PD-L1 ANTAGONIST COMBINATION TREATMENTS

Field

The present invention relates to combination therapies useful for the treatment of cancer. In particular, the invention relates to a combination therapy which comprises an antagonist of a Programmed Death-Ligand 1 protein (PD-L1) and one or more additional therapeutic agent(s).

Background

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults. Until 2005, interferon-alpha (IFN-α) and high-dose interleukin (IL)-2 therapies were the standards of care for patients with advanced RCC (aRCC), albeit with modest efficacy. Since then, development and approval of multiple vascular endothelial growth factor (VEGF) pathway and mammalian target of rapamycin (mTOR) inhibitors have significantly improved the outcomes of aRCC patients. These agents include the VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, axitinib and sorafenib, the mTOR inhibitors temsirolimus and everolimus, and the anti-VEGF monoclonal antibody bevacizumab. However, despite the substantial improvement of patient outcomes with these agents, durable and complete responses in aRCC patients are uncommon; the majority of patients will eventually develop resistance, exhibit disease progression while on therapy, and succumb to death due to metastatic disease.

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1 and PD-L2, respectively) play integral roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 (also known as B7-H1) and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T-cell death and localized immune suppression (Dong et al., Nat Med 1999; 5:1365-69; Freeman et al. J Exp Med 2000; 192:1027-34), potentially providing an immune-toleraant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate antitumor activity in nonclinical animal models (Iwai Y, et al. Proc Natl Acad Sci USA 2002; 99:12293-97). Avelumab is a fully human mAb of the IgG1 isotype that specifically targets and blocks PD-L1. Avelumab is the International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody MSB0010718C.

Axitinib is a VEGF receptor (VEGFR) TKI. The antitumor activity of single-agent axitinib 5 mg twice daily (BID) in previously untreated patients with clear cell aRCC was assessed against sorafenib in a randomized, open-label, Phase 3 trial. Although the study did not demonstrate a statistically significant difference in progression-free survival (PFS) between patients treated with axitinib or sorafenib, axitinib was associated with a longer median PFS (mPFS) time (mPFS of 10.1 months (95% CI 7.2,12.1) with axitinib vs. 6.5 months (95% CI 4.7, 8.3) with sorafenib, stratified hazard ratio 0.77 (95% CI 0.56, 1.05).

4-1BB (CD137 and TNFRSF9), which was first identified as an inducible costimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated NK and NKT cells; regulatory T cells; dendritic cells (DC) including follicular DC; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils, and activated B cells. 4-1BB expression has also been demonstrated on tumor vasculature (19-20) and atherosclerotic endothelium. The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells. 4-1BB agonist mAbs increase costimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T cell memory responses

Macrophage colony stimulating factor (M-CSF) is a member of the family of proteins referred to as colony stimulating factors (CSFs). M-CSF, also known as CSF-1, is a secreted or a cell surface glycoprotein comprised of two subunits that are joined by a disulfide bond with a total molecular mass varying from 40 to 90 kD ((Stanley E. R., et al., *Mol. Reprod. Dev.*, 46:4-10 (1997)). Similar to other CSFs, M-CSF is produced by macrophages, monocytes, and human joint tissue cells, such as chondrocytes and synovial fibroblasts, in response to proteins such as interleukin-1 or tumor necrosis factor-alpha. M-CSF stimulates the formation of macrophage colonies from pluripotent hematopoietic progenitor stem cells (Stanley E. R., et al., *Mol. Reprod. Dev.*, 46:4-10 (1997)). M-CSF typically bind to its receptor, c-fms, in order to exert a biological effect.

c-fms contains five extracellular Ig domains, one transmembrane domain, and an intracellular domain with two kinase domains. Upon M-CSF binding to c-fms, the receptor homo-dimerizes and initiates a cascade of signal transduction pathways including the JAK/STAT, PI3K, and ERK pathways.

The OX40 receptor (OX40, also known as CD134, TNFRSF4, ACT-4, ACT35, and TXGP1L) is a member of the TNF receptor superfamily. OX40 is found to be expressed on activated CD4+ T-cells. High numbers of OX40+ T cells have been demonstrated within tumors (tumor infiltrating lymphocytes) and in the draining lymph nodes of cancer patients (Weinberg, A. et al., J. Immunol. 164: 2160-69, 2000; Petty, J. et al., Am. J. Surg. 183: 512-518, 2002). It was shown in tumor models in mice that engagement of OX40 in vivo during tumor priming significantly delayed and prevented the appearance of tumors as compared to control treated mice (Weinberg et al., 2000). Therefore, it has been contemplated to enhance the immune response of a mammal to an antigen by engaging OX40 through the use of an OX40 binding agent (WO 99/42585; Weinberg et al., 2000).

The rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. Rituximab is the antibody called “C2B8” in U.S. Pat. No. 5,736,137 issued Apr. 7, 1998 (Anderson et al.). rituximab is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma. In vitro mechanism of action studies have demonstrated that rituximab binds human complement and lyses lymphoid B cell lines through complement-dependent cytotoxicity (CDC) (Reff et al. *Blood* 83(2):435-445 (1994)). Additionally, it has significant activity in assays for antibody-dependent cellular cytotoxicity (ADCC).

There is a need for improved therapies for the treatment of cancers. Furthermore, there is a need for therapies having greater efficacy than existing therapies. Preferred combination therapies of the present invention show greater efficacy than treatment with either therapeutic agent alone.

Summary

This invention relates to therapeutic regimens for treatment of cancer.

Provided herein are methods for treating a cancer in a subject. Also provided are methods of inhibiting tumor growth or progression in a subject who has malignant cells. Also provided are methods of inhibiting metastasis of malignant cells in a subject. Also provided are methods of inducing tumor regression in a subject who has malignant cells.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist and a VEGFR inhibitor. In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with a VEGFR inhibitor for treating a cancer. In some embodiments, the invention provides a medicament comprising a VEGFR inhibitor for use in combination with a PD-L1 antagonist for treating a cancer. Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with a VEGFR inhibitor and use of a VEGFR inhibitor in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist. In some embodiments, the invention provides use of a PD-L1 antagonist and a VEGFR inhibitor in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with a VEGFR inhibitor to treat a cancer in a subject. In all of the above embodiments of the treatment method, medicaments and uses herein, the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide or a pharmaceutically acceptable salt thereof.

Also provided are kits comprising a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising an anti-PD-L1 antagonist, the second container comprises at least one dose of a medicament comprising a VEGFR inhibitor, and the package insert comprises instructions for treating a subject for cancer using the medicaments.

In some embodiments of the above methods, medicaments, uses or kits, the VEFR inhibitor can be axitinib and can be formulated as a 1 mg tablet, 3 mg tablet, or a 5 mg tablet.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-4-1BB antibody. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-M-CSF antibody. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-OX40 antibody. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and an anti-M-CSF antibody. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and an anti-OX40 antibody.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist and a CD20 antagonist. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, a CD20 antagonist, and an anti-4-1BB antibody. In some embodiments, the PD-L1 antagonist is avelumab and the CD20 antagonist is rituximab. In some embodiments, the anti-4-1BB antibody is PF-05082566. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 2 of each cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 1 of each cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 1 of each cycle, and avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 2 of each cycle, and

avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, avelumab is administered at least 3 hours after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, avelumab is administered about 60 minutes after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, avelumab is administered about 30 minutes after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, the cancer is R/R DLBCL.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, a CD20 antagonist, and bendamustine. In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, a CD20 antagonist, and bendamustine. In some embodiments, the PD-L1 antagonist is avelumab and the CD20 antagonist is rituximab. In some embodiments, the method comprises administering rituximab at a dose of 375 mg/m^2 IV on Day 1 of a 28 day cycle, bendamustine at a dose of 90 mg/m^2 IV on Day 2 and Day 3 of each 28 day cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, bendamustine at a dose of 90 mg/m^2 IV on Day 1 and Day 2 of each 28 day cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, bendamustine at a dose of 90 mg/m^2 IV on Day 2 and Day 3 of each 28 day cycle, and avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering rituximab at a dose of IV on Day 1 of a 28 day cycle, bendamustine at a dose of 90 mg/m^2 IV on Day 1 and Day 2 of each 28 day cycle, and avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, avelumab is administered at least 3 hours after bendamustine when avelumab and bendamustine are administered on the same day. In some embodiments, the cancer is R/R DLBCL.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises a PD-L1 antagonist, azacitidine, and an anti-4-

1BB antibody. In some embodiments, the method comprises administering to the subject a combination therapy which comprises avelumab, azacitidine, and PF-05082566. In some embodiments, the method comprises administering azacitidine at a daily dose of 75 mg/m^2 subcutaneously (SC) each day from Day 1 to Day 7 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 2 of each cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering azacitidine at a daily dose of 75 mg/m^2 SC each day from Day 1 to Day 7 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 1 of each cycle, and avelumab as a 1 hour IV infusion on Day 2 and Day 16 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering azacitidine at a daily dose of 75 mg/m^2 SC each day from Day 1 to Day 7 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 1 of each cycle, and avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, the method comprises administering azacitidine at a daily dose of 75 mg/m^2 SC each day from Day 1 to Day 7 of a 28 day cycle, PF-05082566 at a fixed dose of 100 mg as a 1 hour IV infusion on Day 2 of each cycle, and avelumab as a 1 hour IV infusion on Day 1 and Day 15 of each cycle at a dose of 10 mg/kg. In some embodiments, on the days when avelumab is administered on the same day as azacitidine, avelumab is administered at least 3 hours after administration of azacitidine. In some embodiments, avelumab is administered at least 3 hours after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, avelumab is administered about 60 minutes after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, avelumab is administered about 30 minutes after PF-05082566 when avelumab and PF-05082566 are administered on the same day. In some embodiments, the cancer is R/R DLBCL.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises avelumab and PF-05082566. In some embodiments, the cancer is advanced NSCLC, RCC, or urothelial cancer which was resistant (responded and then progressed) or refractory (never responded) to prior therapy(ies), including for example a single-agent immune checkpoint inhibitor (e.g., anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody treatment). In some

embodiments, avelumab is administered as a 1 hour IV infusion every 2 weeks at a dose of 10 mg/kg, PF-05082566 is administered at fixed dose of 10 mg as a 1 hour IV infusion once every four weeks on Day 1 of each cycle, and on days when both avelumab and PF-05082566 are administered, PF-05082566 is administered first, followed by avelumab infusion within 30 mintues after the end of the PF-05082566 infusion.

In some embodiments, the method comprises administering to the subject a combination therapy which comprises avelumab and chemoradiotherapy. In some embodiments, the chemoradiotherapy comprises cisplatin and definitive radiation therapy. In some embodiments, subject has locally-advanced squamous cell carcinoma of the head and neck (SCCHN). In some embodiments, the SCCHN is localized to the oral cavity, oropharynx, larynx, or hypopharynx. In some embodiments, the method comprises a lead-in phase and a chemoradiotherapy (CRT) phase, wherein the lead-in phase begins seven days prior to initiation of the CRT phase. In some embodiments, avelumab is administered at a dose of 10 mg/kg on Day 1 of the lead-in phase, and on Day 8, Day 29, and Day 39 of the CRT phase; cisplatin is administered at a dose of 100 mg/m^2 on Day 1, Day 22, and Day 23 of the CRT phase; and radiation therapy is 70 Gy/33-35 fractions/day, 5 fractions/week intensity modulated radiation therapy (IMRT). In some embodiments, the method comprises a maintenance phase which begins two weeks after completion of the CRT phase. In some embodiments the maintenance phase comprises administration of avelumab at a dose of 10 mg/kg every two weeks (Q2W) after completion of the CRT phase.

In all of the above treatment methods, medicaments and uses, the PD-L1 antagonist inhibits the binding of PD-L1 to PD-1. In some embodiments of the above treatment methods, medicaments and uses, the PD-L1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to PD-L1 or to PD-L1 and blocks the binding of PD-L1 to PD-1. In some embodiments, the PD-L1 antagonist is an anti-PD-L1 antibody which comprises three complementarity determining regions (CDRs) from a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 8 and three CDRs from a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 9. In some embodiments, the PD-L1 antagonist is an anti-PD-L1 antibody which comprises heavy

and light chain variable regions comprising the amino acid sequences shown in SEQ ID NO: 8 and SEQ ID NO: 9, respectively.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-4-1BB antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-4-1BB antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-4-1BB antibody and use of an anti-4-1BB antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-4-1BB antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-4-1BB antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-M-CSF antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-M-CSF antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-M-CSF antibody and use of an anti-M-CSF antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-M-CSF antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-M-CSF antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-OX40 antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-OX40 antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-OX40 antibody and use of an anti-OX40 antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-OX40 antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-OX40 antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-M-CSF antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-M-CSF antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-M-CSF antibody and use of an anti-M-CSF antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-M-CSF antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-M-CSF antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-OX40 antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-OX40 antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-OX40 antibody and use of an anti-OX40 antibody in the manufacture of a

medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-OX40 antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-OX40 antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-4-1BB antibody and an anti-M-CSF antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-4-1BB antibody and an anti-M-CSF antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-4-1BB antibody and an anti-M-CSF antibody and use of an anti-4-1BB antibody and an anti-M-CSF antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-4-1BB antibody and an anti-M-CSF antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-4-1BB antibody and an anti-M-CSF antibody to treat a cancer in a subject.

In some embodiments, the invention provides a medicament comprising a PD-L1 antagonist for use in combination with an anti-4-1BB antibody and an anti-OX40 antibody for treating a cancer.

In some embodiments, the invention provides a medicament comprising an anti-4-1BB antibody and an anti-OX40 antibody for use in combination with a PD-L1 antagonist for treating a cancer.

Other embodiments provide use of a PD-L1 antagonist in the manufacture of medicament for treating a cancer in a subject when administered in combination with an anti-4-1BB antibody and an anti-OX40 antibody and use of an anti-4-1BB antibody and

an anti-OX40 antibody in the manufacture of a medicament for treating a cancer in a subject when administered in combination with a PD-L1 antagonist.

In some embodiments, the invention provides use of a PD-L1 antagonist and an anti-4-1BB antibody and an anti-OX40 antibody in the manufacture of medicaments for treating a cancer in a subject. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-L1 antagonist in combination with an anti-4-1BB antibody and an anti-OX40 antibody to treat a cancer in a subject.

In all of the above treatment methods, medicaments and uses, the PD-L1 antagonist inhibits the binding of PD-L1 to PD-1. In some embodiments of the above treatment methods, medicaments and uses, the PD-L1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to PD-L1 or to PD-L1 and blocks the binding of PD-L1 to PD-1. In some embodiments, the PD-L1 antagonist is an anti-PD-L1 antibody which comprises three CDRs from a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 8 and three CDRs from a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 9. In some embodiments, the PD-L1 antagonist is an anti-PD-L1 antibody which comprises heavy and light chain variable regions comprising the amino acid sequences shown in SEQ ID NO: 8 and SEQ ID NO: 9, respectively. In some embodiments, the anti-PD-L1 antibody is Avelumab.

In some embodiments, the anti-4-1BB antibody can comprise a heavy chain variable region comprising three CDRs from the heavy chain variable region having the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region comprising three CDRs from the light chain variable region having the amino acid sequence shown in SEQ ID NO: 19. In some embodiments, the anti-4-1BB antibody can comprise heavy and light chain variable regions comprising the amino acid sequences shown in SEQ ID NO: 18 and SEQ ID NO: 19, respectively. In some embodiments, the anti-4-1BB antibody is PF-05082566.

