereof administered in a combination therapy is administered over a two-week treatment period, over a four-week treatment period, over a six-week treatment period, over an eight-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered in a combination therapy over a three-week treatment period, over a six-week treatment period, over a nine-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered in a combination therapy over a two-month treatment period, over a four-month treatment period, or over a six-month or more treatment period (e.g., during a maintenance phase).

**[0077]** In particular embodiments, MEDI0562 or an antigen-binding fragment thereof is administered in a combination therapy every two weeks, every four weeks, every six weeks, every eight weeks, every 10 weeks, or every twelve weeks.

**[0078]** In particular embodiments, the administration of MEDI0562 in a combination therapy is repeated every 14 to 28 days. In other embodiments, the administration is repeated about every 14 days. In further embodiments, the administration is repeated every 28 days.

**[0079]** In particular embodiments, durvalumab or tremelimumab is administered about as frequently as MEDI0562. In certain embodiments, MEDI0562 is administered about two times as frequently as durvalumab or tremelimumab.

**[0080]** In particular embodiments, the administration of durvalumab or tremelimumab is repeated every 14 to 28 days. In other embodiments the administration of durvalumab or tremelimumab is repeated every 14 days. In further embodiments, the administration of durvalumab or tremelimumab is repeated every 28 days.

**[0081]** The combination therapy dose of MEDI0562 with durvalumab will vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. In particular embodiments, the patient is administered one or more doses of MEDI0562 or an antigen-binding fragment thereof as a combination therapy wherein the dose is 2.25 mg, 7.5 mg, 22.5 mg, 75 mg, 225 mg, or 750 mg.

**[0082]** The combination therapy dose of durvalumab with MEDI0562 will vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. In particular embodiments, the patient is administered one or more doses of durvalumab or an antigen-binding fragment thereof as a combination therapy wherein the dose is 750 mg or 1500 mg.

**[0083]** In particular embodiments, the patient is administered 2.25 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 7.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In other embodiments, the patient is administered 22.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 75 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In other embodiments, the patient is administered 225 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 750 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 1500 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks.

**[0084]** In particular embodiments, the patient is administered 2.25 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 7.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In other embodiments, the patient is administered 22.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 75 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In other embodiments, the patient is administered 225 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks. In some embodiments, the patient is administered 750 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of durvalumab or an antigen-binding fragment thereof every 4 weeks.

**[0085]** When the MEDI0562 or an antigen-binding fragment thereof is administered in combination with an immune therapeutic agent, the combination can be administered in either order or simultaneously. In particular embodiments, the MEDI0562 or an antigen-binding fragment thereof is administered first followed by administration of the durvalumab or an antigen-binding fragment. In some embodiments, the durvalumab or an antigen-binding fragment is administered first followed by administration of the administration of MEDI0562 or an antigen-binding fragment thereof. In other embodiments, the MEDI0562 or an antigen-binding fragment thereof and the durvalumab or an antigen-binding fragment are administered simultaneously.

**[0086]** The combination therapy dose of tremelimumab with MEDI0562 will vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. In particular embodiments, the patient is administered one or more doses of tremelimumab or an antigen-binding fragment thereof as a combination therapy wherein the dose is 75 mg, 225 mg, or 750 mg. In other embodiments, a patient is administered four doses of tremelimumab. In some embodiments, this combination treatment can be repeated upon disease progression.

**[0087]** In particular embodiments, the patient is administered 2.25 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the

patient is administered 7.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In other embodiments, the patient is administered 22.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 75 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In other embodiments, the patient is administered 225 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 750 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 75 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses.

**[0088]** In particular embodiments, the patient is administered 2.25 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 7.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In other embodiments, the patient is administered 22.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 75 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In other embodiments, the patient is administered 225 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 750 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 225 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses.

**[0089]** In particular embodiments, the patient is administered 2.25 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 7.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4

weeks for four doses. In other embodiments, the patient is administered 22.5 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 75 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In other embodiments, the patient is administered 225 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses. In some embodiments, the patient is administered 750 mg of MEDI0562 or an antigen-binding fragment thereof every two weeks and 750 mg of tremelimumab or an antigen-binding fragment thereof every 4 weeks for four doses.

**[0090]** In particular embodiments, the MEDI0562 or an antigen-binding fragment thereof is administered first followed by administration of the tremelimumab or an antigen-binding fragment thereof. In some embodiments, the tremelimumab or an antigen-binding fragment thereof is administered first followed by administration of the administration of MEDI0562 or an antigen-binding fragment thereof. In other embodiments, the MEDI0562 or an antigen-binding fragment thereof and the tremelimumab or an antigen-binding fragment thereof are administered simultaneously.

**[0091]** The antibodies of the disclosure can be selected for parenteral administration. For example, the antibodies of the disclosure can be administered by intravenous infusion or by subcutaneous injection. In particular embodiments, the administration is by intravenous infusion.

**[0092]** Response Evaluation Criteria In Solid Tumors (RECIST) refers to a set of published rules that define when cancer patients improve, stay the same or worsen during treatments. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD).

**[0093]** The methods provided herein can be used for disease control (DC) of a tumor. Disease control can be a complete response (CR), partial response (PR), or stable disease (SD).

**[0094]** A "complete response" (CR) refers to the disappearance of all lesions, whether measurable or not, and no new lesions. Confirmation of a complete response can be obtained using a repeat, consecutive assessment no less than four weeks from the date of first documentation. New, non-measurable lesions preclude CR.

**[0095]** A "partial response" (PR) refers to a decrease in tumor burden of ≥ 50% relative to baseline. Confirmation can be obtained using a consecutive repeat assessment at least 4 weeks from the date of first documentation.

**[0096]** "Progressive disease" (PD) refers to an increase in tumor burden of ≥ 25% relative to the minimum recorded (nadir). Confirmation can be obtained by a consecutive repeat assessment at least 4 weeks from the date of first documentation. New, non-measurable lesions do not define PD.

**[0097]** "Stable disease" (SD) refers to not meeting the criteria for CR, PR, or PD.

**[0098]** According to the methods provided herein, administration of MEDI0562 or an antigen-binding fragment thereof can result in desirable pharmacokinetic parameters. Total drug exposure can be estimated using the "area under the curve" (AUC). "AUC (tau)" refers to AUC until the end of the dosing period, whereas "AUC (inf)"refers to the AUC until infinite time.

**[0099]** Without limiting the disclosure, a number of embodiments of the disclosure are described below for purpose of illustration.

## EXAMPLES

**[00100]** The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only, and should not be construed as limiting the scope of the invention in any way.

### Methods

*RNA Isolation*

**[00101]** Total RNA was extracted from PAXgene blood tubes using the PAXgene Blood RNA kit (Qiagen®, Hilden, Germany). For core needle biopsy samples, tissue was homogenized in RNA lysis buffer and isolated using the RNeasy Fibrous Tissue kit (Qiagen®) according to manufacturer's instructions. RNA purity and concentration were determined spectrophotometrically (260/280>1.9). RNA quality was assessed on an Agilent 2100 Bioanalyzer using the RNA 6000 Nano LabChip®.

*TaqMan Q-PCR*

**[00102]** For TaqMan Q-PCR, cDNA was generated using SuperScript® III First-Strand Synthesis SuperMix kit (Life Technologies, Carlsbad, CA) and random primers. Samples were prepared using the TaqMan Pre-Amp Master Mix Kit and analyzed with the BioMark Real-Time PCR System. Cycle threshold (Ct) values above 28 were excluded from calculations. Delta-delta Ct values (ΔΔCt) were calculated using the mean of two reference genes (β-actin and GAPDH) and each patient's baseline expression level as controls. Fold change values were determined by calculating $2^{-\Delta\Delta Ct}$.

*MEDI0562 PK*

**[00103]** MEDI0562 was measured in serum samples using a colorimetric ELISA method that was developed and validated by MedImmune. Samples were diluted 1:40 in assay buffer and incubated on microtiter plate coated with anti-idiotype antibody (clone 2E3.1.1) for capture of MEDI0562. Plates were washed and biotin-labeled anti-idiotype antibody (clone 1A4.1) added for binding MEDI0562 at a separate site. Streptavidin horseradish peroxidase conjugate and tetramethylbenzidine enzyme substrate were sequentially added for generation of a colorimetric reaction measured at a wavelength of 450 nm. MEDI0562 concentrations in samples were determined by interpolation from a standard curve using a four-parameter curve fit with $1/Y^2$ weight value relating color intensity to concentrations of MEDI0562. The quantitative range of the assay was 25 to 1600 ng/mL in 100% serum.

*MEDI0562 ADA*

**[00104]** Anti-drug-antibodies (ADA) to MEDI0562 were measured using a solution-phase, Meso Scale Discovery (MSD) bridging assay that was developed and validated by MedImmune. Serum samples were tested for detection, confirmation, and titer determination of ADA using a tiered analysis approach and statistically-based cut points. Positive control (rabbit anti-MEDI0562 polyclonal antibody), negative control serum, and test samples at a 1:30 dilution were incubated with biotin-conjugated MEDI0562 and ruthenium-conjugated MEDI0562 to form an immunocomplex. The ADA immunocomplexes were captured on streptavidin-coated MSD plates and measured on an MSD Sector Imager, producing signal intensity proportional to the levels of ADA in the sample. Samples that measured above the screening assay cut point (signal to background >= 1.21) were retested for confirmation in both the absence and presence of excess MEDI0562. Samples with inhibition levels at or above the confirmatory cut point (19.2%) were classified as positive and titered for determination of relative amounts of ADA. The assay could detect 13.0 ng/mL of positive control in the absence of MEDI0562 and 250 ng/mL positive control in the presence of 50 μg/mL MEDI0562.

**Example 1. Combination checkpoint blockade and OX40 costimulation enhanced antitumor activity as compared to monotherapy**

**[00105]** OX86 is a rat anti-mOX40 IgG1 antibody that specifically binds to and triggers signaling of mOX40 and has anti-tumor activity in immunocompetent mouse models of cancer. To more fully study the effects of OX40 agonism using a mouse surrogate antibody with functional properties similar to MEDI0562, a rat/mouse anti-mOX40 IgG2a chimera antibody (OX86 mIgG2a; rat anti-OX40 light and heavy chain variable regions with mouse IgG2a constant regions) was generated from OX86. This example was designed to determine if OX40 mAb OX86 mouse IgG2a is effective in a combination therapy for the treatment of tumors.

**1. Establishment and Implantation of Syngeneic Tumors**

**[00106]** The CT26 cell line (mouse colon carcinoma) was obtained from ATCC, Manassas, VA, and the cell line MCA 205 (chemically-induced mouse soft tissue sarcoma)

was obtained from the Providence Cancer Center, Portland, OR. Both cell lines were maintained in RPMI 1640 medium +10% FBS at 37°C, 5% $CO_2$.

**[00107]** Allografts were established by subcutaneous (SC) injection of 5.0 x $10^5$ CT26 cells, resuspended in 0.1 mL of PBS, into BALB/c mice. Allografts were also established by SC injection of 2.5 x $10^5$ MCA205 cells, resuspended in 0.1 mL of PBS, into C57BL/6 mice.

**2. Tumor Measurements**

**[00108]** Tumors were measured by caliper twice weekly and tumor volumes were calculated using the following formula:

$$\text{tumor volume} = [\text{length (mm)} \times \text{width (mm)}^2] /2$$

where length was defined as the larger side, and width as the smaller side perpendicular to the length.

Antitumor effects of each group were expressed as tumor growth inhibition (TGI), which was calculated as follows:

% TGI = (1 - [mean tumor V of treatment group] ÷ [mean tumor V of control group]) x 100

**3. Dosing Protocols**

**[00109]** The first dosing protocol included tumor-bearing mice inoculated SC on day 1 with CT26 cells that were randomized on day 17 and administered intraperitoneally an isotype control, the 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 20 mg/kg anti-CTLA-4 mAb 9D9 mouse IgG2b, 20 mg/kg anti-PD-1 mAb RMP1-14 rat IgG2a, and 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b. All antibodies were administered twice a week for 2 weeks, except OX86, which was administered twice a week for only the first week.

**[00110]** The second dosing protocol included tumor-bearing mice inoculated SC on day 1 with MCA205 cells that were randomized on day 14 and control article (isotype control) and test articles (20 mg/kg mouse OX40 ligand mouse IgG1 fusion protein, 20 mg/kg anti-CTLA-4 mAb 9D9 mouse IgG2b, and 20 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b) were administered twice a week for 2 weeks, except for the OX40 ligand fusion protein, which was administered twice a week for only the first week.

**[00111]** The third dosing protocol included concurrent OX40 agonist and PD-L1 blockade on study days 15 and 18 as illustrated in Table 1. Tumor-bearing mice inoculated SC on day 1 with CT26 cells were randomized on day 14 and on study days 15 and 18 administered intraperitoneally isotype control, the 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30

mg/kg anti-PD-L1 mAb clone 80 mouse IgG1 and 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b.

**Table 1**

| Study day | | | | | | Activity / Treatment | Label |
|---|---|---|---|---|---|---|---|
| 1 | 14 | 15 | 18 | 22 | 25 | | |
| x | | | | | | Tumor implantation | |
| | x | | | | | Randomize | |
| | | x | x | x | x | Isotype | Isotype (d15, 18, 22, 25) |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) |
| | | x | x | | | PDL1 mIgG1 | PDL1 G1 (d15, 18) |
| | | x | x | | | PDL1 rIgG2b | PDL1 G2b (d15, 18) |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + Iso (d15, 18) |
| | | x | x | | | Isotype | |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + PDL1 G1 (d15, 18) |
| | | x | x | | | PDL1 mIgG1 | |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + PDL1 G2b (d15, 18) |
| | | x | x | | | PDL1 rIgG2b | |

**[00112]** The fourth dosing protocol included concurrent OX40 agonist and PD-L1 blockade on study days 15, 18, 22, and 25 as illustrated in Table 2. Tumor-bearing mice inoculated SC on day 1 with CT26 cells were randomized on day 14 and on study days 15, 18, 22, and 25 administered intraperitoneally isotype control, the 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b.

**Table 2**

| Study day | | | | | | Activity / Treatment | Label |
|---|---|---|---|---|---|---|---|
| 1 | 14 | 15 | 18 | 22 | 25 | | |
| x | | | | | | Tumor implantation | |
| | x | | | | | Randomize | |
| | | x | x | x | x | Isotype | Isotype (d15, 18, 22, 25) |
| | | x | x | x | x | OX86 mIgG2a | OX86 (d15, 18, 22, 25) |
| | | x | x | x | x | PDL1 mIgG1 | PDL1 G1 (d15, 18, 22, 25) |
| | | x | x | x | x | PDL1 rIgG2b | PDL1 G2b (d22, 25) |
| | | x | x | x | x | OX86 mIgG2a | OX86 + Iso (d15, 18, 22, 25) |
| | | x | x | x | x | Isotype | |
| | | x | x | x | x | OX86 mIgG2a | OX86 + PDL1 G1 (d15, 18, 22, 25) |
| | | x | x | x | x | PDL1 mIgG1 | |
| | | x | x | x | x | OX86 mIgG2a | OX86 + PDL1 G2b (d15, 18, 22, 25) |
| | | x | x | x | x | PDL1 rIgG2b | |

**[00113]** The fifth dosing protocol included sequential administration of OX40 agonist followed by PD-L1 blockade as illustrated in Table 3. Tumor-bearing mice inoculated SC on day 1 with CT26 cells were randomized on day 14 and were administered intraperitoneally isotype control, the 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b.

**Table 3**

| Study day | | | | | | Activity / Treatment | Label |
|---|---|---|---|---|---|---|---|
| 1 | 14 | 15 | 18 | 22 | 25 | | |
| x | | | | | | Tumor implantation | |
| | x | | | | | Randomize | |
| | | x | x | x | x | Isotype | Isotype (d15, 18, 22, 25) |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) |
| | | | | x | x | PDL1 mIgG1 | PDL1 G1 (d22, 25) |
| | | | | x | x | PDL1 rIgG2b | PDL1 G2b (d22, 25) |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + Iso (d22, 25) |
| | | | | x | x | Isotype | |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + PDL1 G1 (d22, 25) |
| | | | | x | x | PDL1 mIgG1 | |
| | | x | x | | | OX86 mIgG2a | OX86 (d15, 18) + PDL1 G2b (d22, 25) |
| | | | | x | x | PDL1 rIgG2b | |

**[00114]** The sixth dosing protocol included sequential administration of PD-L1 blockade followed by OX40 agonist as illustrated in Table 4. Tumor-bearing mice inoculated SC on day 1 with CT26 cells were randomized on day 14 and were administered intraperitoneally isotype control, the 0.1 mg/kg anti-OX40 mAb OX86 mouse IgG2a, 30 mg/kg anti-PD-L1 mAb clone 80 mouse IgG1, and 30 mg/kg anti-PD-L1 mAb 10F.9G2 rat IgG2b.

**Table 4**

| Study day | | | | | | Activity / Treatment | Label |
|---|---|---|---|---|---|---|---|
| 1 | 14 | 15 | 18 | 22 | 25 | | |
| x | | | | | | Tumor implantation | |
| | x | | | | | Randomize | |
| | | x | x | x | x | Isotype | Isotype (d15, 18, 22, 25) |
| | | | | x | x | OX86 mIgG2a | OX86 (d22, 25) |
| | | x | x | | | PDL1 mIgG1 | PDL1 G1 (d15, 18) |
| | | x | x | | | PDL1 rIgG2b | PDL1 G2b (d15, 18) |
| | | | | x | x | OX86 mIgG2a | OX86 (d22, 25) + Iso (d15, 18) |
| | | x | x | | | Isotype | |
| | | | | x | x | OX86 mIgG2a | OX86 (d22, 25) + PDL1 G1 (d15, 18) |
| | | x | x | | | PDL1 mIgG1 | |
| | | | | x | x | OX86 mIgG2a | OX86 (d22, 25) + PDL1 G2b (d15, 18) |
| | | x | x | | | PDL1 rIgG2b | |

## 4. Results

**[00115]** Concurrent checkpoint blockade using anti-CTLA-4, anti-PD-1 or anti-PD-L1 in combination with OX-40 costimulation using either two or four doses of a rat/mouse anti-mOX40 IgG2a chimera antibody (OX86 mIgG2a) or mOX40L fusion protein enhanced antitumor activity as compared to monotherapy (Figures 1A-1I; Figures 4A-4F; Figure 5; Figures 6A- 6F; Figure 7). Concurrent immune checkpoint blockade using anti-CTLA-4 and/or anti-PD-L1 and OX40 costimulation enhanced survival as compared to monotherapy

or dual immunotherapy (Figures 2A and 2B) and triple combination of immunotherapy agents (anti-CTLA-4, anti-PD-L1 and anti-OX-40) improved antitumor activity in mice bearing MCA205 sarcoma as compared to monotherapy or dual immunotherapy (Figures 3A-3I). A summary of antitumor activity of concurrent dosing of OX40 combined with PD-L1 antibodies in a preclinical mouse tumor model is shown in Table 5.

**Table 5**

| | PDL1 mAb type | Combo Activity Compared to Single Agent Controls | | |
|---|---|---|---|---|
| | | Attenuated | Equivalent | Enhanced |
| OX40 concurrent (2 doses) | Null | | | ☑ |
| | ADCC | | | ☑ |
| OX40 concurrent (4 doses) | Null | | | ☑ |
| | ADCC | | | ☑ |
| OX40 before PDL1 mAb (2 doses each) | Null | | ☑ | |
| | ADCC | | | ☑ |
| PDL1 mAb before OX40 (2 doses each) | Null | | | ☑ |
| | ADCC | | ☒ | |

**[00116]** Sequential OX40 costimulation followed by checkpoint blockade using anti-PD-L1 enhanced antitumor activity (Figures 8A-8F) and inhibited tumor growth as compared to monotherapy (Figure 9). Sequential checkpoint blockade followed by OX40 costimulation enhanced antitumor activity as compared to monotherapy (Figures 10A-10F), but did not inhibit tumor growth as compared to monotherapy (Figure 11).

**[00117]** These results demonstrate that a rat/mouse anti-mOX40 IgG2a chimera antibody (OX86 mIgG2a) with functional properties similar to MEDI0562 was effective in dual or triple combination therapy with immune checkpoint inhibitors CTLA-4, PD-1, and PD-L1 to provide enhanced treatment of tumors.

**Example 2. Cell surface expression on peripheral blood cells following OX86 administration**

**[00118]** C57BL/6 mice (n=5) were administered 30 mg/kg isotype control antibody or 2.5 mg/kg OX86 mIgG2a intraperitoneally on study day 0 and/or day 21. Peripheral blood cells were tested for cell surface expression of CD45, CD4, and CD25, intracellular FoxP3, Ki67, free OX40 (as determined by staining with OX86 mAb), and total OX40 (as determined by staining with mouse OX40 ligand mouse IgG1 fusion protein; non-competitive to OX86 binding to mouse OX40) .

### 1. Tissue Collection and Single Cell Isolation

**[00119]** Red blood cell lysis (RBCL) buffer (2 mL) was added to blood (50 µL) and incubated for 5 min. Volumes obtained from in-life bleeds ranged from 20 µL to 50 µL. Terminal bleeds were 50 µL. RPMI +10% fetal bovine serum (FBS) (8 mL) was added to each sample. Cells in each sample were pelleted (300 x g, 5 min) and then resuspended in 0.3 mL Flow Buffer. Cell suspensions (200 µL) were added to each well of a 96-well round-bottomed plate for staining with fluorescent antibodies. Pooled group samples were used for unstained, the single antibody control staining, isotype control staining and the fluorescence-minus-one (FMO) antibody staining controls.

### 2. Flow Cytometry Analysis of Tissues

**[00120]** Single-cell suspensions of blood were pelleted (300 x g, 5 min), resuspended in 50 µL of Fc Block solution (1:50), diluted in eBiosciences Flow buffer and incubated for 10 min on ice. Fifty microliters of fluorescently labelled antibodies (2X stock solution) were added to each sample (final volume 100 µL). Single antibody staining solutions (extracellular) were added at 1 µL per well and cell/antibody mixtures were incubated for 30 min on ice. Cells were pelleted (300 x g, 5 min), washed twice (200 µL Flow buffer per well, 300 x g, 5 min), resuspended in 50 µL Fix/Perm buffer (one part concentrate to three part diluent) and then incubated overnight at 4°C in the dark.

**[00121]** Treated cells were washed twice in 1X Permeabilization Buffer (diluted in water). Intracellular labelling antibodies were diluted into Permeabilization Buffer (100 µL per well) and added to the cells, which were then incubated at room temperature in the dark for 30 minutes. Antibodies for single marker staining (intracellular) were added to cells at 1 µL per well into 100 µL Permeabilization Buffer and incubated for 30 min on ice in the dark. Cells were washed once in Permeabilization Buffer and resuspended in 3.7% formaldehyde solution (100 µL) before being analyzed on a LSRII flow cytometer (BD Biosciences, San Jose, CA).

### 3. Results

**[00122]** As shown in Figures 12A-12B, OX40 agonist antibody OX86 mIgG2a induced a transient increase in T-cell activation and proliferation as measured by increased expression of CD25 and Ki67, respectively (Figures 12A-12B).

**[00123]** As shown in Figures 13A-13B, OX40 agonist antibody OX86 altered the levels of free and total OX40 on live peripheral blood CD45+CD4+FoxP3+ cells in C57BL/6 mice.

## Example 3. Dosing of MEDI0562 Monotherapy

### 1. Design of the Study

**[00124]** The study was a first-time-in-human Phase 1, multicenter, open-label, single-arm, dose-escalation, and dose-expansion study of MEDI0562 to evaluate the safety, tolerability, PK, immunogenicity, pharmacodynamics, and preliminary antitumor activity in adult subjects with selected advanced solid tumors. The study flow diagram is illustrated in Figure 14. The following abbreviations and legends are used to describe the study flow diagram illustrated in Figure 14: CNS = central nervous system; Q2W = every 2 weeks.

**[00125]** All subjects were evaluated for antitumor activity on a regular basis and their clinical status classified according to irRECIST guidelines. All subjects were followed for survival until the end of study (3 years after the final subject is entered into the study or when the sponsor stops the study).

### 2. Patients and Methods

**[00126]** Subjects in this study included adult subjects, $\geq$ 18 years of age with advanced solid tumors that have received and have progressed, were refractory, or were intolerant to standard therapy appropriate for the specific tumor type and had not received more than 3 prior lines of therapy for recurrent or metastatic disease including both standards of care and investigational therapies.

**[00127]** During dose-escalation, subjects had histologic or cytologic documentation of advanced solid tumors, excluding primary CNS tumors and advanced solid tumors with CNS-only disease. In the dose-expansion phase, subjects had histologic or cytologic diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) that was incurable by local therapy, cervical cancer (CC), microsatellite stable (MSS) colorectal cancer (CRC), PD-L1+ non-small cell lung cancer, pancreatic cancer, prostate cancer, urothelial bladder cancer (UBC), or immunotherapy-relapsed or -refractory select solid tumors.

**[00128]** All subjects were required to have at least 1 lesion that was measurable using irRECIST guidelines, an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 as well as adequate organ function. Adequate organ function was defined as: absolute neutrophil count $\geq$ 1,500/mm$^3$; platelet count $\geq$ 75,000/ mm$^3$; hemoglobin $\geq$ 9.0 g/dL; creatinine clearance or 24-hour urine CrCl > 50 mL/min as determined by the Cockcroft-Gault formula; total bilirubin $\leq$ 1.5 $\times$ ULN except in the case of subjects with documented or suspected Gilbert's disease (for these subjects, bilirubin must be $\leq$ 3 $\times$ ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of normal (ULN) (AST/ALT can be up to 5 $\times$ ULN in the presence of liver metastasis, but cannot be associated with concurrent elevated bilirubin); and potassium, sodium, magnesium, and calcium (corrected for serum albumin) $\leq$ Grade 1 or within the institutional ranges of normal.

**[00129]** Subjects were excluded from participation in the study if administered prior treatment with a TNFRSF agonist, prior treatment with CTLA-4, PD-L1, or PD-1 antagonists, a history of severe allergic reactions to any unknown allergens or any components of the study drug formulations, active or prior documented autoimmune disease within the past two years, untreated CNS metastatic disease, unresolved toxicities from prior anticancer therapy, had a medical condition requiring current systemic anticoagulation or a history of congenital hypercoagulable condition, had current or prior use of immunosuppressive medication within 14 days prior to the first dose of MEDI0562, a history of primary immunodeficiency, solid organ transplantation, tuberculosis or active infection with human immunodeficiency virus (HIV) or hepatitis B or C, receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational product, had major surgery within 28 days prior to first dose of MEDI0562 or still recovering from prior surgery, prior malignancy active within the previous 2 years, or uncontrolled intercurrent illness.

**[00130]** Subjects were not permitted to have any conventional or investigational anticancer therapy within 28 days prior to the first dose of MEDI0562, concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, but concurrent use of hormones for non-cancer related conditions and local palliative treatment of lesions was allowed.

### 3. Dose Escalation

**[00131]** Dose-escalation was conducted in subjects with advanced solid tumors, excluding primary CNS tumors and advanced solid tumors with CNS-only disease. Figure 15 demonstrates the dosing schema. Sequential cohorts of 3 to 6 subjects each received 1 of 6

dose levels of MEDI0562 (0.03, 0.1, 0.3, 1.0, 3.0, or 10 mg/kg) via intravenous (IV) infusion every 2 weeks (Q2W), unless the maximum tolerated dose (MTD) was reached before all dose-escalation cohorts were completed. The MTD was determined based on the assessment of dose limiting toxicities (DLT) during the DLT-evaluation period, which was defined as the time from the first dose of investigational product through 28 days post Dose 1 (i.e., until the planned administration of the third dose). Subjects remained on treatment until unacceptable toxicity, documentation of confirmed disease progression, or other reason for treatment discontinuation developed. Ongoing surveillance of pharmacodynamic, PK, clinical, safety, and antitumor activity data was performed throughout dose-escalation.

**[00132]** Alternate treatment schedules of MEDI0562 (e.g., every 4 weeks (Q4W)) were explored based on PK, pharmacodynamic, safety, and response data. The first cohort of 3 to 6 subjects on a Q4W schedule received MEDI0562 at the highest Q2W dose level that had not exceeded the MTD. If the MTD was not exceeded at that dose level on a Q4W schedule and provided this was not the highest protocol-defined dose, MEDI0562 Q4W dose escalation proceeded with additional sequential cohorts of 3 to 6 subjects according to the aforementioned dose levels.

**5. Pharmacokinetic, Antitumor, and Safety Assessments**

**[00133]** Assessment of antitumor activity was conducted using objective response (OR), disease control (DC), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Immune-related response criteria (irRECIST) was used for assessment of tumor response. Tumor assessments included the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable), and cross-sectional imaging using computed tomography or magnetic resonance imaging (MRI) scans.

**[00134]** The PK of MEDI0562 was assessed using individual subject MEDI0562 concentrations in serum at different time points after MEDI0562 administration measured utilizing a validated immunoassay method. Pharmacokinetic parameters included but were not limited to maximum observed concentration, area under the concentration-time curve from day 1 to day 15, clearance, and terminal half-life.

**[00135]** Immunogenicity of MEDI0562 was assessed by the number and percentage of subjects who develop detectable anti-drug antibodies. The endpoints for assessment of pharmacodynamic activity included induction of Ki67 on peripheral cluster of differentiation (CD)4+ and CD8+ memory T-cell populations and assessment of programmed death ligand 1 (PD-L1) and tumor-infiltrating lymphocytes (TILs) in tumor biopsy specimens.

For Ki67 and OX40 cell assessments by flow cytometry, blood was drawn in an appropriate blood collection tube and evaluated in fit for purpose validated assays. For OX40 evaluations, samples were stained with a panel of fluorochrome conjugated antibodies that included antibodies to CD4/CD8/CD3/GITR/CD279/CD73/CD278/CD45/CD45RA and CD134. The anti-CD134 stain utilized clone ACT35, which is not competitive with MEDI0562 in its binding for OX40, to generate a percent OX40+ positive (against a negative control) as well as OX40 expression levels on positive cells as measured by the instruments median fluorescence intensity. Conversions from percent positive to absolute cell counts, where performed, multiplied the available percentage of CD4 and CD8 cell measures against CD4 and/or CD8 T cells counts per volume of whole blood generated from a separate fit for purposed validated test that quantifies these populations in whole blood. For Ki67 cell proliferation evaluations, samples were first surface stained with fluorochorme conjugated mAb that included CD4/CD8/CD3/CD45RA/CCR7/CD19/CD56 followed by permeabilization and staining with a fluorochome labelled mAb to Ki67. %Ki67+ for cell subsets was determined by comparison to a staining of an identical sample that lacked the Ki67 mAb.

**[00136]** Plasma was isolated from blood and analyzed for a range of oncology biomarkers that may correlate with drug response including protein, small molecule, and nucleic acid biomarkers that relate to MEDI0562 treatment.

**[00137]** The safety evaluation was based on the presence of adverse event (AE), serious adverse event (SAE), DLT, abnormal laboratory parameter, vital sign, and electrocardiogram results.

## 6. Results

**[00138]** In the study, 55 subjects were treated with MEDI0562 monotherapy every 2 weeks (Q2W) across 6 dose-level cohorts (10 subjects, 0.03 mg/kg; 10 subjects, 0.1 mg/kg; 12 subjects, 0.3 mg/kg; 8 subjects, 1.0 mg/kg; 8 subjects, 3.0 mg/kg; 7 subjects, 10.0 mg/kg). No dose-limiting toxicities (DLTs) were observed in the dose escalation cohorts. The safety data indicates that MEDI0562 was well tolerated. MEDI0562 was well tolerated at all doses and the related adverse events profile was similar across different doses of MEDI0562.

**[00139]** For MEDI0562 administered Q2W as a monotherapy, the maximum administered dose (MAD) and maximum tolerated dose (MTD) were not reached and DLTs were observed.