In some embodiments, the anti-M-CSF antibody can comprise a heavy chain variable region comprising three CDRs from the heavy chain variable region having the amino acid sequence shown in SEQ ID NO: 30, and a light chain variable region comprising three CDRs from the light chain variable region having the amino acid sequence shown in SEQ ID NO: 31. In some embodiments, the anti-M-CSF antibody

can comprise heavy and light chain variable regions comprising the amino acid sequences shown in SEQ ID NO: 30 and SEQ ID NO: 31, respectively. In some embodiments, the anti-M-CSF antibody is PD-0360324.

In some embodiments, the anti-OX40 antibody can comprise a heavy chain variable region comprising three CDRs from the heavy chain variable region having the amino acid sequence shown in SEQ ID NO: 38, and a light chain variable region comprising three CDRs from the light chain variable region having the amino acid sequence shown in SEQ ID NO: 39. In some embodiments, the anti-OX40 antibody can comprise a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 39. In some embodiments, the anti-OX40 antibody is PF-04518600.

In some embodiments of the above treatment methods, medicaments and uses of the invention, the individual is a human and the cancer is a solid tumor. In some embodiments, the solid tumor is renal cell carcinoma (RCC), bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma (SCCHN), lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, small-cell lung cancer (SCLC) or triple negative breast cancer.

In other embodiments of the above treatment methods, medicaments and uses of the invention, the individual is a human and the cancer is a Heme malignancy and in some embodiments, the Heme malignancy is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

Also, in some embodiments of any of the above treatment methods, medicaments and uses, the cancer tests positive for the expression of one or both of PD-L1 and PD-L2. In still other embodiments, the cancer has elevated PD-L1 expression.

In some embodiments of the above treatment methods, medicaments and uses, the subject is a human and the cancer is RCC that tests positive for human PD-L1.

In some embodiments of the above treatment methods, medicaments and uses, the cancer is advanced RCC with clear cell subtype and is present in a human who has not been previously treated for RCC.

In some embodiments of the above treatment methods, medicaments and uses, the cancer is relapsed or refractory (R/R) cancer. In some embodiments, the R/R cancer is R/R DLBCL.

In some embodiments of the above treatment methods, medicaments and uses, the cancer is locally advanced cancer. In some embodiments, the locally advanced cancer is locally advanced SCCHN. In some embodiments, the SCCHN is localized to the oral cavity, oropharynx, larynx, or hypopharynx.

.Brief Description of the Figures/Drawings

Figure 1 depicts a graph summarizing infiltration of T cells in response to treatment.

Figure 2 depicts a graph summarizing ratio of CD8+ T cells/Treg in response to treatment.

Figure 3 depicts a graph summarizing Eomes induction in response to treatment.

Detailed Description

I. Definitions

So that the invention may be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

“About” when used to modify a numerically defined parameter (e.g., the dose of a PD-L1 antagonist or VEGFR inhibitor, or the length of treatment time with a combination therapy described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg/kg may vary between 4.5 mg/kg and 5.5 mg/kg.

As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

"Administration" and "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. "Administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term "subject" includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, rabbit) and most preferably a human.

An “antibody” is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab’, F(ab’)2, Fv), single chain (scFv) and domain antibodies (including, for example, shark and camelid antibodies), and fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "antigen binding fragment" or “antigen binding portion” of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (e.g., PD-L1). Antigen binding functions of

an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen binding fragment" of an antibody include Fab; Fab'; F(ab')2; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., Nature 341:544-546, 1989), and an isolated complementarity determining region (CDR).

An antibody, an antibody conjugate, or a polypeptide that "preferentially binds" or "specifically binds" (used interchangeably herein) to a target (e.g., PD-L1 protein) is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically or preferentially binds to a PD-L1 epitope is an antibody that binds this epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other PD-L1 epitopes or non-PD-L1 epitopes. It is also understood that by reading this definition, for example, an antibody (or moiety or epitope) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda MD)); and (2) an approach based

on crystallographic studies of antigen-antibody complexes (Al-lazikani et al., 1997, J. Molec. Biol. 273:927-948). As used herein, a CDR may refer to CDRs defined by either approach or by a combination of both approaches.

A “CDR” of a variable domain are amino acid residues within the variable region that are identified in accordance with the definitions of the Kabat, Chothia, the accumulation of both Kabat and Chothia, AbM, contact, and/or conformational definitions or any method of CDR determination well known in the art. Antibody CDRs may be identified as the hypervariable regions originally defined by Kabat et al. See, e.g., Kabat et al., 1992, Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, NIH, Washington D.C. The positions of the CDRs may also be identified as the structural loop structures originally described by Chothia and others. See, e.g., Chothia et al., Nature 342:877-883, 1989. Other approaches to CDR identification include the “AbM definition,” which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now Accelrys®), or the “contact definition” of CDRs based on observed antigen contacts, set forth in MacCallum et al., J. Mol. Biol., 262:732-745, 1996. In another approach, referred to herein as the “conformational definition” of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., Journal of Biological Chemistry, 283:1156-1166, 2008. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, AbM, contact, and/or conformational definitions.

"Isolated antibody" and “isolated antibody fragment” refers to the purification status and in such context means the named molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to a complete absence of such material or to an absence of water,

buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

"Monoclonal antibody" or “mAb” or “Mab”, as used herein, refers to a population of substantially homogeneous antibodies, i.e., the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, which are often specific for different epitopes. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler et al. (1975) Nature 256: 495, or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al. (1991) Nature 352: 624-628 and Marks et al. (1991) J. Mol. Biol. 222: 581-597, for example. See also Presta (2005) J. Allergy Clin. Immunol. 116:731.

"Chimeric antibody" refers to an antibody in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in an antibody derived from a particular species (e.g., human) or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in an antibody derived from another species (e.g., mouse) or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

“Human antibody” refers to an antibody that comprises human immunoglobulin protein sequences only. A human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” or “rat antibody” refer to an antibody that comprises only mouse or rat immunoglobulin sequences, respectively.

"Humanized antibody" refers to forms of antibodies that contain sequences from non-human (e.g., murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the

humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix “hum”, “hu” or “h” is added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

The terms “cancer”, “cancerous”, or “malignant” refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer, glioma, hodgkin's lymphoma, non-hodgkin's lymphoma, acute myeloid leukemia (AML), multiple myeloma, gastrointestinal (tract) cancer, renal cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. Another particular example of cancer includes renal cell carcinoma.

“Biotherapeutic agent” means a biological molecule, such as an antibody or fusion protein, that blocks ligand / receptor signaling in any biological pathway that supports tumor maintenance and/or growth or suppresses the anti-tumor immune response.

“Chemotherapeutic agent” is a chemical compound useful in the treatment of cancer. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, kinase inhibitors, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topisomerase inhibitors, photosensitizers, anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen

receptor down-regulators (ERDs), estrogen receptor antagonists, leutinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit expression of genes implicated in abnormal cell proliferation or tumor growth. Chemotherapeutic agents useful in the treatment methods of the present invention include cytostatic and/or cytotoxic agents.

"Conservatively modified variants" or "conservative substitution" refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (e.g. charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.), such that the changes can frequently be made without altering the biological activity or other desired property of the protein, such as antigen affinity and/or specificity. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. (1987) Molecular Biology of the Gene, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth in Table 1 below.

TABLE 1. Exemplary Conservative Amino Acid Substitutions

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys; His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

"Consists essentially of," and variations such as "consist essentially of" or "consisting essentially of," as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified dosage regimen, method, or composition. As a non-limiting example, a PD-L1 antagonist that consists essentially of a recited amino acid sequence may also include one or more amino acids, including substitutions of one or more amino acid residues, which do not materially affect the properties of the binding compound.

“Diagnostic anti-PD-L1 monoclonal antibody” means a mAb which specifically binds to PD-L1 that is expressed on the surface of certain mammalian cells. A mature PD-L1 lacks the presecretory leader sequence, also referred to as leader peptide The terms "PD-L1" and "mature PD-L1" are used interchangeably herein, and shall be understood to mean the same molecule unless otherwise indicated or readily apparent from the context.

As used herein, an anti-human PD-L1 mAb or a diagnostic anti-hPD-L1 mAb refers to a monoclonal antibody that specifically binds to mature human PD-L1. A mature human PD-L1 molecule consists of amino acids 19-290 of the following sequence (SEQ ID NO: 1): MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIEC KFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAA LQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQA EGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDP EENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQD TNSKKQSDTHLEET (SEQ ID NO: 1).

"Homology" refers to sequence similarity between two polypeptide sequences when they are optimally aligned. When a position in both of the two compared sequences is occupied by the same amino acid monomer subunit, e.g., if a position in a light chain CDR of two different Abs is occupied by alanine, then the two Abs are homologous at that position. The percent of homology is the number of homologous positions shared by the two sequences divided by the total number of positions compared ×100. For example, if 8 of 10 of the positions in two sequences are matched or homologous when the sequences are optimally aligned then the two sequences are

80% homologous. Generally, the comparison is made when two sequences are aligned to give maximum percent homology. For example, the comparison can be performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences.

The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., et al., (1990) J. Mol. Biol. 215:403-410; Gish, W., et al., (1993) Nature Genet. 3:266-272; Madden, T.L., et al., (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., et al., (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., et al., (1997) Genome Res. 7:649-656; Wootton, J.C., et al., (1993) Comput. Chem. 17:149-163; Hancock, J.M. et al., (1994) Comput. Appl. Biosci. 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., et al., "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., et al., "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., et al., (1991) Methods 3:66-70; Henikoff, S., et al., (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., et al., (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., et al., (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., et al., (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., et al., (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

"Patient" or "subject" refers to any single subject for which therapy is desired or that is participating in a clinical trial, epidemiological study or used as a control, including humans and mammalian veterinary patients such as cattle, horses, dogs, and cats.

"PD-L1 antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1. In any of the treatment method, medicaments and uses of the present invention in which a human subject is being treated, the PD-L1 antagonist blocks binding of human PD-L1 to human PD-1.

PD-L1 antagonists useful in the any of the treatment methods, medicaments, and uses of the present invention include a monoclonal antibody (mAb) which specifically binds to PD-L1, and preferably specifically binds to human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')2, scFv and Fv fragments.

Examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present invention, are described in WO2013079174, WO2015061668, WO2010089411, WO/2007/005874, WO/2010/036959, WO/2014/100079, WO2013/019906, WO/2010/077634, and US Patent Nos. 8552154, 8779108, and 8383796. Specific anti-human PD-L1 mAbs useful as the PD-L1 antagonist in the treatment method, medicaments and uses of the present invention include, for example without limitation: avelumab (MSB0010718C), nivolumab (BMS-936558), MPDL3280A (an IgG1-engineered, anti–PD-L1 antibody), BMS-936559 (a fully human, anti–PD-L1, IgG4 monoclonal antibody), MEDI4736 (an engineered IgG1 kappa monoclonal antibody with triple mutations in the Fc domain to remove antibody-dependent, cell-mediated cytotoxic activity), and an antibody which comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

Other PD-L1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include an immunoadhesin that specifically binds to PD-L1, and preferably specifically binds to human PD-L1, e.g., a fusion protein containing the PD-L1 binding portion of PD-1 fused to a constant region such as an Fc region of an immunoglobulin molecule.

Table 2 below provides exemplary anti-PD-L1 antibody sequences for use in the treatment method, medicaments and uses of the present invention.

Table 2. EXEMPLARY ANTI-HUMAN PD-L1 MONOCLONAL ANTIBODY SEQUENCES	
Heavy chain CDR1 (CDRH1)	SYIMM (SEQ ID NO:2)
Heavy chain CDR2 (CDRH2)	SIYPSGGITFY (SEQ ID NO:3)

Table 2. EXEMPLARY ANTI-HUMAN PD-L1 MONOCLONAL ANTIBODY SEQUENCES	
Heavy chain CDR3 (CDRH3)	IKLGTVTTVDY (SEQ ID NO:4)
Light chain CDR1 (CDRL1)	TGTSSDVGGYNYVS (SEQ ID NO:5)
Light chain CDR2 (CDRL2)	DVSNRPS (SEQ ID NO:6)
Light chain CDR3 (CDRL3)	SSYTSSSTRV (SEQ ID NO:7)
Heavy chain variable region (VR)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGL EWVSSIYPSGGITFYADKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARIKLGTVTTVDYWGQGTLVTVSS (SEQ ID NO: 8)
Light chain VR	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTRVFGTGTKVTVL (SEQ ID NO: 9)
Heavy chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGL EWVSSIYPSGGITFYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 10)
Light chain	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTRVFGTGTKVTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSL TPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 11)

"PD-L1" expression as used herein means any detectable level of expression of PD-L1 protein on the cell surface or of PD-L1 mRNA within a cell or tissue. PD-L1 protein expression may be detected with a diagnostic PD-L1 antibody in an IHC assay of a tumor tissue section or by flow cytometry. Alternatively, PD-L1 protein expression by tumor cells may be detected by PET imaging, using a binding agent (e.g., antibody fragment, affibody and the like) that specifically binds to PD-L1. Techniques for detecting and measuring PD-L1 mRNA expression include RT-PCR and real-time quantitative RT-PCR.

Several approaches have been described for quantifying PD-L1 protein expression in IHC assays of tumor tissue sections. See, e.g., Thompson, R. H., et al., PNAS 101 (49); 17174-17179 (2004); Thompson, R. H. et al., Cancer Res. 66:3381-3385 (2006); Gadiot, J., et al., Cancer 117:2192-2201 (2011); Taube, J. M. et al., Sci Transl Med 4, 127ra37 (2012); and Toplian, S. L. et al., New Eng. J Med. 366 (26): 2443-2454 (2012).

One approach employs a simple binary end-point of positive or negative for PD-L1 expression, with a positive result defined in terms of the percentage of tumor cells that exhibit histologic evidence of cell-surface membrane staining. A tumor tissue section is counted as positive for PD-L1 expression is at least 1%, and preferably 5% of total tumor cells.

In another approach, PD-L1 expression in the tumor tissue section is quantified in the tumor cells as well as in infiltrating immune cells, which predominantly comprise lymphocytes. The percentage of tumor cells and infiltrating immune cells that exhibit membrane staining are separately quantified as < 5%, 5 to 9%, and then in 10% increments up to 100%. For tumor cells, PD-L1 expression is counted as negative if the score is < 5% score and positive if the score is ≥ 5%. PD-L1 expression in the immune infiltrate is reported as a semi-quantitative measurement called the adjusted inflammation score (AIS), which is determined by multiplying the percent of membrane staining cells by the intensity of the infiltrate, which is graded as none (0), mild (score of 1, rare lymphocytes), moderate (score of 2, focal infiltration of tumor by lymphohistiocytic aggregates), or severe (score of 3, diffuse infiltration). A tumor tissue section is counted as positive for PD-L1 expression by immune infiltrates if the AIS is ≥ 5.

The level of PD-L1 mRNA expression may be compared to the mRNA expression levels of one or more reference genes that are frequently used in quantitative RT-PCR, such as ubiquitin C.

In some embodiments, a level of PD-L1 expression (protein and/or mRNA) by malignant cells and/or by infiltrating immune cells within a tumor is determined to be “overexpressed” or “elevated” based on comparison with the level of PD-L1 expression (protein and/ or mRNA) by an appropriate control. For example, a control PD-L1 protein or mRNA expression level may be the level quantified in nonmalignant cells of the same type or in a section from a matched normal tissue.