**Table 6: Subject disposition (as-treated population)**

| Parameter | MEDI0562 0.03 mg/kg Q2W (N = 10) | MEDI0562 0.1 mg/kg Q2W (N = 10) | MEDI0562 0.3 mg/kg Q2W (N = 12) | MEDI0562 1.0 mg/kg Q2W (N = 8) | MEDI0562 3.0 mg/kg Q2W (N = 8) | MEDI0562 10.0 mg/kg Q2W (N = 7) | Total (N = 55) |
|---|---|---|---|---|---|---|---|
| Subjects who received treatment | 10 | 10 | 12 | 8 | 8 | 7 | 55 |
| Subjects who discontinued treatment | 10 (100%) | 10 (100%) | 12 (100%) | 8 (100%) | 8 (100%) | 7 (100%) | 55 (100%) |
| Adverse event | 0 | 1 (10.0%) | 2 (16.7%) | 0 | 0 | 1 (14.3%) | 4 (7.3%) |
| Death | 1 (10.0%) | 0 | 1 (8.3%) | 0 | 0 | 0 | 2 (3.6%) |
| Progressive disease | 6 (60.0%) | 7 (70.0%) | 6 (50.0%) | 6 (75.0%) | 3 (37.5%) | 6 (85.7%) | 34 (61.8%) |
| Initiation of alternate treatment | 0 | 0 | 0 | 0 | 1 (12.5%) | 0 | 1 (1.8%) |
| Lost to follow-up | 0 | 1 (10.0%) | 0 | 0 | 0 | 0 | 1 (1.8%) |
| Withdrawal by subject | 1 (10.0%) | 1 (10.0%) | 2 (16.7%) | 2 (25.0%) | 4 (50.0%) | 0 | 10 (18.2%) |
| Other | 2 (20.0%) | 0 | 1 (8.3%) | 0 | 0 | 0 | 3 (5.5%) |
| Subjects who are ongoing on treatment | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | |
| End of study status | | | | | | | |
| Completed protocol-defined end of study [a] | 0 | 1 (10.0%) | 1 (8.3%) | 4 (50.0%) | 4 (50.0%) | 3 (42.9%) | 13 (23.6%) |
| Withdrawal of consent | 1 (10.0%) | 2 (20.0%) | 3 (25.0%) | 3 (37.5%) | 4 (50.0%) | 1 (14.3%) | 14 (25.5%) |
| Death | 9 (90.0%) | 4 (40.0%) | 8 (66.7%) | 1 (12.5%) | 0 | 3 (42.9%) | 25 (45.5%) |
| Lost to follow-up | 0 | 3 (30.0%) | 0 | 0 | 0 | 0 | 3 (5.5%) |

Q2W = every 2 weeks. The denominator for all percentages is the number of subjects enrolled and treated in each group. [a] Subjects completed the protocol-defined end of study if they were on study at the time of study termination.

**Table 7: related adverse events for treatment of human patients administered varying MEDI0562 doses Q2W**

| Subjects[a] | MEDI0562 dose Q2W (mg/kg), n (%) | | | | | | Total N = 55 |
|---|---|---|---|---|---|---|---|
| | 0.03 N = 10 | 0.1 N = 10 | 0.3 N = 12 | 1.0 N = 8 | 3.0 N = 8 | 10.0 N = 7 | |
| Any event | 10 (100%) | 10 (100%) | 11 (91.7%) | 8 (100%) | 6 (75%) | 7 (100%) | 52 (94.5%) |
| Any drug-related event | 5 (50%) | 4 (40%) | 9 (75%) | 7 (87.5%) | 5 (63%) | 7 (100%) | 37 (67%) |
| Any ≥grade 3 event[b] | 6 (60%) | 5 (50%) | 10 (83%) | 4 (50%) | 1 (13%) | 5 (57%) | 30 (55%) |
| Any serious event | 4 (40%) | 3 (30%) | 7 (58%) | 3 (38%) | 2 (25%) | 3 (43%) | 22 (40%) |
| Any drug-related serious event | 0 | 0 | 2 (17%) | 1 (13%) | 0 | 0 | 3 (5.5%) |
| Any drug-related ≥grade 3 event[c] | 2 (20%) | 1 (10%) | 4 (33%) | 2 (25%) | 0 | 0 | 9 (16%) |
| Drug-related death (grade 5 severity[d]) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any event leading to drug discontinuation | 0 | 1 (10%) | 3 (25%) | 0 | 1 (13%) | 2 (29%) | 7 (13%) |
| Any drug-related event leading to drug discontinuation | 0 | 0 | 1 (8%) | 0 | 0 | 0 | 1 (2%) |

**[00140] Objective response.** For the As-treated Population, the objective response rate (ORR) based on an application of immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (N = 32, Response-evaluable Population) to investigator-assessed tumor measurements was 3.6% (2/55 subjects; 95% CI: 0.4%, 12.5%; Table 8). Two subjects (0.03 mg/kg MEDI0562 and 3.0 mg/kg MEDI0562) had a BOR of irPR observed at DA1. None of the subjects had an unconfirmed response. ORR in the Response-evaluable Population was 4.0% (2/50 subjects; 95% CI: 0.5%, 13.7%).

**Table 8: Disease Response Based on Application of irRECIST to Investigator-assessed Tumor Measurements (As-treated Population)**

| | MEDI0562 0.03 mg/kg Q2W (N = 10) | MEDI0562 0.1 mg/kg Q2W (N = 10) | MEDI0562 0.3 mg/kg Q2W (N = 12) | MEDI0562 1.0 mg/kg Q2W (N = 8) | MEDI0562 3.0 mg/kg Q2W (N = 8) | MEDI0562 10.0 mg/kg Q2W (N = 7) | Total (N = 55) |
|---|---|---|---|---|---|---|---|
| OR, n (%) [a] | 1 (10.0%) | 0 | 0 | 0 | 1 (12.5%) | 0 | 2 (3.6%) |
| 95% CI | (0.3%, 44.5%) | (0.0%, 30.8%) | (0.0%, 26.5%) | (0.0%, 36.9%) | (0.3%, 52.7%) | (0.0%, 41.0%) | (0.4%, 12.5%) |
| | | | | | | | |
| Best overall response, n (%) | | | | | | | |
| irCR | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| irPR | 1 (10.0%) | 0 | 0 | 0 | 1 (12.5%) | 0 | 2 (3.6%) |
| irSD | 2 (20.0%) | 5 (50.0%) | 4 (33.3%) | 2 (25.0%) | 4 (50.0%) | 5 (71.4%) | 22 (40.0%) |
| irPD | 5 (50.0%) | 4 (40.0%) | 6 (50.0%) | 4 (50.0%) | 0 | 0 | 19 (34.5%) |
| Non-evaluable | 2 (20.0%) | 1 (10.0%) | 2 (16.7%) | 2 (25.0%) | 3 (37.5%) | 2 (28.6%) | 12 (21.8%) |
| | | | | | | | |
| Median time to response (months) [b] | 1.9 | NA | NA | NA | 1.8 | NA | 1.9 |
| 95% CI | NA | NA | NA | NA | NA | NA | (1.8, 1.9) |
| (Min - Max) | (1.9 - 1.9) | NA | NA | NA | (1.8 - 1.8) | NA | (1.8 - 1.9) |
| | | | | | | | |
| Median DoR (months) [b] | 3.7 | NA | NA | NA | 3.7 | NA | 3.7 |
| 95% CI | NA | NA | NA | NA | NA | NA | NA |
| (Min - Max) | (3.7 - 3.7) | NA | NA | NA | (3.7 - 3.7) | NA | (3.7 - 3.7) |
| | | | | | | | |
| DC-8, n (%) [c] | 3 (30.0%) | 4 (40.0%) | 4 (33.3%) | 2 (25.0%) | 5 (62.5%) | 5 (71.4%) | 23 (41.8%) |
| 95% CI | (6.7%, 65.2%) | (12.2%, 73.8%) | (9.9%, 65.1%) | (3.2%, 65.1%) | (24.5%, 91.5%) | (29.0%, 96.3%) | (28.7%, 55.9%) |

**[00141] Change in tumor size.** Figure 16 illustrates the best percent change from baseline in tumor burden based on irRECIST. Two subjects had a significant reduction in tumor burden, one subject receiving 0.03 mg/kg MEDI0562 and one subject receiving 3.0 mg/kg MEDI0562.

**[00142] Disease control rate (DCR).** For the As-treated Population, DCR $\geq$ 8 weeks was 41.8% (23/55 subjects; 95% CI: 28.7%, 55.9%) (Table 11). DCR $\geq$ 8 weeks was achieved by 2 subjects in the 1.0 mg/kg MEDI0562 cohort, 3 subjects in the 0.03 mg/kg MEDI0562 cohort, 4 subjects in each of the 0.1 and 0.3 mg/kg MEDI0562 cohorts, and 5 subjects in each

of the 3.0 and 10.0 mg/kg MEDI0562 cohorts. For the Response-evaluable Population, DCR ≥ 8 weeks was 46.0% (23/50 subjects; 95% CI: 31.8%, 60.7%).

**[00143] Progression-free Survival (PFS).** The median PFS based on an application of irRECIST to investigator-assessed tumor measurements for the As-treated Population was 3.1 months (95% CI: 1.8, 3.7 months; Table 9). Median PFS across the MEDI0562 cohorts ranged from 1.8 (in the 0.03 and 1.0 mg/kg MEDI0562 cohorts) to 7.4 months (in the 10 mg/kg MEDI0562 cohort). PFS rates at 3 months and 6 months were 52.7% (95% CI: 36.6%, 66.5%) and 25.3% (95% CI: 12.2%, 40.7%), respectively. Comparable results were observed for PFS when censored prior to subsequent anticancer treatment (median PFS 3.4 months; 95% CI: 1.8, 3.7 months).

**Table 9: Progression-free Survival Based on Application of irRECIST to Investigator-assessed Tumor Measurements (As-treated Population)**

| | MEDI0562 0.03 mg/kg Q2W (N = 10) | MEDI0562 0.1 mg/kg Q2W (N = 10) | MEDI0562 0.3 mg/kg Q2W (N = 12) | MEDI0562 1.0 mg/kg Q2W (N = 8) | MEDI0562 3.0 mg/kg Q2W (N = 8) | MEDI0562 10.0 mg/kg Q2W (N = 7) | Total (N = 55) |
|---|---|---|---|---|---|---|---|
| PFS (months) | | | | | | | |
| Number of events | 6 | 7 | 9 | 6 | 3 | 1 | 32 |
| Median PFS [a] | 1.8 | 3.0 | 1.9 | 1.8 | 4.6 | 7.4 | 3.1 |
| 95% CI | (1.4, NA) | (0.8, 3.6) | (1.8, 3.4) | (1.8, 7.4) | (3.7, NA) | (NA, NA) | (1.8, 3.7) |
| (Min, Max) | (1.4, 5.6) | (0.8, 7.4) | (1.3, 4.6) | (1.8, 7.4) | (2.8, 10.3) | (1.9, 7.4) | (0.8, 10.3) |
| | | | | | | | |
| PFS at 3 months [a] | 37.5% | 46.7% | 30.3% | 33.3% | 100% | 100% | 52.7% |
| At risk | 3 | 3 | 3 | 2 | 4 | 4 | 19 |
| 95% CI | (8.7%, 67.4%) | (11.5%, 76.5%) | (7.2%, 58.2%) | (4.6%, 67.6%) | 0 | 0 | (36.6%, 66.5%) |
| | | | | | | | |
| PFS at 6 months [a] | 0 | 15.6% | 0 | 16.7% | 25% | 100% | 25.3% |
| At risk | 0 | 1 | 0 | 1 | 1 | 1 | 4 |
| 95% CI | 0 | (0.8%, 49.1%) | 0 | (0.8%, 51.7%) | (0.9%, 66.5%) | 0 | (12.2%, 40.7%) |

CI = confidence interval; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; Min = minimum; Max = maximum; PFS = progression-free survival; Q2W = every 2 weeks.

[a] Median PFS and PFS at 3 and 6 months were assessed via Kaplan-Meier methods.

**[00144] Overall Survival (OS).** The median OS for the As-treated Population was 10.4 months (95% CI: 7.4, not applicable months; Table 10). OS rates at 3, 6, 9, and 12 months were 89.2% (95% CI: 76.0%, 95.4%), 70.2% (95% CI: 54.1%, 81.5%), 57.2% (95% CI: 40.8%, 70.7%), and 46.6% (95% CI: 30.7%, 61.0%), respectively.

**Table 10: Overall Survival (As-treated Population)**

| | MEDI0562 0.03 mg/kg Q2W (N = 10) | MEDI0562 0.1 mg/kg Q2W (N = 10) | MEDI0562 0.3 mg/kg Q2W (N = 12) | MEDI0562 1.0 mg/kg Q2W (N = 8) | MEDI0562 3.0 mg/kg Q2W (N = 8) | MEDI0562 10.0 mg/kg Q2W (N = 7) | Total (N = 55) |
|---|---|---|---|---|---|---|---|
| OS (months) | | | | | | | |
| Number of events | 9 | 4 | 8 | 1 | 0 | 3 | 25 |
| Median OS [a] | 6.7 | 9.9 | 6.1 | 0 | 0 | 0 | 10.4 |
| 95% CI | (2.1, 10.4) | (3.1, NA) | (3, 18.9) | (9.8, NA) | (NA, NA) | (1.3, NA) | (7.4, NA) |
| (Min, Max) | (2.1, 13.8) | (1, 22.2) | (1.3, 18.9) | (0.6, 24) | (1, 20.4) | (1.3, 17.1) | (0.6, 24) |
| | | | | | | | |
| OS at 3 months [a] | 80% | 100% | 81.5% | 100% | 100% | 85.7% | 89.2% |
| At risk | 8 | 6 | 8 | 6 | 5 | 6 | 39 |
| 95% CI | (40.9%, 94.6%) | 0 | (43.5%, 95.1%) | 0 | 0 | (33.4%, 97.9%) | (76%, 95.4%) |
| | | | | | | | |
| OS at 6 months [a] | 50% | 66.7% | 58.2% | 100% | 100% | 71.4% | 70.2% |
| At risk | 4 | 4 | 5 | 6 | 4 | 5 | 28 |
| 95% CI | (18.4%, 75.3%) | (19.5%, 90.4%) | (22.4%, 82.2%) | 0 | 0 | (25.8%, 92%) | (54.1%, 81.5%) |
| | | | | | | | |
| OS at 9 months [a] | 37.5% | 50% | 34.9% | 100% | 100% | 57.1% | 57.2% |
| At risk | 3 | 3 | 3 | 5 | 4 | 4 | 22 |
| 95% CI | (9.9%, 65.9%) | (11.1%, 80.4%) | (8.4%, 64%) | 0 | 0 | (17.2%, 83.7%) | (40.8%, 70.7%) |
| | | | | | | | |
| OS at 12 months [a] | 12.5% | 50% | 23.3% | 80% | 100% | 57.1% | 46.6% |
| At risk | 1 | 2 | 2 | 4 | 3 | 3 | 15 |
| 95% CI | (0.7%, 41.8%) | (11.1%, 80.4%) | (3.6%, 52.9%) | (20.4%, 96.9%) | 0 | (17.2%, 83.7%) | (30.7%, 61%) |

CI = confidence interval; Min = minimum; Max = maximum; OS = overall survival; Q2W = every 2 weeks.

[a] Median OS and OS at 3, 6, 9 and 12 months were assessed via Kaplan-Meier methods.

**[00145]** **Pharmacodynamics.** For the As-treated Population, the mean percentages of Ki67+CD4+ and Ki67+CD8+ memory T cells in the peripheral blood were plotted over time by dose cohort (Figures 17A and 17B). At doses of 0.03 to 10.0 mg/kg MEDI0562 IV Q2W, the mean percentage of Ki67+CD4+/CD8+ memory T cells increased following the first dose. The mean peak percentages of Ki67+CD4+ and Ki67+CD8+ memory T cells increased by approximately 1.5 fold to 3 fold compared to the respective baselines.

**[00146]** In all available tumor biopsy samples, PD-L1+ cell and CD8+ TIL densities were reported pre- and post-MEDI0562. Samples collected at screening demonstrated a range of

PD-L1+ cell and CD8+ TIL densities, from 0 to 1400 cells/mm$^2$ and 0 to 2000 cells/mm$^2$, respectively. This type of variability is consistent with that reported for both immune markers (*see* Steele et al., 2018, J. Immunother. Cancer. 6:20; Rebelatto et al., 2016, Diagn. Pathol. 11:95). A subset of all enrolled patients provided post-treatment biopsy samples that were evaluable (n = 14 across 5 dose levels). As seen in Figures 18A and 18B, some subjects demonstrated an increase in the density of PD-L1+ cells and CD8+ TILs compared to the baseline pre-treatment biopsies; however, some subjects had decreased numbers of PD-L1+ cells or CD8+ TILs, or no significant change. No dose-dependent response was evident, which was not unexpected given the low number of patients ($\leq$ 3 patients) having evaluable post-treatment biopsies at each dose level. However, the increase observed in CD8+ TILs and PD-L1 densities in a subset of patients indicated that MEDI0562 was active and able to modify the tumor microenvironment in a manner consistent with its mechanism of action.

**[00147] T cell effects.** MEDI0562 at varying doses was shown to reduce the number of OX40+FOXP3+ T cells indicating a reduction in Tregs in tumors in a dose dependent manner (Figures 21A-101C). Treatment with varying doses of MEDI0562 also demonstrated increased T effector cell function across all doses of MEDI0562 in tumors and the T effector:T regulatory cell ratio increased in tumors at higher doses of MEDI0562 monotherapy (Figures 22A-22C). Human patients with high exposure to MEDI0562 and/or high baseline of OX40 levels exhibited dual mechanisms of action on T cells by increasing T-cell effector function as well as decreasing Tregs in tumors (Figures 23A-23C).

**Pharmacogenomics.** Pharmacogenomics analysis of patterns of gene expression consistent with immune activation was conducted and the results are illustrated in Figure 24. MEDI0562 at varying doses was shown to increase expression of PD-L1, T effector cell signature, T effector cell/ T regulatory cell ratio, CXCL9, and interferon-gamma signature in whole blood within one week of treatment. Increased expression of these genes and signatures indicate increased immune function and increased effector capabilities of circulating T cells, as seen for tumor T cells. A dose-dependent decrease in OX40 gene expression in circulating blood cells was also observed within one week of MEDI0562 treatment. This was similarly shown by flow cytometry analysis. Although not explicitly tested, this decrease may reflect OX40+ cells moving from peripheral blood to the tumor.

**[00148] Pharmacokinetics (PK).** For subjects in the As-treated Population, mean concentration-time profiles of serum MEDI0562 following the first dose and multiple Q2W doses are plotted by dose cohort in Figure 19A and 19B, respectively. The PK parameters for

MEDI0562 following the first dose were calculated using non-compartmental analysis and were summarized by dose cohort (Table 11).

**[00149]** Following IV infusion of 0.03 to 10 mg/kg MEDI0562, peak serum MEDI0562 concentrations were reached immediately after dosing. Thereafter, the serum concentrations declined in a biexponential manner (Figure 19A). Following multiple Q2W dosing, MEDI0562 serum concentrations were maintained, with the exception of the 0.03 mg/kg MEDI0562 cohort, and no or minimal accumulation was observed (Figure 19B).

**[00150]** Following IV infusion of 0.03 to 10 mg/kg MEDI0562, $C_{max}$ increased from 0.957 to 193 μg/mL, and the area under the concentration-time curve from time 0 to the time of last quantifiable concentration ($AUC_{last}$) during the first dosing interval increased from 3.11 to 823 μg*day/mL at 0.03 to 10 mg/kg, after the first dose (Table 11). The increases in $C_{max}$ and $AUC_{last}$ were proportional to dose. The serum clearance was 0.483 to 0.808 L/day and terminal half-life was 3.81 to 5.92 days.

**Table 11: MEDI0562 Pharmacokinetic Parameters Summary after First Dose (As-treated Population)**

| Dose | | $C_{max}$ (µg/mL) | $T_{max}$ (day) | $AUC_{last}$ (day*µg/mL) [a] | $T_{last}$ (day) | $AUC_{inf}$ (day*µg/mL) | AUC %Extrap (%) | CL (L/day) | $V_z$ (L) | $V_{ss}$ (L) | $T_{1/2}$ (day) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.03 mg/kg | N | 10 | 10 | 10 | 10 | 8 | 8 | 8 | 8 | 8 | 8.00 |
| | Mean | 0.957 | 0.108 | 3.11 | 10.1 | 4.12 | 11.6 | 0.705 | 3.61 | 3.57 | 3.81 |
| | SD | 0.478 | 0.0750 | 2.68 | 5.39 | 3.13 | 4.99 | 0.418 | 2.09 | 2.10 | 1.07 |
| 0.1 mg/kg | N | 10.0 | 10.0 | 10.0 | 10.0 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| | Mean | 2.43 | 0.102 | 10.1 | 11.9 | 14.5 | 16.1 | 0.483 | 3.77 | 3.70 | 5.49 |
| | SD | 0.447 | 0.118 | 4.62 | 5.57 | 3.43 | 5.08 | 0.122 | 0.847 | 0.803 | 0.835 |
| 0.3 mg/kg | N | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| | Mean | 6.33 | 0.0661 | 23.4 | 13.5 | 27.9 | 13.3 | 0.808 | 4.55 | 4.52 | 4.36 |
| | SD | 1.77 | 0.0230 | 9.97 | 2.06 | 14.6 | 10.3 | 0.299 | 1.65 | 1.60 | 1.91 |
| 1.0 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | Mean | 22.5 | 0.0879 | 115 | 13.2 | 147 | 20.1 | 0.524 | 4.12 | 4.04 | 5.80 |
| | SD | 4.62 | 0.0374 | 36.8 | 2.56 | 53.2 | 5.26 | 0.178 | 1.08 | 1.04 | 1.67 |
| 3.0 mg/kg | N | 8 | 8 | 8 | 8 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 59.3 | 0.0716 | 279 | 14.0 | 363 | 20.5 | 0.767 | 6.37 | 6.29 | 5.92 |
| | SD | 12.9 | 0.0322 | 68.3 | 0.0794 | 119 | 5.20 | 0.296 | 2.17 | 1.76 | 1.12 |
| 10.0 mg/kg | N | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | Mean | 193 | 0.141 | 823 | 13.0 | 1040 | 20.6 | 0.755 | 5.57 | 5.52 | 5.53 |
| | SD | 63.4 | 0.0803 | 269 | 2.59 | 350 | 8.18 | 0.290 | 1.07 | 0.991 | 1.54 |

AUC%Extrap = extrapolated area under the concentration versus time curve expressed as percent of the total AUCinf; AUClast = area under the concentration-time curve from the start of dosing to the time of the last quantifiable concentration; AUCinf = area under the concentration time curve from the start of dosing to infinity; CL = systemic clearance; Cmax = maximum concentration; SD = standard deviation; T1/2 = terminal elimination half-life; Tlast = time of last quantifiable concentration; Tmax = time to maximum concentration; Vss = volume of distribution at steady state; Vz = volume of distribution during terminal phase.

For parameters dependent on terminal phase (ie, AUCinf, AUC%Extrap, CL, T1/2, Vz, Vss), subjects who had insufficient data to calculate the terminal slope or with AUC%Extrap > 30% were excluded from the calculation of summary statistics. All PK parameters were rounded to 3 significant figures.

[a] $AUC_{Day1-Day15}$ is reported as $AUC_{last}$ following the first dose.

**[00151] Immunogenicity.** Anti-drug antibodies (ADAs) against MEDI0562 at baseline were detected in 3/54 (5.6%) subjects who had a baseline ADA sample (one subject in each of the 0.1, 1.0, and 10.0 mg/kg MEDI0562 dose cohorts). ADAs against MEDI0562 post-baseline were detected in all dose cohorts. Of the 51 subjects who had an ADA sample post-baseline, 26 (51.0%) subjects had a positive ADA result post-baseline (4 [50%], 3 [33.3%], 7 [58.3%], 6 [85.7%], 3 [37.5%], and 3 [42.9%] at 0.03, 0.1, 0.3, 1.0, 3.0, and 10 mg/kg MEDI0562, respectively). No apparent trend was observed between dose level and ADA

incidence rate; note, however, that the sample sizes in each dose cohort were too small for a meaningful comparison. Among the 26 subjects who had ADA detected post-baseline, 24 subjects had persistent positive ADA responses (i.e., positive at ≥ 2 post-baseline assessments, with ≥ 16 weeks between first and last positive, or positive at last post-baseline assessment); the remaining 2 subjects had a transient positive ADA response.

**[00152]** The impact of ADA on MEDI0562 PK was observed at all doses less than 3 mg/kg (Figure 20). In the 3 and 10 mg/kg MEDI0562 cohorts, no apparent impact of ADA was observed on the PK of MEDI0562. There was no correlation between the presence of ADAs and safety or efficacy findings.

**[00153]** **Adverse events.** A total of 53 (96.4%) subjects had at least one treatment-emergent adverse event (TEAE), and 37 (67.3%) subjects had at least one TEAE considered to be related to MEDI0562 (Table 12). TEAEs ≥ Grade 3 were experienced by 33 (60.0%) subjects; 8 (14.5%) subjects had ≥ Grade 3 events that were considered to be related to MEDI0562. A total of 24 (43.6%) subjects experienced a serious adverse event (SAE); 2 (3.61%) subjects experienced SAEs considered to be related to MEDI0562. Four (7.3%) subjects had TEAEs that led to discontinuation of MEDI0562. There was one death with a contributing AE in the study, which was not considered to be related to MEDI0562. Eight (14.5%) subjects had at least one infusion-related reaction, all of which were considered to be related to MEDI0562. All infusion-related reactions were non-serious, low grade, and did not result in discontinuation of MEDI0562.

**[00154]** A total of 53 (96.4%) subjects had at least one TEAE (Table 12). TEAEs were most frequently reported (> 40% subjects overall) in the SOCs of General Disorders and Administration Site Conditions (32 [58.2%] subjects) and Gastrointestinal Disorders, and Metabolism and Nutrition Disorders (23 [41.8%] subjects each). The most frequently reported TEAEs regardless of causality (occurring in ≥ 20% of subjects overall) were fatigue, nausea, and hyponatremia.

## 7. Discussion

**[00155]** The study described above was a FTIH Phase 1, multicenter, open-label, single-arm, dose-escalation, and dose-expansion study of MEDI0562 to evaluate the safety, tolerability, PK, immunogenicity, pharmacodynamics, and preliminary antitumor activity of MEDI0562 administered as a single agent in adult subjects with selected advanced solid tumors.

**[00156]** Two subjects (one in each of the 0.03 mg/kg and 3.0 mg/kg MEDI0562 cohorts) had a BoR of irPR; all other subjects who were evaluable for efficacy had a BoR of either irSD or irPD. The sensitivity analysis was supportive of the main analysis and the irRECIST data was comparable with the RECIST v1.1 analysis. The lack of efficacy with MEDI0562 contributed to the sponsor's decision to discontinue the study and to focus further MEDI0562 development as part of a combination therapy.

**[00157]** MEDI0562 exhibited linear PK with a mean serum clearance of 0.483 to 0.808 L/day and terminal half-life of 3.81 to 5.92 days. Treatment with MEDI0562 increased percentages of Ki67+CD4+ and Ki67+CD8+ memory T cells in the peripheral blood. Treatment with MEDI0562 also increased CD8+ T cell and PD-L1 densities in the tumors of a subset of patients. The small number of evaluable pre/post-treatment biopsies coupled with patient heterogeneity limited the ability to observe a dose-dependent change in these immune markers post-MEDI0562. ADAs against MEDI0562 were detected in 51.0% of subjects post-baseline, and the impact of ADAs on MEDI0562 PK was observed at all doses less than 3 mg/kg.

**[00158]** MEDI0562 was reasonably well tolerated, considering the patient population. At least one Grade 3 or 4 TEAE was reported in 33 (60.0%) of 55 subjects; 1 [1.8%] subject had a Grade 5 TEAE; 4 (7.3%) subjects had TEAEs that led to permanent discontinuation of MEDI0562. Twenty-four of the 25 deaths that occurred during the study were due to the disease under study. The MAD was identified as 10 mg/kg; this dose as monotherapy was considered safe and tolerable.

**[00159]** Overall, MEDI0562 was reasonably well tolerated in the study population. The MAD was 10 mg/kg. No dose-response relationship was observed between MEDI0562 and the emergence of AEs. Two subjects (one in each of the 0.03 mg/kg and 3.0 mg/kg MEDI0562 cohorts) had a BoR of irPR; all other subjects who were evaluable for efficacy had a BoR of either irSD or irPD. Peak serum MEDI0562 concentrations were reached immediately following IV infusion and declined thereafter in a biexponential manner. Serum MEDI0562 concentrations increased in a dose-proportional manner. The serum clearance was 0.483 to 0.808 L/day and terminal half-life was 3.81 to 5.92 days. ADAs against MEDI0562 were detected in approximately half of subjects with ADA results post-baseline. The impact of ADA on MEDI0562 PK was observed at all doses less than 3 mg/kg.

## Example 4. Dosing of MEDI0562 and Durvalumab or Tremelimumab Combination Therapy

**[00160]** The mouse studies described above demonstrated that combination treatment of tumor-bearing mice with OX86 mIgG2 and anti-CTLA-4, anti-PD-1, and/or anti-PD-L1 resulted in anti-tumor activity that reduced growth of multiple tumors. The positive mouse data were used as the rationale for conducting a human clinical trial using MEDI0562/durvalumab combination therapy and MEDI0562/tremelimumab combination therapy for the treatment of tumors.

**1. Design of the Study**

**[00161]** The study was a Phase 1, multicenter, open-label study of MEDI0562 in combination with immune therapeutic agents to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and antitumor activity in adult subjects with advanced solid tumors, excluding primary CNS tumors and hematologic malignancies.

**[00162]** The study included two phases, dose escalation and dose expansion, with two treatment arms in each phase: MEDI0562/durvalumab combination therapy (Arm A) and MEDI0562/tremelimumab combination therapy (Arm B). Subjects remained on treatment until unacceptable toxicity, progressive disease (PD), or development of other reason for treatment discontinuation. The study flow diagrams for Arms A and B are illustrated in Figures 26 and 27. The following abbreviations and legends are used to describe the study flow diagram illustrated in Figures 26 and 22: Approx = approximately; CNS = central nervous system; DLT = dose-limiting toxicity; EXP = expansion; HCC = hepatocellular carcinoma; IMT- = immunotherapy; MAD = maximum administered dose; MEL = melanoma; MSS CRC = microsatellite stable colorectal cancer; MTD = maximum tolerated dose; NSCLC = non-small-cell lung cancer; PD-L1+ = programmed death ligand 1 positive; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; ref = refractory; rel = relapsed; SCCHN = squamous cell carcinoma of head and neck. (a) Enrollment in Arm A and Arm B will proceed at least 2 dose-level cohorts below the actively enrolling monotherapy dose-escalation cohort in Study D6060C00001. As of Study D6060C00002 Protocol Amendment 2, Study D6060C00001 completed MEDI0562 monotherapy dose escalation without reaching the MTD; the MAD was 10 mg/kg MEDI0562 (or 750 mg for a 75-kg individual) via intravenous infusion Q2W. (b) Any dose level evaluated through the DLT-evaluation period that did not exceed the MTD can be expanded to a total of 18 subjects (pharmacodynamics expansion). (c) The selection of dose level to be utilized during the dose-expansion phase will be made by the dose-escalation committee, with the limitation that the dose level will not exceed the applicable MTD or MAD. (d) If the MTD is not exceeded in

Cohort B-a1 and based on observed PK, pharmacodynamic, safety, and clinical activity, concurrent dose-escalation ofMEDI0562 in combination with 75 mg tremelimumab may be initiated.

**[00163]** Subjects were treated in either Arm A or Arm B within the dose-escalation or dose-expansion phase of the study. MEDI0562 was administered first as an IV infusion over approximately 60 to 90 minutes, followed by durvalumab or tremelimumab approximately 50 minutes after the end of MEDI0562 infusion. Durvalumab and tremelimumab was administered over approximately 1 hour. The dosing schedule is illustrated in Figure 23.