"RECIST 1.1 Response Criteria" as used herein means the definitions set forth in Eisenhauer et al., E.A. et al., Eur. J Cancer 45:228-247 (2009) for target lesions or nontarget lesions, as appropriate based on the context in which response is being measured.

"Sustained response" means a sustained therapeutic effect after cessation of treatment with a therapeutic agent, or a combination therapy described herein. In some embodiments, the sustained response has a duration that is at least the same as the treatment duration, or at least 1.5, 2.0, 2.5 or 3 times longer than the treatment duration.

"Tissue Section" refers to a single part or piece of a tissue sample, e.g., a thin slice of tissue cut from a sample of a normal tissue or of a tumor.

"Treat" or "treating" a cancer as used herein means to administer a combination therapy of a PD-L1 antagonist and another therapeutic agent to a subject having a cancer, or diagnosed with a cancer, to achieve at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth. Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A. Weber, J. Nucl. Med. 50:1S-10S (2009)). For example, with respect to tumor growth inhibition, according to National Cancer Institute (NCI) standards, a T/C less than or equal to 42% is the minimum level of anti-tumor activity. A T/C < 10% is considered a high anti-tumor activity level, with T/C (%) = Median tumor volume of the treated/Median tumor volume of the control × 100. In some embodiments, the treatment achieved by a combination of the invention is any of partial response (PR), complete response (CR), overall response (OR), progression free survival (PFS), disease free survival (DFS) and overall survival (OS). PFS, also referred to as "Time to Tumor Progression" indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a CR or PR, as well as the amount of time patients have experienced stable disease (SD). DFS refers to the length of time during and after treatment that the patient remains free of disease. OS refers to a prolongation in life expectancy as compared to naive or untreated subjects or patients. In some embodiments, response to a combination of the invention is any of PR, CR, PFS, DFS, OR, or OS that is assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response criteria. The treatment

regimen for a combination of the invention that is effective to treat a cancer patient may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the therapy to elicit an anti-cancer response in the subject. While an embodiment of any of the aspects of the invention may not be effective in achieving a positive therapeutic effect in every subject, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student's t-test, the chi2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

The terms "treatment regimen", "dosing protocol" and dosing regimen are used interchangeably to refer to the dose and timing of administration of each therapeutic agent in a combination of the invention.

As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: reducing the proliferation of (or destroying) neoplastic or cancerous cells, inhibiting metastasis of neoplastic cells, shrinking or decreasing the size of tumor, remission of a PD-L1 associated disease (e.g., cancer), decreasing symptoms resulting from a PD-L1 associated disease (e.g., cancer), increasing the quality of life of those suffering from a PD-L1 associated disease (e.g., cancer), decreasing the dose of other medications required to treat a PD-L1 associated disease (e.g., cancer), delaying the progression of a PD-L1 associated disease (e.g., cancer), curing a PD-L1 associated disease (e.g., cancer), and/or prolong survival of patients having a PD-L1 associated disease (e.g., cancer).

"Ameliorating" means a lessening or improvement of one or more symptoms as compared to not administering a PD-L1 antibody. "Ameliorating" also includes shortening or reduction in duration of a symptom.

As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect any one or more beneficial or desired results. For prophylactic use, beneficial or desired results include eliminating or reducing the risk, lessening the severity, or delaying the outset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing incidence or amelioration of one or more symptoms of

various PD-L1 associated diseases or conditions (such as for example advanced RCC), decreasing the dose of other medications required to treat the disease, enhancing the effect of another medication, and/or delaying the progression of the PD-L1 associated disease of patients. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective dosage” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

"Tumor" as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors (National Cancer Institute, Dictionary of Cancer Terms).

"Tumor burden" also referred to as "tumor load", refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone narrow. Tumor burden can be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

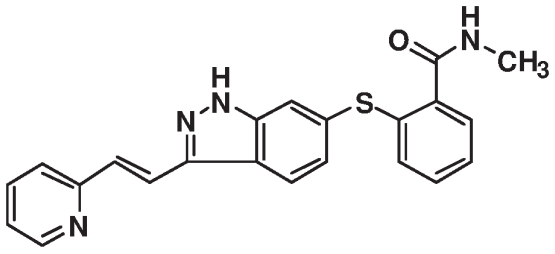
The term "tumor size" refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of

tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., bone scan, ultrasound, CT or MRI scans.

"Variable regions" or "V region" as used herein means the segment of IgG chains which is variable in sequence between different antibodies. It extends to Kabat residue 109 in the light chain and 113 in the heavy chain.

"VEGFR inhibitor" means a small molecule inhibitor of vascular endothelial growth factor (VEGF) receptor or a monoclonal antibody against vascular endothelial growth factor (VEGF). In an embodiment, a "VEGFR inhibitor" means a small molecule inhibitor of vascular endothelial growth factor (VEGF) receptor. Specific VEGFR inhibitors useful as the VEGFR inhibitor in the treatment method, medicaments and uses of the present invention, include axitinib, sunitinib, sorafenib, tivozanib, and bevacizumab. In an embodiment, specific VEGFR inhibitors useful as the VEGFR inhibitor in the treatment method, medicaments and uses of the present invention, include axitinib, sunitinib, sorafenib, and tivozanib.

In an embodiment of the treatment method, medicaments and uses of the present invention, the VEGFR inhibitor is the compound, N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide or 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridin-2-yl)ethenyl]indazole, of the following structure:



which is known as axitinib or AG-013736.

Axitinib is a potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival (Hu-Lowe, D.D., et al., Clin Cancer Res 14: 7272-7283 (2008); Solowiej, S., et al., Biochemistry 48: 7019-31 (2009)). Clinical trials are currently on-going or have been conducted to study the use of axitinib for the treatment of various cancers, including

liver cancer, melanoma, mesothelioma, non-small cell lung cancer, prostate cancer, renal cell carcinoma, soft tissue sarcomas and solid tumors. Inlyta® (axitinib) has been approved in the United States, Europe, Japan and other jurisdictions for the treatment of renal cell carcinoma.

Axitinib, as well as pharmaceutically acceptable salts thereof, is described in U.S. Patent No. 6,534,524. Methods of making axitinib are described in U.S. Patent Nos. 6,884,890 and 7,232,910, in U.S. Publication Nos. 2006-0091067 and 2007-0203196 and in International Publication No. WO 2006/048745. Dosage forms of axitinib are described in U.S. Publication No. 2004-0224988. Polymorphic forms and pharmaceutical compositions of axitinib are also described in U.S. Publication Nos. 2006-0094763, 2008-0274192 and 2010-0179329 and International Publication No. WO 2013/046133. The patents and patent applications listed above are incorporated herein by reference.

Axitinib is understood to include reference to salts thereof, unless otherwise indicated. Axitinib is basic in nature and capable of forming a wide variety of salts with various inorganic and organic acids. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids. Pharmaceutically acceptable salts of axitinib may be formed, for example, by reacting axitinib with an amount of acid, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts of the compound of Formula I include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

All such acid salts are intended to be pharmaceutically acceptable salts within the scope of axitinib, as used in the present invention and all acid salts are considered equivalent to the free forms of the corresponding compound for purposes of the invention.

Prodrugs of axitinib are also contemplated for use in the methods, medicaments and uses of the present invention. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield axitinib or a salt thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

The term “4-1BB antibody” as used herein means an antibody, as defined herein, capable of binding to human 4-1BB receptor.

The terms "4-1BB” and “4-1BB receptor” are used interchangeably in the present application, and refer to any form of 4-1BB receptor, as well as variants, isoforms, and species homologs thereof that retain at least a part of the activity of4-1BB receptor. Accordingly, a binding molecule, as defined and disclosed herein, may also bind 4-1BB from species other than human. In other cases, a binding molecule may be completely specific for the human 4-1BB and may not exhibit species or other types of cross-reactivity. Unless indicated differently, such as by specific reference to human4-1BB,4-1BB includes all mammalian species of native sequence4-1BB, e.g., human, canine, feline, equine and bovine. One exemplary human 4-1BB is a 255 amino acid protein (Accession No. NM_001561; NP_001552).

4-1BB comprises a signal sequence (amino acid residues 1-17), followed by an extracellular domain (169 amino acids), a transmembrane region (27 amino acids), and an intracellular domain (42 amino acids) (Cheuk ATC et al. 2004 Cancer Gene Therapy 11: 215-226). The receptor is expressed on the cell surface in monomer and dimer forms and likely trimerizes with 4-1BB ligand to signal.

“4-1BB agonist” as used herein means, any chemical compound or biological molecule, as defined herein, which upon binding to 4-1BB, (1) stimulates or activates 4-1BB, (2) enhances, increases, promotes, induces, or prolongs an activity, function, or

presence of 4-1BB, or (3) enhances, increases, promotes, or induces the expression of 4-1BB. 4-1BB agonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to 4-1BB. Alternative names or synonyms for 4-1BB include CD137 and TNFRSF9. In any of the treatment method, medicaments and uses of the present invention in which a human individual is being treated, the 4-1BB agonists increase a 4-1BB-mediated response. In some embodiments of the treatment method, medicaments and uses of the present invention, 4-1BB agonists markedly enhance cytotoxic T-cell responses, resulting in anti-tumor activity in several models.

Human 4-1BB comprises a signal sequence (amino acid residues 1-17), followed by an extracellular domain (169 amino acids), a transmembrane region (27 amino acids), and an intracellular domain (42 amino acids) (Cheuk ATC et al. 2004 Cancer Gene Therapy 11: 215-226). The receptor is expressed on the cell surface in monomer and dimer forms and likely trimerizes with 4-1BB ligand to signal.

Examples of mAbs that bind to human 4-1BB, and useful in the treatment method, medicaments and uses of the present invention, are described in US 8,337,850 and US20130078240. In some embodiments an anti-4-1BB antibody useful in the treatment, method, medicaments and uses disclosed herein is a fully humanized IgG2 agonist monoclonal antibody comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 18 and SEQ ID NO: 19, respectively.

Table 3A below provides exemplary anti-4-1BB antibody sequences for use in the treatment method, medicaments and uses of the present invention.

Table 3A. EXEMPLARY ANTI-HUMAN 4-1BB MONOCLONAL ANTIBODY SEQUENCES	
CDRH1	STYWIS (SEQ ID NO:12)
CDRH2	KIYPGDSYTNYSPSFQG (SEQ ID NO:13)
CDRH3	RGYGIFDY (SEQ ID NO:14)
CDRL1	SGDNIGDQYAH (SEQ ID NO:15)
CDRL2	QDKNRPS (SEQ ID NO:16)
CDRL3	ATYTGFGSLAV (SEQ ID NO:17)
Heavy chain VR	EVQLVQSGAEVKKPGESLRISCKGSGYSFSTYWISWVRQMPGKGL EWMGKIYPGDSYTNYSPSFQGQVTISADKSISTAYLQWSSLKASDT AMYYCARGYGIFDYWGQGTLVTVSS (SEQ ID NO: 18)
Light chain VR	SYELTQPPSVSVSPGQTASITCSGDNIGDQYAHWYQQKPGQSPVL VIYQDKNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYT

	GFGSLAVFGGGTKLTVL (SEQ ID NO: 19)
Heavy chain	EVQLVQSGAEVKKPGESLRISCKGSGYSFSTYWISWVRQMPGKGL EWMGKIYPGDSYTNYSPSFQGQVTISADKSISTAYLQWSSLKASDT AMYYCARGYGIFDYWGQGTLVTVSSastkgpsvfplapcsrstsestaalgclvk dyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpssnfgtqtytcnvdhkpsntkvd ktverkccvecppcpappvagpsvflfppkpkdtlmisrtpevtcvvvdvshedpevqfnwyv dgvevhnaktkpreeqfnstfrvvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqpr epqvytlppsreemtknqvsltclvkgfypsdiavewesngqpennykttppmldsdgsfflys kltvdksrwqqgnvfscsvmhealhnhytqkslslspgk (SEQ ID NO: 20)
Light chain	SYELTQPPSVSVSPGQTASITCSGDNIGDQYAHWYQQKPGQSPVL VIYQDKNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYT GFGSLAVFGGGTKLTVLgqpkaapsvtlfppsseelqankatlvclisdfypgavtva wkadsspvkagvetttpskqsnnkyaassylsltpeqwkshrsyscqvthegstvektvapte cs (SEQ ID NO: 21)

The term “M-CSF antibody” as used herein means an antibody, as defined herein, capable of binding to human M-CSF receptor.

The terms "M-CSF” and “M-CSF receptor” are used interchangeably in the present application, and refer to any form of M-CSF receptor, as well as variants, isoforms, and species homologs thereof that retain at least a part of the activity of M-CSF receptor. Accordingly, a binding molecule, as defined and disclosed herein, may also bind M-CSF from species other than human. In other cases, a binding molecule may be completely specific for the human M-CSF and may not exhibit species or other types of cross-reactivity. Unless indicated differently, such as by specific reference to human M-CSF, M-CSF includes all mammalian species of native sequence M-CSF, e.g., human, canine, feline, equine and bovine. One exemplary human M-CSF is a 554 amino acid protein (UniProt Accession No. P09603).

“M-CSF antagonist antibody” as used herein means, any antibody, as defined herein, which upon binding to M-CSF, inhibits the binding of a M-CSF to c-fms receptor and blocks or prevents activation of c-fms. M-CSF antagonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb) which specifically binds to M-CSF.

Examples of mAbs that bind to human M-CSF, and useful in the treatment method, medicaments and uses of the present invention, are described in, for example, U.S. Patent No. 7,326,414, PCT Patent Application Publication No. WO2014167088, and U.S. Patent Application Publication No. 20140242071. In some embodiments an anti-M-CSF antibody useful in the treatment, method, medicaments and uses disclosed

herein is a fully human IgG2 antagonist monoclonal antibody comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 30 and SEQ ID NO: 31, respectively.

Table 3B below provides exemplary anti-M-CSF antibody sequences for use in the treatment method, medicaments and uses of the present invention.

Table 3B. EXEMPLARY ANTI-HUMAN M-CSF MONOCLONAL ANTIBODY SEQUENCES	
CDRH1	SFSMT (SEQ ID NO: 24)
CDRH2	YISSRSSTISYADSVKG (SEQ ID NO: 25)
CDRH3	DPLLAGATFFDY (SEQ ID NO: 26)
CDRL1	RASQSVSSSYLA (SEQ ID NO: 27)
CDRL2	GASSRAT (SEQ ID NO: 28)
CDRL3	QQYGSSPLT (SEQ ID NO: 29)
Heavy chain VR	MELGLCWVFLVAILEGVQCEVQLVESGGGLVQPGGSLRLSCAASG FTFSSFSMTWVRQAPGKGLEWVSYISSRSSTISYADSVKGRFTISR DNAKNSLYLQMNSLRDEDTAVYYCARDPLLAGATFFDYWGQGTLV TVSSA (SEQ ID NO: 30)
Light chain VR	METPAQLLFLLLLWLPDTTGEFVLTQSPGTLSLSPGERATLSCRAS QSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIK (SEQ ID NO: 31)
Heavy chain	MELGLCWVFLVAILEGVQCEVQLVESGGGLVQPGGSLRLSCAASG FTFSSFSMTWVRQAPGKGLEWVSYISSRSSTISYADSVKGRFTISR DNAKNSLYLQMNSLRDEDTAVYYCARDPLLAGATFFDYWGQGTLV TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHK PSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK (SEQ ID NO: 22)
Light chain	METPAQLLFLLLLWLPDTTGEFVLTQSPGTLSLSPGERATLSCRAS QSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC (SEQ ID NO: 23)

The term “OX40 antibody” as used herein means an antibody, as defined herein, capable of binding to human OX40 receptor.