**[00164]** All subjects were evaluated regularly and their clinical status classified according to RECIST Version 1.1 until confirmed radiologic PD. All subjects were followed for survival until the end of study (3 years after the final subject is entered into the study or when the sponsor stops the study, whichever occurs earlier).

## 2. Patients and Methods

**[00165]** Subjects in this study included adult subjects, ≥ 18 years of age, with advanced solid tumors relapsed following or refractory to standard therapy and have not received more than 3 prior lines of systemic therapy for recurrent or metastatic disease (including both standard of care and investigational therapies). Subjects in the dose-escalation phase had histologic documentation of advanced solid tumors, excluding primary CNS tumors and hematologic malignancies. Subjects in the dose-expansion phase had recurrent or metastatic disease for the following tumor types based on treatment arm as described below: (i) Arm A: UC, MSS, CRC, NSCLC, or SCCHN; (ii) Arm B: HCC or MEL.

**[00166]** All subjects were required to have at least 1 lesion that was measurable using RECIST guidelines, an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 as well as adequate organ function. Adequate organ function was defined as: absolute neutrophil count ≥ 1,000/$mm^3$; absolute lymphocyte count ≥ 500/$mm^3$; platelet count ≥ 100,000/ $mm^3$; hemoglobin ≥ 9.0 g/dL; creatinine clearance or 24-hour urine CrCl > 50 mL/min as determined by the Cockcroft-Gault formula; total bilirubin ≤ 1.5 × ULN except in the case of subjects with documented or suspected Gilbert's disease (for these subjects, bilirubin must be ≤ 3 × ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) (AST/ALT can be up to 5 × ULN in the presence of liver metastasis, but cannot be associated with concurrent elevated bilirubin); and potassium, sodium, magnesium, and calcium (corrected for serum albumin) ≤ Grade 1 or within the

institutional ranges of normal. Subjects with CNS metastases must have been treated and must be asymptomatic at day 1 of the study.

**[00167]** Subjects were excluded from participation in the study if administered prior treatment with a TNFRSF agonist, prior treatment with IMT for subjects with UC, a history of severe allergic reactions to any unknown allergens or any components of the study drug formulations, active or prior documented autoimmune disease within the past 2 years, unresolved toxicities from prior anticancer therapy, use of a systemic therapeutic anticoagulation or daily aspirin dose exceeding 325 mg/per day, current or prior use of immunosuppressive medication within 14 days prior to the first dose of MEDI0562, a history of primary immunodeficiency, solid organ transplantation, tuberculosis or active infection with human immunodeficiency virus (HIV) or hepatitis B or C, receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational product, had major surgery within 28 days prior to first dose of MEDI0562 or still recovering from prior surgery, invasive malignancy within the previous 2 years, or uncontrolled intercurrent illness.

**[00168]** Subjects were not permitted to have any conventional or investigational anticancer therapy within 28 days prior to the first dose of MEDI0562 and durvalumab or tremelimumab combination treatment, concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, but concurrent use of hormones for non-cancer related conditions and local palliative treatment of lesions was allowed.

### 3. Dose Escalation

**[00169]** The dose-escalation phase enrolled subjects with previously treated advanced solid tumors, excluding those with primary CNS tumors or hematologic malignancies. Enrollment began with the first dose-level cohort in Arm A, followed immediately with enrollment in the first dose-level cohort of Arm B. Enrollment into both Arm A and Arm B proceeded such that the dose level of MEDI0562 administered did not exceed the MEDI0562 monotherapy dose. Arm A and Arm B dose escalation proceeded independently.

**[00170]** In Arm A, sequential cohorts of 3 to 6 subjects each received 1 of 6 dose levels of MEDI0562 (2.25, 7.5, 22.5, 75, 225, or 750 mg) Q2W in combination with 1500 mg durvalumab every 4 weeks (Q4W) via IV infusion, unless the MEDI0562 MTD was reached before all dose-escalation cohorts was completed. If the MTD was exceeded at the 1500 mg durvalumab dose level in combination with MEDI0562, a lower dose level of 750 mg durvalumab was explored.

**[00171]** In Arm B, sequential cohorts of 3 to 6 subjects each received 1 of 6 dose levels of MEDI0562 (2.25, 7.5, 22.5, 75, 225, or 750 mg) Q2W and 1 of 3 dose levels of tremelimumab (75, 225, or 750 mg) via IV infusion, unless the MEDI0562 MTD was reached before all dose-escalation cohorts were completed (Arm B-a). The first cohort of subjects received 2.25 mg MEDI0562 and 75 mg tremelimumab. Dose escalation proceeded initially with 2.25 mg MEDI0562 and increasing dose levels of tremelimumab. Once the MTD/MAD of tremelimumab in combination with 2.25 mg MEDI0562 was reached, subsequent dose escalation was initiated with the aforementioned dose levels of MEDI0562 (7.5, 22.5, 75, 225, and 750 mg) Q2W in combination with the MTD/MAD of tremelimumab. Tremelimumab was administered Q4W for 4 doses only in combination with MEDI0562 Q2W followed by monotherapy MEDI0562 Q2W thereafter.

**[00172]** If the MTD was not exceeded at the first dose-level cohort of 2.25 mg MEDI0562 in combination with 75 mg tremelimumab and based on observed PK, pharmacodynamic, safety, and clinical activity, concurrent dose escalation was initiated with escalating doses of MEDI0562 (7.5, 22.5, 75, 225, and 750 mg) Q2W in combination with 75 mg tremelimumab (Arm B-b). Tremelimumab was administered Q4W for 4 doses only in combination with MEDI0562 Q2W followed by monotherapy MEDI0562 Q2W thereafter. If enrollment was initiated in Arm B-b, dose escalation proceeded independently between the 2 dose-escalation pathways (Arm B-a and Arm B-b). The 2 dose-escalation pathways permitted determination of an MTD/MAD of MEDI0562 in combination with 75 mg tremelimumab.

**[00173]** Ongoing surveillance of pharmacodynamic, PK, safety, and antitumor activity data was performed throughout the dose-escalation phase.

**4. Dose Expansion**

**[00174]** Independent dose expansion of Arm A and Arm B was initiated following completion of the dose-escalation phase in the respective arm.

**[00175]** Arm A of the dose-expansion phase began with enrollment in the urothelial carcinoma (UC) cohort, and proceeded with enrollment in up to 5 additional tumor-type cohorts. The UC cohort included approximately 40 immunotherapy (IMT)-naive first-line cisplatin-ineligible UC subjects. Following initiation of the UC cohort in Arm A, up to 5 additional expansion cohorts, with up to 40 subjects each, IMT-naive/PD-L1 high non-small-cell lung cancer (NSCLC), IMT-refractory NSCLC, IMT-relapsed NSCLC, or IMT-pretreated squamous cell carcinoma of the head and neck (SCCHN) was initiated. In the event of observed antitumor activity and any correlation with potential predictive biomarkers

in these initial 40 subjects with UC, enrollment of additional UC subjects according to molecular features of their tumors was initiated through a protocol amendment.

**[00176]** Arm B of the dose-expansion phase included up to 2 tumor-type cohorts, with up to 40 subjects each. Enrollment began in the cohort of IMT-pretreated, unresectable hepatocellular carcinoma (HCC) subjects. Following initiation of the HCC cohort in Arm B, an additional expansion cohort of IMT-pretreated melanoma (MEL) subjects was initiated.

**[00177]** The selection of dose level and treatment schedule to be utilized during the dose-expansion phase was made by the dose-escalation committee, with the limitation that the dose level did not exceed the applicable MTD or MAD. Factors to be considered when selecting the dose level included PK, safety, and comparative pharmacodynamic effects. In Arm B, only a single MEDI0562/tremelimumab dose-level combination was explored in dose expansion. If Arm B-b was initiated, the dose level for the dose-expansion phase was selected based on assessment of both dose-escalation pathways. The selected dose level of MEDI0562 for expansion may have differed between Arm A and Arm B, however, the MEDI0562 dose level in either arm did not exceed the MEDI0562 MTD/MAD, and may have included an alternate lower dose.

### 5. Pharmacokinetic, Antitumor, and Safety Assessments

**[00178]** Assessment of antitumor activity will include best overall response, objective response (OR), disease control (DC), time to response (TTR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and the percent change from baseline in target lesion sum of diameters. RECIST Version 1.1 will be used for assessment of tumor response.

**[00179]** The PK of MEDI0562 and durvalumab or tremelimumab will be assessed by individual MEDI0562, durvalumab, and tremelimumab concentrations at different time points after administration. PK parameters that may be modeled on these data include but are not limited to Cmax, area under the concentration-time curve (AUC), CL, and t½.

**[00180]** The endpoints for assessment of immunogenicity of MEDI0562, durvalumab, and tremelimumab include the number and percentage of subjects who develop detectable antidrug antibodies. The endpoints for assessment of pharmacodynamic activity include induction of Ki67 on peripheral cluster of differentiation (CD)4+ and CD8+ memory T-cell populations.

**[00181]** The safety evaluation was based on the presence of adverse event (AE), serious adverse event (SAE), DLT, abnormal laboratory parameter, vital sign, and electrocardiogram results.

## 6. Results

**[00182]** Twenty-two subjects were treated with MEDI0562 in combination with durvalumab (Arm A, 13 subjects) or tremelimumab (Arm B, 9 subjects). Arm A included 3 subjects in Cohort A-1 (2.25 mg MEDI0562 + 1500 mg durvalumab), 5 subjects in Cohort A-2 (7.5 mg MEDI0562 + 1500 mg durvalumab), and 5 subjects in Cohort A-3 (22.5 mg MEDI0562 + 1500 mg durvalumab). Arm B included 5 subjects in Cohort B-a1 (2.25 mg MEDI0562 + 75 mg tremelimumab) and 4 subjects in Cohort B-a2 (2.25 mg MEDI0562 + 225 mg tremelimumab). Two DLTs were observed among these treated subjects: 1 subject in Cohort A-3 with neuroendocrine carcinoma experienced Grade 3 lipase that did not resolve within 3 days and was treated for autoimmune pancreatitis prior to disease progression, and 1 subject in Cohort B-a2 with colorectal carcinoma had pneumonitis.

**[00183]** To date, safety data is available for 10 subjects treated with MEDI0562 in combination with durvalumab or tremelimumab (3 subjects, Cohort A-1; 3 subjects, Cohort A-2; and 4 subjects, Cohort B-a1). Adverse events (AEs) have been reported in 8 of the 10 treated subjects.

**[00184]** Four subjects have experienced serious adverse events (SAEs); none of the SAEs were considered to be treatment-related. To date, PK and immunogenicity, and PD data are available from 19 subjects from 5 dose cohorts (2.25 mg MEDI0562 Q2W + 1500 mg durvalumab/75 mg tremelimumab/225 mg tremelimumab Q4W, 7.5 mg MEDI0562 Q2W+ 1500 mg durvalumab Q4W, and 22.5 mg MEDI0562 Q2W + 1500 mg durvalumab Q4W). The mean MEDI0562 concentration-time profiles are presented in Figure 29. Following IV infusion of 2.25 – 22.5 mg MEDI0562, serum MEDI0562 concentration increased approximately dose-proportionally (Figure 29). The MEDI0562 exposure were similar following combination therapy of 2.25 mg MEDI0562 with durvalumab or tremelimumab (Figure 24).

**[00185]** ADA was not detected at pre-dose day 1 in any subject. After treatment with MEDI0562 in combination with durvalumab or tremelimumab, 13 of 19 subjects tested positive for ADA against MEDI0562. Some of the ADA-positive subjects showed reduced exposure compared to ADA-negative subjects at the time ADA was detected, indicating impact of ADA on MEDI0562 PK.

**[00186]** The mean %Ki67+ CD4+ memory T cell, %Ki67+ CD8+ memory T cell and %OX40+ CD4+ memory T cells over time are shown in Figures 30A-30C. The mean %Ki67+ CD4+ memory T cell and %Ki67+ CD8+ memory T cell increased while %OX40+ CD4+ memory T cells decreased following the first IV dose of MEDI0562 in combination with durvalumab or tremelimumab (Figures 30A-30C).

**[00187]** While the invention has been described in terms of various embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the invention as claimed. In addition, the section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

**[00188]** Each embodiment herein described may be combined with any other embodiment or embodiments unless clearly indicated to the contrary. In particular, any feature or embodiment indicated as being preferred or advantageous may be combined with any other feature or features or embodiment or embodiments indicated as being preferred or advantageous, unless clearly indicated to the contrary.

**[00189]** All references cited in this application are expressly incorporated by reference herein.

**Table 12: Disclosed Sequences**

| SEQ ID NO: | Sequence | Description |
|---|---|---|
| 1 | DIQMTQSPSSLSASVGDRVTITCRASQDISNY LNWYQQKPGKAPKLLIYYTSKLHSGVPSRFSG SGSGTDYTLTISSLQPEDFATYYCQQGSALPW TFGQGTKVEIK | Light chain variable domain of MEDI0562 |
| 2 | QVQLQESGPGLVKPSQTLSLTCAVYGGSFSSG YWNWIRKHPGKGLEYIGYISYNGITYHNPSLK SRITINRDTSKNQYSLQLNSVTPEDTAVYYCA RYKYDYDGGHAMDYWGQGTLVTVSS | Heavy chain variable domain of MEDI0562 |
| 3 | SGYWN | CDRH1 of MEDI0562 |
| 4 | YISYNGITYHNPSLKS | CDRH2 of MEDI0562 |
| 5 | YKYDYDGGHAMDY | CDRH3 of MEDI0562 |
| 6 | RASQDISNYLN | CDRL1 of MEDI0562 |
| 7 | YTSKLHS | CDRL2 of MEDI0562 |
| 8 | QQGSALPWT | CDRL3 of MEDI0562 |
| 9 | EIVLTQSPGTLSLSPGERATLSCRASQRVSSS YLAWYQQKPGQAPRLLIYDASSRATGIPDRFS | Light chain variable domain of durvalumab |

| | | |
|---|---|---|
| | GSGSGTDFTLTISRLEPEDFAVYYCQQYGSLP WTFGQGTKVEIK | |
| 10 | EVQLVESGGGLVQPGGSLRLSCAASGFTFSRY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AREGGWFGELAFDYWGQGTLVTVSS | Heavy chain variable domain of durvalumab |
| 11 | GFTFSRYWMS | CDRH1 of durvalumab |
| 12 | NIKQDGSEKYYVDSVKG | CDRH2 of durvalumab |
| 13 | EGGWFGELAFDY | CDRH3 of durvalumab |
| 14 | RASQRVSSSYLA | CDRL1 of durvalumab |
| 15 | DASSRAT | CDRL2 of durvalumab |
| 16 | QQYGSLPWT | CDRL3 of durvalumab |
| 17 | PSSLSASVGDRVTITCRASQSINSYLDWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQYYSTPFTFGPGTK VEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKV | Light chain variable domain of tremelimumab |
| 18 | GVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARDPRGATL YYYYYGMDVWGQGTTVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVH | Heavy chain variable domain of tremelimumab |
| 19 | GFTFSSYGMH | CDRH1 of Tremelimumab |
| 20 | VIWYDGSNKYYADSV | CDRH2 of tremelimumab |
| 21 | TAVYYCARDPRGATLYYYYYGMDV | CDRH3 of tremelimumab |
| 22 | RASQSINSYLD | CDRL1 of tremelimumab |
| 23 | AASSLQS | CDRL2 of tremelimumab |
| 24 | QQYYSTPFT | CDRL3 of tremelimumab |

**WHAT IS CLAIMED IS:**

Claim 1. A method of treating a tumor in a human patient, comprising administering MEDI0562 to the patient.

Claim 2. The method of claim 1, wherein MEDI0562 is administered at a dose of 3 mg/kg.

Claim 3. The method of claim 1, wherein MEDI0562 is administered at a dose of 10 mg/kg.

Claim 4. The method of any one of claims 1-3, wherein MEDI0562 is administered every 14 to 28 days.

Claim 5. The method of claim 4, wherein MEDI0562 is administered every 14 days.

Claim 6. The method of claim 4, wherein MEDI0562 is administered every 28 days.

Claim 7. The method of any one of claims 1-6, wherein the administration of MEDI0562 results in a partial response.

Claim 8. The method of any one of claims 1-6, wherein the administration of MEDI0562 results in a complete response.

Claim 9. The method of any one of claims 1-6, wherein the tumor is a solid tumor.

Claim 10. The method of claim 9, wherein the solid tumor is squamous cell carcinoma of the head and neck, cervical cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, or urothelial bladder cancer.

Claim 11. The method of any one of claims 1-6, wherein the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Claim 12. A method of treating a solid tumor in a human patient, comprising administering 3 mg/kg of MEDI0562 to the patient.

Claim 13. A method of treating a tumor in a human patient, comprising administering MEDI0562 and an immune therapeutic agent to the patient.

Claim 14. The method of claim 13, wherein the immune therapeutic agent is durvalumab or tremelimumab.

Claim 15. The method of either of claims 13 or 14, wherein MEDI0562 is administered at a dose of 2.25 mg, 7.5 mg, 22.5 mg, 75 mg, 225 mg, or 750 mg.

Claim 16. The method of claim 15, wherein durvalumab is additionally administered at a dose of 750 mg or 1500 mg.

Claim 17. The method of claim 15, wherein tremelimumab is additionally administered at a dose of 75 mg, 225 mg, or 750 mg.

Claim 18. The method of either of claims 13 or 14, wherein MEDI0562 is administered every 14 days.

Claim 19. The method of claim 16, wherein durvalumab is administered every 28 days.

Claim 20. The method of claim 17, wherein tremelimumab is administered every 28 days.

Claim 21. The method of claim 20, wherein tremelimumab is administered four times.

Claim 22. The method of either of claims 13 or 14, wherein the tumor is a solid tumor.

Claim 23. The method of claim 22, wherein the solid tumor is squamous cell carcinoma of the head and neck, colorectal cancer, or non-small cell lung cancer.

Claim 24. The method of either of claims 13 or 14, wherein the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Figure 1

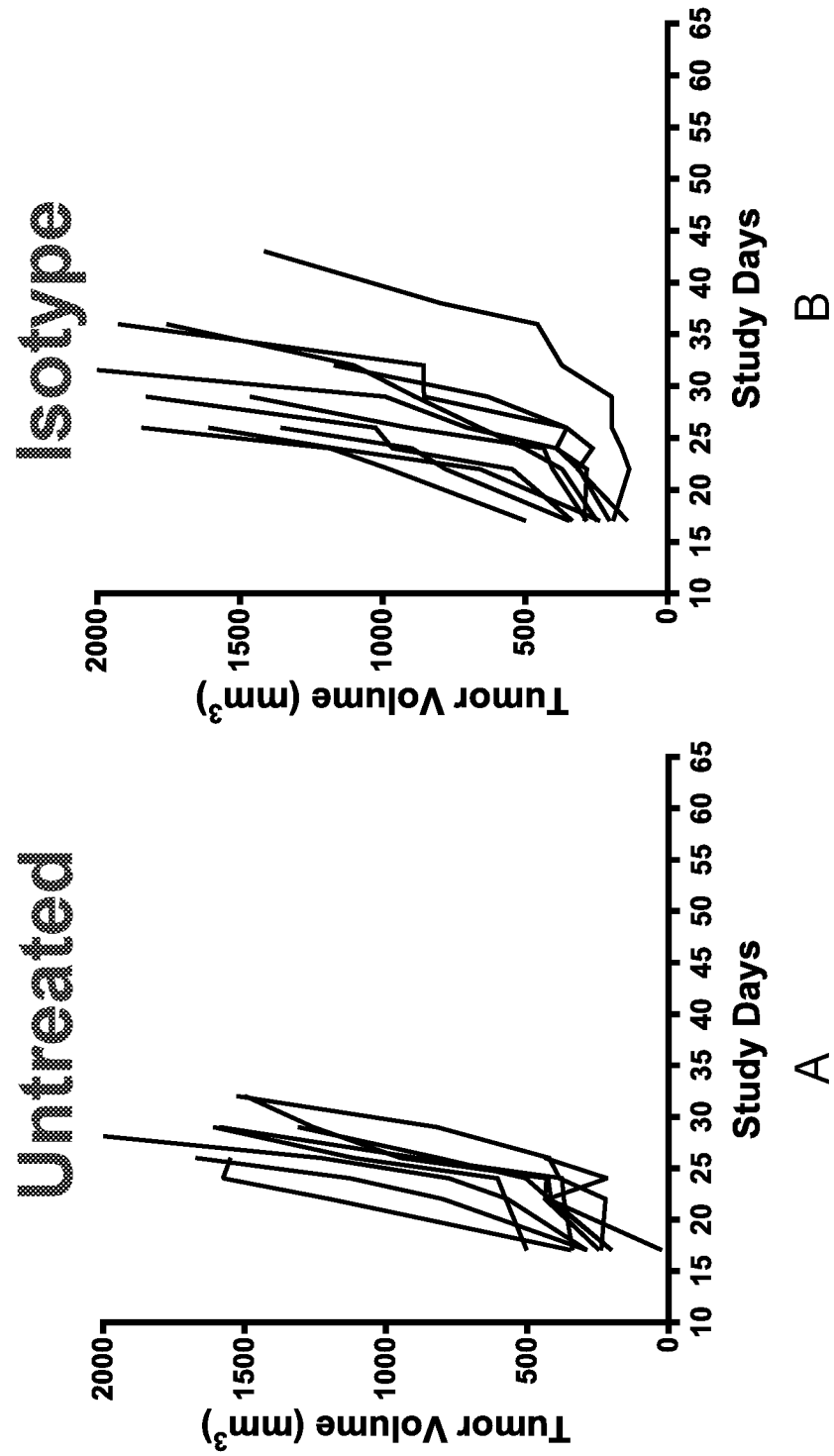

Untreated
Isotype
Tumor Volume (mm3)
2000
1500
1000
500
0
10 15 20 25 30 35 40 45 50 55 60 65
Study Days
A
B

Figure 1 Cont'd.

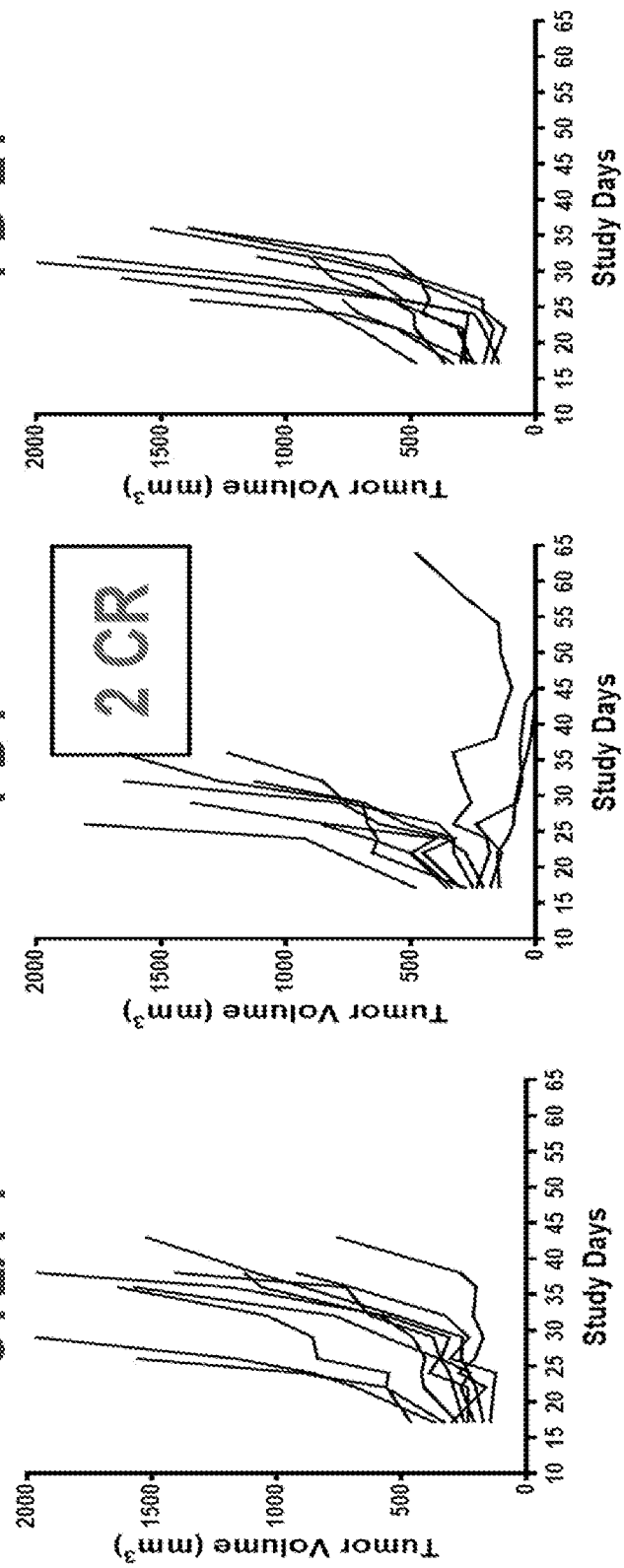


Figure 1 Cont'd.

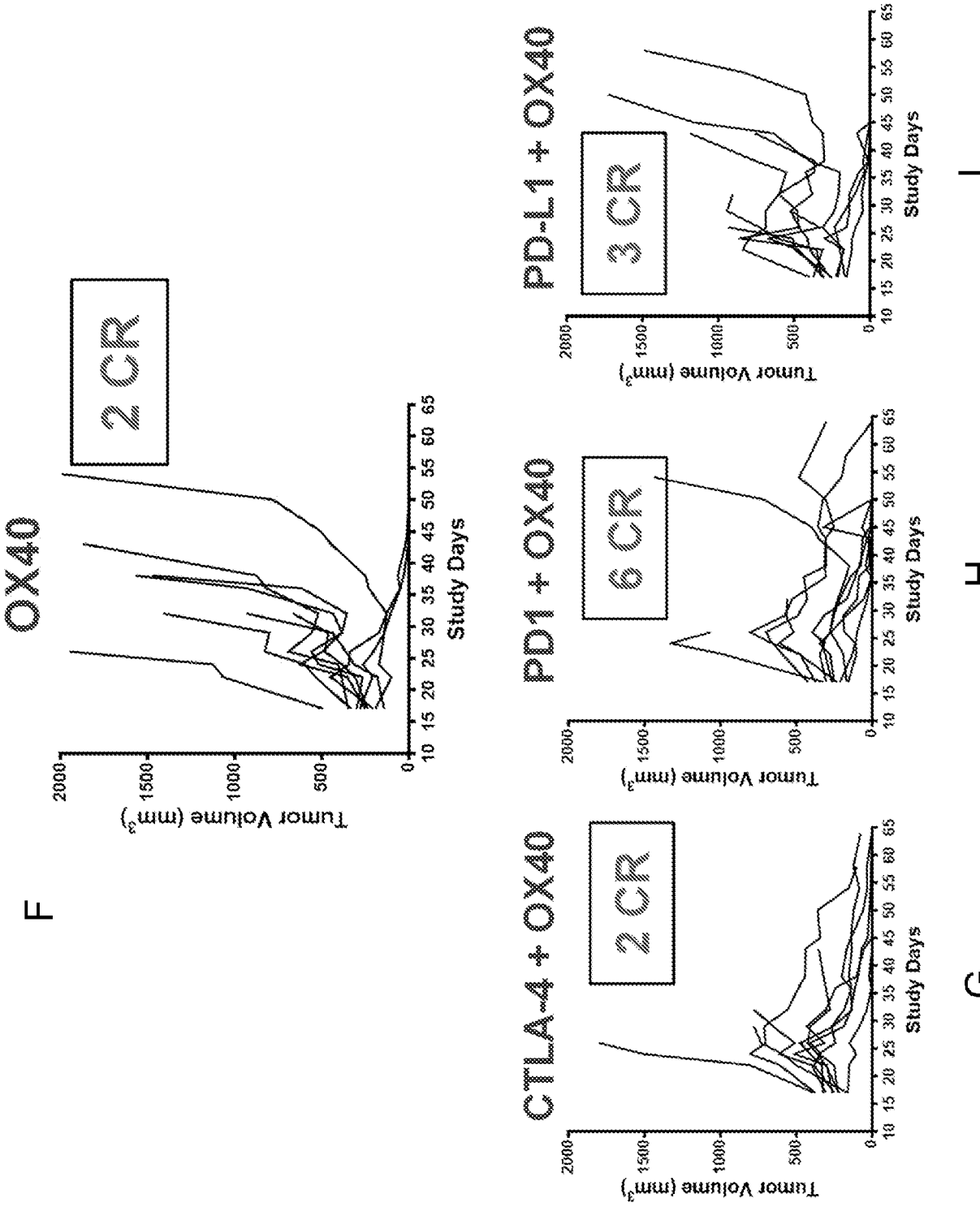


Figure 2

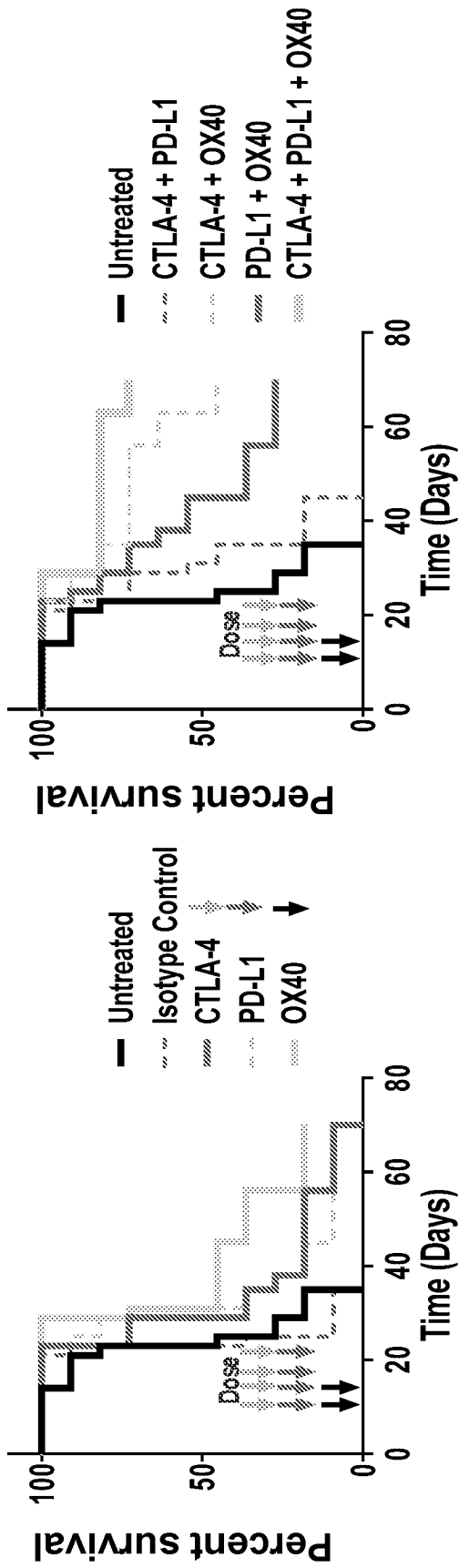

Untreated
Isotype Control
CTLA-4
PD-L1
OX40
Percent survival
Time (Days)
Dose
0
50
100
0
20
40
60
80
A
Untreated
CTLA-4 + PD-L1
CTLA-4 + OX40
PD-L1 + OX40
CTLA-4 + PD-L1 + OX40
Percent survival
Time (Days)
Dose
B

Figure 3

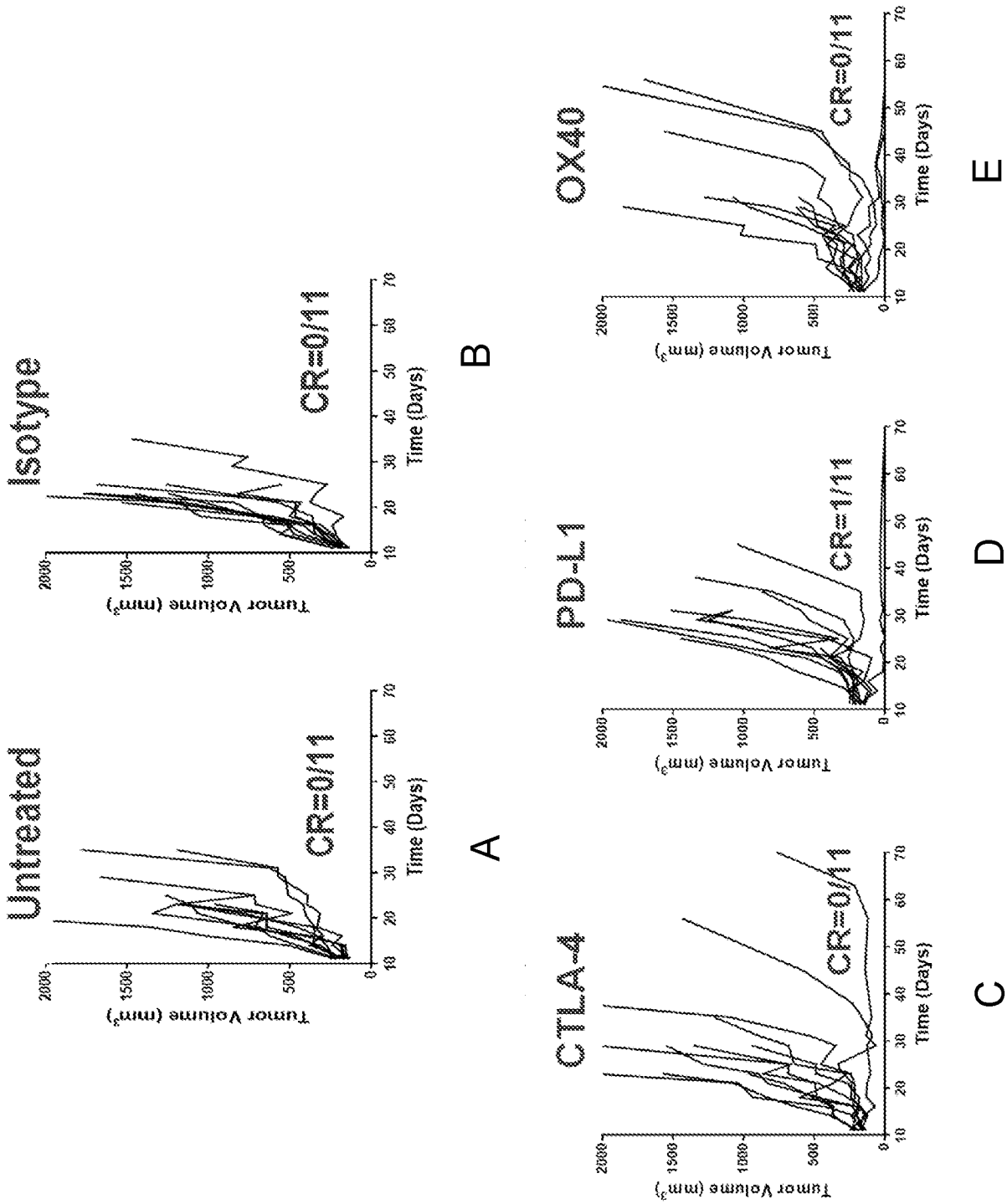

Untreated
CR=0/11
Isotype
CR=0/11
CTLA-4
CR=0/11
PD-L1
CR=1/11
OX40
CR=0/11
Tumor Volume (mm³)
Time (Days)
A
B
C
D
E

Figure 3 Cont'd.