The terms "OX40” and “OX40 receptor” are used interchangeably in the present application, and refer to any form of OX40 receptor, as well as variants, isoforms, and species homologs thereof that retain at least a part of the activity of OX40 receptor.

Accordingly, a binding molecule, as defined and disclosed herein, may also bind OX40 from species other than human. In other cases, a binding molecule may be completely specific for the human OX40 and may not exhibit species or other types of cross-reactivity. Unless indicated differently, such as by specific reference to human OX40, OX40 includes all mammalian species of native sequence OX40, e.g., human, canine, feline, equine and bovine. One exemplary human OX40 is a 277 amino acid protein (UniProt Accession No. P43489).

"OX40 agonist antibody" as used herein means, any antibody, as defined herein, which upon binding to OX40, (1) stimulates or activates OX40, (2) enhances, increases, promotes, induces, or prolongs an activity, function, or presence of OX40, or (3) enhances, increases, promotes, or induces the expression of OX40. OX40 agonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb) which specifically binds to OX40.

Examples of mAbs that bind to human OX40, and useful in the treatment method, medicaments and uses of the present invention, are described in, for example, U.S. Patent No. 7,960,515, PCT Patent Application Publication Nos. WO2013028231 and WO2013/119202, and U.S. Patent Application Publication No. 20150190506. In some embodiments an anti-OX40 antibody useful in the treatment, method, medicaments and uses disclosed herein is a fully human agonist monoclonal antibody comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 38 and SEQ ID NO: 39, respectively. In some embodiments, the anti-OX40 antibody is a fully human IgG2 or IgG1 antibody.

Table 3C below provides exemplary anti-OX40 antibody sequences for use in the treatment method, medicaments and uses of the present invention.

Table 3C. EXEMPLARY ANTI-HUMAN OX40 MONOCLONAL ANTIBODY SEQUENCES	
CDRH1	SYSMN (SEQ ID NO: 32)
CDRH2	YISSSSSTIDYADSVKG (SEQ ID NO: 33)
CDRH3	ESGWYLFDY (SEQ ID NO: 34)
CDRL1	RASQGISSWLA (SEQ ID NO: 35)
CDRL2	AASSLQS (SEQ ID NO: 36)
CDRL3	QQYNSYPPT (SEQ ID NO: 37)
Heavy chain VR	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSYISSSSSTIDYADSVKGRFTISRDNAKNSLYLQMNSLRDEDT AVYYCARESGWYLFDYWGQGTLVTVSS (SEQ ID NO: 38)

Light chain VR	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKS LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNS YPPTFGGGTKVEIK (SEQ ID NO: 39)
Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSYISSSSSTIDYADSVKGRFTISRDNAKNSLYLQMNSLRDEDT AVYYCARESGWYLFDYWGQGTLVTVSSastkgpsvfplapcsrstsestaalg clvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpssnfgtqtytcnvdhkpsnt kvdktverkccvecppcpappvagpsvflfppkpkdtlmisrtpevtcvvvdvshedpevqfn wyvdgvevhnaktkpreeqfnstfrvvsvltvvhqdwlngkeykckvsnkglpapiektisktk gqprepqvytlppsreemtknqvsltclvkgfypsdiavewesngqpennykttppmldsdg sfflyskltvdksrwqqgnvfscsvmhealhnhytqkslslspgk (SEQ ID NO: 40)
Light chain	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKS LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNS YPPTFGGGTKVEIKrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdna lqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec (SEQ ID NO: 41)

The “CD20” antigen is a ˜35 kDa, non-glycosylated phosphoprotein found on the surface of greater than 90% of B cells from peripheral blood or lymphoid organs. CD20 is expressed during early pre-B cell development and remains until plasma cell differentiation. CD20 is present on both normal B cells as well as malignant B cells. Other names for CD20 in the literature include “B-lymphocyte-restricted antigen” and “Bp35”. The CD20 antigen is described in Clark et al. *PNAS* (*USA*) 82:1766 (1985), for example.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the invention. The materials, methods, and examples are illustrative only and not intended to be limiting.

II. METHODS, USES AND MEDICAMENTS

In one aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist and a VEGR inhibitor.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-4-1BB antibody.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-M-CSF antibody.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist and an anti-OX40 antibody.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and an anti-M-CSF antibody.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and an anti-OX40 antibody.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and a CD20 antagonist. In some embodiments, the PD-L1 antagonist is avelumab, the anti-4-1BB antibody is PF-05082566, and the CD20 antagonist is rituximab. In some embodiments, the method comprises a 28-day cycle wherein rituximab is administered on Day 1 of each 28-day cycle at a dose of 375 mg/m^2, PF-05082566 is administered on Day 1 or Day 2 at a fixed dose of 100 mg, and avelumab is administered at a dose of 10 mg/kg on Day 2 and Day 15 or 16 of each 28-day cycle. In some embodiments on Day 2, avelumab is administered at least 3 hours after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 30 minutes after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 60 minutes after administration of PF-05082566.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist, an anti-4-1BB antibody, and azacitidine. In some embodiments, the PD-L1 antagonist is avelumab, and the anti-4-1BB antibody is PF-05082566. In some embodiments, the method comprises a 28-day cycle wherein azacitidine is administered subcutaneously at a daily dose of 75 mg/m^2 on Day 1 to Day 7 consecutively of each 28-day cycle, PF-05082566 is administered intravenously at a fixed dose of 100 mg on Day 1 or Day 2, and avelumab is administered at a dose of 10 mg/kg on Day 2 and either Day 15 or Day 16 of each 28-day cycle. In some embodiments on Day 2, avelumab is administered at least 3 hours after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 30 minutes after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 60 minutes after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered at least 3 hours after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 30 minutes after administration of PF-05082566. In some embodiments on Day 2, avelumab is administered about 60 minutes after administration of PF-05082566. In some embodiments, azacitidine is administered at least 3 hours prior to PF-05082566 when dosed on the same day.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist, bendamustine, and a CD20 antagonist. In some embodiments, the PD-L1 antagonist is avelumab, and the CD20 antagonist is rituximab. In some embodiments, the method comprises a 28-day cycle wherein rituximab is administered on Day 1 of each 28-day cycle at a dose of 375 mg/m^2, bendamustine is administered intravenously at a dose of 90 mg/m^2 on Day 2 and Day 3, and avelumab is administered at a dose of 10 mg/kg on Day 2 and Day 15 or 16 of each 28-day cycle. In some embodiments, the method comprises a 28-day cycle wherein rituximab is administered on Day 1 of each 28-day cycle at a dose of 375 mg/m^2, bendamustine is administered intravenously at a dose of 90 mg/m^2 on Day 1 and Day 2, and avelumab is administered at a dose of 10 mg/kg on Day 2 and Day 15 or 16 of each 28-day cycle. In some embodiments on Day 2, avelumab is administered at least 3 hours after administration of bendamustine. In some embodiments on Day 2, avelumab is

administered about 30 minutes after administration of bendamustine. In some embodiments on Day 2, avelumab is administered about 60 minutes after administration of bendamustine.

In another aspect of the invention, the invention provides a method for treating a cancer in a subject comprising administering to the subject a combination therapy which comprises a PD-L1 antagonist and chemoradiotherapy.

The combination therapy may also comprise one or more additional therapeutic agents. The additional therapeutic agent may be, e.g., a chemotherapeutic other than a VEGR inhibitor, a biotherapeutic agent (including but not limited to antibodies to VEGF, EGFR, Her2/neu, other growth factor receptors, CD40, CD-40L, CTLA-4, and ICOS), an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNα2, GM-CSF), a chimeric antigen receptior (CAR)-T cell, and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF).

Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, especially calicheamicin gamma1I and calicheamicin phiI1, see, e.g., Agnew, Chem. Intl. Ed. Engl., 33:183-186 (1994); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as

neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (“Ara-C”); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators

(SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole, letrozole, and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Each therapeutic agent in a combination therapy of the invention may be administered either alone or in a medicament (also referred to herein as a pharmaceutical composition) which comprises the therapeutic agent and one or more pharmaceutically acceptable carriers, excipients and diluents, according to standard pharmaceutical practice.

Each therapeutic agent in a combination therapy of the invention may be administered simultaneously (i.e., in the same medicament), concurrently (i.e., in separate medicaments administered one right after the other in any order) or sequentially in any order. Sequential administration is particularly useful when the therapeutic agents in the combination therapy are in different dosage forms (one agent is a tablet or capsule and another agent is a sterile liquid) and/or are administered on different dosing schedules, e.g., a chemotherapeutic that is administered at least daily and a biotherapeutic that is administered less frequently, such as once weekly, once every two weeks, or once every three weeks.

In some embodiments, the VEGFR inhibitor or anti-4-1BB antibody is administered before administration of the PD-L1 antagonist, while in other embodiments, the VEGFR inhibitor or anti-4-1BB antibody is administered after administration of the PD-L1 antagonist.

In some embodiments, at least one of the therapeutic agents in the combination therapy is administered using the same dosage regimen (dose, frequency and duration of treatment) that is typically employed when the agent is used as monotherapy for treating the same cancer. In other embodiments, the patient receives a lower total amount of at least one of the therapeutic agents in the combination therapy than when the agent is used as monotherapy, e.g., smaller doses, less frequent doses, and/or shorter treatment duration.

Each small molecule therapeutic agent in a combination therapy of the invention can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, topical, and transdermal routes of administration.

A combination therapy of the invention may be used prior to or following surgery to remove a tumor and may be used prior to, during or after radiation therapy.

In some embodiments, a combination therapy of the invention is administered to a patient who has not been previously treated with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-naïve. In other embodiments, the combination therapy is administered to a patient who failed to achieve a sustained response after prior therapy with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-experienced.

A combination therapy of the invention is typically used to treat a tumor that is large enough to be found by palpation or by imaging techniques well known in the art, such as MRI, ultrasound, or CAT scan. In some embodiments, a combination therapy of the invention is used to treat an advanced stage tumor having dimensions of at least about 200 mm^3, 300 mm^3, 400 mm^3, 500 mm^3, 750 mm^3, or up to 1000 mm^3.

In some embodiments, a combination therapy of the invention is administered to a human patient who has a cancer that tests positive for PD-L1 expression. In some embodiments, PD-L1 expression can be detected using a diagnostic anti-human PD-L1 antibody, or antigen binding fragment thereof, in an IHC assay on an FFPE or frozen tissue section of a tumor sample removed from the patient. Typically, the patient's physician would order a diagnostic test to determine PD-L1 expression in a tumor tissue sample removed from the patient prior to initiation of treatment with the PD-L1 antagonist and VEGFR inhibitor, but it is envisioned that the physician could order the first or subsequent diagnostic tests at any time after initiation of treatment, such as for example after completion of a treatment cycle.

Selecting a dosage regimen (also referred to herein as an administration regimen) for a combination therapy of the invention depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells, tissue or organ in the subject being treated. Preferably, a dosage regimen maximizes the amount of each therapeutic agent delivered to the patient consistent with an acceptable level of side effects. Accordingly, the dose amount and dosing frequency of each biotherapeutic and

chemotherapeutic agent in the combination depends in part on the particular therapeutic agent, the severity of the cancer being treated, and patient characteristics. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available. See, e.g., Wawrzynczak (1996) Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, NY; Bach (ed.) (1993) Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, NY; Baert et al. (2003) New Engl. J. Med. 348:601-608; Milgrom et al. (1999) New Engl. J. Med. 341:1966-1973; Slamon et al. (2001) New Engl. J. Med. 344:783-792; Beniaminovitz et al. (2000) New Engl. J. Med. 342:613-619; Ghosh et al. (2003) New Engl. J. Med. 348:24-32; Lipsky et al. (2000) New Engl. J. Med. 343:1594-1602; Physicians' Desk Reference 2003 (Physicians' Desk Reference, 57th Ed); Medical Economics Company; ISBN: 1563634457; 57th edition (November 2002). Determination of the appropriate dosage regimen may be made by the clinician, e.g., using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment, and will depend, for example, the patient's clinical history (e.g., previous therapy), the type and stage of the cancer to be treated and biomarkers of response to one or more of the therapeutic agents in the combination therapy.

Biotherapeutic agents in a combination therapy of the invention may be administered by continuous infusion, or by doses at intervals of, e.g., daily, every other day, three times per week, or one time each week, two weeks, three weeks, monthly, bimonthly, etc. A total weekly dose is generally at least 0.05 μg/kg, 0.2 μg/kg, 0.5 μg/kg, 1 μg/kg, 10 μg/kg, 100 μg/kg, 0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg body weight or more. See, e.g., Yang et al. (2003) New Engl. J. Med. 349:427-434; Herold et al. (2002) New Engl. J. Med. 346:1692-1698; Liu et al. (1999) J. Neurol. Neurosurg. Psych. 67:451-456; Portielji et al. (20003) Cancer Immunol. Immunother. 52:133-144.

In some embodiments that employ an anti-human PD-L1 mAb as the PD-L1 antagonist in the combination therapy, the dosing regimen will comprise administering the anti-human PD-L1 mAb at a dose of about 1, 2, 3, 5 or 10 mg/kg at intervals of about 14 days (± 2 days) or about 21 days (± 2 days) or about 30 days (± 2 days) throughout the course of treatment.

In other embodiments that employ an anti-human PD-L1 mAb as the PD-L1 antagonist in the combination therapy, the dosing regimen will comprise administering the anti-human PD-L1 mAb at a dose of from about 0.005 mg/kg to about 10 mg/kg, with intra-patient dose escalation. In other escalating dose embodiments, the interval between doses will be progressively shortened, e.g., about 30 days (± 2 days) between the first and second dose, about 14 days (± 2 days) between the second and third doses. In certain embodiments, the dosing interval will be about 14 days (± 2 days), for doses subsequent to the second dose.

In certain embodiments, a subject will be administered an intravenous (IV) infusion of a medicament comprising any of the PD-L1 antagonists described herein.

In some embodiments, the PD-L1 antagonist in the combination therapy is avelumab, which is administered intravenously at a dose selected from the group consisting of: about 1 mg/kg Q2W (Q2W = one dose every two weeks), about 2 mg/kg Q2W, about 3 mg/kg Q2W, about 5 mg/kg Q2W, about 10 mg Q2W, about 1 mg/kg Q3W (Q3W = one dose every three weeks), about 2 mg/kg Q3W, about 3 mg/kg Q3W, about 5 mg/kg Q3W, and about 10 mg Q3W.

In some embodiments of the invention, the PD-L1 antagonist in the combination therapy is avelumab, which is administered in a liquid medicament at a dose selected from the group consisting of about 1 mg/kg Q2W, about 2 mg/kg Q2W, about 3 mg/kg Q2W, about 5 mg/kg Q2W, about 10 mg Q2W, about 1 mg/kg Q3W, about 2 mg/kg Q3W, about 3 mg/kg Q3W, about 5 mg/kg Q3W, and about 10 mg Q3W.

In some embodiments, a treatment cycle begins with the first day of combination treatment and last for 2 weeks. In such embodiments, the combination therapy is preferably administered for at least 12 weeks (6 cycles of treatment), more preferably at least 24 weeks, and even more preferably at least 2 weeks after the patient achieves a CR.

In some embodiments, the 4-1BB agonist in the combination therapy comprises an anti-4-1BB monoclonal antibody comprising heavy chain variable region and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 18 and SEQ ID NO: 19, respectively, and is administered in a liquid medicament at a dose selected from the group consisting of 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q2W, 5 mg/kg Q2W, 10 mg Q2W, 1 mg/kg Q3W, 2 mg/kg Q3W, 3 mg/kg Q3W, 5 mg/kg Q3W, and 10 mg Q3W. In some embodiments, the anti-4-1BB monoclonal antibody is

administered as a liquid medicament, and the selected dose of the medicament is administered by IV infusion over a time period of about 60 minutes.

In some embodiments, the anti-4-1BB monoclonal antibody is administered at a starting dose of about 0.6 mg/kg Q4W and avelumab is administered at a starting dose of 10 mg/kg Q2W, and if the starting dose combination is not tolerated by the patient, then the dose of avelumab is reduced to 5 mg/kg Q2W and/or the dose of the anti-4-1BB monoclonal antibody is reduced to 0.3 mg/kg Q4W.

In some embodiments, the patient is selected for treatment with the combination therapy of the invention is the patient has been diagnosed with advanced RCC with predominantly clear cell subtype, and the primary tumor has been resected. In some embodiments, the patient has not received prior systemic therapy for advanced RCC.

The present invention also provides a medicament which comprises a PD-L1 antagonist as described above and a pharmaceutically acceptable excipient. When the PD-L1 antagonist is a biotherapeutic agent, e.g., a mAb, the antagonist may be produced in CHO cells using conventional cell culture and recovery/purification technologies.

In some embodiments, a medicament comprising an anti-PD-L1 antibody as the PD-L1 antagonist may be provided as a liquid formulation or prepared by reconstituting a lyophilized powder with sterile water for injection prior to use.

The present invention also provides a medicament which comprises axitinib and a pharmaceutically acceptable excipient.

The anti-PD-L1 and VEGFR inhibitor medicaments described herein may be provided as a kit which comprises a first container and a second container and a package insert. The first container contains at least one dose of a medicament comprising an anti-PD-L1 antagonist, the second container contains at least one dose of a medicament comprising a VEGFR inhibitor, and the package insert, or label, which comprises instructions for treating a patient for cancer using the medicaments. The first and second containers may be comprised of the same or different shape (e.g., vials, syringes and bottles) and/or material (e.g., plastic or glass). The kit may further comprise other materials that may be useful in administering the medicaments, such as diluents, filters, IV bags and lines, needles and syringes. In some embodiments of the kit, the anti-PD-L1 antagonist is an anti-PD-L1 antibody and the instructions state that

the medicaments are intended for use in treating a patient having a cancer that tests positive for PD-L1 expression by an IHC assay.

The anti-PD-L1 and anti-4-1BB antibody medicaments described herein may be provided as a kit which comprises a first container and a second container and a package insert. The first container contains at least one dose of a medicament comprising an anti-PD-L1 antagonist, the second container contains at least one dose of a medicament comprising an anti-4-1BB antibody, and the package insert, or label, which comprises instructions for treating a patient for cancer using the medicaments. The first and second containers may be comprised of the same or different shape (e.g., vials, syringes and bottles) and/or material (e.g., plastic or glass). The kit may further comprise other materials that may be useful in administering the medicaments, such as diluents, filters, IV bags and lines, needles and syringes. In some embodiments of the kit, the anti-PD-L1 antagonist is an anti-PD-L1 antibody and the instructions state that the medicaments are intended for use in treating a patient having a cancer that tests positive for PD-L1 expression by an IHC assay.

The anti-PD-L1 antibody and CD20 antagonist medicaments described herein may be provided as a kit which comprises a first container and a second container and a package insert. The first container contains at least one dose of a medicament comprising an anti-PD-L1 antagonist, the second container contains at least one dose of a medicament comprising a CD20 antagonist, and the package insert, or label, which comprises instructions for treating a patient for cancer using the medicaments. The first and second containers may be comprised of the same or different shape (e.g., vials, syringes and bottles) and/or material (e.g., plastic or glass). The kit may further comprise other materials that may be useful in administering the medicaments, such as diluents, filters, IV bags and lines, needles and syringes. In some embodiments of the kit, the anti-PD-L1 antagonist is an anti-PD-L1 antibody and the instructions state that the medicaments are intended for use in treating a patient having a cancer that tests positive for PD-L1 expression by an IHC assay.

These and other aspects of the invention, including the exemplary specific embodiments listed below, will be apparent from the teachings contained herein.

III. GENERAL METHODS

Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001) Molecular Cloning, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu (1993) Recombinant DNA, Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, et al. (2001) Current Protocols in Molecular Biology, Vols.1-4, John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, et al. (2000) Current Protocols in Protein Science, Vol. 1, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, e.g., Coligan, et al. (2000) Current Protocols in Protein Science, Vol. 2, John Wiley and Sons, Inc., New York; Ausubel, et al. (2001) Current Protocols in Molecular Biology, Vol. 3, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) Products for Life Science Research, St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) BioDirectory, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, et al. (2001) Current Protcols in Immunology, Vol. 1, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) Using Antibodies, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, supra). Standard techniques for characterizing ligand/receptor interactions are available (see, e.g., Coligan, et al. (2001) Current Protocols in Immunology, Vol. 4, John Wiley, Inc., New York).

Monoclonal, polyclonal, and humanized antibodies can be prepared (see, e.g., Sheperd and Dean (eds.) (2000) Monoclonal Antibodies, Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) Antibody Engineering, Springer-Verlag, New York; Harlow and Lane (1988) Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, et al. (2000) J.

Immunol. 165:6205; He, et al. (1998) J. Immunol. 160:1029; Tang et al. (1999) J. Biol. Chem. 274:27371-27378; Baca et al. (1997) J. Biol. Chem. 272:10678-10684; Chothia et al. (1989) Nature 342:877-883; Foote and Winter (1992) J. Mol. Biol. 224:487-499; U.S. Pat. No. 6,329,511).

An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan et al. (1996) Nature Biotechnol. 14:309-314; Barbas (1995) Nature Medicine 1:837-839; Mendez et al. (1997) Nature Genetics 15:146-156; Hoogenboom and Chames (2000) Immunol. Today 21:371-377; Barbas et al. (2001) Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Kay et al. (1996) Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, San Diego, CA; de Bruin et al. (1999) Nature Biotechnol. 17:397-399).

Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, e.g., Meyaard et al. (1997) Immunity 7:283-290; Wright et al. (2000) Immunity 13:233-242; Preston et al., supra; Kaithamana et al. (1999) J. Immunol. 163:5157-5164).

Antibodies can be conjugated, e.g., to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, e.g., to dyes, radioisotopes, enzymes, or metals, e.g., colloidal gold (see, e.g., Le Doussal et al. (1991) J. Immunol. 146:169-175; Gibellini et al. (1998) J. Immunol. 160:3891-3898; Hsing and Bishop (1999) J. Immunol. 162:2804-2811; Everts et al. (2002) J. Immunol. 168:883-889).

Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, e.g., Owens, et al. (1994) Flow Cytometry Principles for Clinical Laboratory Practice, John Wiley and Sons, Hoboken, NJ; Givan (2001) Flow Cytometry, 2nd ed.; Wiley-Liss, Hoboken, NJ; Shapiro (2003) Practical Flow Cytometry, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, e.g., as diagnostic reagents, are available (Molecular Probesy (2003) Catalogue, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) Catalogue, St. Louis, MO).

Standard methods of histology of the immune system are described (see, e.g., Muller-Harmelink (ed.) (1986) Human Thymus: Histopathology and Pathology, Springer Verlag, New York, NY; Hiatt, et al. (2000) Color Atlas of Histology, Lippincott, Williams, and Wilkins, Phila, PA; Louis, et al. (2002) Basic Histology: Text and Atlas, McGraw-Hill, New York, NY).

Software packages and databases for determining, e.g., antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, e.g., GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, et al. (2000) Bioinformatics 16: 741-742; Menne, et al. (2000) Bioinformatics Applications Note 16:741-742; Wren, et al. (2002) Comput. Methods Programs Biomed. 68:177-181; von Heijne (1983) Eur. J. Biochem. 133:17-21; von Heijne (1986) Nucleic Acids Res. 14:4683-4690).

IV. Examples

Example 1: Combination Treatment with Avelumab and Axitinib

This example illustrates a clinical trial study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of avelumab (MSB0010718C) in combination with axitinib (AG-013736) in patients with previously untreated advanced renal cell carcinoma (aRCC).

This study is an open-label, multi-center, multiple-dose trial designed to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 dose (RP2D) of avelumab (MSB0010718C) in combination with axitinib (AG-013736). Once the MTD of avelumab administered in combination with axitinib is estimated (dose finding portion), the dose expansion phase will be opened to further characterize the combination in term of safety profile, anti-tumor activity, pharmacokinetics, pharmacodynamics and biomarker modulation. Protocol design is set forth in Table 4.

The Dose Finding Phase will estimate the MTD and RP2D in patients with aRCC with clear cell histology who did not receive prior systemic therapy for advanced disease, using the modified toxicity probability interval (mTPI) method.35 Dose finding will follow an “Up-and-Down” design, with up to 4 potential dose levels (DL) to be tested, shown in Table 4.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for avelumab in combination with axitinib in patients with aRCC who did not receive prior systemic therapy for their advanced disease. The Expansion Test Dose will either be the MTD (i.e., the highest dose of avelumab and axitinib associated with the occurrence of DLTs in <33% of patients) or the RP2D, i.e., the highest tested dose that is declared safe and tolerable by the investigators and sponsor. Once the Expansion Test Dose is identified, the Dose Expansion Phase will be opened, and avelumab in combination with axitinib will be evaluated in up to approximately 20-40 patients with previously untreated aRCC.

Table 4

Arms	Assigned Interventions	
Dose finding phase	**Group 1:**	avelumab 10 mg/kg IV Q2W; axitinib 5 mg oral BID
	Group 2:	avelumab 5 mg/kg IV Q2W; axitinib 5 mg oral BID
	Group 3:	avelumab 10 mg/kg IV Q2W; axitinib 3 mg oral BID
	Group 4:	avelumab 5 mg/kg IV Q2W; axitinib 3 mg oral BID
Dose expansion phase	**Group 1:**	avelumab 10 mg/kg IV Q2W; axitinib 5 mg oral BID
	Group 2:	avelumab 5 mg/kg IV Q2W; axitinib 5 mg oral BID
	Group 3:	avelumab 10 mg/kg IV Q2W; axitinib 3 mg oral BID
	Group 4:	avelumab 5 mg/kg IV Q2W; axitinib 3 mg oral BID

Inclusion Criteria: Histologically or cytologically confirmed advanced RCC with clear cell component. Primary tumor resected. Mandatory archival formalin fixed, paraffin embedded (FFPE) tumor tissue block from primary tumor resection specimen (all patients). For Extension Cohort only, mandatory de novo tumor biopsy from a locally recurrent or metastatic lesion unless obtained from a procedure performed within 6 months of study entry and if the patient has received no intervening systemic anti-cancer treatment. At least one measureable lesion as defined by RECIST version 1.1. Age ≥18 years. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Adequate bone marrow function, renal and liver functions.

The number of patients to be enrolled in the Dose Finding Phase will depend on the observed safety profile, and the number of tested dose levels. Up to approximately

55 patients (including Dose Finding Phase and Dose Expansion Phase) are projected to be enrolled in the study.

Study Treatment: Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule. Avelumab will be given as a 1-hour intravenous infusion (IV) every two weeks (Q2W). In all patients, treatment with study drugs may continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first.

In order to mitigate avelumab infusion-related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) may be administered approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

Tumor Assessment: Anti-tumor activity will be assessed by radiological tumor assessments at 6-week intervals, using RECIST version 1.1. Complete and partial responses will be be confirmed on repeated imaging at least at 4 weeks after initial documentation. After 1 year from enrollment in the study, tumor assessments should be conducted less frequently, i.e., at 12-week intervals. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (e.g., symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). If radiologic imaging shows progressive disease (PD), tumor assessment should be repeated at least $\geq$4 weeks later in order to confirm PD.

Brain Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans are required at baseline and when there is a suspected brain metastasis. Bone scan (bone scintigraphy) or 18fluorodeoxyglucose-positron emission tomography/CT(18FDG-PET/CT) are required at baseline, then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of CR for patients who have bone metastases.

Pharmacokinetic/Immunogenicity Assessments: PK/immunogenicity sampling will be collected. To understand the PK effects of avelumab on axitinib, a 7-day lead-in period with single-agent axitinib will be included prior to Cycle 1 in all patients in the Dose Finding Phase and in at least 8 patients in the Dose Expansion Phase of the

study. Since avelumab has a long half-life (3-5 days), it would not be feasible to run a lead-in to study the PK of avelumab alone. Therefore, the effect of axitinib on avelumab will be evaluated by comparing avelumab trough concentrations at steady state in the presence of axitinib with those reported for avelumab alone in prior studies.

Biomarker Assessments: A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and axitinib. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the avelumab in combination with axitinib, as well as potential mechanisms of resistance.

Tumor biospecimens from archived tissue samples and metastatic lesions will be used to analyze candidate DNA, RNA, or protein markers, or a relevant signature of markers, for their ability to identify those patients who are most likely to benefit from treatment with the study drugs. Markers that may be analyzed include, but not be limited to, PD-L1 expression tumor-infiltrating CD8+ T lymphocytes, and T-cell receptor gene sequence quantitation. Optional tumor biopsies obtained upon disease progression will be used to investigate acquired mechanisms of resistance. Only core needle or excisional biopsies, or resection specimen are suitable.

Peripheral Blood: Specimens will be retained as whole blood, serum, and plasma in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to avelumab used in combination with axitinib. These include biomarkers that may aid in the identification of those patients who might preferentially benefit from treatment with avelumab in combination with axitinib, including but not limited to biomarkers related to anti-tumor immune response or target modulation, such as soluble VEGF-A, IL-8, IFNγ and/or tissue FoxP3, PD-1, PD-L2. Biospecimens should be obtained pre-dose and at the same time as PK samples whenever possible.

Example 2: Combination Treatment with Axitinib and Avelumab Versus Sunitinib

This example illustrates a clinical trial study to evaluate safety and efficacy of avelumab (MSB0010718C) in combination with axitinib (AG-013736) and to

demonstrate the superiority of this combination versus standard-of-care sunitinib monotherapy in the first-line treatment of patients with advanced RCC (aRCC). Sunitinib malate (SUTENT®) is an oral multitargeted TKI of stem cell receptor factor (KIT), platelet derived growth factor-receptors (PDGFRs), VEGFRs, glial cell-line neurotrophic factor receptor (RET), and FMS-like tyrosine kinase 3 (FLT3), and colony stimulating factor receptor Type 1 (CSR-1R) approved multinationally for the treatment of aRCC, imatinib-resistant or intolerant gastrointestinal stromal tumor (GIST), and unresectable, well-differentiated metastatic pancreatic neuroendocrine tumors (NET).