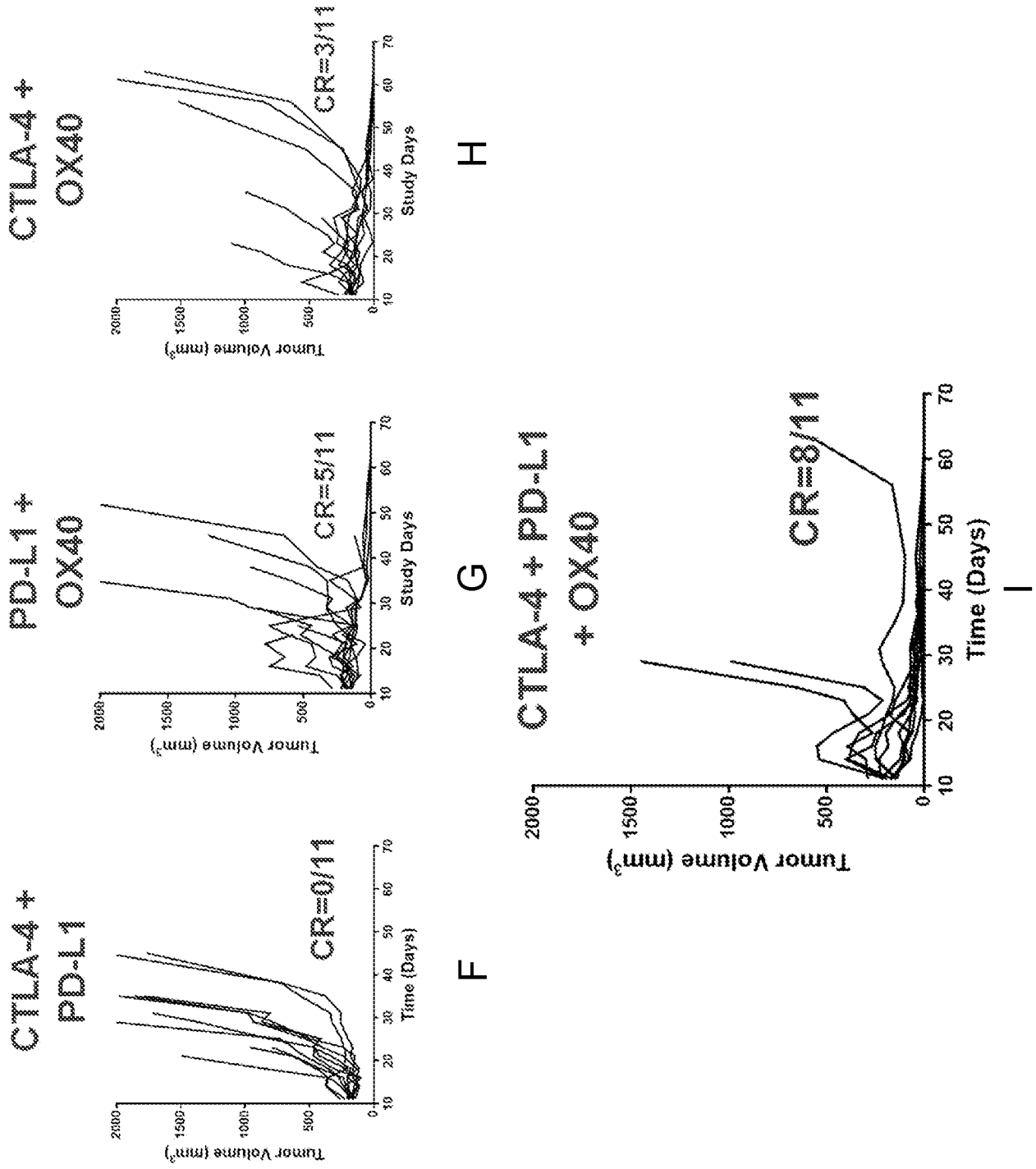
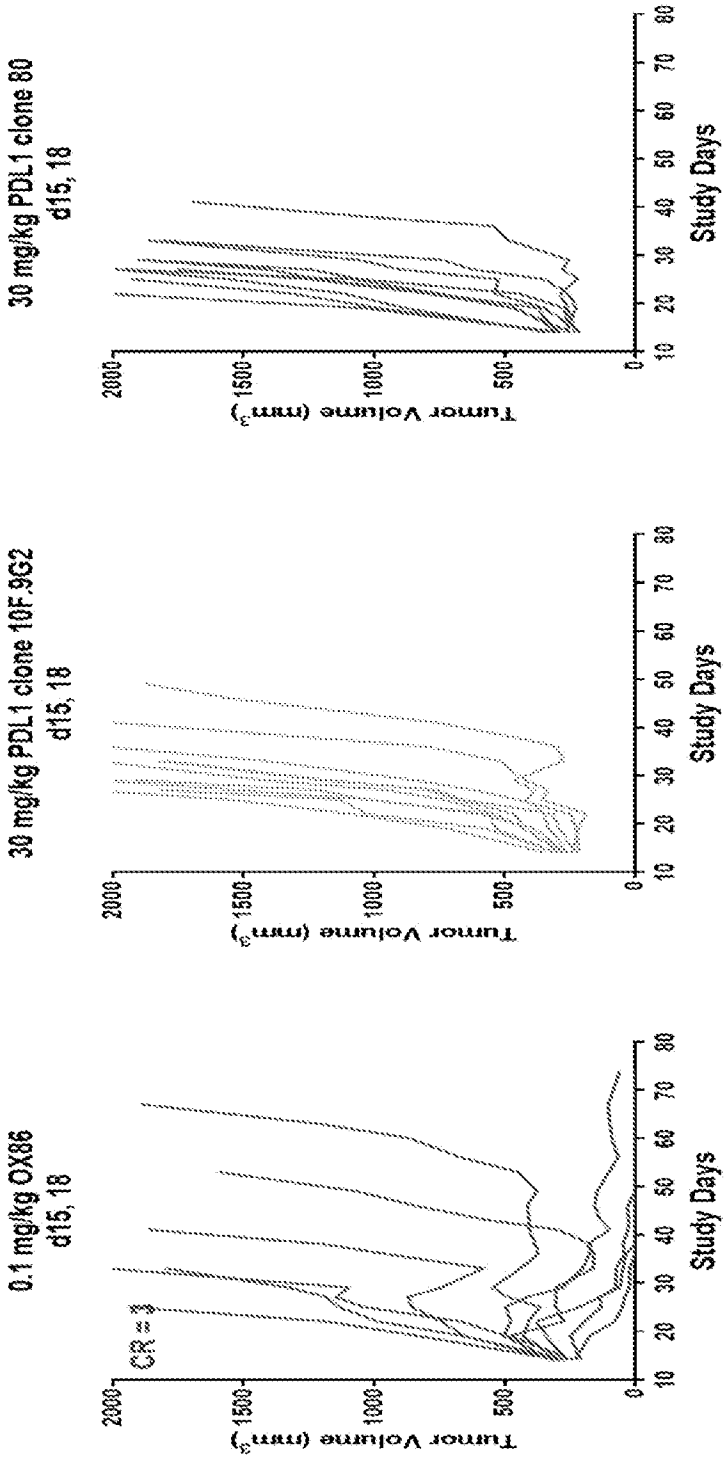
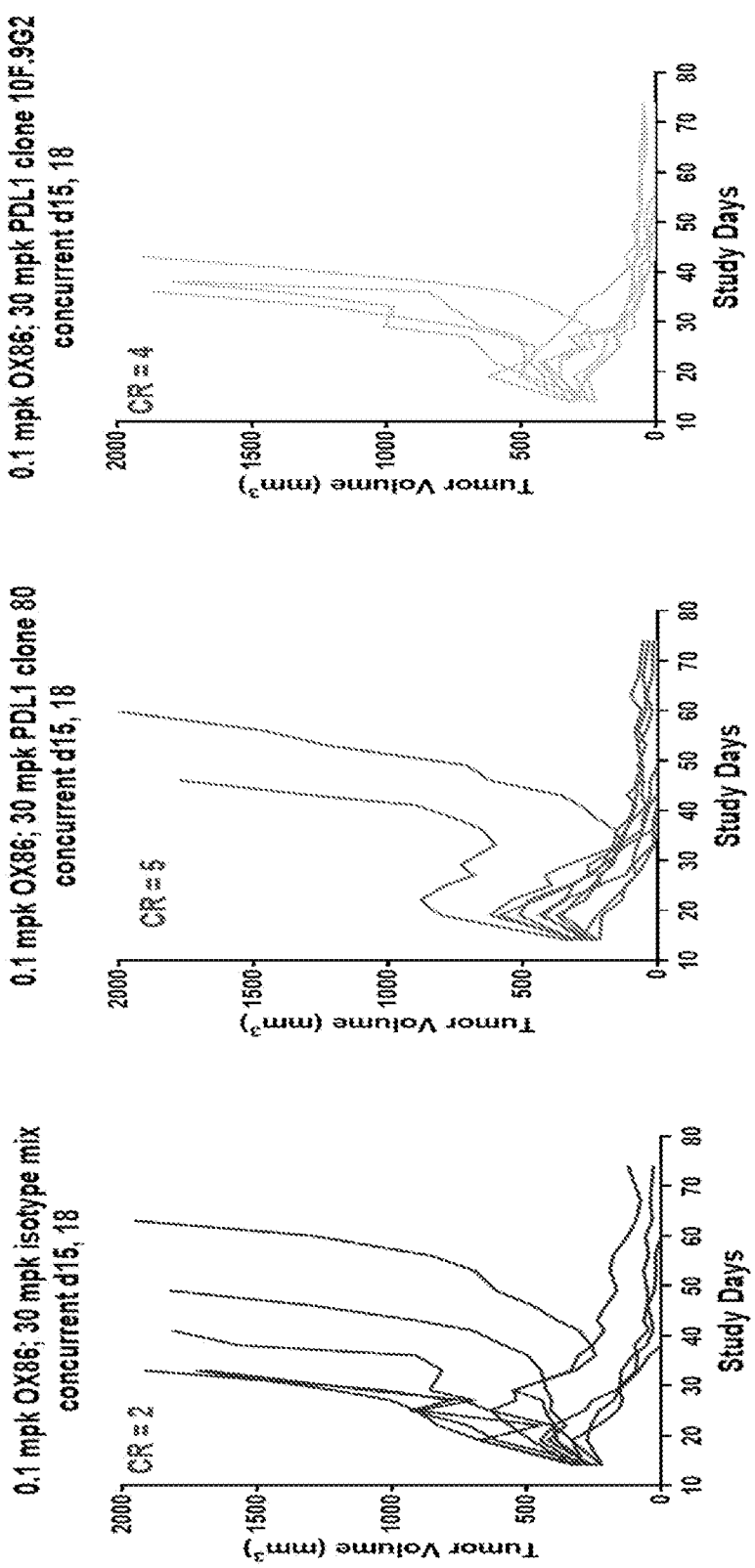


Figure 4


0.1 mg/kg OX86
d15, 18
CR = 3
30 mg/kg PDL1 clone 10F.9G2
d15, 18
30 mg/kg PDL1 clone 80
d15, 18
Tumor Volume (mm3)
Study Days
0
500
1000
1500
2000
10
20
30
40
50
60
70
80

A B C

Figure 4 Cont'd.




D E F

Figure 5

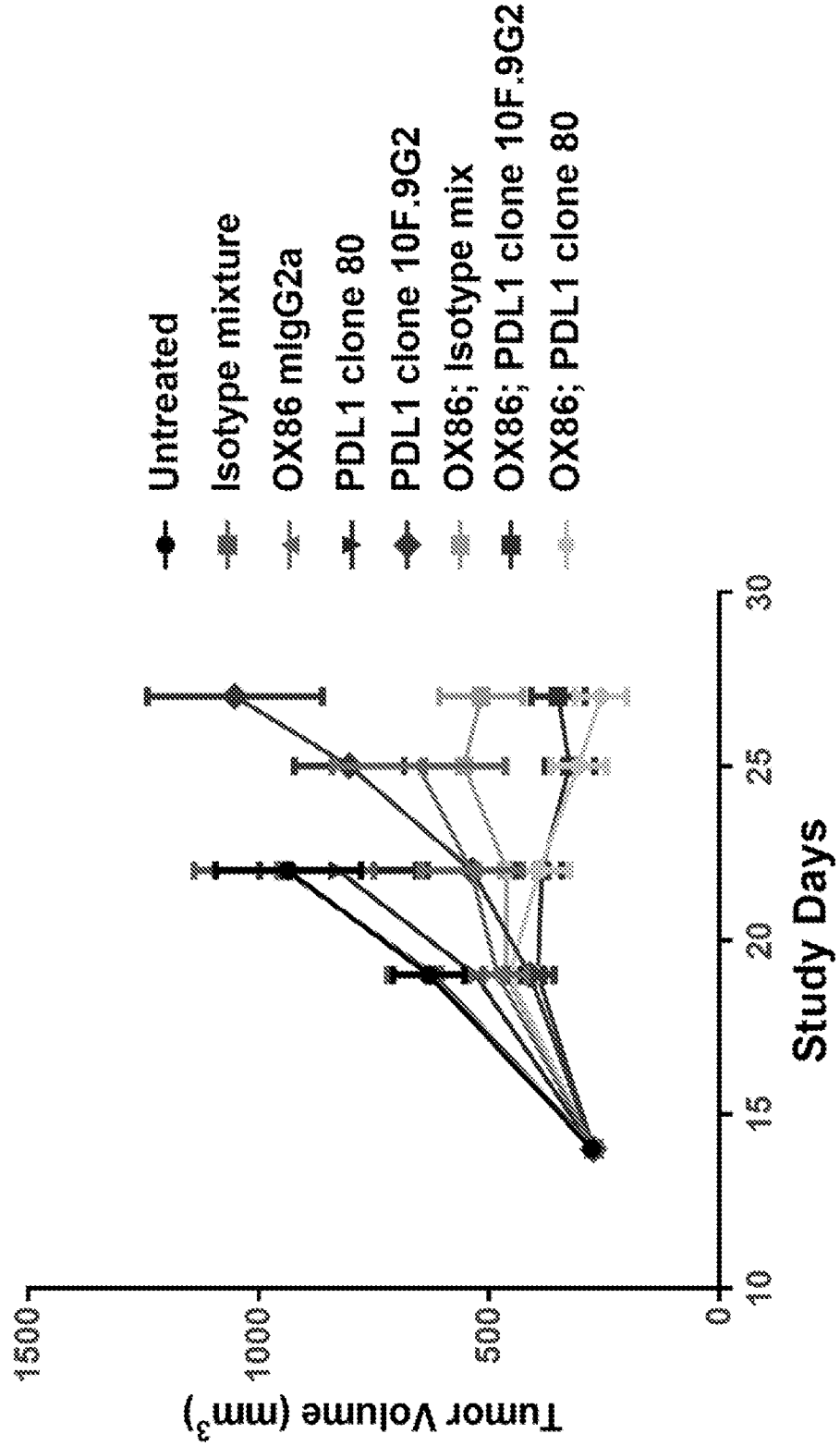

Untreated
Isotype mixture
OX86 mIgG2a
PDL1 clone 80
PDL1 clone 10F.9G2
OX86; Isotype mix
OX86; PDL1 clone 10F.9G2
OX86; PDL1 clone 80
Tumor Volume (mm³)
1500
1000
500
0
10
15
20
25
30
Study Days

Figure 6

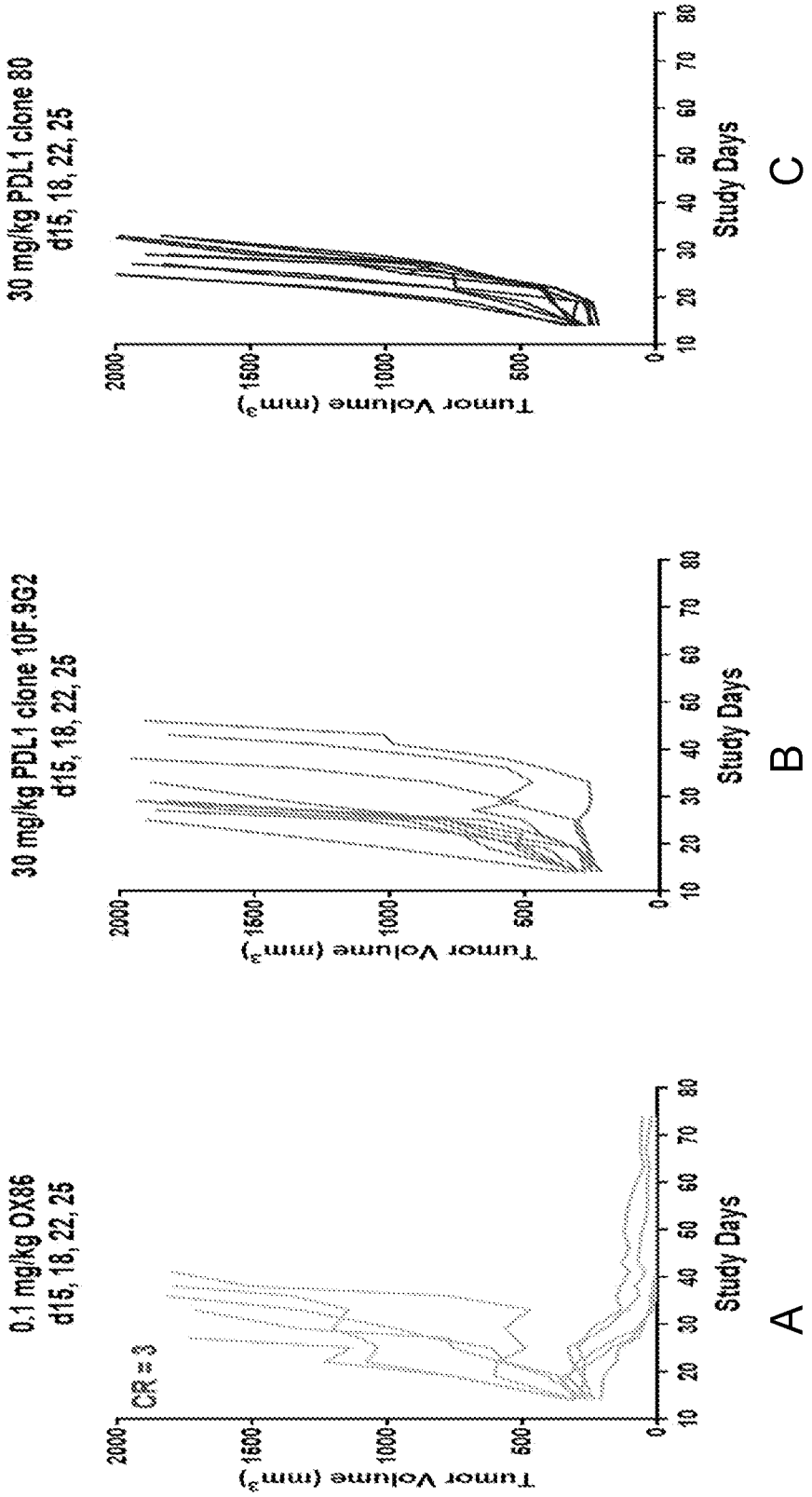

0.1 mg/kg OX86
d15, 18, 22, 25
CR = 3
30 mg/kg PDL1 clone 10F.9G2
d15, 18, 22, 25
30 mg/kg PDL1 clone 80
d15, 18, 22, 25
Tumor Volume (mm³)
Study Days
A
B
C

Figure 6 Cont'd.

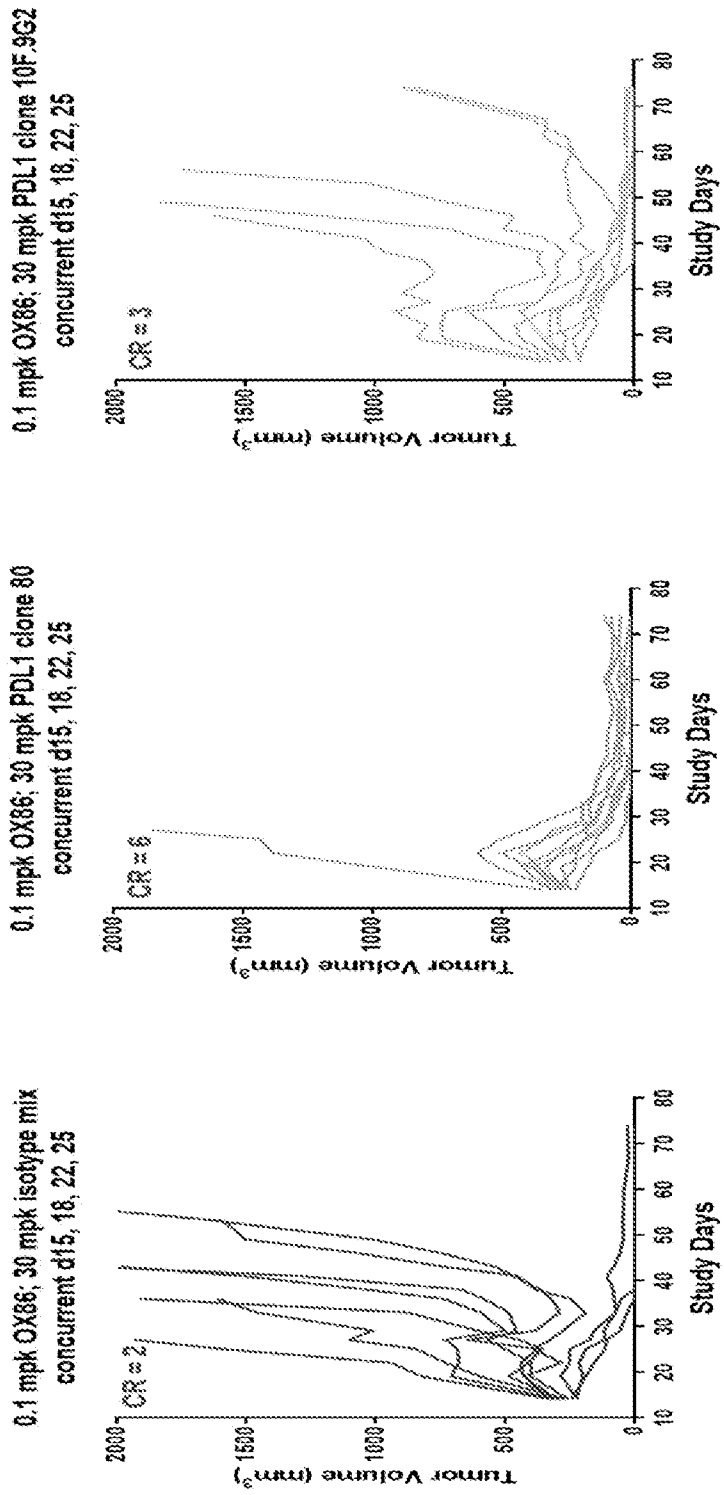


Figure 7

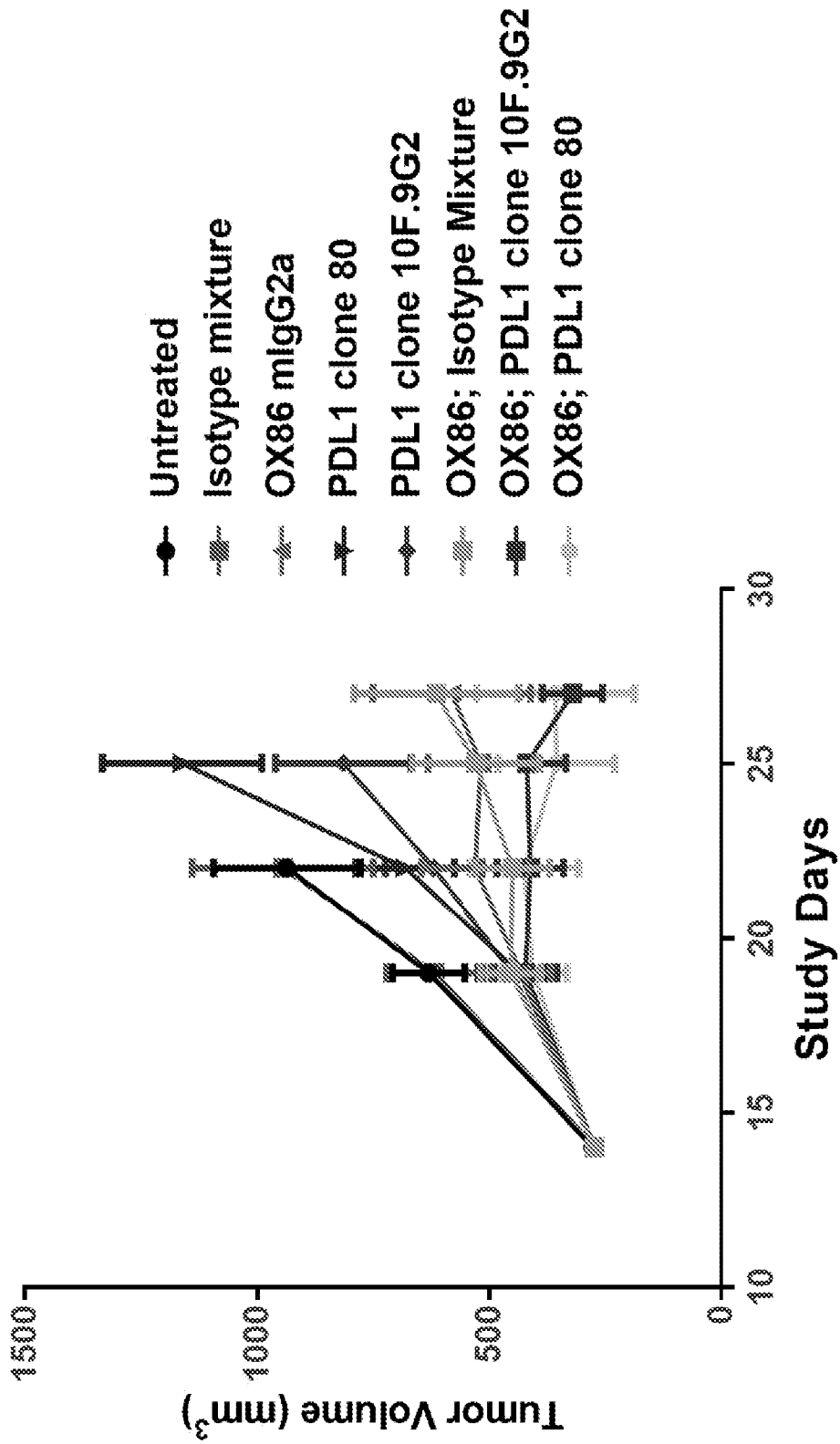

Untreated
Isotype mixture
OX86 mIgG2a
PDL1 clone 80
PDL1 clone 10F.9G2
OX86; Isotype Mixture
OX86; PDL1 clone 10F.9G2
OX86; PDL1 clone 80
Tumor Volume (mm3)
1500
1000
500
0
10
15
20
25
30
Study Days

Figure 8

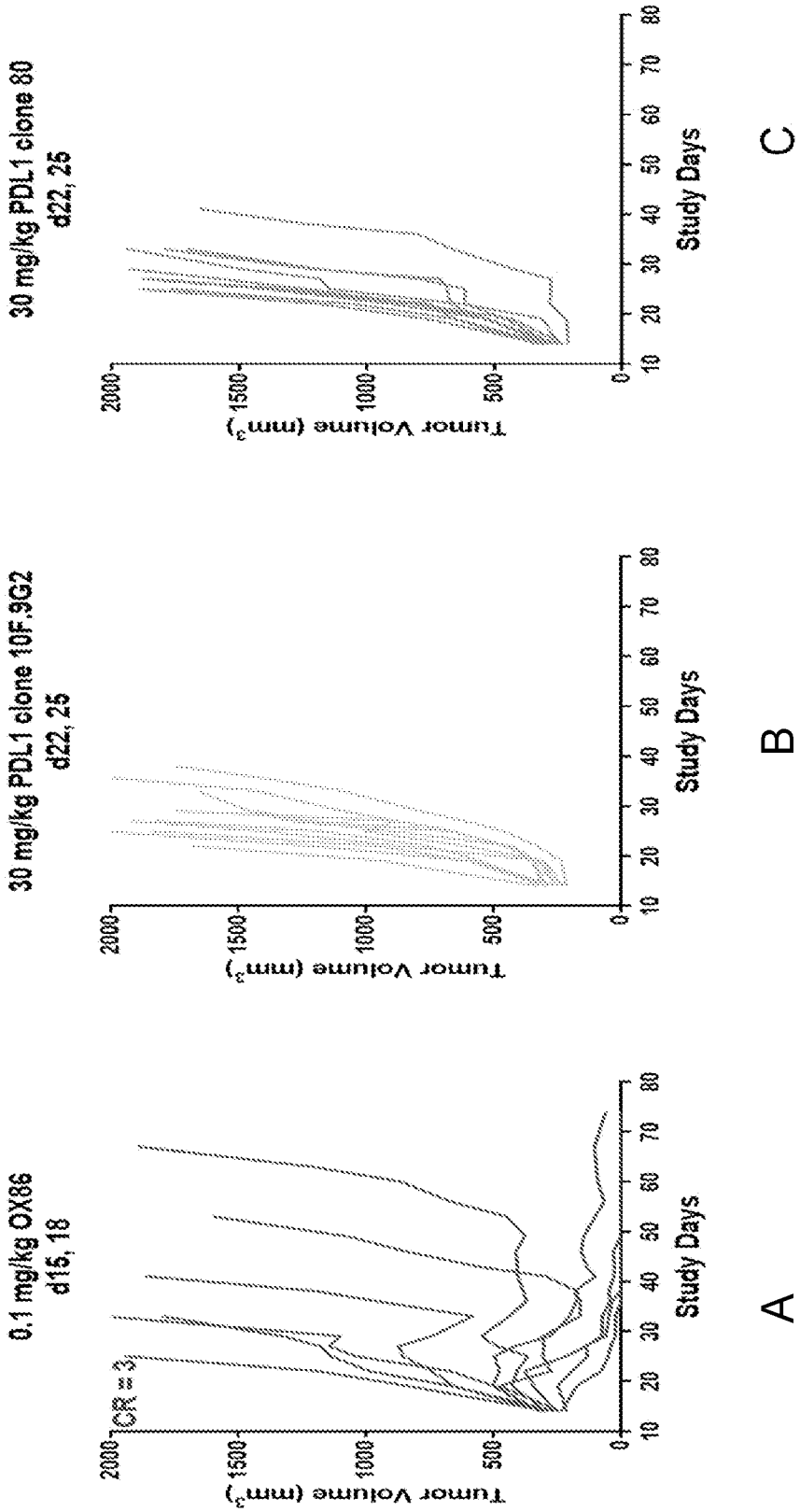

0.1 mg/kg OX86
d15, 18
CR = 3
30 mg/kg PDL1 clone 10F.9G2
d22, 25
30 mg/kg PDL1 clone 80
d22, 25
Tumor Volume (mm³)
Study Days
A
B
C

Figure 8 Cont'd.

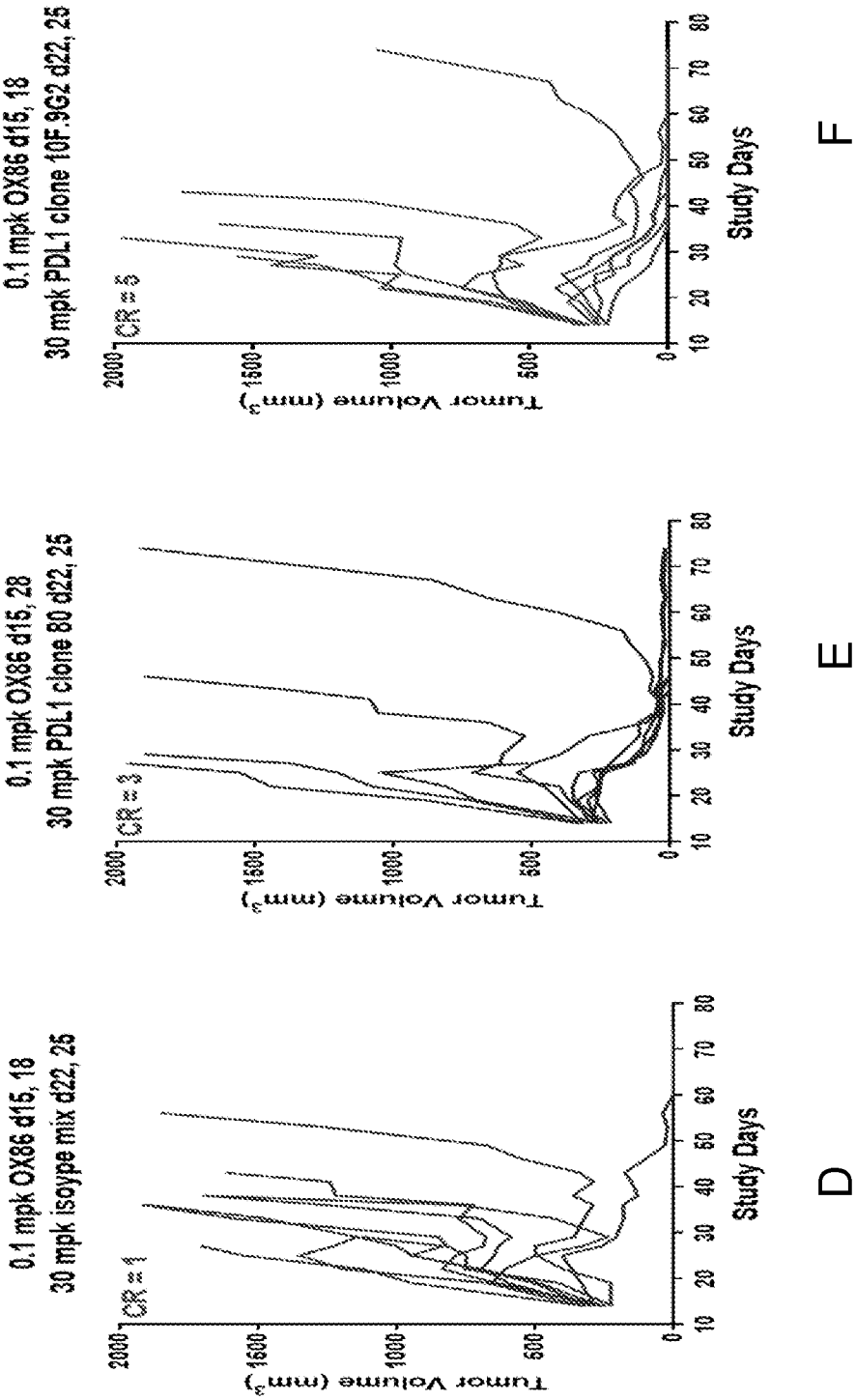


Figure 9

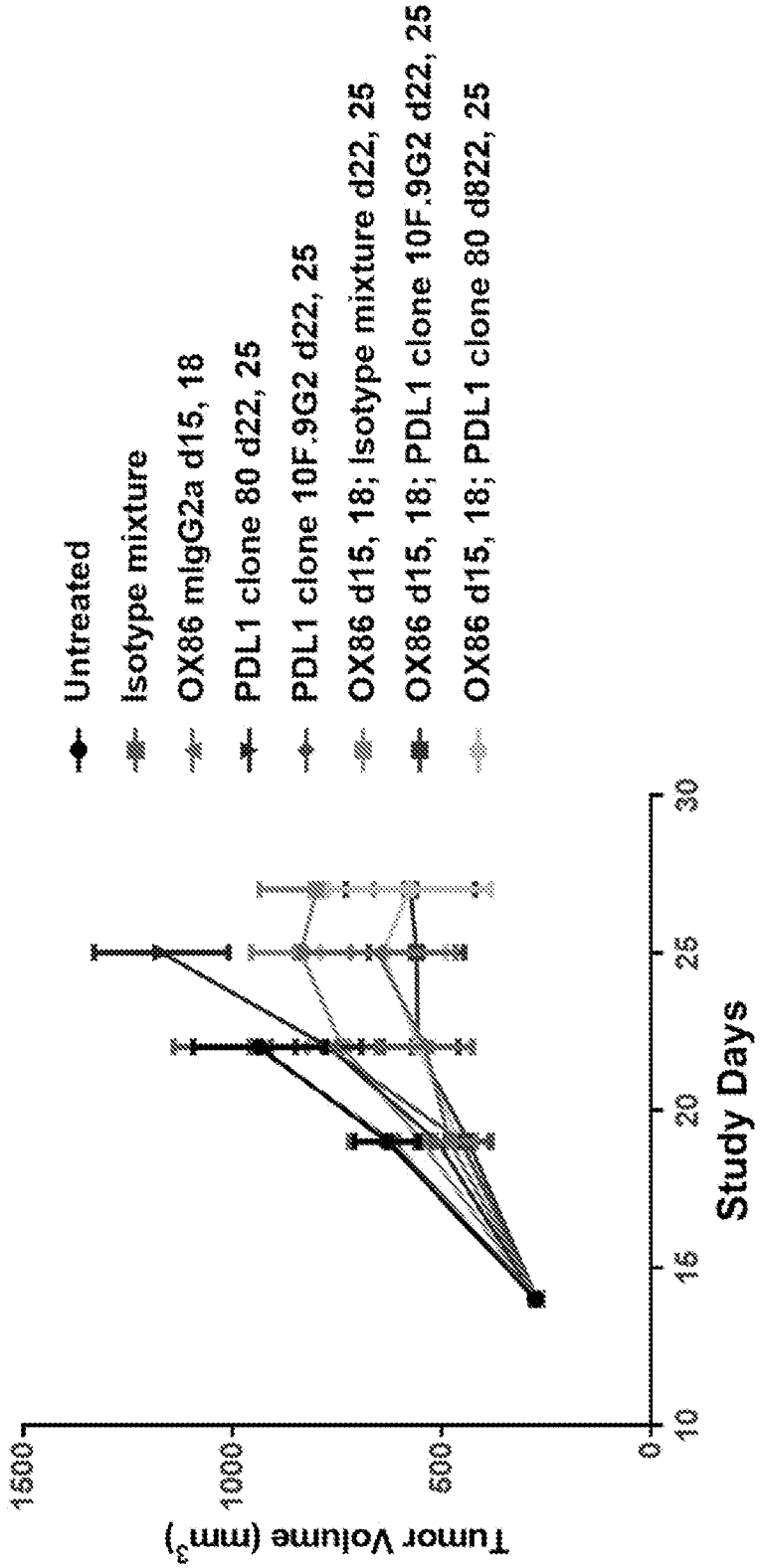

Untreated
Isotype mixture
OX86 mIgG2a d15, 18
PDL1 clone 80 d22, 25
PDL1 clone 10F.9G2 d22, 25
OX86 d15, 18; Isotype mixture d22, 25
OX86 d15, 18; PDL1 clone 10F.9G2 d22, 25
OX86 d15, 18; PDL1 clone 80 d822, 25
Tumor Volume (mm3)
1500
1000
500
0
10
15
20
25
30
Study Days

Figure 10

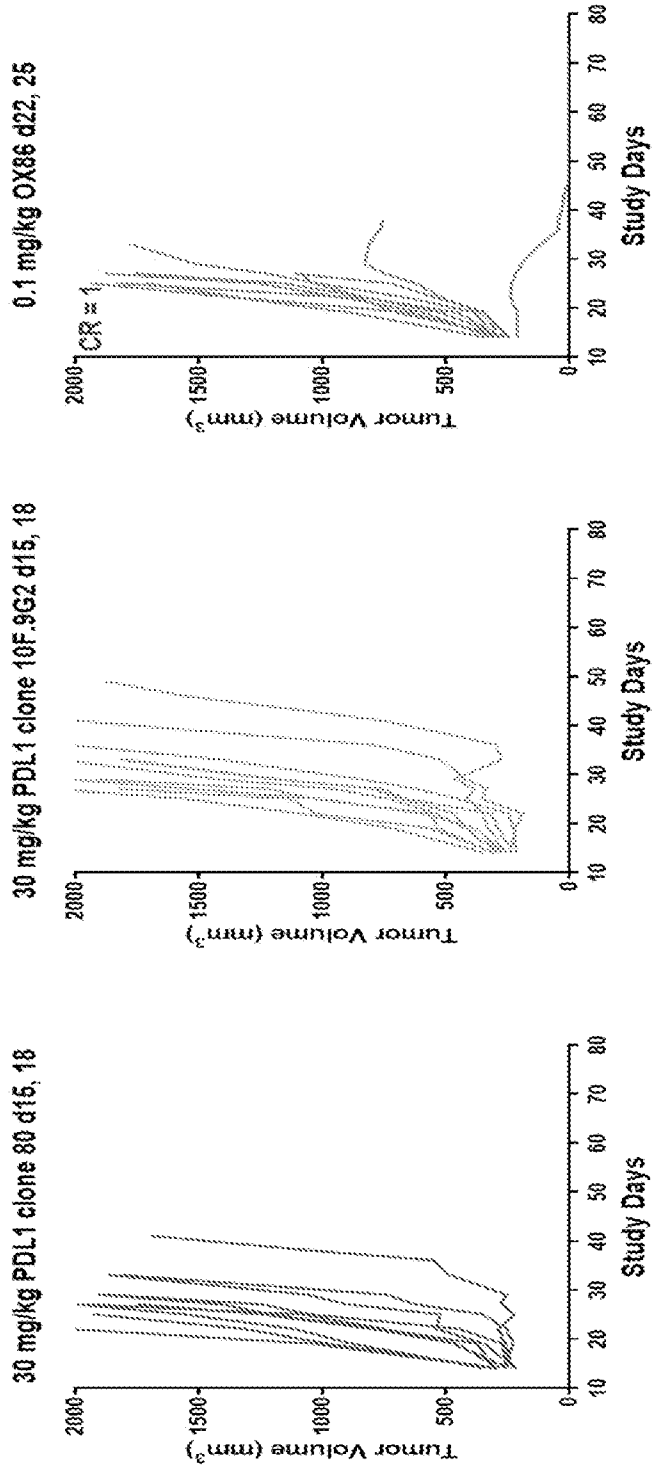

30 mg/kg PDL1 clone 80 d15, 18
30 mg/kg PDL1 clone 10F.9G2 d15, 18
0.1 mg/kg OX86 d22, 25
CR = 1
Tumor Volume (mm³)
Study Days
A
B
C

Figure 10 Cont'd.

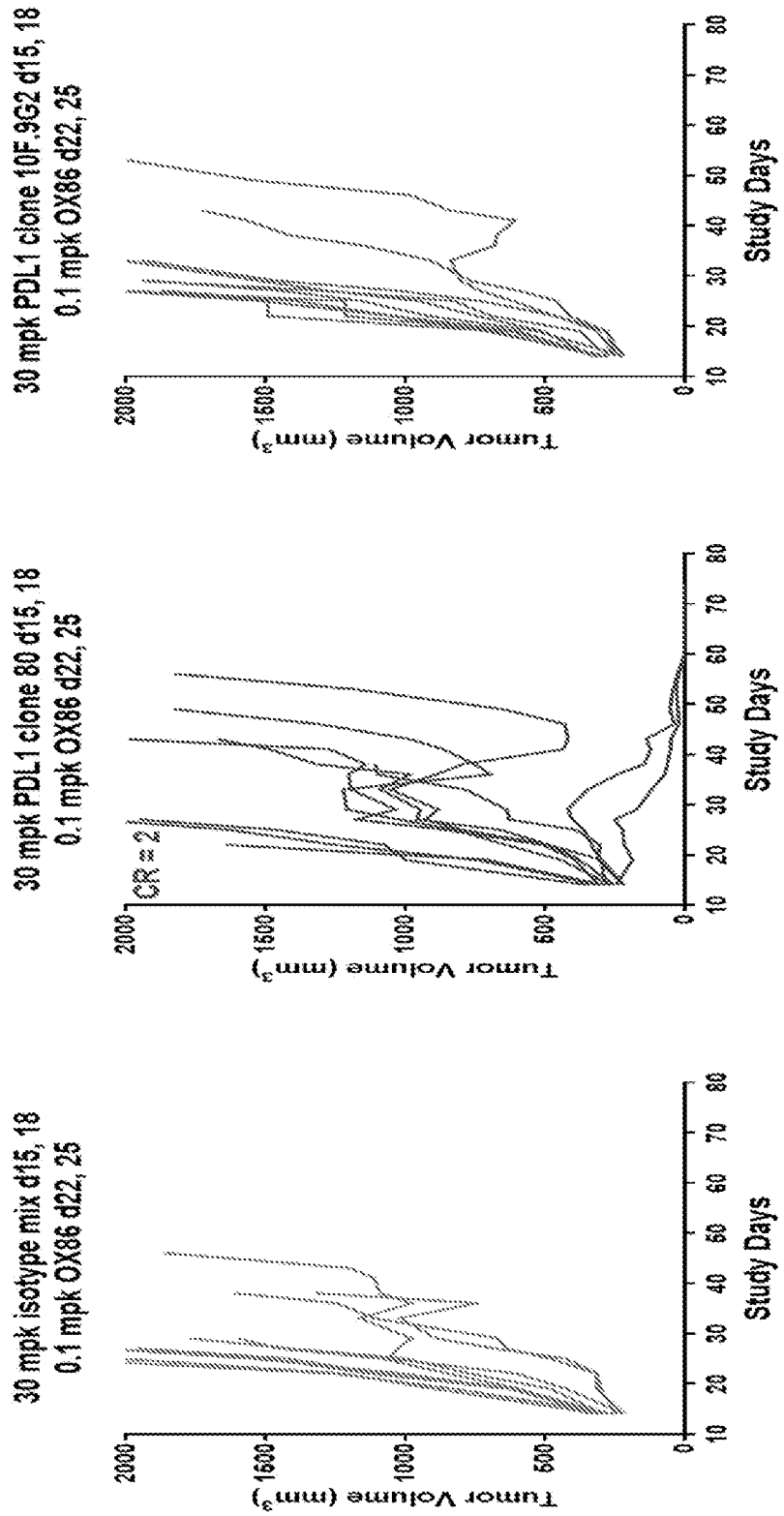


Figure 11

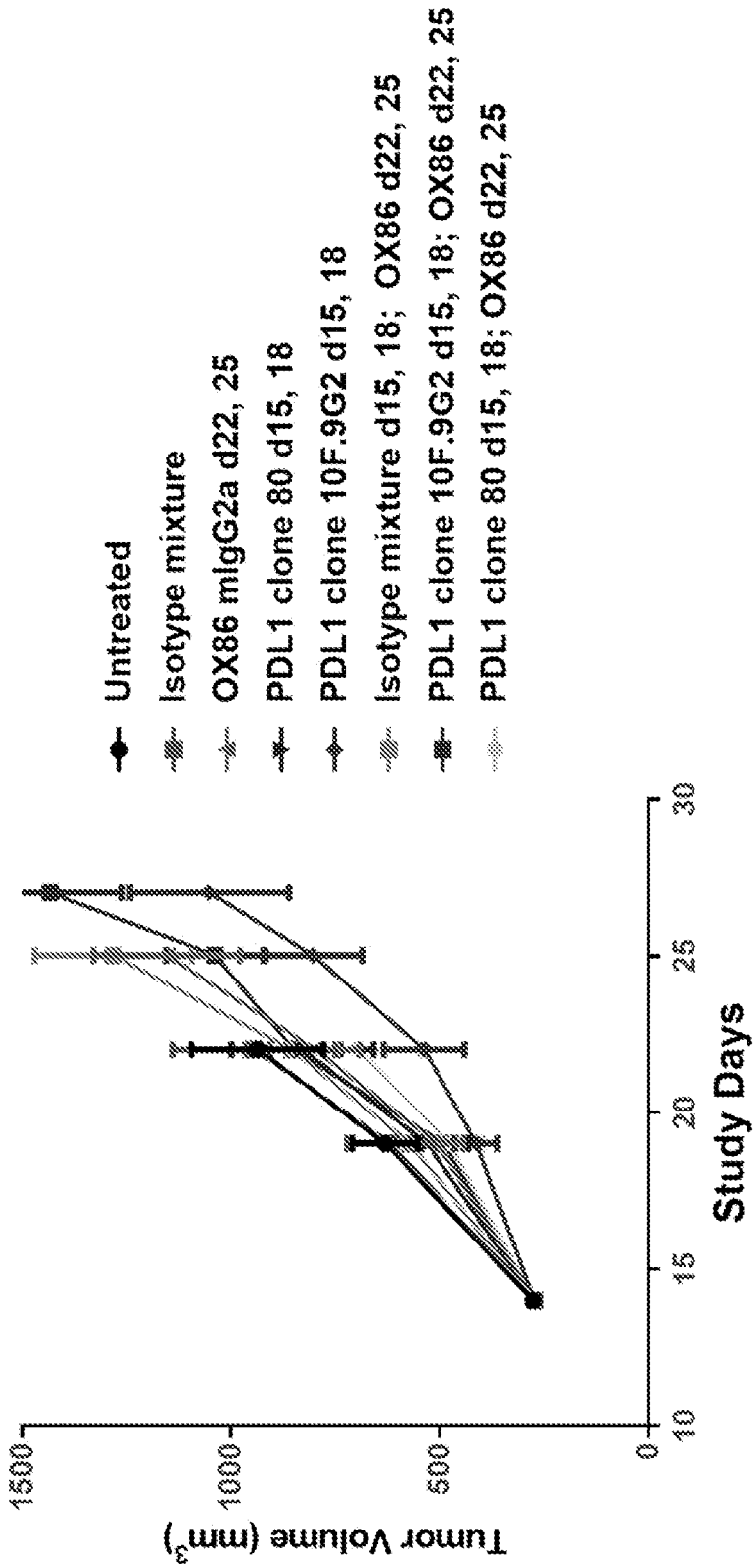

Untreated
Isotype mixture
OX86 mIgG2a d22, 25
PDL1 clone 80 d15, 18
PDL1 clone 10F.9G2 d15, 18
Isotype mixture d15, 18; OX86 d22, 25
PDL1 clone 10F.9G2 d15, 18; OX86 d22, 25
PDL1 clone 80 d15, 18; OX86 d22, 25
Tumor Volume (mm3)
1500
1000
500
0
10
15
20
25
30
Study Days

Figure 12

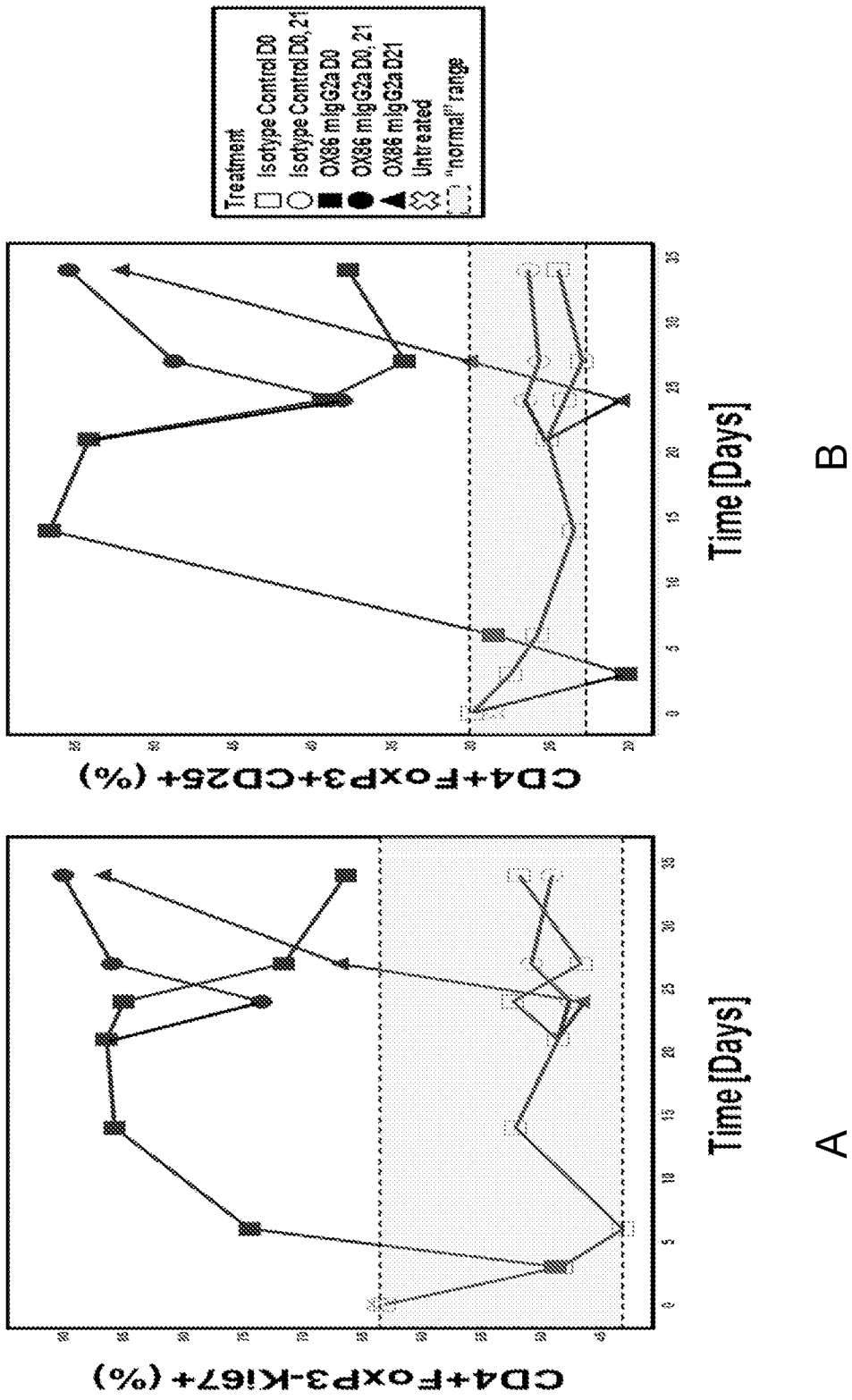

Treatment
Isotype Control D0
Isotype Control D0, 21
OX86 mIgG2a D0
OX86 mIgG2a D0, 21
OX86 mIgG2a D21
Untreated
"normal" range
CD4+FoxP3+CD25+ (%)
CD4+FoxP3-Ki67+ (%)
Time [Days]
Time [Days]
B
A

Figure 13

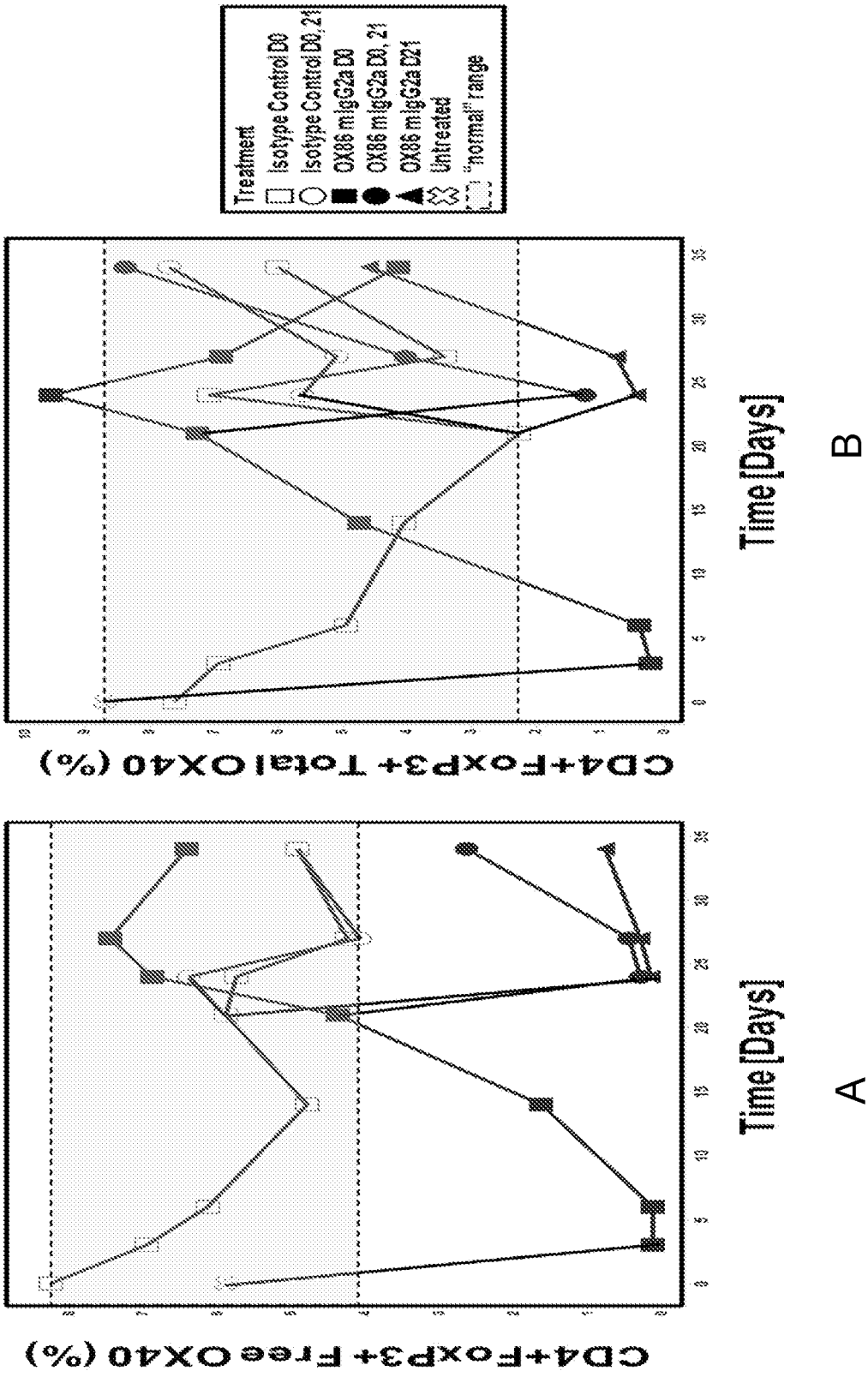

Treatment
Isotype Control D0
Isotype Control D0, 21
OX86 mIgG2a D0
OX86 mIgG2a D0, 21
OX86 mIgG2a D21
Untreated
"normal" range
CD4+FoxP3+ Free OX40 (%)
Time [Days]
A
CD4+FoxP3+ Total OX40 (%)
Time [Days]
B

Figure 14

**DOSE-ESCALATION PHASE**
**(Advanced solid tumors; excluding primary CNS tumors and advanced solid tumors with CNS-only disease)**

| Q2W (3 + 3 Design)[a] | | |
|---|---|---|
| Cohort | Dose Level MEDI0562 | Subjects[b] |
| 1 | 0.03 mg/kg | n = 3 - 6 |
| 2 | 0.1 mg/kg | n = 3 - 6 |
| 3 | 0.3 mg/kg | n = 3 - 6 |
| 4 | 1.0 mg/kg | n = 3 - 6 |
| 5 | 3.0 mg/kg | n = 3 - 6 |
| 6 | 10 mg/kg | n = 3 - 6 |