The study is a Phase 3, randomized, multination, multicenter, open-label, parallel 2-arm study in which approximately 465 patients are planned to be randomized to receive avelumab in combination with axitinib or sunitinib monotherapy: Arm A: avelumab in combination with axitinib; Arm B: sunitinib. Patients will be stratified according to ECOG performance status (0 versus 1) and LDH (>1.5 ULN vs. ≤1.5 ULN). In arm A (avelumab in combination with axitinib), avelumab will be given as a 1 hour intravenous infusion (IV) every 2 weeks in a 6-week cycle. Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule.

Treatment with study drugs may continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first. Axitinib treatment may be adjusted by dosing interruption with or without dose reduction. Intrapatient axitinib dose escalation may occur if the intrapatient escalation criteria are met.

Study Treatment: Axitinib will be given orally twice daily PO on a continuous daily dosing schedule. Avelumab will be given as a 1 hour intravenous infusion every 2 weeks in a 6-week cycle. Sunitinib will be given orally 50 mg taken once daily, on a schedule 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). Patients who develop disease progression on study treatment but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab combined with axitinib, or single-agent avelumab, or single-agent axitinib, or single-agent sunitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Tumor Assessments: Anti-tumor activity will be assessed by radiological tumor assessments and will be based on RECIST guidelines version 1.1 for primary and secondary endpoints and on immune-related RECIST (irRECIST) guidelines for

exploratory endpoints. Tumor assessments will be performed every 6 weeks (Q6W) up to 1 year from first dose therapy; thereafter, tumor assessments will be performed every 2 cycles. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (e.g., symptomatic deterioration), at the time of the End of Treatment/Withdrawal visit (if not done in the previous 6 weeks), and during the Short term Follow-up period (at the 90-day visit only); subsequent tumor assessments during the Long term Follow-up period can be collected in absence of withdrawal of consent, regardless of initiation of subsequent anti-cancer therapies.

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18FDG PET (required at baseline then every 16 weeks only if bone metastases are present at baseline). Otherwise, bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, at 6 weeks after the first dose of therapy, then every 6 weeks up to 1 year from the first dose of therapy and every 12 weeks thereafter, (if not done in the previous 6 weeks), and during the Short term Follow-up period (at the 90-day visit only); subsequent tumor assessments during the Long term Follow-up period can be collected in absence of withdrawal of consent, regardless of initiation of subsequent anti-cancer therapies. Further imaging assessments may be performed at any time if clinically indicated (e.g., suspected PD, symptomatic deterioration, etc.). Assessment of response will be made using RECIST version 1.1 and as per immune-related response criteria (irRC) (Nishino 2013). All radiographic images will be collected and may be objectively verified by a BICR independent third-party core imaging laboratory.

Primary Endpoint: Progression-Free Survival (PFS) as assessed by Blinded Independent Central Review (BICR) per RECIST v1.1. Secondary Endpoints: Overall Survival (OS); objective tumor response rate (OR), as assessed by BICR per RECIST version 1.1.; disease Control (DC), as assessed by BICR per RECIST version 1.1.; time

to event: time to response (TTR), Duration of Response (DR); adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03), timing, seriousness, and relationship to study therapy; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), and timing; PK parameters including trough concentrations (Ctrough) of avelumab and trough concentrations (Ctrough) and maximum concentrations (Cmax) of axitinib; tumor tissue biomarker status (i.e., positive or negative; based on for example, PD-L1 expression and/or quantitation of tumor infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry); measures of clinical outcome (PFS, OS, OR, DCR, DR and TTR) in biomarker-positive and biomarker-negative sub-groups; anti-drug antibodies (ADAs; neutralizing antibodies) of avelumab when in combination with axitinib; patient-Reported Outcomes (PRO): FACT-Kidney Symptom Index (FKSI-19), EuroQol 5 Dimension (EQ 5D).

Example 3: Combination Treatment with Anti-4-1BB Antibody and Avelumab

This example illustrates the therapeutic activity of anti-4-1BB antibody and avelumab combination therapy in murine B16F10 melanoma and MC38 colon carcinoma models.

Six (6)- to 8-week old female C57BL/6 mice were purchased from the Jackson Laboratories. All animals were housed in a pathogen free vivarium facility at Rinat and experiments were conducted according to the protocols in accordance with the Institutional Animal Care and Use Committee (IACUC) guidelines.

The B16F10 melanoma cell line was purchased from American Type Culture Collection (ATCC). The MC38 colon carcinoma cell line was kindly provided by Dr. Antoni Ribas at University of California, Los Angeles, CA. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine at 37°C in 5% carbon dioxide (CO_2), and IMPACT-tested for pathogens at Research Animal Diagnostic Laboratory (RADIL) (Columbia, MO). Pathogen-free cells growing in an exponential growth phase were harvested and used for tumor inoculation.

Antibodies used for cell surface or intracellular staining were purchased from BD Biosciences or eBioscience. They were rat anti-mouse CD4-PerCP-Cy5.5 (clone

RM4-5, BD Biosciences), rat anti-mouse CD8a-APC-H7 (clone 53-6.7, BD Biosciences), rat anti-mouse CD25-PE-Cy7 (clone PC61, BD Biosciences), rat anti-mouse CD45-BV510 (clone 30-F11, BD Biosciences), rat anti-mouse CD90.2-FITC (clone 53-2.1, BD Biosciences), rat anti-mouse Eomes-PE (clone: Dan11mag, eBioscience), rat anti-mouse FoxP3-eFluor450 (clone FJK-16s, eBioscience), and rat anti-mouse NKp46-BV421 or -AF647 (clone 29A1.4, BD Biosciences). Live cells were separated from dead cells using LIVE/DEAD Fixable Blue Dead Cell Stain Kit (Invitrogen).

Therapeutic mouse anti-mouse 4-1BB mAb (mouse immunoglobulin G1 [mIgG1]), derived from the parental clone MAB9371 (R&D Systems), was prepared in-house. Avelumab was provided by Merck Serono. Isotype control mIgG1 (clone: MOPC-21) was purchased from BioXcell. Human IgG1 was prepared in-house. Anti-4-1BB and avelumab were diluted to concentrations of 0.1 mg/mL and 1 mg/mL, respectively, in phosphate buffered saline (PBS) (Life Technologies), and dosed at 0.2 mL per mouse intraperitoneally (ip) for 3 doses 3 to 4 days apart.

C57BL/6 mice were inoculated subcutaneously at the right flank with 0.2×10^6 B16F10 or 0.5×10^6 MC38 cells in 0.1 mL of serum-free DMEM. When tumors reached target size, mice were randomized into treatment groups. Treatment was started on the same day as randomization. Tumor size was measured twice weekly in 2 dimensions using a caliper, and the volume was expressed in cubic millimeters using the formula: $V = 0.5\ L \times W^2$ where L is the longest diameter of the tumor and W is the diameter perpendicular to L. Body weight was recorded weekly.

Tumors were disseminated into single cell suspension using gentle MACS and Miltenyi Mouse Dissociation Kit (Miltenyi Biotec) according to manufacturer's protocol with modification. Ammonium-Chloride-Potassium (ACK) Lysing Buffer (Life Technologies) was used to remove red blood cells. Cells were washed twice with FACS staining buffer (PBS supplemented with 2% FBS and 0.9% sodium azide [NaN_3]), and finally resuspended in FACS staining buffer.

An aliquot of cells was pre-incubated with 10 µg/mL of mouse BD Fc Block (BD Biosciences) for 10 minutes before phenotyping mAbs were added to specifically stain immune cells. Cell surface antigens were labeled by incubating cells at 4°C for 30 minutes. After removing unbound mAbs, cells were washed twice with FACS staining buffer, fixed in fixative buffer (PBS + 2% FBS + 1% paraformaldehyde), and

stored at 4°C in the dark until analyzed by flow cytometry. Intracellular staining was carried out using Foxp3/Transcription Factor Staining Buffer set (eBioscience) according to the manufacturer's protocol. Flow cytometry data were acquired using LSR Fortessa (BD Biosciences) and analyzed using FlowJo (TreeStar Inc.).

Results were expressed as mean ± SEM. Statistical analyses were performed using GraphPad Prism 6.0. One-way or 2-way ANOVA was applied to compare the statistical differences among multiple groups relative to the isotype control. $P < 0.05$ was considered as significant difference.

Two murine models were used to evaluate the therapeutic efficacy of anti-4-1BB in combination with avelumab. In the B16F10 melanoma model, the average starting tumor size was 67 to 78 mm^3 (range 44 to 114 mm^3; n = 7 animals per group) (Table 5). By Day 26 post tumor inoculation, the tumors for isotype, anti-4-1BB alone, and avelumab alone groups reached an average of 1206 ± 397 mm^3, 1979 ± 425 mm^3, and 2112 ± 429 mm^3, respectively (Table 5). By contrast, dramatic tumor suppression (average of 341 ± 146 mm^3) was observed when animals were administered with anti-4-1BB and avelumab concurrently ($p < 0.0001$ vs single agent alone groups) (Table 5).

Table 5. Tumor Measurements (Mean ± SEM) of Subcutaneous B16F10 Melanoma over Time

Days	Isotypes			Anti-4-1BB			Avelumab			Anti-4-1BB / Avelumab		
	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
13	67	4	7	69	6	7	78	8	7	70	10	7
17	251	109	7	364	87	7	327	78	7	219	57	7
20	475	222	7	725	266	7	654	174	7	272	94	7
24	909	368	7	1511	417	7	1304	274	7	243	106	6
26	1206	397	7	1979	425	7	2112	429	7	341	146	6

Tumor volume is expressed in mm^3.

N = Number of animals within each group; SEM = Standard error of the mean.

In the MC38 colon carcinoma model, the average starting tumor size was approximately 60 mm^3 (range 41 - 92 mm^3; n = 10 animals per group) (Table 6). At the end of study (Day 23 post tumor implantation), the average tumor volumes of isotype, anti-4-1BB alone, avelumab alone, and anti-4-1BB antibody/avelumab combination groups were 1177 ± 252 mm^3, 1093 ± 183 mm^3, 901 ± 206 mm^3, and 530 ± 190 mm^3,

respectively (Table 6). The reduction in tumor size by the combination treatment was significant, compared to the isotype control ($p < 0.001$) and 4-1BB alone groups ($p < 0.01$), but not to the avelumab group ($p > 0.05$) (Table 6).

Table 6. Tumor Measurements (Mean ± SEM) of Subcutaneous MC38 Colon Carcinoma over Time

Days	Isotypes			Anti-4-1BB			Avelumab			Anti-4-1BB / Avelumab		
	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
7	60	5	10	62	3	10	63	5	10	64	5	10
10	130	21	10	122	15	10	127	19	10	117	13	10
14	357	72	10	250	30	10	254	42	10	146	42	10
16	501	108	10	355	56	10	384	86	10	176	64	10
18	680	148	10	508	76	10	523	114	10	246	93	10
21	987	236	9	785	143	10	714	158	9	416	149	10
23	1177	252	9	1093	183	10	901	206	9	530	190	10

Tumor volume is expressed in mm^3.

N = Number of animals within each group; SEM = Standard error of the mean.

Tumor-infiltrating lymphocytes (TILs) were isolated from MC38 tumors after treatment and analyzed for markers associated with anti-tumor immune response. The combination treatment facilitated the infiltration of T cells into tumors with an average of 53% of total CD45+ cells, while T-cell frequency (of CD45+ cells) was 25%, 31%, and 36% in the isotype, anti-4 1BB antibody treatment alone, and avelumab alone groups, respectively (Figure 1). The ratio of CD8+ T cells/ regulatory T cell (Treg) in the isotype and avelumab groups was 1.2 and 2.5, respectively. This ratio increased to 10 and 21 in anti-4-1BB antibody treatment alone and in combination with avelumab, respectively (Figure 2). Furthermore, the induction of Eomes, a marker associated with T-cell effector/memory differentiation, was observed in the anti-4-1BB antibody treatment alone and anti-4-1BB and avelumab combination groups (Figure 3).

These results demonstrate that treatment with anti-4-1BB antibody in combination with avelumab has a synergistic anti-tumor effect accompanied by the enrichment of T cells in tumor, increased $CD8^+$ T cell/regulatory T cell (Treg) ratio, and induction of eomesodermin (Eomes) expression. Furthermore, the combination therapy elicited an anti-tumor immune response in the tumor microenvironment.

Example 4: Combination Treatment of Advanced Malignancies with Avelumab and PF-05082566

This example illustrates a clinical trial study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of avelumab (MSB0010718C) in combination with PF-05082566, an anti-4-1BB agonist IgG2 antibody, in patients with with locally advanced or metastatic solid tumors (e.g., non-small cell lung cancer (NSCLC), melanoma, and squamous cell carcinoma (SCCHN)). Protocol design is set forth in Table 7.

Table 7

Arms	Assigned Interventions
Cohort A1: NSCLC patients treated with 10 mg/kg avelumab + 500 mg PF-05082566	Avelumab 10 mg/kg IV Q2W; PF-05082566 500 mg IV every 4 weeks. Treatment with the combination of avelumab with PF-05082566 will continue until disease progression.
Cohort A2: NSCLC patients treated with 10 mg/kg avelumab + 100 mg PF-05082566	Avelumab 10 mg/kg IV Q2W; PF-05082566 100 mg IV every 4 weeks. Treatment with the combination of avelumab with PF-05082566 will continue until disease progression.
Cohort A3: NSCLC patients treated with 10 mg/kg avelumab + 20 mg PF-05082566	Avelumab 10 mg/kg IV Q2W; PF-05082566 20 mg IV every 4 weeks. Treatment with the combination of avelumab with PF-05082566 will continue until disease progression.
Cohort A4: Melanoma patients treated with 10 mg/kg avelumab + 100 mg PF-05082566	Avelumab 10 mg/kg IV Q2W; PF-05082566 100 mg IV every 4 weeks. Treatment with the combination of avelumab with PF-05082566 will continue until disease progression.

Arms	Assigned Interventions
Cohort A5: SCCHN patients treated with 10 mg/kg avelumab + 100 mg PF-05082566	Avelumab 10 mg/kg IV Q2W; PF-05082566 100 mg IV every 4 weeks. Treatment with the combination of avelumab with PF-05082566 will continue until disease progression.

Example 5: Combination Treatment of Cancer with Avelumab, Anti-4-1BB antibody, and Anti-M-CSF Antibody

This example illustrates the therapeutic activity of anti-4-1BB antibody, anti-M-CSF antibody, and the anti-PD-L1 antibody Avelumab triple combination therapy in murine MC38 colon carcinoma models.

Six (6)- to 8-week old female C57BL/6 mice were purchased from the Jackson Laboratories. All animals were housed in a pathogen free vivarium facility at Rinat and experiments were conducted according to the protocols in accordance with the Institutional Animal Care and Use Committee (IACUC) guidelines.

The MC38 colon carcinoma cell line was kindly provided by Dr. Antoni Ribas at University of California, Los Angeles, CA. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L glutamine at 37℃ in 5% carbon dioxide (CO2), and IMPACT-tested for pathogens at Research Animal Diagnostic Laboratory (RADIL) (Columbia, MO). Pathogen-free cells growing in an exponential growth phase were harvested and used for tumor inoculation.

Therapeutic mouse anti-mouse 4-1BB mAb (mouse immunoglobulin G1 [mIgG1]), derived from the parental clone MAB9371 (R&D Systems), was prepared in-house. Avelumab was provided by Merck Serono. Rat anti-mouse M-CSF (clone 5A1), rat IgG1 (clone HRPN) and mIgG1 (clone: MOPC-21) isotype controls were purchased from BioXcell. Human IgG1 isotype was prepared in-house. Anti-4-1BB, avelumab and anti-M-CSF mAbs were diluted to concentrations of 0.1 mg/mL and 1 mg/mL, and 1.5 mg/mL, respectively, in phosphate buffered saline (PBS) (Life Technologies), and dosed at 0.2 mL per mouse intraperitoneally (ip) for 3 doses 3 to 4 days apart.