Figure 15

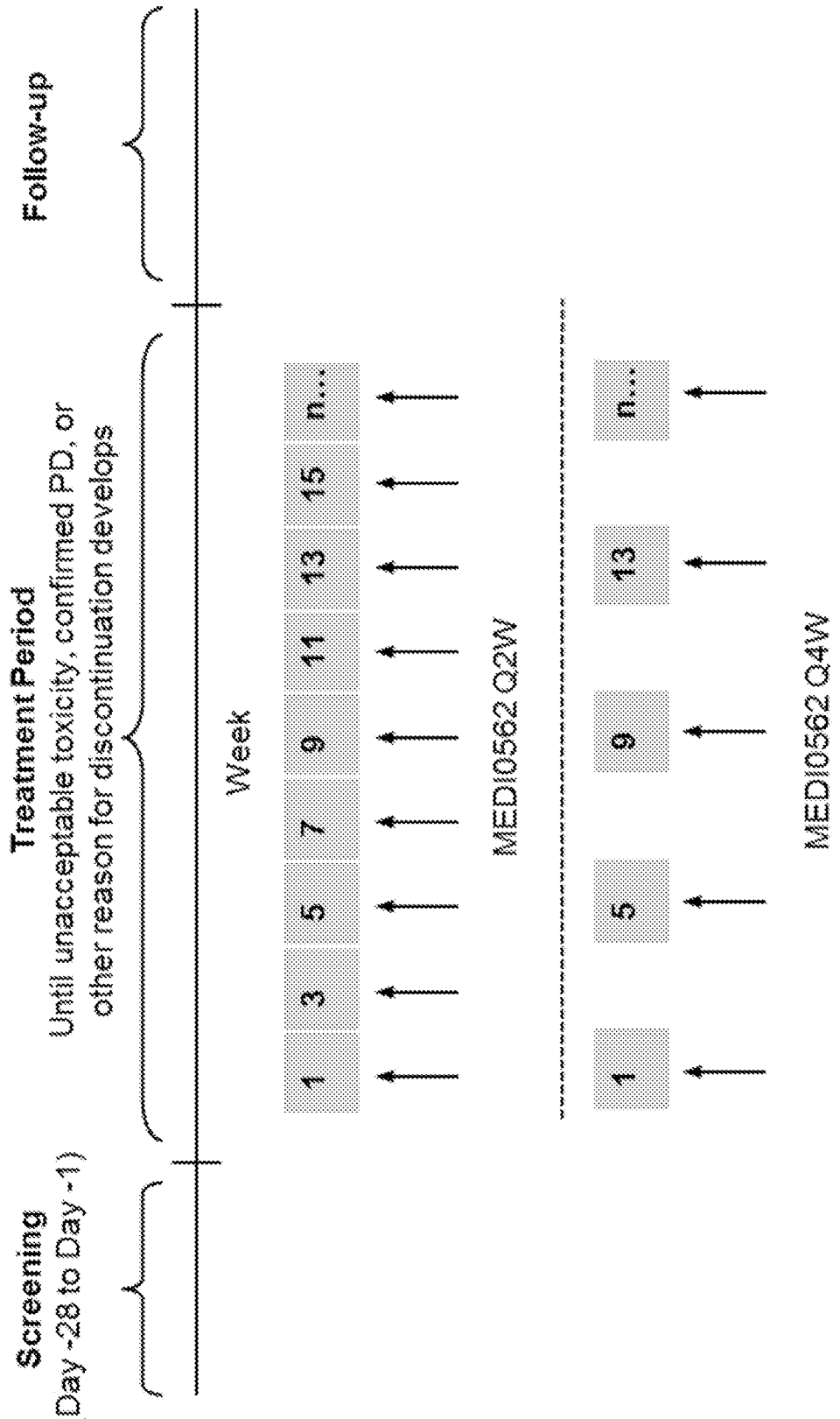

Screening
(Day -28 to Day -1)
Treatment Period
Until unacceptable toxicity, confirmed PD, or other reason for discontinuation develops
Follow-up
Week
1
3
5
7
9
11
13
15
n...
MEDI0562 Q2W
1
5
9
13
n...
MEDI0562 Q4W

Figure 16

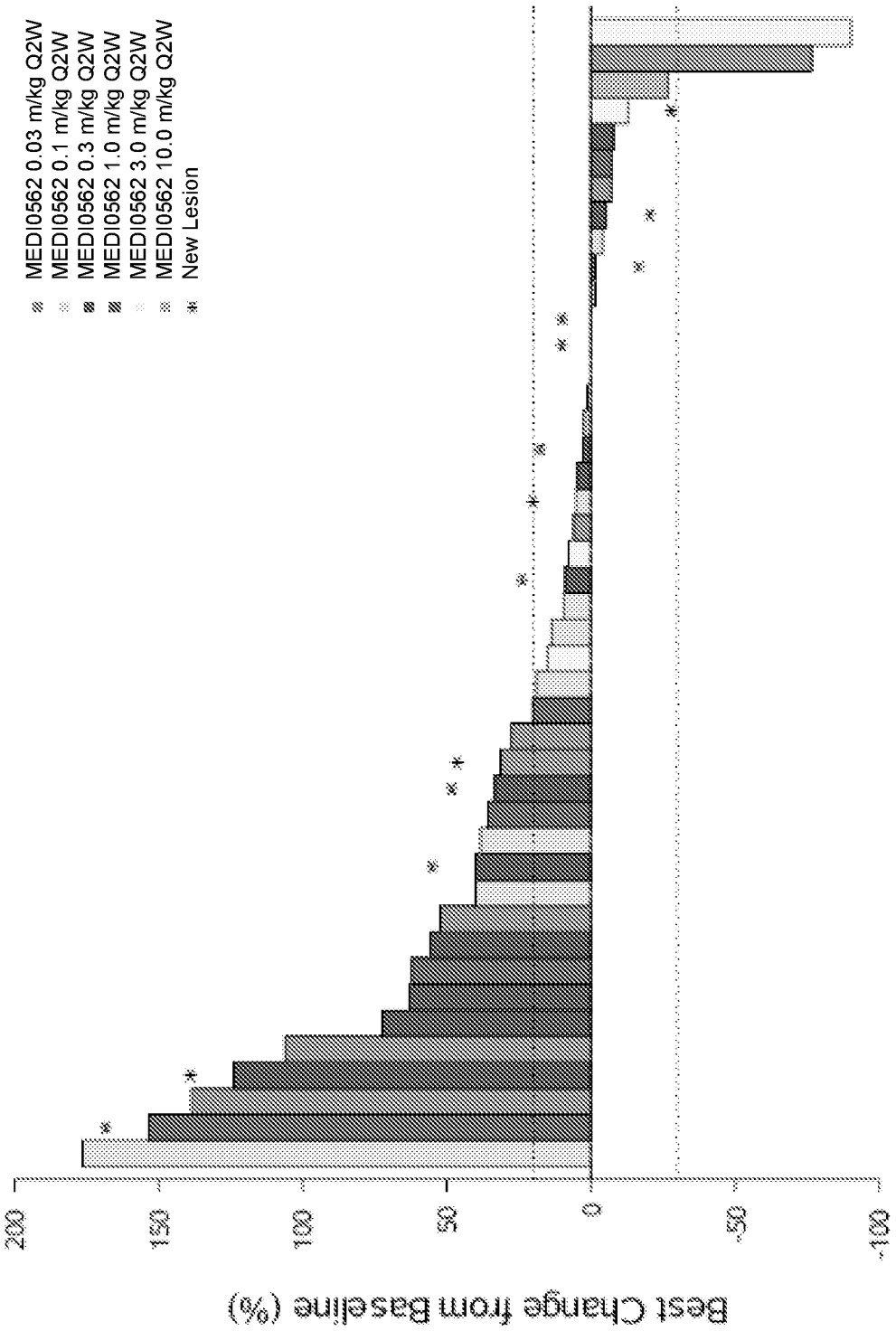

MEDI0562 0.03 m/kg Q2W
MEDI0562 0.1 m/kg Q2W
MEDI0562 0.3 m/kg Q2W
MEDI0562 1.0 m/kg Q2W
MEDI0562 3.0 m/kg Q2W
MEDI0562 10.0 m/kg Q2W
New Lesion
200
150
100
50
0
-50
-100
Best Change from Baseline (%)

Figure 17A

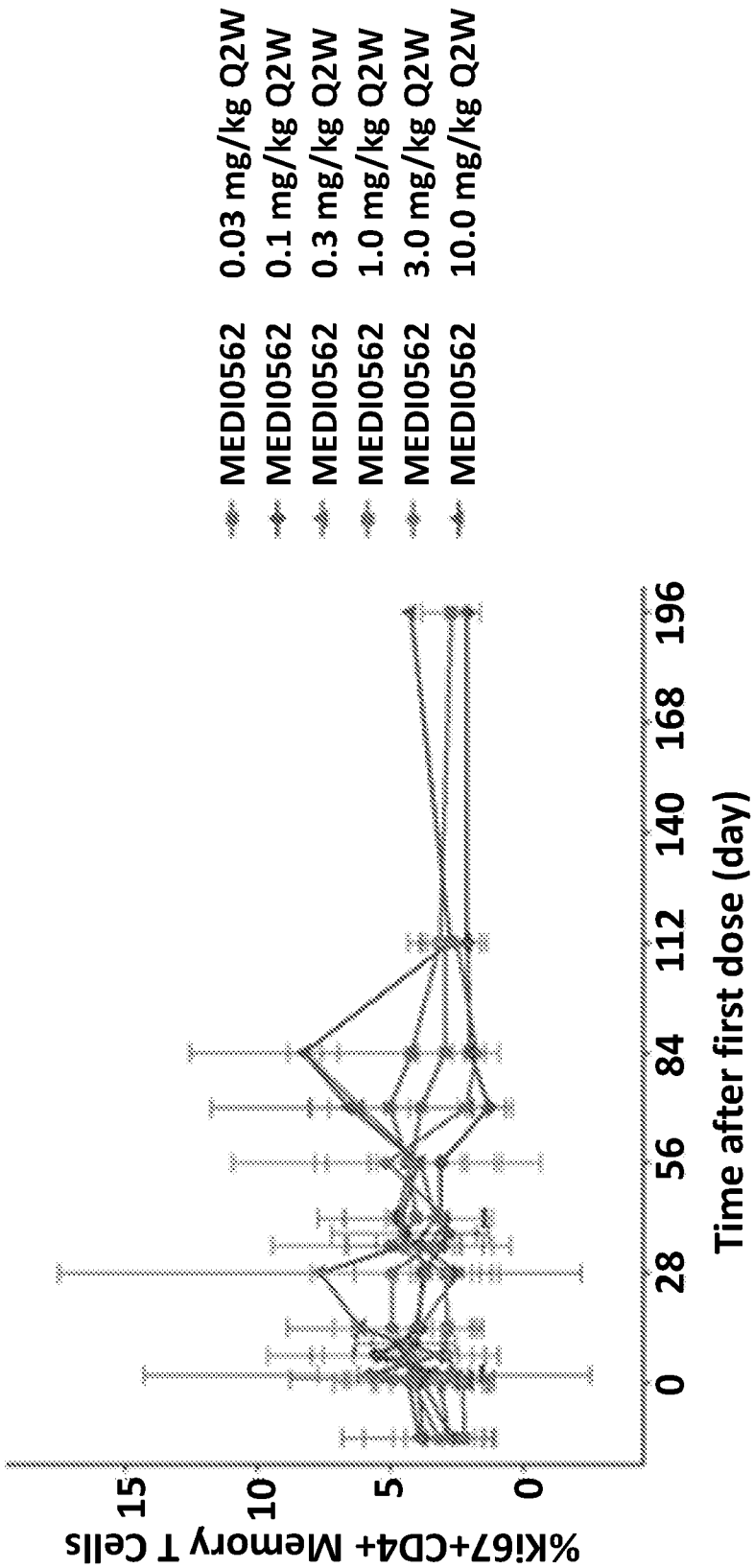

%Ki67+CD4+ Memory T Cells
0
5
10
15
0
28
56
84
112
140
168
196
Time after first dose (day)
MEDI0562 0.03 mg/kg Q2W
MEDI0562 0.1 mg/kg Q2W
MEDI0562 0.3 mg/kg Q2W
MEDI0562 1.0 mg/kg Q2W
MEDI0562 3.0 mg/kg Q2W
MEDI0562 10.0 mg/kg Q2W

Figure 17B

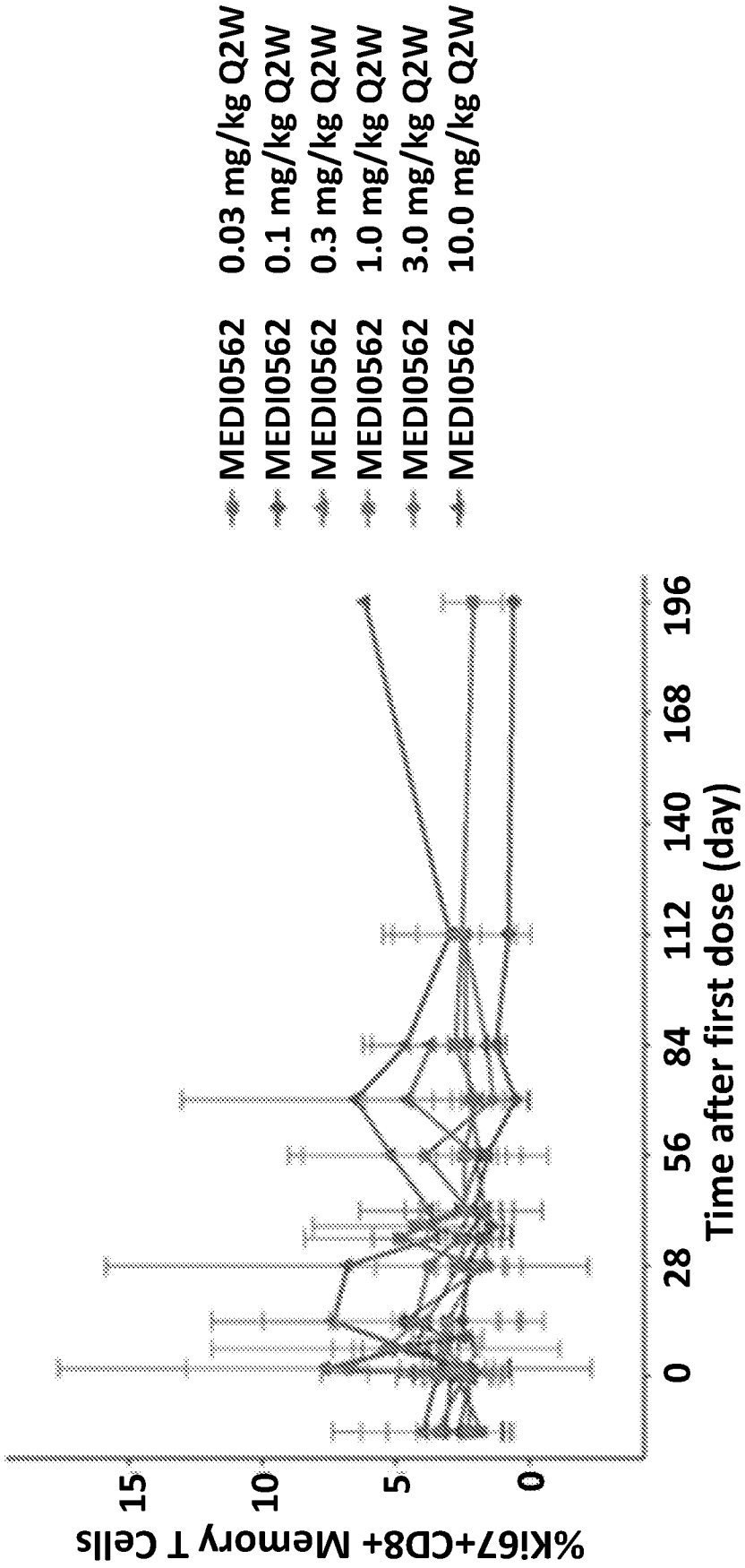

MEDI0562 0.03 mg/kg Q2W
MEDI0562 0.1 mg/kg Q2W
MEDI0562 0.3 mg/kg Q2W
MEDI0562 1.0 mg/kg Q2W
MEDI0562 3.0 mg/kg Q2W
MEDI0562 10.0 mg/kg Q2W
%Ki67+CD8+ Memory T Cells
0
5
10
15
0
28
56
84
112
140
168
196
Time after first dose (day)

Figure 18A

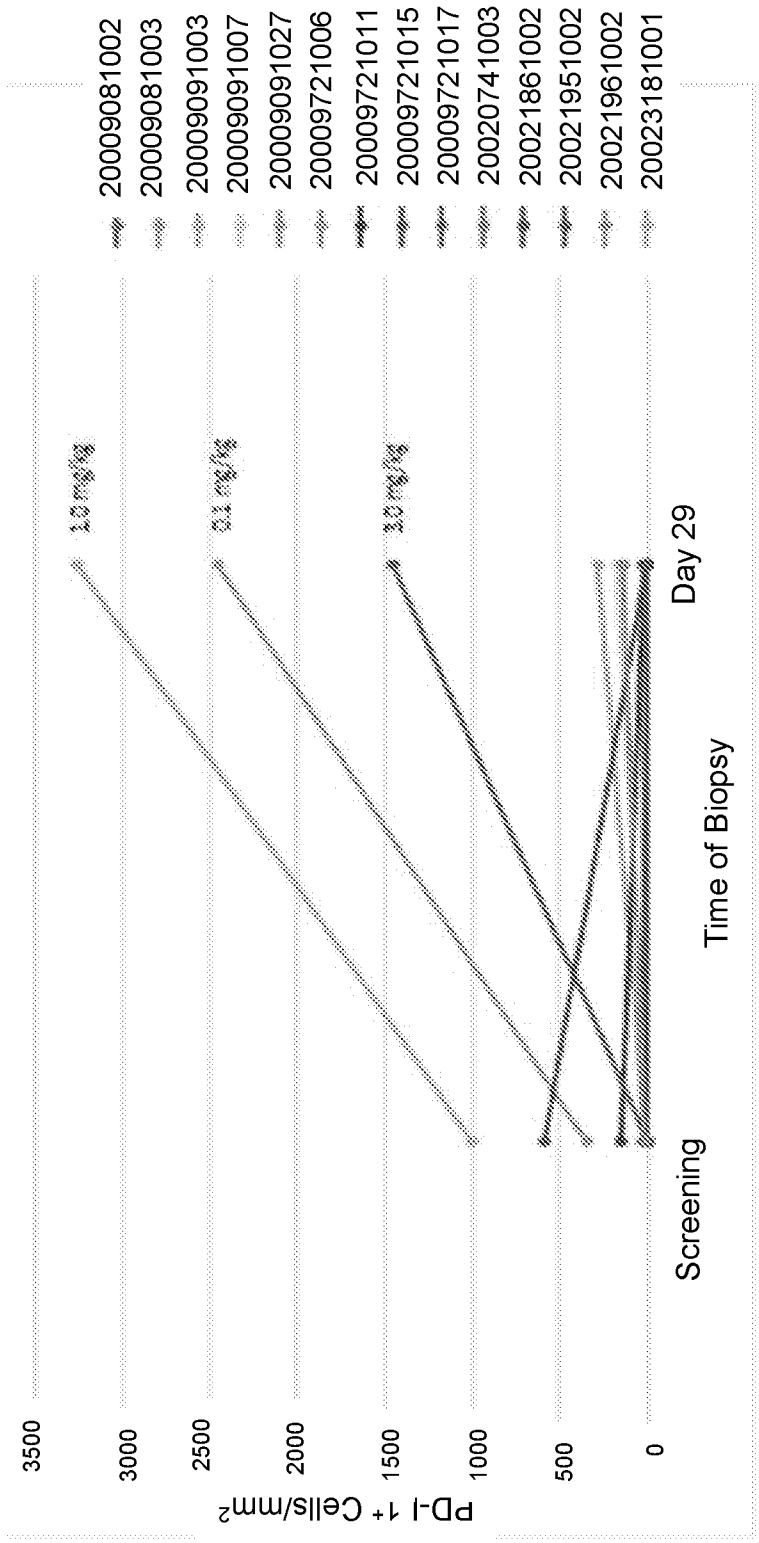

PD-1 1+ Cells/mm2
3500
3000
2500
2000
1500
1000
500
0
Screening
Time of Biopsy
Day 29
1.0 mg/kg
0.1 mg/kg
1.0 mg/kg
20009081002
20009081003
20009091003
20009091007
20009091027
20009721006
20009721011
20009721015
20009721017
20020741003
20021861002
20021951002
20021961002
20023181001

Figure 18B

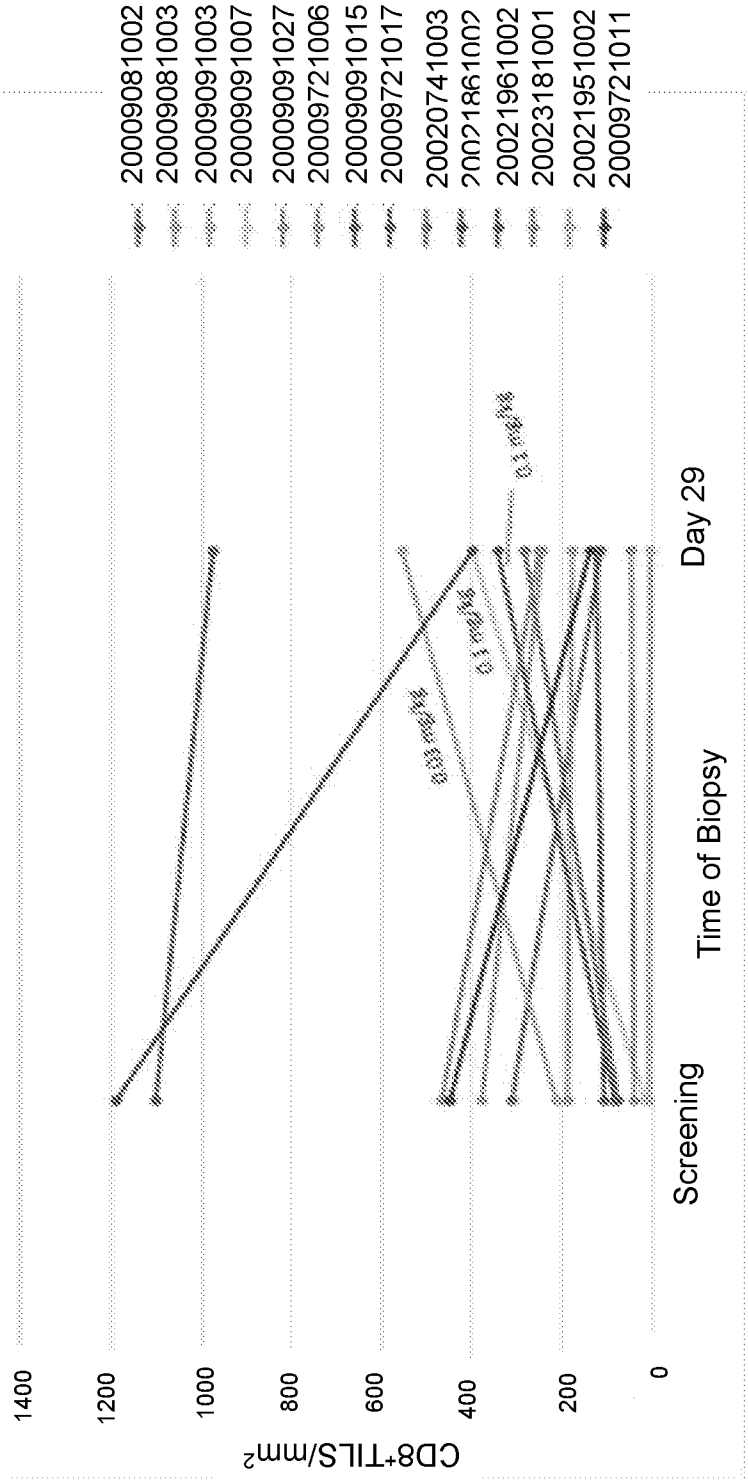

20009081002
20009081003
20009091003
20009091007
20009091027
20009721006
20009091015
20009721017
20020741003
20021861002
20021961002
20023181001
20021951002
20009721011
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
1400
1200
1000
800
600
400
200
0
CD8+TILS/mm2
Screening
Time of Biopsy
Day 29

Figure 19A

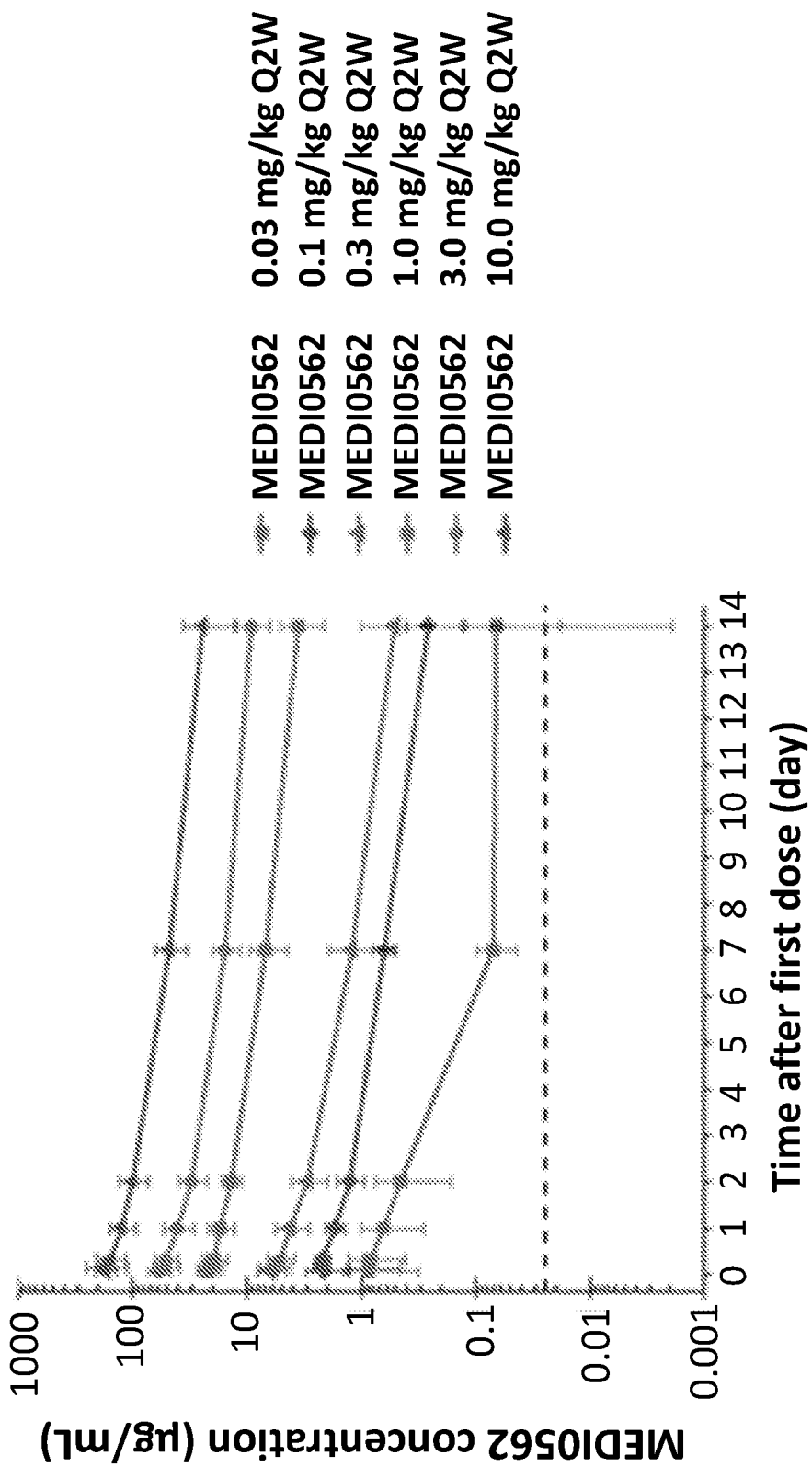

MEDI0562 0.03 mg/kg Q2W
MEDI0562 0.1 mg/kg Q2W
MEDI0562 0.3 mg/kg Q2W
MEDI0562 1.0 mg/kg Q2W
MEDI0562 3.0 mg/kg Q2W
MEDI0562 10.0 mg/kg Q2W
MEDI0562 concentration (µg/mL)
1000
100
10
1
0.1
0.01
0.001
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time after first dose (day)

Figure 19B

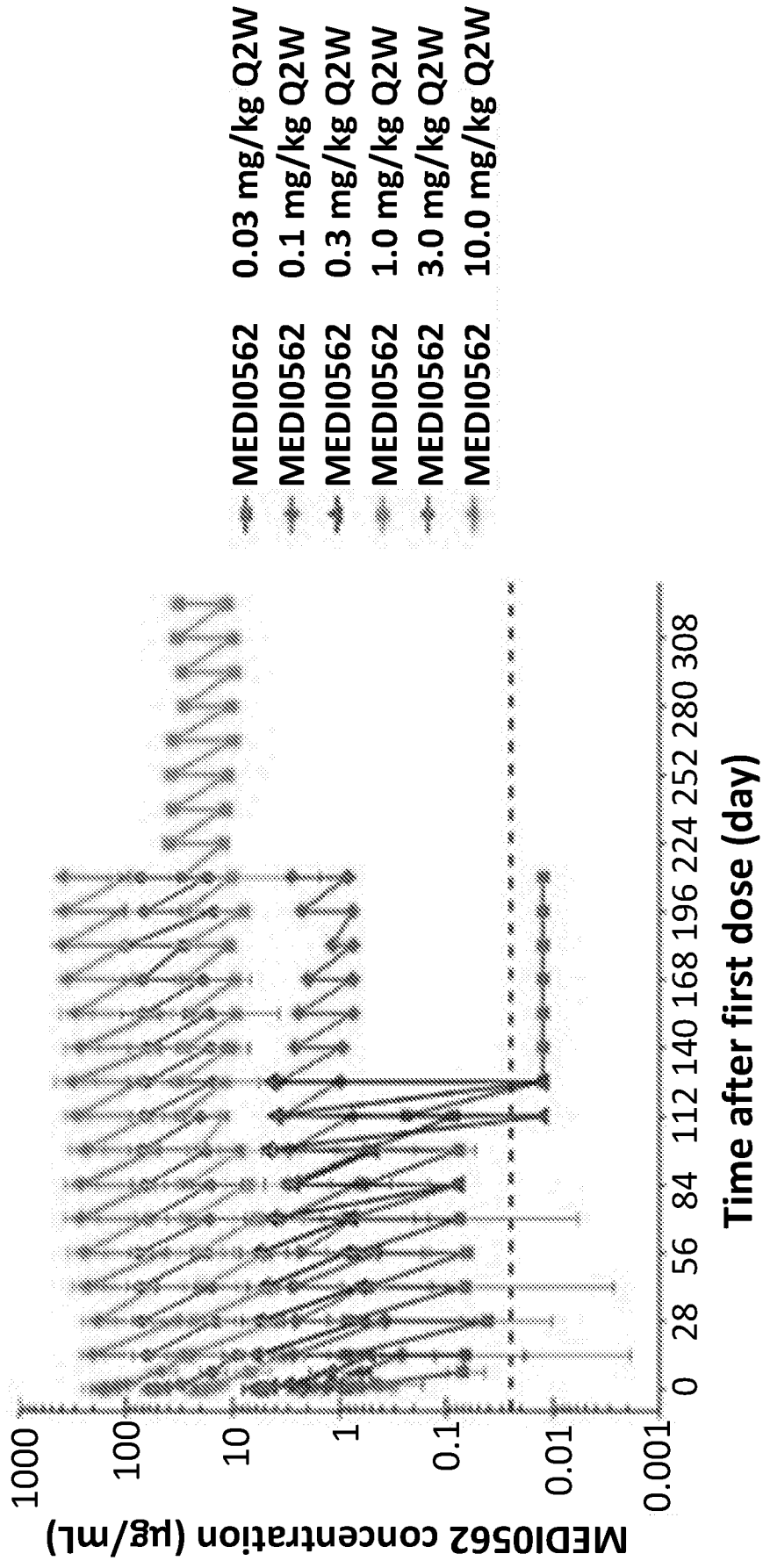

MEDI0562 0.03 mg/kg Q2W
MEDI0562 0.1 mg/kg Q2W
MEDI0562 0.3 mg/kg Q2W
MEDI0562 1.0 mg/kg Q2W
MEDI0562 3.0 mg/kg Q2W
MEDI0562 10.0 mg/kg Q2W
MEDI0562 concentration (µg/mL)
1000
100
10
1
0.1
0.01
0.001
0 28 56 84 112 140 168 196 224 252 280 308
Time after first dose (day)