C57BL/6 mice were inoculated subcutaneously at the right flank with 0.5-1 x 106 MC38 cells in 0.1 mL of DMEM. When tumors reached an average of ~ 60 mm^3 (range 41 – 93 mm^3), mice were randomized into groups of 10 animals per group, and

treatment was started at the same day. Tumor size was measured in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: V = 0.5 L x W2 where L and W are the long and short diameters of the tumor, respectively. Body weight was recorded weekly.

Results were expressed as mean ± SEM (Table 8). Statistical analyses were performed using GraphPad Prism 6.0. One-way or two-way ANOVA was applied to compare the statistical differences among multiple groups relative to isotype controls. $P<0.05$ was considered as significant difference.

Table 8

Group 1. Isotype control			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	60	5	10
10	130	21	10
14	357	72	10
16	501	108	10
18	680	148	10
21	987	236	9
23	1177	252	9
Group 2. Anti-4-1BB antibody (1 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	62	3	10
10	122	15	10
14	250	30	10
16	355	56	10
18	508	76	10
21	785	143	10
23	1093	183	10
Group 3. Anti-M-CSF antibody (15 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	58	4	10
10	138	27	10
14	196	32	10
16	268	43	10
18	350	56	10

21	432	84	9
23	572	123	9
Group 4. Anti-PD-L1 antibody (Avelumab, 10 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	63	5	10
10	127	19	10
14	254	42	10
16	384	86	10
18	523	114	10
21	714	158	9
23	901	206	9
Group 5. Anti-4-1BB antibody (1 mg/kg) + Anti-PD-L1 antibody (Avelumab, 10 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	64	5	10
10	117	13	10
14	146	42	10
16	176	64	10
18	246	93	10
21	416	149	10
23	530	190	10
Group 6. Anti-M-CSF antibody (15 mg/kg) + Anti-PD-L1 antibody (Avelumab, 10 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	62	4	10
10	106	10	10
14	182	29	10
16	211	32	9
18	297	65	9
21	436	112	9
23	499	145	9
Group 7. Anti-4-1BB antibody (1 mg/kg) + Anti-M-CSFantibody (15 mg/kg) + Anti-PD-L1 antibody (Avelumab, 10 mg/kg)			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
7	61	4	10
10	120	16	10

14	139	15	10
16	145	20	10
18	166	20	10
21	214	28	10
23	277	39	10

Treatment with the triple combination anti-4-1BB antibody, Avelumab, and anti-M-CSF antibody delayed MC38 tumor growth compared to isotype control (Table 8). The triple antibody combination (Table 8, Group 7) was more efficacious that either double combination of avelumab and anti-4-1BB antibody (Table 8, Group 5) or avelumab and anti-CSF-1 antibody (Table 8, Group 6). For example, at day 23 post-tumor inoculation, tumors in animals treated with the triple combination of avelumab, anti-4-1BB antibody, and anti-CSF-1 antibody had a mean size of 277 mm^3. In comparison, tumors in animals treated with either the double combination of avelumab and anti-4-1BB antibody or avelumab and anti-CSF-1 antibody had a mean size of 530 mm^3 and 499 mm^3, respectively, at day 23. Tumors in animals given isotype control had a mean size of 1177 mm^3 at day 23. Tumors in animals given anti-4-1BB antibody had a mean size of 1093 mm^3 at day 23. Tumors in animals given anti-CSF-1 antibody had a mean size of 572 mm^3 at day 23. Tumors in animals given anti-PD-L1 antibody (Avelumab) had a mean size of 901 mm^3 at day 23. These results demonstrate that treatment with the triple combination of anti-4-1BB antibody, Avelumab, and anti-M-CSF-antibody is more efficacious in treating cancer than single antibody or double antibody combination treatment.

Example 6: Combination Treatment of Colon Carcinoma with Avelumab, Anti-4-1BB antibody, and Anti-OX40 Antibody

This example illustrates the therapeutic activity of the anti-PD-L1 antibody Avelumab, anti-4-1BB antibody, and anti-OX40 antibody triple combination therapy in murine cancer models.

Two murine models were used to evaluate the therapeutic efficacy of combinatorial treatment of anti-OX40 antibody, anti-4-1BB and Avelumab. Six (6)- to 8-week old female C57BL/6 mice or Balb/C mice were purchased from the Jackson Laboratories. All animals were housed in a pathogen free vivarium facility at Rinat and

experiments were conducted according to the protocols in accordance with the Institutional Animal Care and Use Committee (IACUC) guidelines.

The B16F10 melanoma cell line was purchased from American Type Culture Collection (ATCC). The MC38 colon carcinoma cell line was kindly provided by Dr. Antoni Ribas at University of California, Los Angeles, CA. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine at 37°C in 5% carbon dioxide (CO_2). Cells growing in an exponential growth phase were harvested and used for tumor inoculation.

Therapeutic mouse anti-OX40 antibodies with either the mIgG1 or the mIgG2a isotype (anti-OX40 mIgG1 and anti-OX40 mIgG2a, respectively) were derived from parental clone OX86 in house. Therapeutic mouse anti-mouse 4-1BB antibody (mouse immunoglobulin G1 [mIgG1]), derived from the parental clone MAB9371 (R&D Systems), was prepared in-house. Avelumab was provided by Merck Serono. Isotype control mIgG1 (clone: MOPC-21) and mIgG2a (C1.18.4) was purchased from BioXcell. Human IgG1 was prepared in-house. Anti-OX40 antibody, anti-4-1BB antibody, and avelumab were dosed at 3 mg/kg, 1 mg/kg and 20 mg/kg in the B16F10 model and 1 mg/kg, 1 mg/kg and 10 mg/kg in the MC38 model, respectively, in phosphate buffered saline (PBS) (Life Technologies), and dosed at 0.2 mL per mouse intraperitoneally (ip) for 3 doses 3 to 4 days apart.

C57BL/6 mice were inoculated subcutaneously at the right flank with 0.3×10^6 B16F10 cells in 0.1 mL of PBS. Balb/C mice were inoculated subcutaneously at the right flank with 0.5×10^6 MC38 cells in 0.1 mL of PBS. When tumors reached target size, mice were randomized into treatment groups. Treatment was started on the same day as randomization. Tumor size was measured twice weekly in 2 dimensions using a caliper, and the volume was calculated in cubic millimeters using the formula: $V = 0.5\ L \times W^2$ where L is the longest diameter of the tumor and W is the diameter perpendicular to L. Body weight was recorded weekly.

Results are summarized in Table 9 (B16F10 melanoma) and Table 10 (MC38 colon carcinoma) below (mean tumor size ± SEM). Statistical analyses were performed using GraphPad Prism 6.0. 2-way ANOVA was applied to compare the statistical differences among multiple groups relative to the isotype control or other treatment groups. $P < 0.05$ was considered as significant difference. Tumor measurements are in mm^3.

Table 9. Tumor Measurements of Subcutaneous B16F10 Melanoma over Time

Group 1. Isotype control			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	74	11	8
15	214	46	8
18	392	67	8
22	1015	204	8
25	1897	310	8
29	2233	249	8
32	2311	228	8
Group 2. Anti-4-1BB antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	73	9	8
15	282	67	8
18	413	98	8
22	742	155	8
25	1392	278	8
29	2620	518	8
32	2759	493	8
Group 3. Anti-OX40 mIgG2a antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	71	7	9
15	198	51	9
18	370	105	9
22	783	293	9
25	1147	283	9
29	2046	433	9
32	2576	360	9
Group 4. Avelumab			
Days Post-Tumor	**Mean Tumor Size**	**SEM**	**N**

Inoculation	(mm^3)		
12	77	15	5
15	236	71	5
18	396	137	5
22	750	134	5
25	1291	210	5
29	2159	326	5
32	2352	264	5
Group 5. Anti-4-1BB antibody + Anti-OX40 mIgG2a antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	78	14	9
15	155	23	9
18	313	50	9
22	595	87	9
25	861	65	9
29	1453	137	9
32	2003	245	9
Group 6. Anti-OX40 mIgG1 antibody + Avelumab			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	76	15	8
15	228	77	8
18	336	80	8
22	648	149	8
25	1009	248	8
29	1381	228	8
32	1908	261	8
Group 7. Avelumab + Anti-OX40 mIgG2a antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**

12	75	11	8
15	184	37	8
18	297	61	8
22	505	111	8
25	833	191	8
29	1731	392	8
32	2056	371	8
Group 8. Avelumab + Anti-4-1BB antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	73	10	8
15	229	52	8
18	274	52	8
22	537	117	8
25	803	192	8
29	1435	305	8
32	1572	307	8
Group 9. Avelumab + Anti-4-1BB antibody + Anti-OX40 mIgG1 antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	72	9	9
15	176	32	9
18	228	60	9
22	373	114	9
25	585	192	9
29	788	267	9
32	979	329	9
Group 10. Avelumab + Anti-4-1BB antibody + Anti-OX40 mIgG2a antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
12	74	10	9
15	104	17	9

18	120	17	9
22	155	49	9
25	208	54	9
29	365	93	9
32	442	114	9

Table 10. Tumor Measurements of Subcutaneous MC38 Colon Carcinoma over Time

Group 1. Isotype control			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	7	9
13	162	23	9
16	305	41	9
21	696	66	9
24	1064	112	9
28	1830	214	9
Group 2. Anti-OX40 mIgG1 antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	6	9
13	160	15	9
16	280	28	9
21	751	79	9
24	1238	139	9
28	2223	270	9
Group 3. Anti-OX40 mIgG2a antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	7	9
13	154	11	9
16	247	18	9

21	455	64	9
24	648	102	9
28	1053	181	9
Group 4. Anti-4-1BB antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	84	7	8
13	161	11	8
16	264	19	8
21	585	37	8
24	909	65	8
28	1494	129	8
Group 5. Anti-OX40 mIgG1 antibody + Anti-4-1BB antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	7	9
13	171	11	9
16	246	20	9
21	492	27	9
24	737	62	9
28	1241	217	9
Group 6. Anti-OX40 mIgG2a antibody + Anti-4-1BB antibody			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	7	8
13	175	15	8
16	248	29	8
21	387	74	8
24	567	119	8
28	854	163	8
Group 7. Anti-4-1BB antibody + Avelumab			

Days Post-Tumor Inoculation	Mean Tumor Size (mm^3)	SEM	N
10	85	6	9
13	152	8	9
16	195	27	9
21	349	89	9
24	573	157	9
28	1026	255	9
Group 8. Anti-OX40 mIgG1 antibody + Anti-4-1BB antibody + Avelumab			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	6	9
13	167	12	9
16	170	32	9
21	228	65	9
24	304	86	9
28	448	108	9
Group 9. Anti-OX40 mIgG2a antibody + Anti-4-1BB antibody + Avelumab			
Days Post-Tumor Inoculation	**Mean Tumor Size (mm^3)**	**SEM**	**N**
10	85	6	9
13	153	17	9
16	127	23	9
21	116	37	9
24	165	67	9
28	260	107	9

Two murine models were used to evaluate the therapeutic efficacy of triple combinatorial treatment of anti-OX40 antibody, anti-4-1BB antibody, and Avelumab. In the B16F10 melanoma model, the average tumor size when treatment was started was 71-78 mm^3 (Table 9). By day 32 post tumor innoculation, the tumors in animals treated

with isotype control, anti-4-1BB antibody alone, avelumab alone, anti-OX40 mIgG2a antibody alone and anti-OX40 mIgG1 antibody plus Avelumab groups were either very close to or over 2000 mm^3; they were 2311 ± 228 mm^3, 2759 ± 493 mm^3, 2352 ± 264 mm^3, 2576 ± 360 mm^3 and 1908 ± 261 mm^3, respectively. Treatment of animals with anti-4-1BB antibody plus anti-OX40 mIgG2a antibody, anti-OX40 mIgG2a antibody plus Avelumab, or anti-4-1BB antibody plus Avelumab had better treatment efficacy by day 25 as comparing to isotype control treated animals; however the difference in tumor size became insignificant on day 32. By contrast, dramatic tumor suppression was observed when animals were administered Avelumab, anti-4-1BB antibody, and anti-OX40 mIgG1 antibody concurrently (Table 9, Group 9), or Avelumab, anti-4-1BB antibody, and anti-OX40 mIgG2a antibody concurrently (Table 9, Group 10). Tumors were 979 ± 329 mm^3 (Table 9, Group 9; $p < 0.001$ vs isotype control and single agent alone groups) and 442 ± 114 mm^3 (Table 9, Group 10; $p < 0.00001$ vs isotype control and single agent alone groups), respectively. In the case of triple combination with anti-4-1BB antibody, anti-OX40 mIgG2a antibody, and Avelumab combination, it is also significantly better than the double combination groups ($p < 0.01$) (Table 9).

In the MC38 colon carcinoma model, the average tumor size when treatment was started was 84-85 mm^3. By day 28 post tumor implantation, tumors in animals treated with anti-OX40 mIgG2a antibody (Table 10, Group 3), anti-OX40 mIgG1 antibody plus anti-4-1BB antibody (Table 10, Group 5), anti-OX40 mIgG2a plus anti-4-1BB antibody (Table 10, Group 6), or anti-4-1BB antibody plus Avelumab (Table 10, Group 7) had tumors sizes of 1053 ± 181 mm^3, 1241 ± 217 mm^3, 854± 163 mm^3 and 1026± 255 mm^3, respectively, which is significantly lower than that of the isotype control treated group (1830 ± 214 mm^3) ($p < 0.001$) (Table 10, Group 1). Treatment with anti-OX40 mIgG1 antibody alone (Table 10, Group 2) or anti-4-1BB antibody alone (Table 10, Group 4) did not inhibit tumor growth. By contrast, treatment with the triple combination of anti-4-1BB antibody and Avelumab with either anti-OX40 mIgG1 antibody (Table 10, Group 8) or anti-OX40 mIgG2a antibody (Table 10, Group 9) antibody significantly inhibited tumor growth with the tumor size averaging 448 ± 108 mm^3 and 260 ± 107 mm^3, respectively. In both cases this is not only significant comparing to the isotype control group ($p < 0.0001$), both triple combinations were also significantly better than any of the double combinations ($p < 0.001$) (Table 10).

These results demonstrate that treatment with the triple combination of anti-4-1BB antibody, Avelumab, and anti-OX40 antibody is more efficacious in treating cancer than single antibody or double antibody combination treatment.

Example 7: Combination Treatment of relapsed or refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL) with Avelumab in Combination with Anti-4-1BB Antibody, Azacitidine, Anti-CD20 Antagonist Antibody, and/or Conventional Chemotherapy (Bendamustine).

In this study example, three treatment regiments are illustrated:

• Avelumab in combination with rituximab and PF-05082566 for the treatment of patients with relapsed or refractory DLBCL

• Avelumab in combination with azacitidine and PF-05082566 for the treatment of patients with relapsed or refractory DLBCL

• Avelumab in combination with rituximab and bendamustine is indicated for the treatment of patients with relapsed or refractory DLBCL

The target population for the study is patients with R/R DLBCL defined as follows: (i) patients with R/R DLBCL following failure of at least 2 lines (and a maximum of 4 lines) of prior rituximab/multi-agent chemotherapy and/or (ii) failure of ASCT, or (iii) who are not candidates for ASCT (refusal or no available donor), or (iv) who are not candidates for intensive second-line chemotherapy.