Figure 20

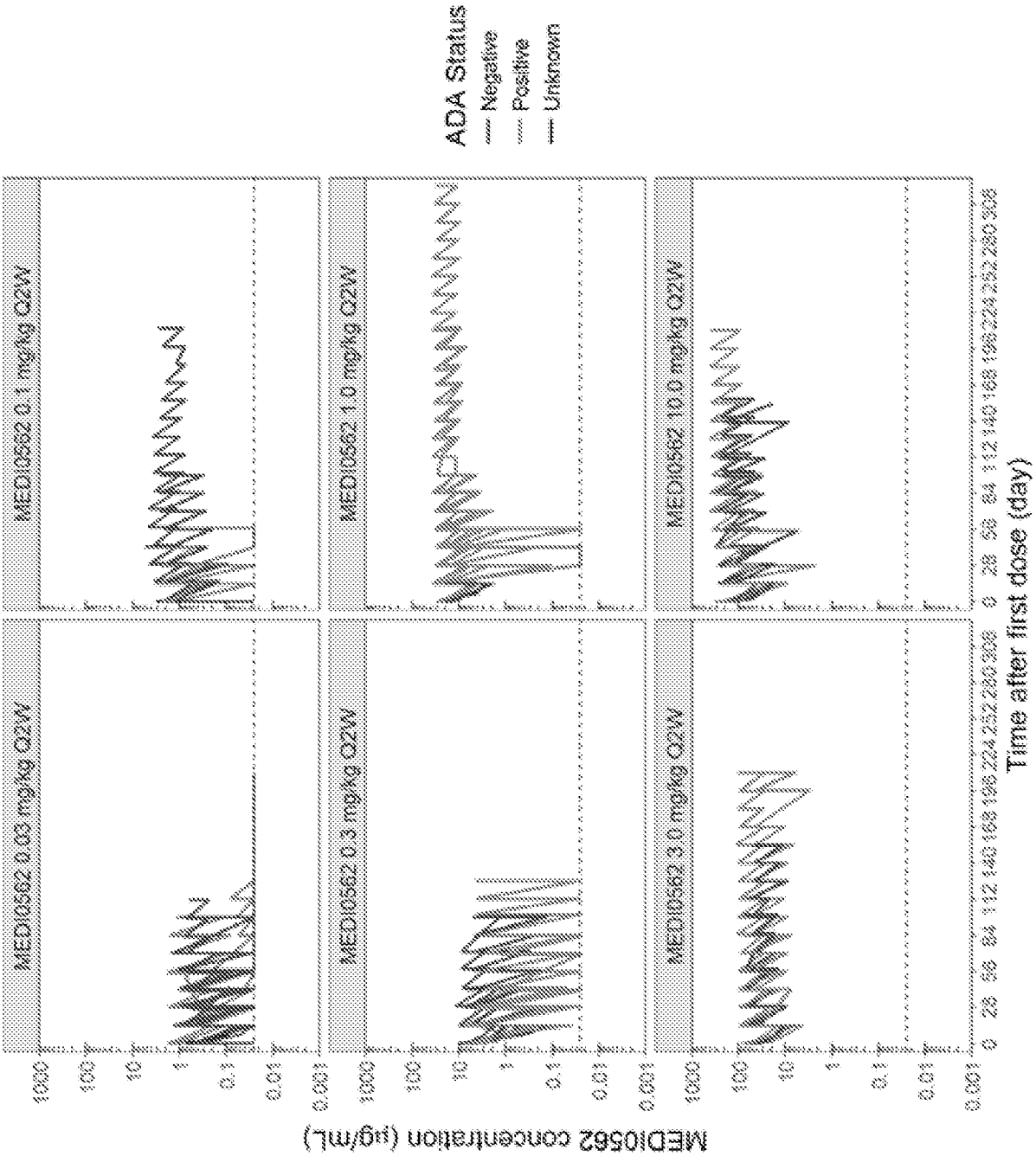

MED10562 0.03 mg/kg Q2W
MED10562 0.1 mg/kg Q2W
MED10562 0.3 mg/kg Q2W
MED10562 1.0 mg/kg Q2W
MED10562 3.0 mg/kg Q2W
MED10562 10.0 mg/kg Q2W
ADA Status
Negative
Positive
Unknown
MED10562 concentration (µg/mL)
Time after first dose (day)

Figure 21

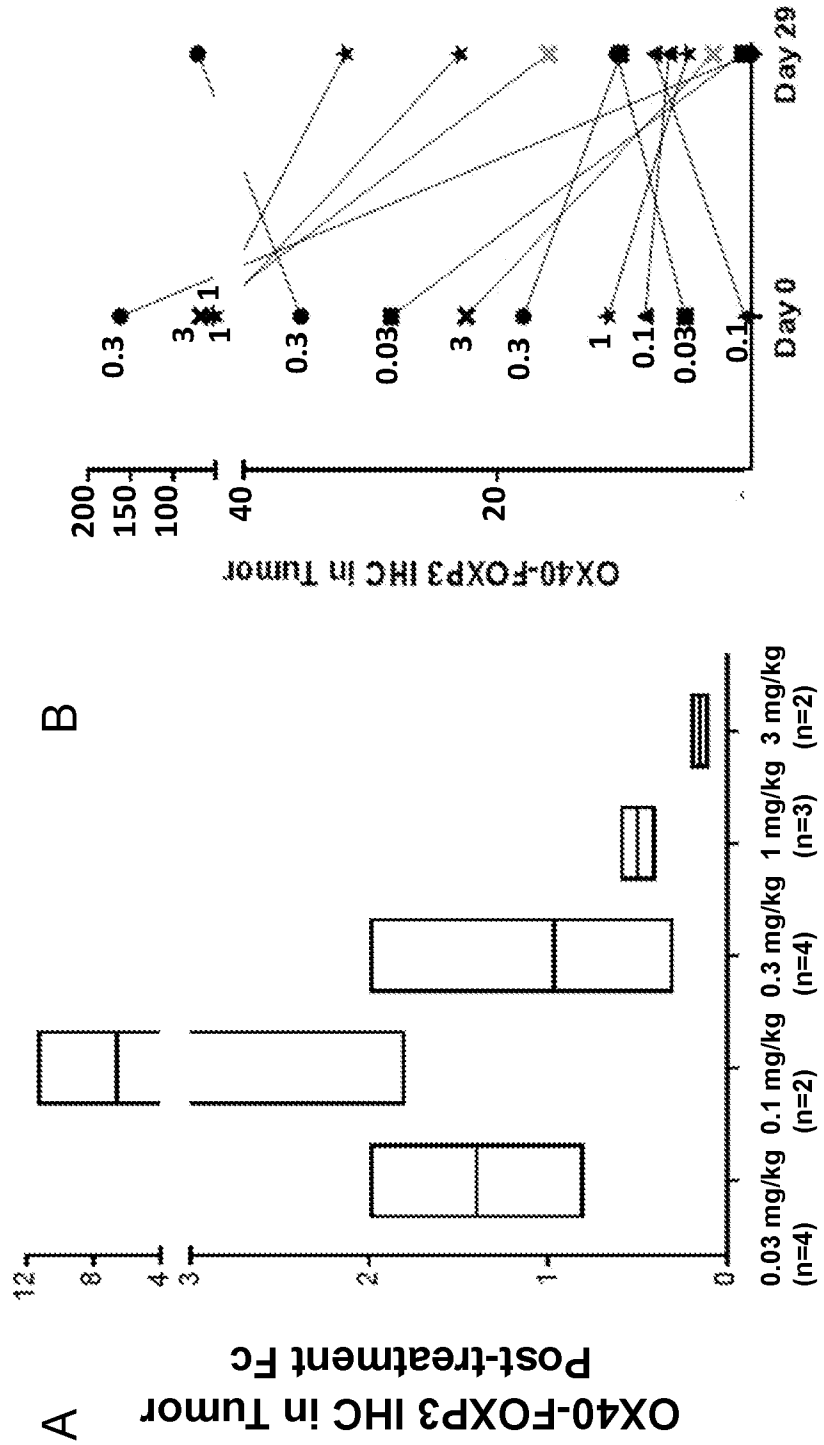

A
OX40-FOXP3 IHC in Tumor
Post-treatment Fc
12
8
4
3
2
1
0
0.03 mg/kg (n=4)
0.1 mg/kg (n=2)
0.3 mg/kg (n=4)
1 mg/kg (n=3)
3 mg/kg (n=2)
B
OX40-FOXP3 IHC in Tumor
200
150
100
40
20
Day 0
Day 29
0.3
3
1
0.3
0.03
3
0.3
1
0.1
0.03
0.1

Figure 21 Cont'd.

C


Representative data from tumor samples pre/post treatment with MEDI0562

Figure 22A

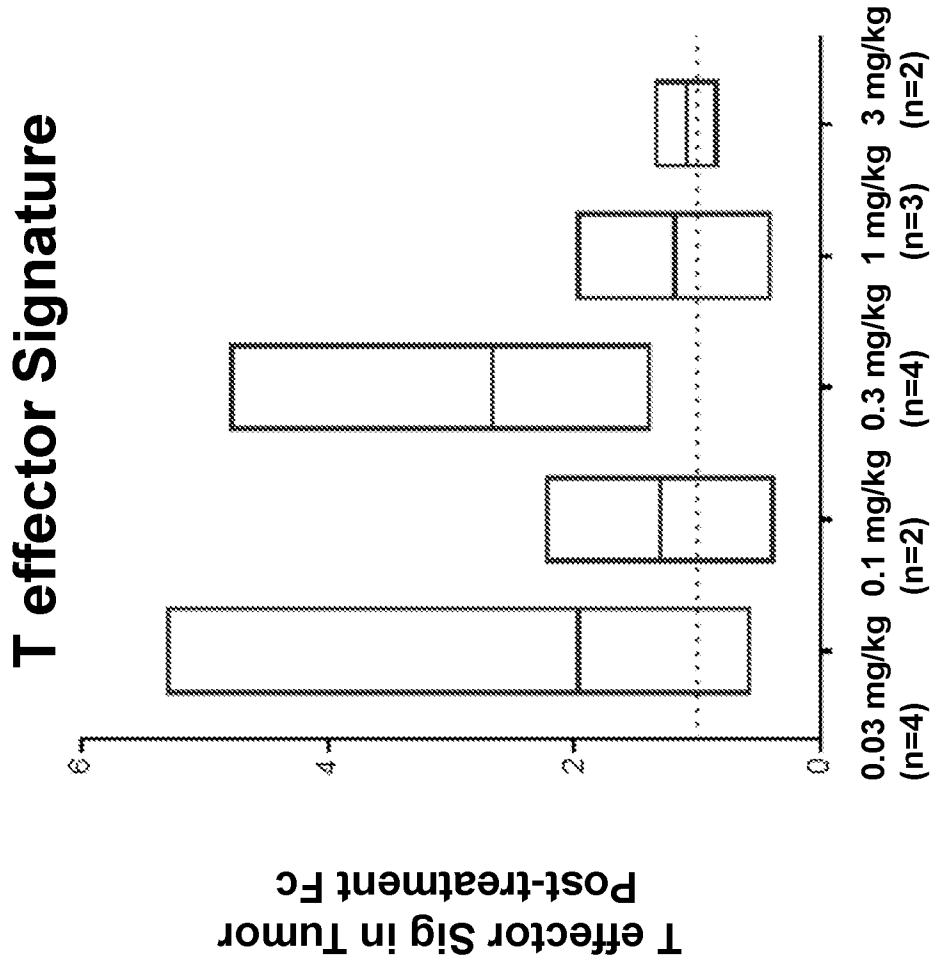

T effector Signature
T effector Sig in Tumor
Post-treatment Fc
0
2
4
6
0.03 mg/kg (n=4)
0.1 mg/kg (n=2)
0.3 mg/kg (n=4)
1 mg/kg (n=3)
3 mg/kg (n=2)

Figure 22B

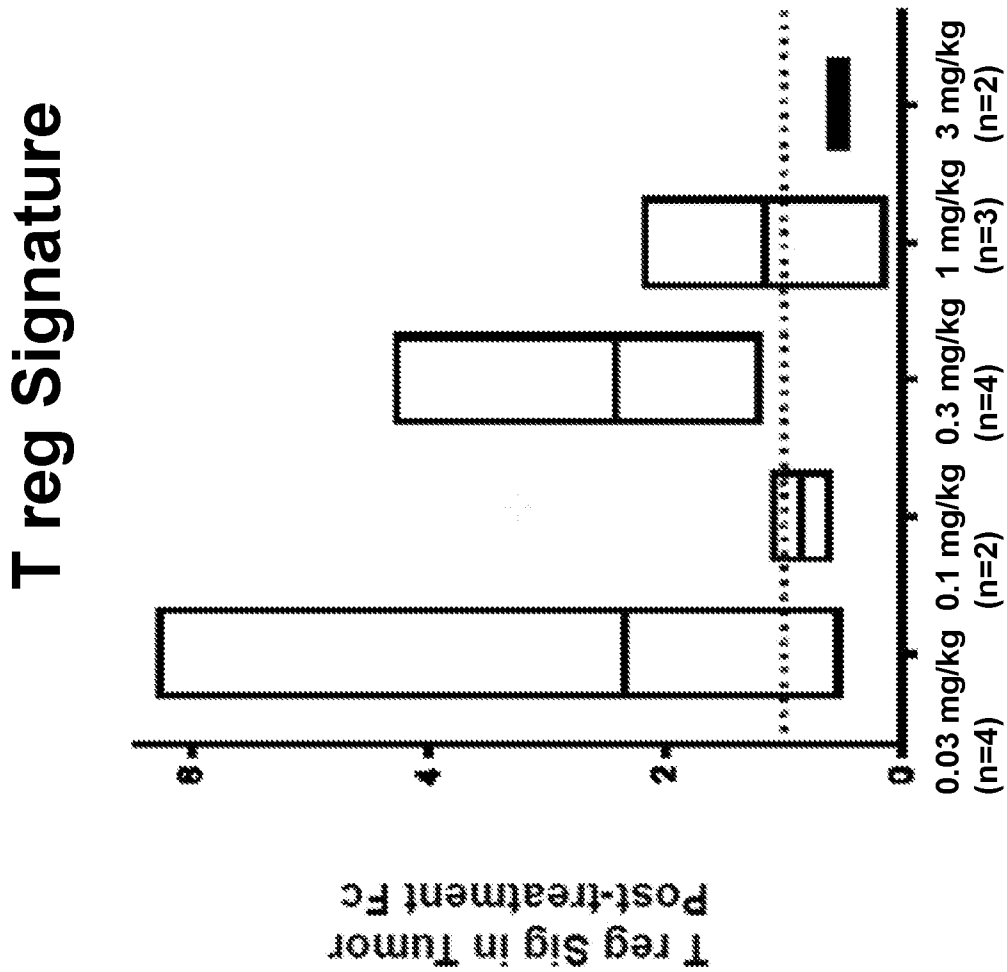

T reg Signature
T reg Sig in Tumor
Post-treatment Fc
0
2
4
6
0.03 mg/kg (n=4)
0.1 mg/kg (n=2)
0.3 mg/kg (n=4)
1 mg/kg (n=3)
3 mg/kg (n=2)

Figure 22C

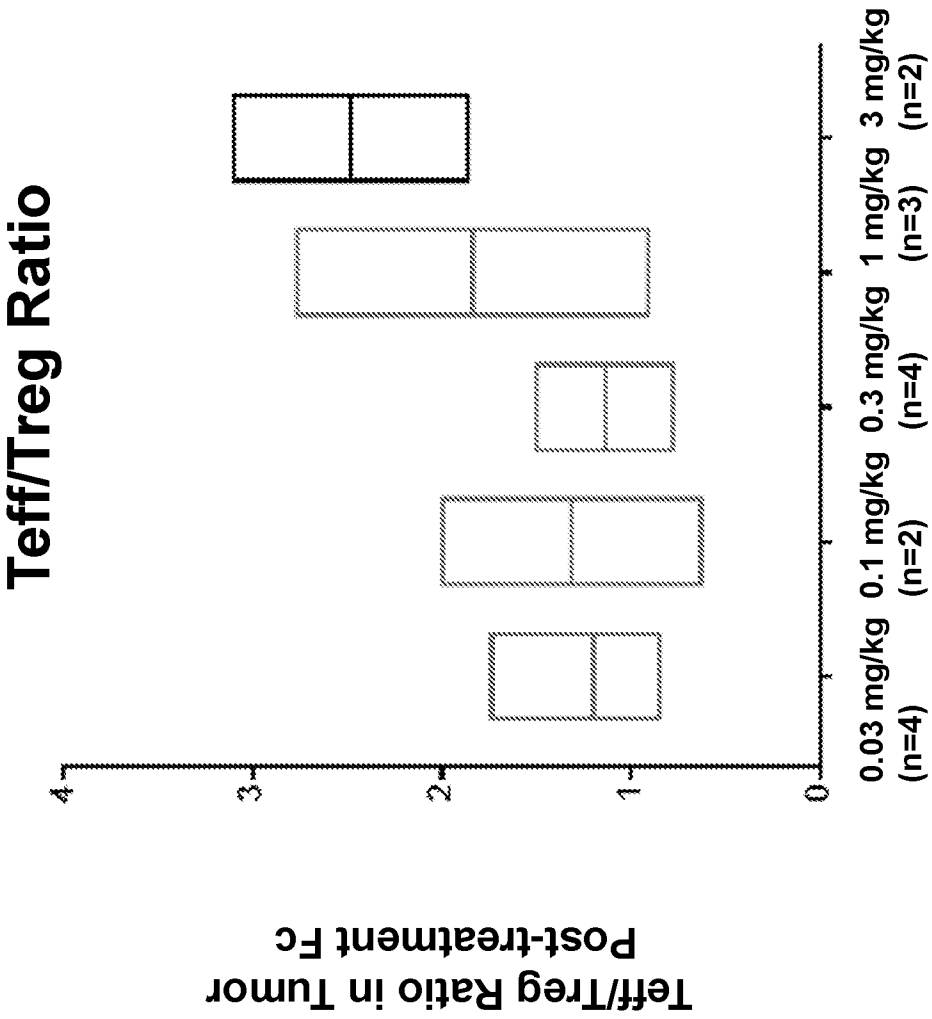

Teff/Treg Ratio
Teff/Treg Ratio in Tumor
Post-treatment Fc
0
1
2
3
4
0.03 mg/kg (n=4)
0.1 mg/kg (n=2)
0.3 mg/kg (n=4)
1 mg/kg (n=3)
3 mg/kg (n=2)

Figure 23A

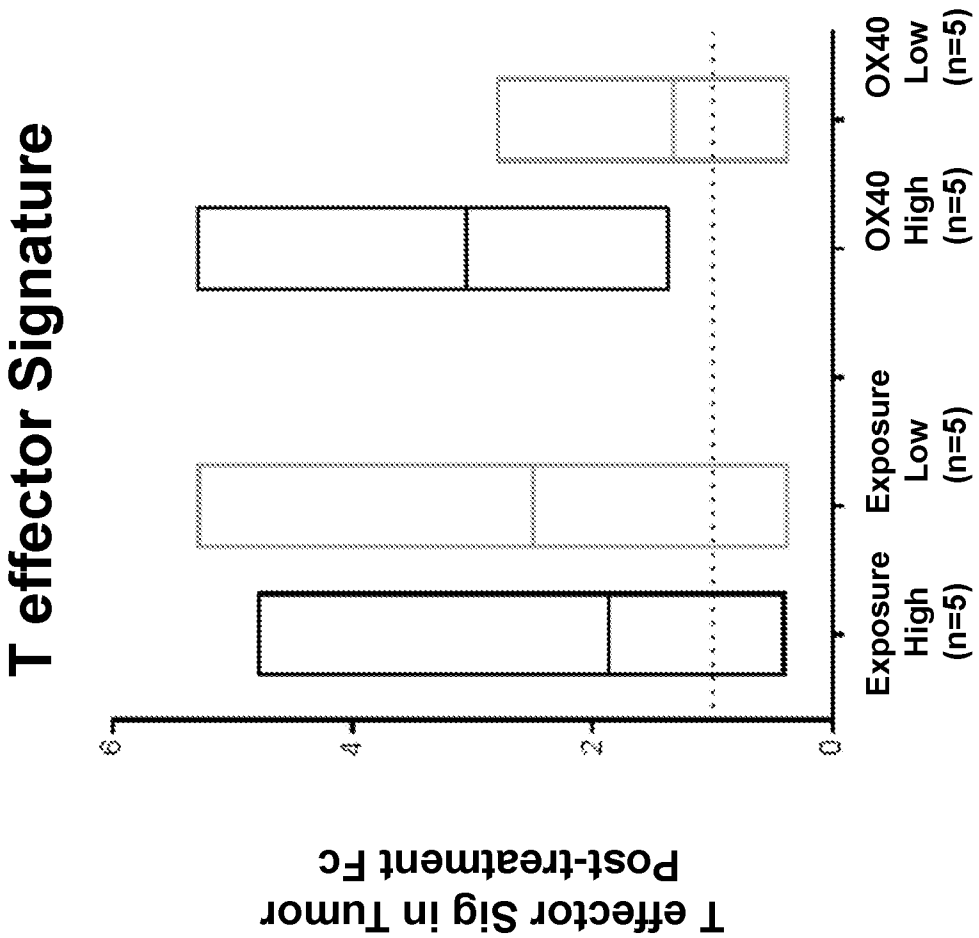

T effector Signature
T effector Sig in Tumor
Post-treatment Fc
0
4
8
Exposure High (n=5)
Exposure Low (n=5)
OX40 High (n=5)
OX40 Low (n=5)

Figure 23B

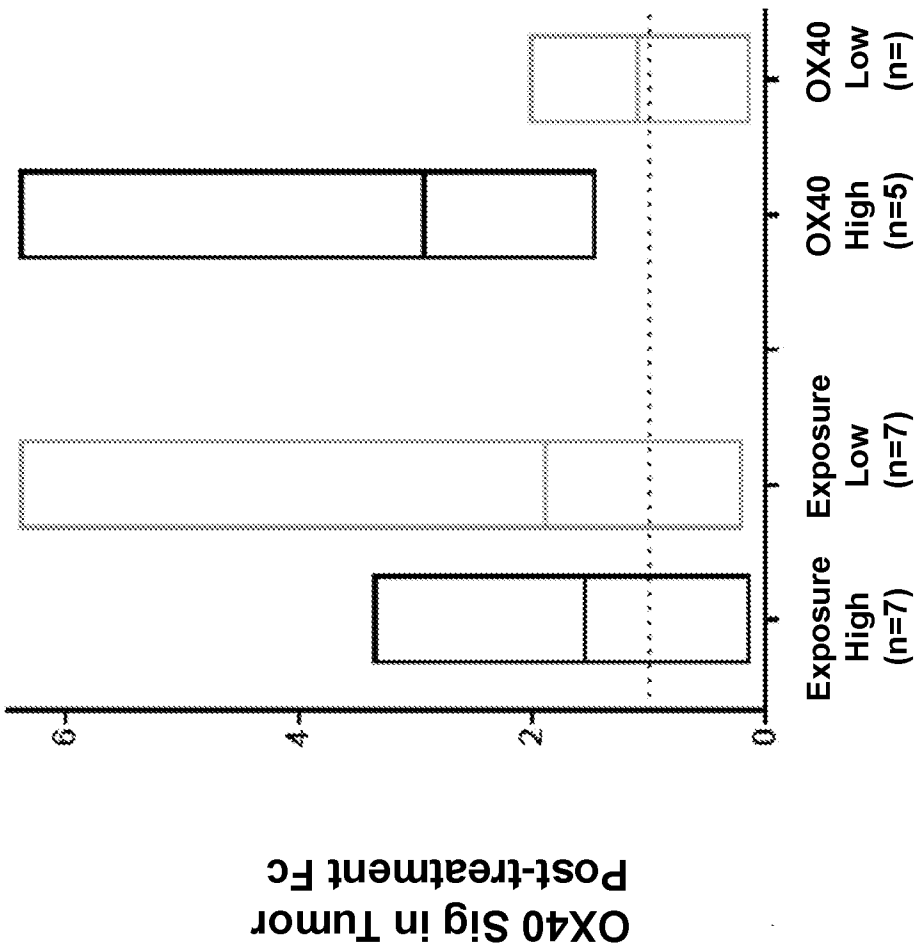

OX40 Signature
OX40 Sig in Tumor Post-treatment Fc
0
2
4
6
Exposure High (n=7)
Exposure Low (n=7)
OX40 High (n=5)
OX40 Low (n=)

Figure 23C

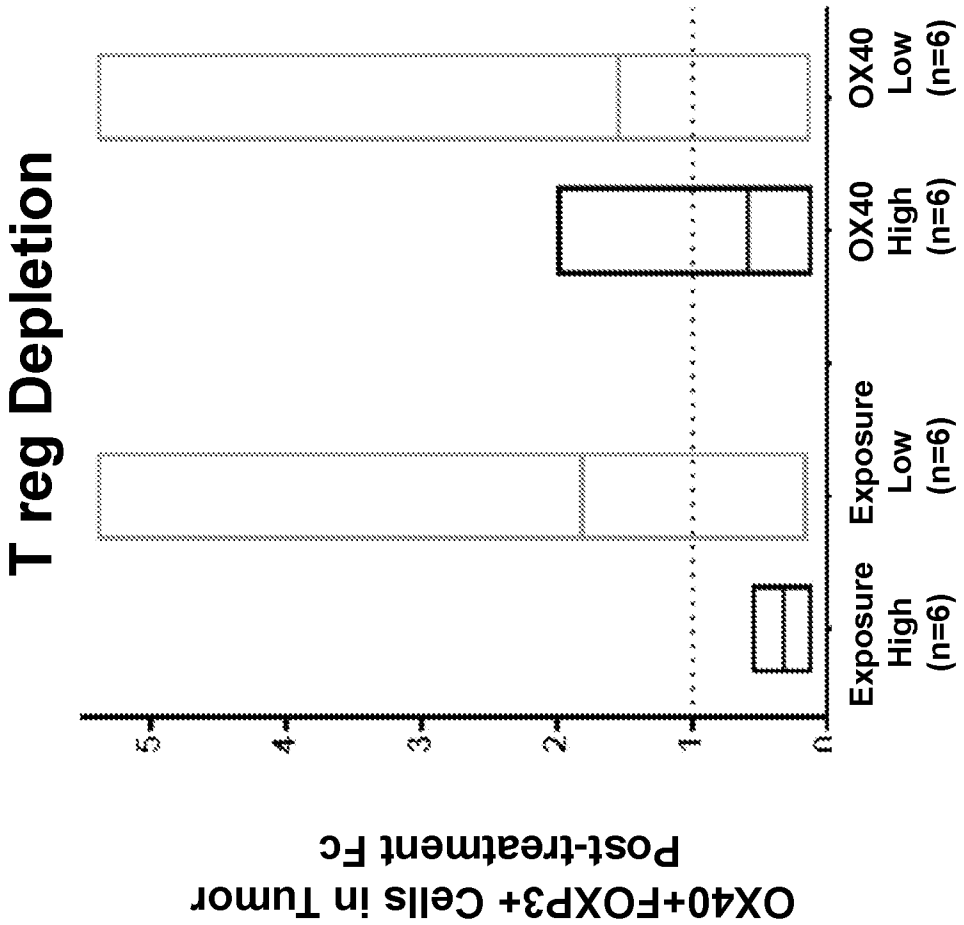

T reg Depletion
OX40+FOXP3+ Cells in Tumor
Post-treatment Fc
0
1
2
3
4
5
Exposure High (n=6)
Exposure Low (n=6)
OX40 High (n=6)
OX40 Low (n=6)

Figure 24

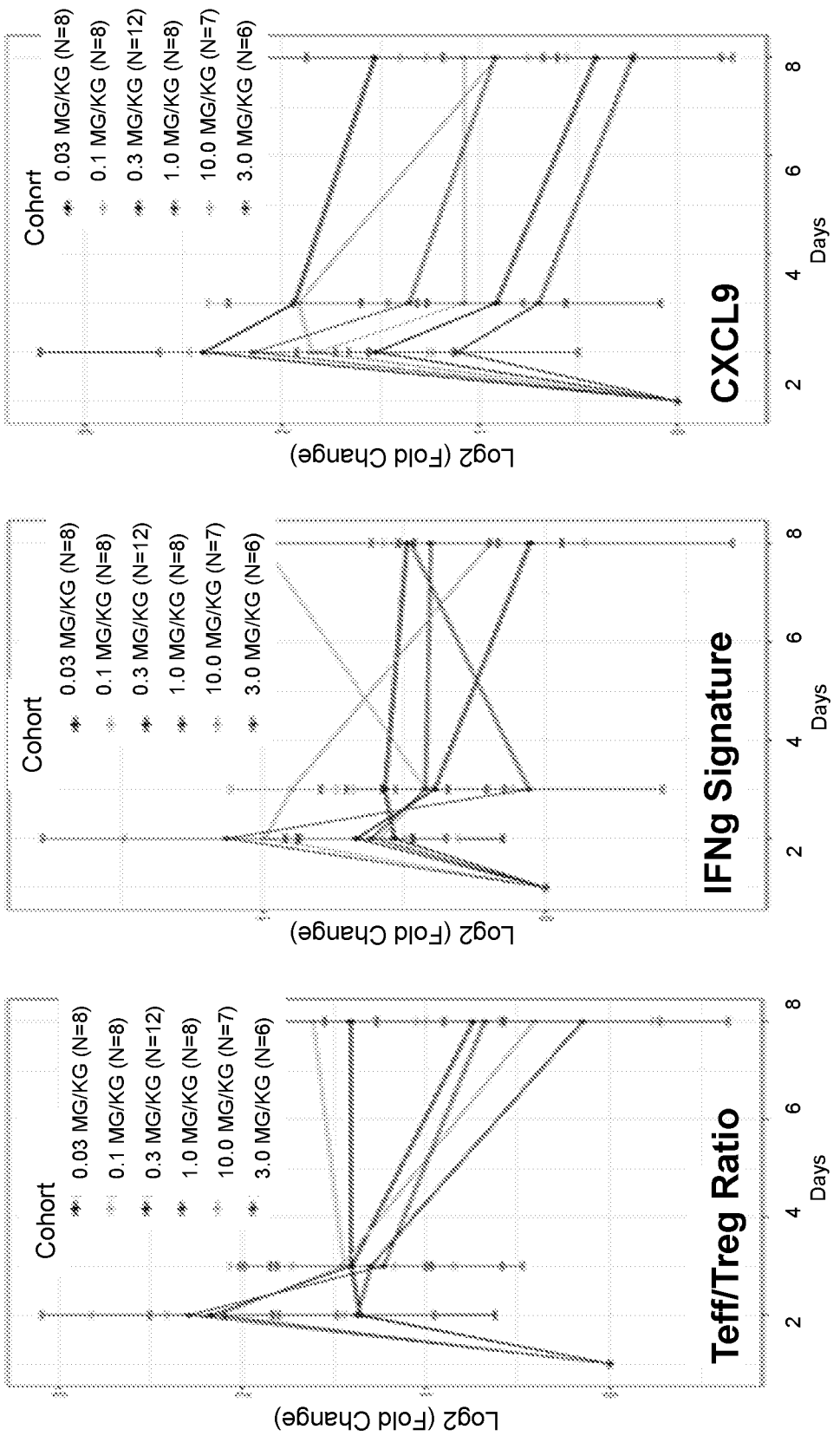

Teff/Treg Ratio
IFNg Signature
CXCL9
Log2 (Fold Change)
Days
Cohort
0.03 MG/KG (N=8)
0.1 MG/KG (N=8)
0.3 MG/KG (N=12)
1.0 MG/KG (N=8)
10.0 MG/KG (N=7)
3.0 MG/KG (N=6)
A
B
C

Figure 24 Cont'd.

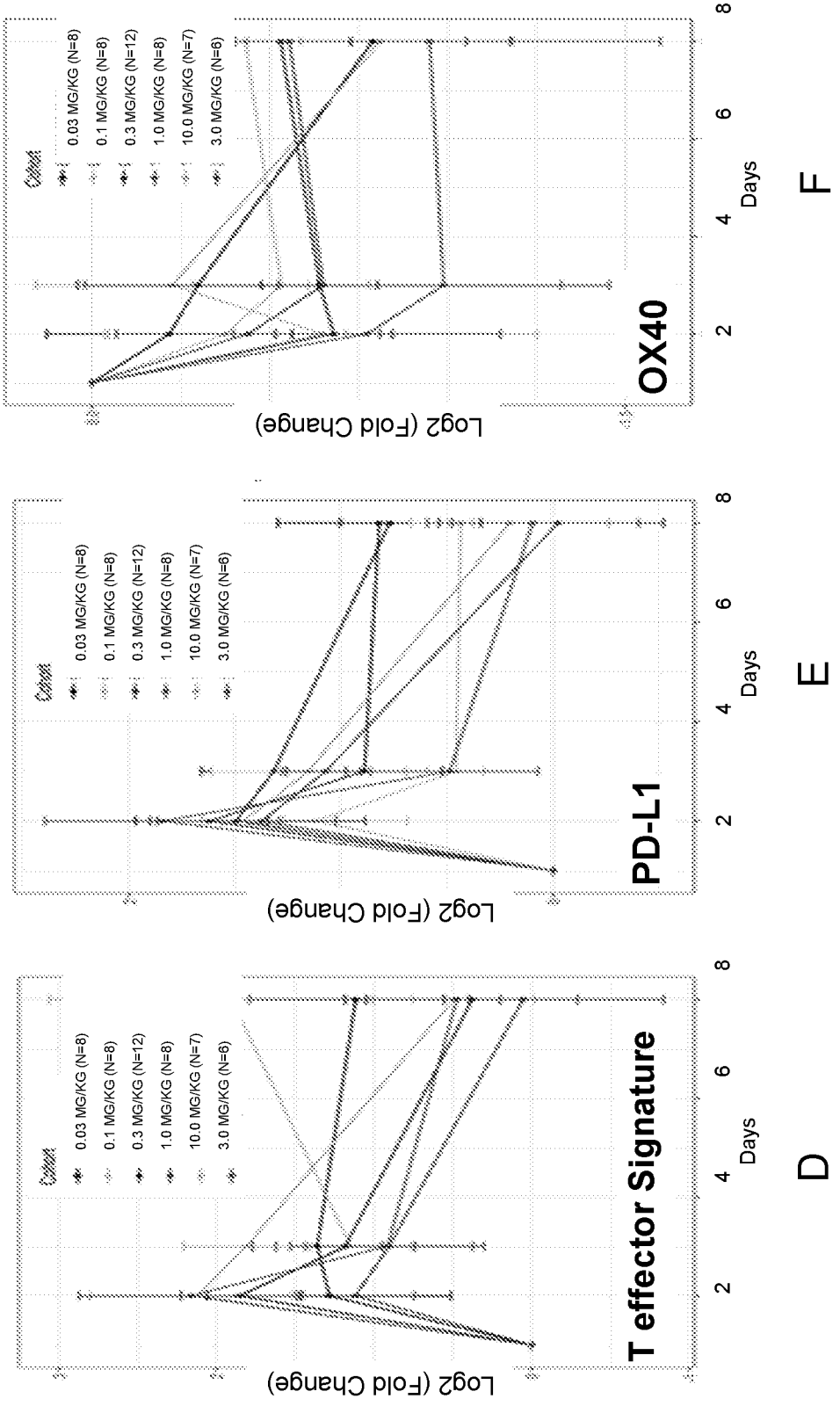


Figure 25

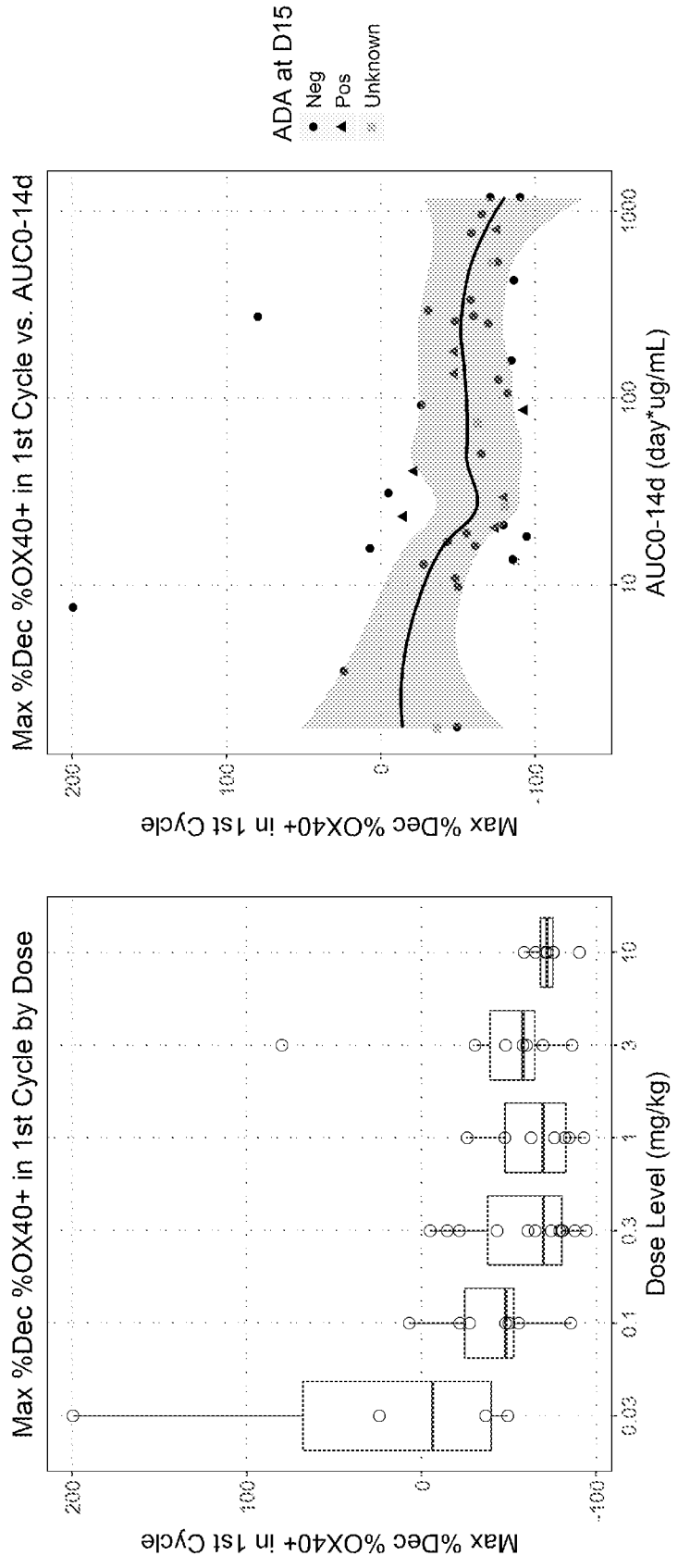
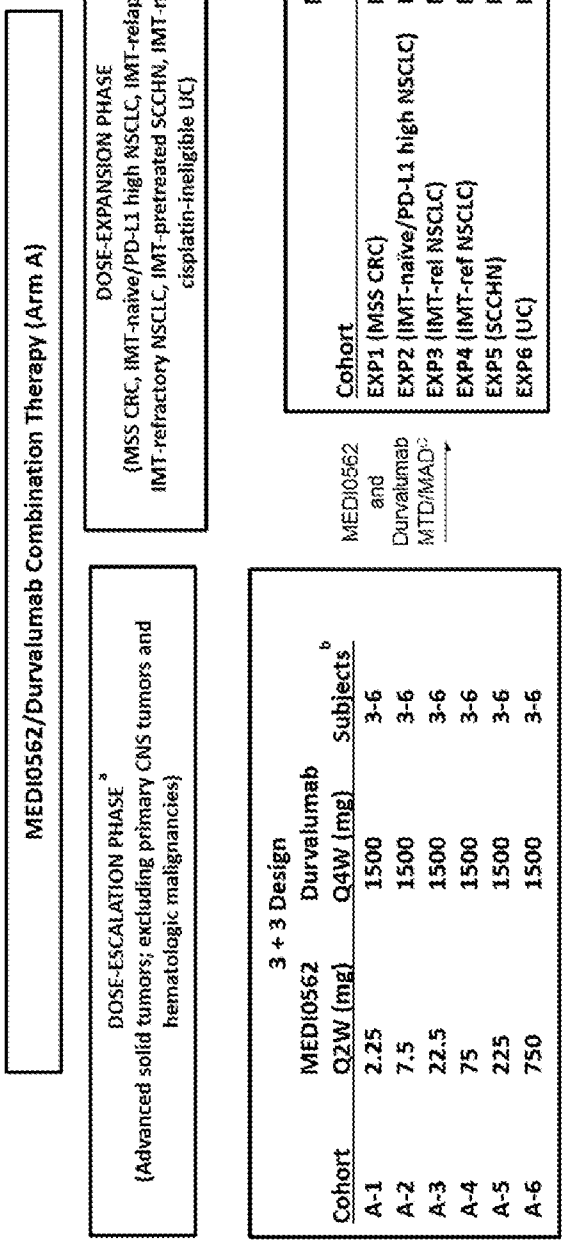

Max %Dec %OX40+ in 1st Cycle by Dose
Max %Dec %OX40+ in 1st Cycle
200
100
0
-100
0.03
0.1
0.3
1
3
10
Dose Level (mg/kg)
A
Max %Dec %OX40+ in 1st Cycle vs. AUC0-14d
ADA at D15
Neg
Pos
Unknown
Max %Dec %OX40+ in 1st Cycle
200
100
0
-100
1
10
100
1000
AUC0-14d (day*ug/mL)
B

Figure 26


MEDI0562/Durvalumab Combination Therapy (Arm A)
DOSE-ESCALATION PHASE[a]
(Advanced solid tumors; excluding primary CNS tumors and hematologic malignancies)
DOSE-EXPANSION PHASE
(MSS CRC, IMT-naive/PD-L1 high NSCLC, IMT-relapsed NSCLC, IMT-refractory NSCLC, IMT-pretreated SCCHN, IMT-naive first-line cisplatin-ineligible UC)
3 + 3 Design
Cohort | MEDI0562 Q2W (mg) | Durvalumab Q4W (mg) | Subjects[b]
A-1 | 2.25 | 1500 | 3-6
A-2 | 7.5 | 1500 | 3-6
A-3 | 22.5 | 1500 | 3-6
A-4 | 75 | 1500 | 3-6
A-5 | 225 | 1500 | 3-6
A-6 | 750 | 1500 | 3-6
MEDI0562 and Durvalumab MTD/MAD[c]
Cohort | MEDI0562 Q2W | Durvalumab Q4W | Subjects
EXP1 (MSS CRC) | MTD/MAD | MTD/MAD | Up to 40
EXP2 (IMT-naive/PD-L1 high NSCLC) | MTD/MAD | MTD/MAD | Up to 40
EXP3 (IMT-rel NSCLC) | MTD/MAD | MTD/MAD | Up to 40
EXP4 (IMT-ref NSCLC) | MTD/MAD | MTD/MAD | Up to 40
EXP5 (SCCHN) | MTD/MAD | MTD/MAD | Up to 40
EXP6 (UC) | MTD/MAD | MTD/MAD | Up to 40

# Figure 27

**MEDI0562/Tremelimumab Combination Therapy (Arm B)**

**DOSE- ESCALATION PHASE[a]**
**(Advanced solid tumors; excluding primary CNS tumors and hematologic malignancies)**

**3 + 3 Design**

| Cohort | MEDI0562 Q2W (mg) | Tremelimumab Q4W x 4 doses only (mg) | Subjects[b] |
|---|---|---|---|
| B-a1 | 2.25 | 75 | 3-6 |
| B-a2 | 2.25 | 225 | 3-6 |
| B-a3 | 2.25 | 750 | 3-6 |
| B-a4 | 7.5 | MTD/MAD | 3-6 |
| B-a5 | 22.5 | MTD/MAD | 3-6 |
| B-a6 | 75 | MTD/MAD | 3-6 |
| B-a7 | 225 | MTD/MAD | 3-6 |
| B-a8 | 750 | MTD/MAD | 3-6 |

***Optional: MEDI0562 + 75 mg Tremelimumab[d]***

**3 + 3 Design**

| Cohort | MEDI0562 Q2W (mg) | Tremelimumab Q4W x 4 doses only (mg) | Subjects[b] |
|---|---|---|---|
| B-b1 | 7.5 | 75 | 3-6 |
| B-b2 | 22.5 | 75 | 3-6 |
| B-b3 | 75 | 75 | 3-6 |
| B-b4 | 225 | 75 | 3-6 |
| B-b5 | 750 | 75 | 3-6 |

MEDI0562 and Tremelimumab MTD/MAD[c]

**DOSE- EXPANSION PHASE**
**(Unresectable IMT-pretreated HCC, IMT-pretreated MEL)**

| Cohort | MEDI0562 Q2W | Tremelimumab Q4W | Subjects[b] |
|---|---|---|---|
| EXP1 (HCC) | MTD/MAD | MTD/MAD | Up to 40 |
| EXP2 (MEL) | MTD/MAD | MTD/MAD | Up to 40 |

Figure 28

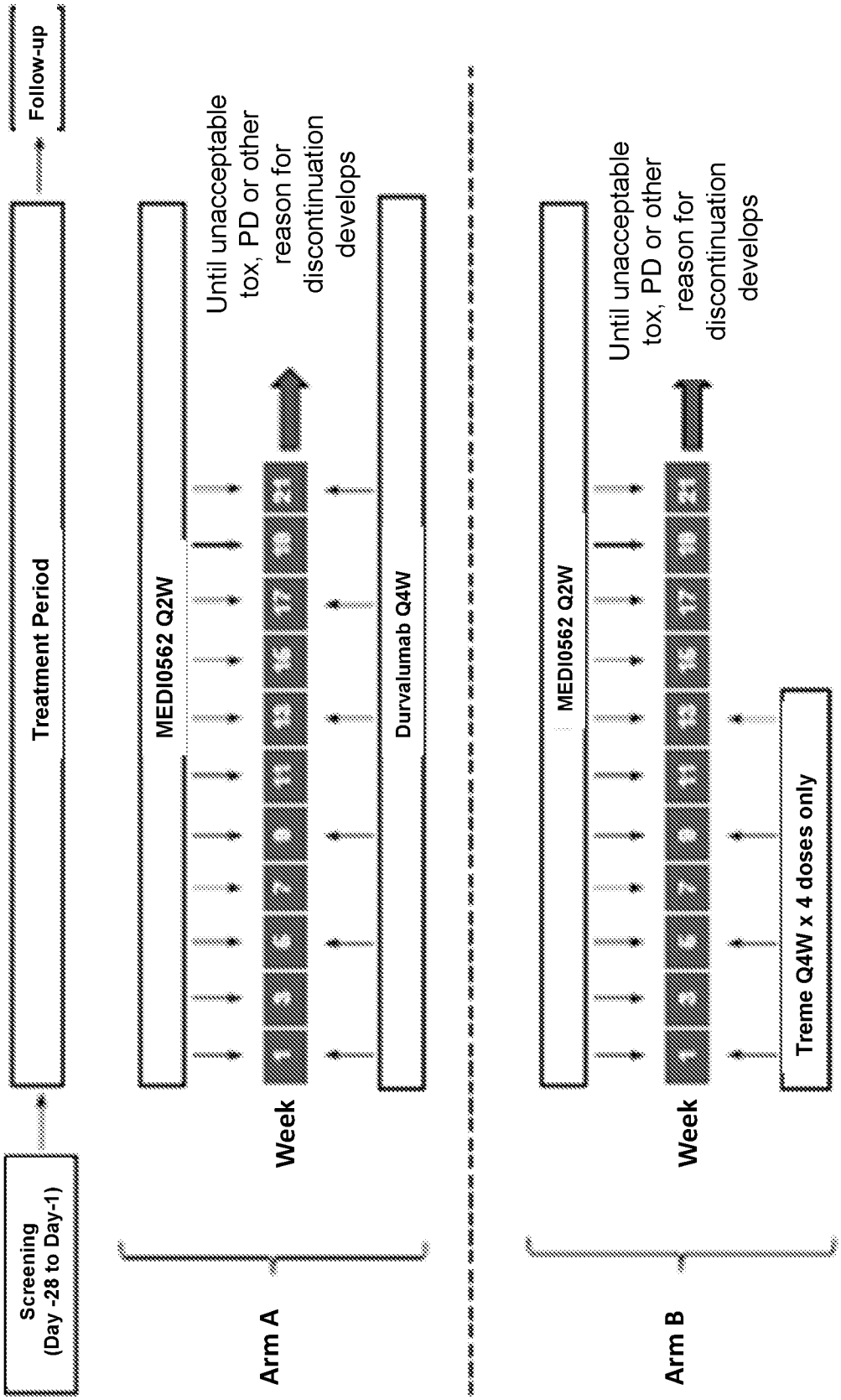

Screening
(Day -28 to Day-1)
Treatment Period
Follow-up
Arm A
MEDI0562 Q2W
Durvalumab Q4W
Week
1
3
5
7
9
11
13
15
17
19
21
Until unacceptable tox, PD or other reason for discontinuation develops
Arm B
MEDI0562 Q2W
Treme Q4W x 4 doses only
Week
1
3
5
7
9
11
13
15
17
19
21
Until unacceptable tox, PD or other reason for discontinuation develops

Figure 29

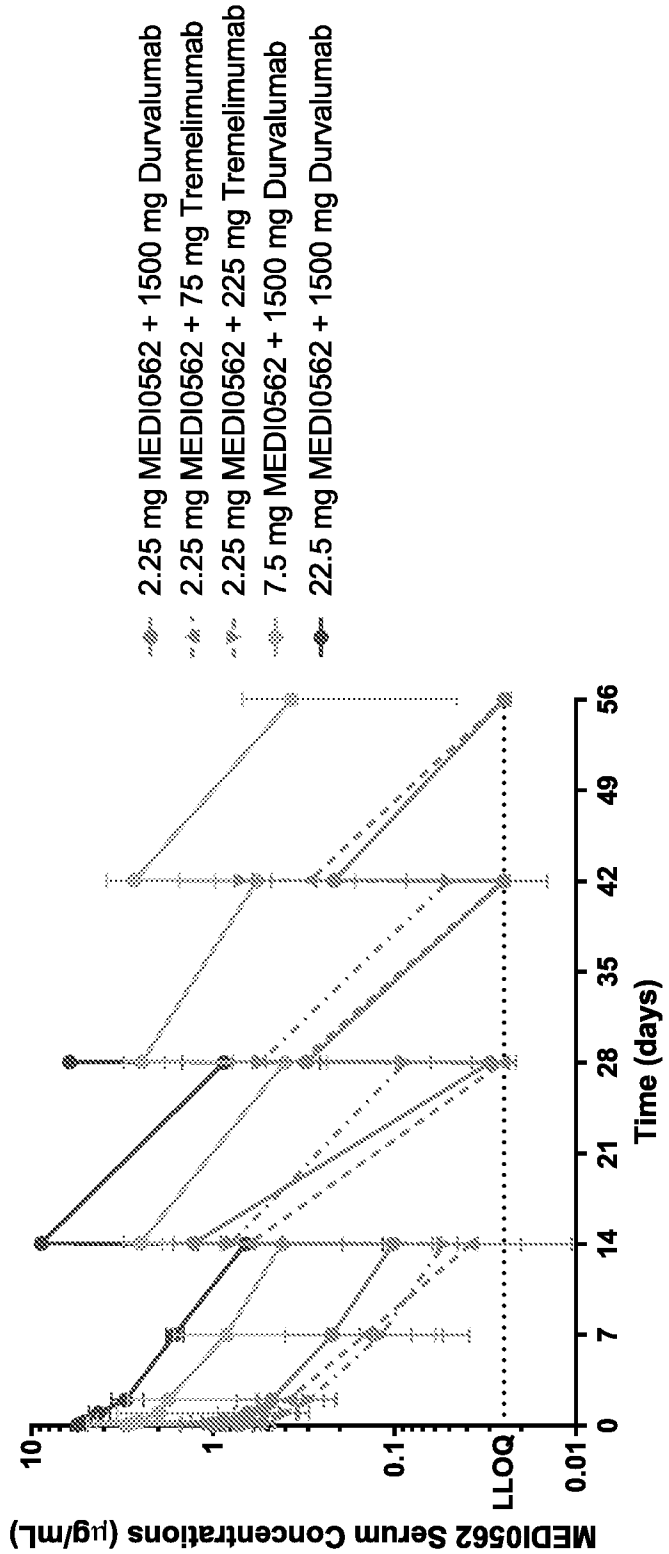

2.25 mg MEDI0562 + 1500 mg Durvalumab
2.25 mg MEDI0562 + 75 mg Tremelimumab
2.25 mg MEDI0562 + 225 mg Tremelimumab
7.5 mg MEDI0562 + 1500 mg Durvalumab
22.5 mg MEDI0562 + 1500 mg Durvalumab
MEDI0562 Serum Concentrations (µg/mL)
10
1
0.1
LLOQ
0.01
0
7
14
21
28
35
42
49
56
Time (days)

Figure 30A

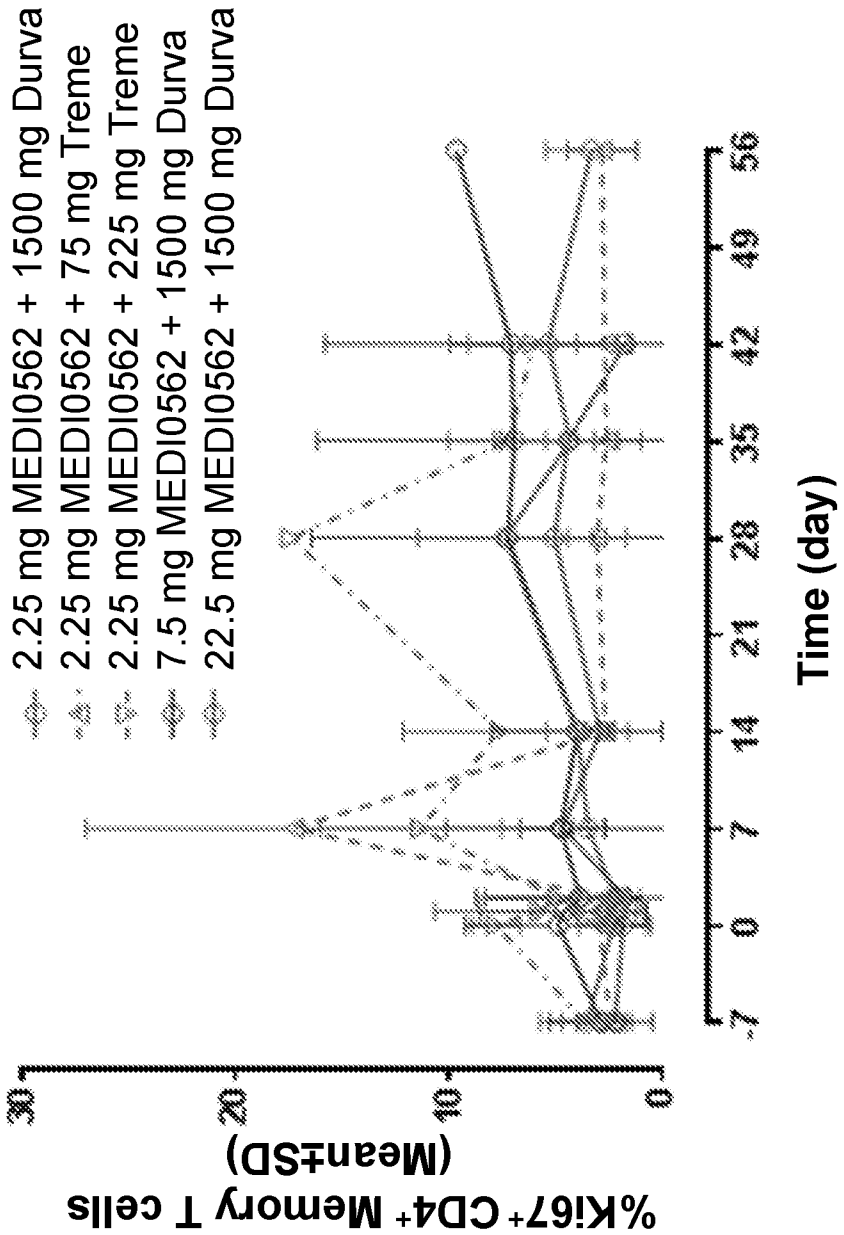

%Ki67+ CD4+ Memory T cells
2.25 mg MEDI0562 + 1500 mg Durva
2.25 mg MEDI0562 + 75 mg Treme
2.25 mg MEDI0562 + 225 mg Treme
7.5 mg MEDI0562 + 1500 mg Durva
22.5 mg MEDI0562 + 1500 mg Durva
%Ki67+ CD4+ Memory T cells (Mean±SD)
30
20
10
0
-7
0
7
14
21
28
35
42
49
56
Time (day)

FIG. 30B

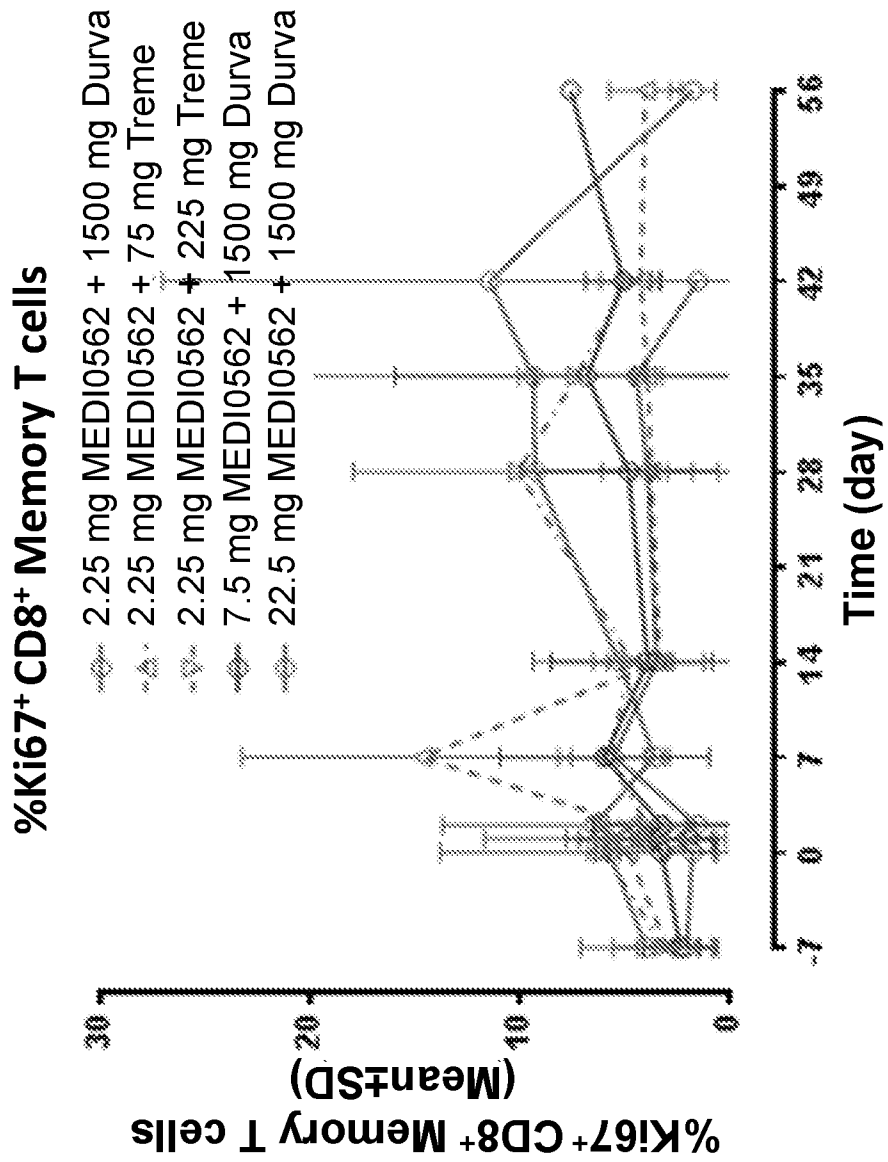
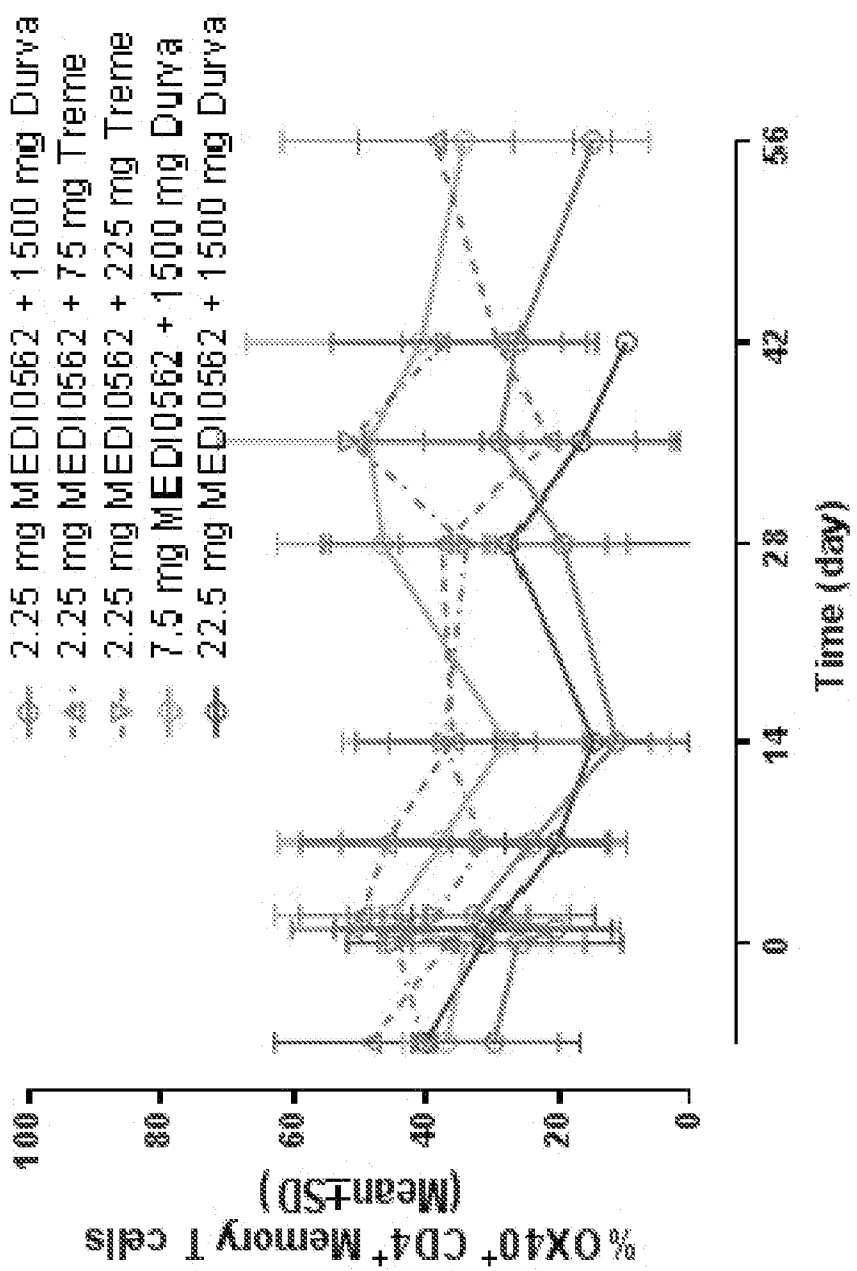

%Ki67+ CD8+ Memory T cells
2.25 mg MEDI0562 + 1500 mg Durva
2.25 mg MEDI0562 + 75 mg Treme
2.25 mg MEDI0562 + 225 mg Treme
7.5 mg MEDI0562 + 1500 mg Durva
22.5 mg MEDI0562 + 1500 mg Durva
%Ki67+ CD8+ Memory T cells (Mean±SD)
30
20
10
0
-7
0
7
14
21
28
35
42
49
56
Time (day)

Figure 30C


% OX40+ CD4+ Memory T cells
2.25 mg MEDI0562 + 1500 mg Durva
2.25 mg MEDI0562 + 75 mg Treme
2.25 mg MEDI0562 + 225 mg Treme
7.5 mg MEDI0562 + 1500 mg Durva
22.5 mg MEDI0562 + 1500 mg Durva
% OX40+ CD4+ Memory T cells (Mean±SD)
100
80
60
40
20
0
0
14
28
42
56
Time (day)