The current NCCN Guidelines (version 1.2016) for DLBCL recommend treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with newly diagnosed disease in all stages of disease, or mini-CHOP in patients >80 years with comorbidities. Approximately 60% of patients with DLBCL are expected to be cured following treatment with R-CHOP. Thirty to 50% of those with advanced disease will, however, have disease that is either primary refractory (~15%) or resistant (~25%) to R-CHOP (NCCN Guidelines, 2016; Sehn & Gascoyne, 2015; Vacirca et al, 2014).

High-dose chemotherapy followed by ASCT provides the best chance of a cure in patients with R/R DLBCL in the second-line setting; however, due to advanced age and/or comorbidities, only approximately 50% of patients for whom first-line R-CHOP failures are fit for high-dose chemotherapy, and of these, only about ~50% have chemosensitive disease in the second-line setting and are suitable for ASCT (Sehn &

Gascoyne, 2015). Even if eligible for high-dose chemotherapy, patients may refuse ASCT, lack a good donor, or be ineligible due to a variety of comorbidities. Even in patients treatmed with high-dose chemotherapy followed by ASCT, only a minority (<10%) are cured.

The following rituximab-containing chemotherapy regimens are currently recommended by the NCCN Guidelines (version 1.2016) for second-line salvage therapy and beyond in patients who are not eligible for high-dose chemotherapy and ASCT: bendamustine ± rituximab, brentuximab, cyclophosphamide/etoposide/ procarbazine/prednisone (CEPP), cyclophosphamide/etoposide/ vincristine/prednisone (CEOP), dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) ± rituximab, gemcitabine, dexamethasone and cisplatin (GDP) ± rituximab, gemcitabine/oxaliplatin ± rituximab, lenalidomide ± rituximab, and rituximab (NCCN Guidelines, 2016).

The outcome of patients for whom treatment with R-CHOP failures, and who are not eligible for high-dose chemotherapy or ASCT is dismal, with a median PFS of 3.6 months (Vacirca et al, 2014). The treatment options for these patients remain very limited, and there is consequently a high unmet medical need in patients with R/R DLBCL for the development of more effective salvage strategies that can prolong PFS and overall survival (OS).

The proposed Study is a multicenter, international, parallel design, randomized, open-label, 2-component (Phase 1b followed by Phase 3) study of avelumab in various combinations for the treatment of R/R DLBCL. Agents that will be tested include:

(i) PF-05082566, a novel fully human IgG2 monoclonal antibody agonist of 4-1BB,

(ii) Azacitidine, a DNA methyltransferase inhibitor (DNMTi) and epigenetic agent which has been shown to have potential immune priming activity through various mechanisms including the induction of PD-1 on tumor infiltrating lymphocytes (TILs) and PD-L1 on tumor cells as well as the induction of tumor neo-antigen expression,

(iii) Rituximab, a CD20 antagonist antibody, and

(iv) Bendamustine, an alkylatingchemotherapy agent which is one of the National Comprehensive Cancer Network (NCCN) recommended agents for the salvage therapy of patients with DLBCL who are ineligible for high dose chemotherapy and autologous stem cell transplant (ASCT).

The treatment regimens proposed in the study include avelumab combined with:

(i) Rituximab and PF-05082566

(ii) Azacitidine and PF-05082566, and

(iii) Rituximab and bendamustine

In Phase 3, patients will be randomized in a 1:1 ratio to the treatment regimen selected in Phase 1b versus the Investigator's Choice standard of care (SOC) treatment to determine whether the selected treatment regimen is superior to the Investigator's Choice SOC treatment in prolonging progression-free survival (PFS).

The target study population of this Phase 1b/Phase 3 registrational study will comprise patients with R/R DLBCL who have completed at least 2 (but not more than 4) lines of prior rituximab/multi-agent chemotherapy, or in whom ASCT has been a failure , or who are not candidates for ASCT, or who are not eligible for intensive chemotherapy. The study will assess the safety, efficacy, pharmacokinetics (PK), immunogenicity, and patient reported outcomes.

The primary objective of the Phase 1b component is to make a preliminary assessment of safety for each combination regimen. Each arm without a significant safety signal among the first 6 patients will then be expanded to a total of 28 patients per arm in order to select a treatment regimen to be advanced to the Phase 3 component of the study. This decision will be based upon the investigator observed objective response rate (ORR) and safety profile of each combination regimen. The combination regimens to be assessed in the Phase 1b component of the study in 28-day cycles include:

Arm A: Avelumab/Rituximab/PF-05082566 (4-1BB)

(i) Rituximab 375 mg/m^2 (IV) in the morning on Day 1 of each 28-day cycle. Rituximab is administered for a maximum of 8 cycles.

Rituximab will be administered at least 3 hours prior to PF-05082566 when dosed on the same day.

(ii) PF-05082566 100 mg fixed dose (IV) in the morning on Day 2 of Cycles 1 and 2 of each 28-day cycle. If PF-05082566 is well tolerated in Cycles 1 and 2, administration of PF-05082566 may be on Day 1 in Cycle 3 (and all subsequent cycles).

PF-05082566 will be administered at least 3 hours prior to avelumab in Cycle 1. If PF-05082566 is well tolerated in Cycle 1, in Cycle 2 and all subsequent cycles the

window of dose administration between PF-05082566 and avelumab may be decreased from at least 3 hours apart to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg (IV) every 2-weeks Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 and 2, administration of avelumab may be on Day 1 and Day 15 in Cycle 3 (and all subsequent cycles).

Avelumab will be administered at least 3 hours after PF-05082566 in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 Day 2, in Cycle 2 Day 2 and subsequent cycles the window of dose administration between avelumab and PF-05082566 may be decreased from at least 3 hours apart to 30-60 minutes apart.

Arm B: Avelumab/Azacitidine/PF-05082566 (4-1BB)

(i) Azacitidine 75 mg/m^2 (SC) in the morning on Day 1 - Day 7 consecutively of each 28-day cycle. Azacitidine is administered for a maximum of 6 cycles.

Azacitidine will be administered at least 3 hours prior to PF-05082566 when dosed on the same day.

(ii) PF-05082566 100 mg fixed dose (IV) in the morning on Day 2 for Cycle 1 and Cycle 2, of each 28-day cycle. If PF-05082566 is well tolerated in Cycle 1 and 2, PF-05082566 may be administered on Day 1 commencing with Cycle 3 (and subsequent cycles).

PF-05082566 should be administered at least 3 hours prior to avelumab administration. If PF-05082566 is well tolerated in Cycle 1, in Cycle 2 and all subsequent cycles the window of dose administration between PF-05082566 and avelumab may be decreased from at least 3 hours apart to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg every 2-weeks (IV) Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 and 2, avelumab may be administered on Day 1 and Day 15 in Cycle 3 (and all subsequent cycles).

Avelumab administration should be at least 3 hours after PF-05082566 in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 Day 2, in Cycle 2 Day 2 and subsequent cycles the window of dose administration between avelumab and PF-05082566 may be decreased from at least 3 hours apart to 30-60 minutes apart.

Arm C: Avelumab/Bendamustine/Rituximab

(i) Rituximab 375 mg/m^2 (IV) in the morning on Day 1 of each 28-day cycle. Rituximab is administered for a maximum of 8 cycles.

(ii) Bendamustine 90 mg/m^2 (IV) on Day 2 and Day 3 of each 28-day cycle in Cycle 1 and Cycle 2. If bendamustine is well tolerated in Cycle 1 and 2, bendamustine may be administered on Day 1 and Day 2 in Cycle 3 (and all subsequent cycles). Bendamustine is administered for a maximum of 6 cycles.

(iii) Avelumab 10 mg/kg every 2-weeks (IV) Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 and 2, avelumab may be administered on Day 1 and Day 15 in Cycle 3 (and all subsequent cycles). Avelumab administration should be at least 3 hours after bendamustine.

In Phase 3 (N = 220), the primary objective is to demonstrate superiority in PFS (as assessed by Blinded Independent Central Review [BICR]) of the combination regimen identified in Phase 1b, over the control treatment, namely Investigator's Choice SOC chemotherapy (comprising rituximab/bendamustine or rituximab/ gemcitabine/ oxaliplatin).

The following treatment regimens will be assessed in the Phase 3 component of the study, with all treatments being administered in 28-day cycles:

Arm D (N=110): Regimen Selected from Phase 1b

Arm D will be one of the treatment regimens assessed in Phase 1b, ie, Arm A, B, or C, selected based on safety and efficacy assessments.

Cohort E (N=110): Investigator's Choice Option Between the Following Standard of Care Regimens:

(i) Rituximab/bendamustine

- Rituximab 375 mg/m^2 IV Day 1
- Bendamustine 120 mg/m^2 IV Day 1 and Day 2

(ii) Rituximab/gemcitabine/oxaliplatin

- Rituximab 375 mg/m^2 IV Day 1
- Gemcitabine 1000 mg/m^2 IV on Day 2 and Day 17
- Oxaliplatin 100 mg/m^2 IV on Day 2 and Day 17

Example 8: Combination Treatment of Patients with Advanced Malignancies whose Disease has Progressed on an Immune Checkpoint Inhibitor with Avelumab in Combination with anti-4-1BB antibody.

This example illustrates a Phase 2 study to assess safety and efficacy of avelumab (MSB0010718C) in combination with anti-4-1BB agonist antibody PF-05082566 in patients with advanced NSCLC, RCC, or urothelial cancer (UC) whose disease has progressed on prior therapy(ies), including a single-agent immune checkpoint inhibitor.

The objective of this study is to evaluate the Objective Response Rate (ORR) based on RECIST 1.1 of avelumab plus PF-05082566. Patients must have advanced NSCLC, RCC, or urothelial cancer which was resistant (responded and then progressed) or refractory (never responded) to prior therapy(ies), including a single-agent immune checkpoint inhibitor (e.g.,anti- PD-1/anti-PD-L1 or anti-CTLA-4).

Avelumab will be given as a 1-hour intravenous infusion every 2 weeks at a dose of 10 mg/kg in all three cohorts. PF-05082566 will be administered at 100 mg as a 1-hour IV infusion once every 4 weeks on Day 1 of each cycle.

On days when both drugs are administered, PF 05082566 will be administered first, followed by the avelumab infusion no more than 30 minutes after the end of the PF-05082566 infusion.

Dosing will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, patient is lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first.

The combination of avelumab plus anti-4-1BB antibody PF-05082566 and anti-OX40 antibody PF-04518600 has been evaluated for cytokine release using the standard human PBMC in vitro test. The cytokine release assay was completed for PF-05082566 alone and in combination with avelumab and PF-04518600. Results for the PF-05082566 antibody alone did not show a significant increase in cytokine release. In addition, there was no additive effect on cytokine release when the three monoclonal antibodies were combined.

ORR estimation will be the primary objective in any potential evaluation of avelumab in combination with immunotherapy other that PF-05082566. In each case,

the ORR will be evaluated with the totality of the data for potential cohort expansion or testing of multiple tumor types and/or other combination immunotherapeutic agents.

Example 9: Randomized, Phase 3 Study of Avelumab (MSB0010718C) in Combination with Standard of Care Chemoradiotherapy (Cisplatin and Definitive Radiation Therapy) Versus Standard-of-Care Chemoradiotherapy in the Front-line Treatment of Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

This example illustrates a Phase 3, multicenter, multinational, randomized, placebo controlled study of avelumab (MSB0010718C) in combination with standard of care (SOC) chemoradiotherapy (cisplatin and definitive radiation therapy) versus SOC chemotherapy for front-line treatment of patients with locally-advanced squamous cell carcinoma of the head and neck.

Approximately 640 patients who have received no prior therapy for their SCCHN (oral cavity, oropharynx, larynx, or hypopharynx) HPV-: Stage III, IVa, or IVb or HPV+: T4 or N3 who are eligible for definitive chemoradiotherapy with cisplatin will be randomized 1:1 to treatment with avelumab + SOC chemoradiotherapy vs. placebo + chemoradiotherapy followed by maintenance avelumab or placebo for up to 1 year. Patients will be stratified based on:

- Tumor (T) stage (<T4 vs T4);
- Nodal (N) stage (N0 vs N1/N2a/N2b vs N2c/N3)

Tumor assessment will occur every 12 weeks following the completion of definitive chemoradiotherapy for 2 years, and then every 16 weeks thereafter.

A blinded independent review committee (BICR) will review tumor assessments in addition to investigator reviews.

When the study treatment is discontinued for reasons other than progressive disease (PD), patient withdrawal of consent, or death, patients will be followed and have tumor assessments performed every 12 weeks until: 1) PD, 2) death, 3) patient withdrawal of consent from study, or 4) 2 years from completion of chemoradiotherapy have passed after which tumor assessments can be every 16 weeks, whichever occurs first.

Arm A: Avelumab (MSB0010718C) +SOC Chemoradiotherapy (CRT).

In this study, the lead-in phase is to start seven days prior to initiation of the CRT phase. The maintenance phase will start after completion of the CRT phase (i.e., two weeks following completion of CRT).

- Cisplatin 100 mg/m^2 Days 1, 22, 43. Administered in 500 ml normal saline over a 60-120 minute infusion with an additional 1 to 1.5 L of fluid given post-hydration.
- Radiation therapy (RT) 70 Gy/33-35 fractions/day, 5 fractions/week intensity modulated radiation therapy (IMRT)
- Avelumab: 10 mg/kg administered on Day 1 of the lead-in phase, and Days 8, 29, 39 of the CRT phase, and every 2 weeks (Q2W) thereafter for up to 12 months.

Arm B: SOC Chemoradiotherapy.

- Cisplatin 100 mg/m^2 Days 1, 22, 43
- RT 70 Gy/33-35 fractions/day, 5 fractions/week IMRT
- Placebo: Day 1 of the lead-in phase, Days 8, 29, 39, and Q2W thereafter for up to 12 months.

Avelumab and placebo will be administered as IV infusion.

Patients will receive study treatment until: 1) 12 months after start of maintenance therapy (study intervention completion), 2) PD 3) death, 4) patient withdrawal of consent, 5) patient is lost to follow-up, 6) unacceptable toxicity occurs, or 7) the study is terminated by the Sponsor, whichever occurs first.

The dose of cisplatin may be modified on Days 22 and/or 43 for toxicity as follows: starting dose level is 100 100 mg/m^2, dose level -1 is 75 mg/m^2, and dose level -2 is 50 mg/m^2.

Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to anti-tumor immune response and/or response to or disease progression on avelumab, such as genes related to IFN-γ or transforming growth factor (TGF)-β.

Example 10: Phase 1b dose-finding study of avelumab (MSB0010718C; anti-PD-L1) + axitinib in treatment-naïve patients with advanced renal cell carcinoma

This example illustrates results from the study described in Example 1 above. Eligible patients have histologically confirmed aRCC with a clear-cell component, primary tumour resection, ≥1 measurable lesion, archival/fresh tumour biopsy, ECOG PS ≤1, no preexisting uncontrolled hypertension, and no prior systemic therapy for

aRCC. To determine dose modifications for future cohorts, dose escalation/de-escalation rules that follow the modified toxicity probability interval method were used. Adverse events (AEs) were graded by NCI CTCAE v4. Objective response rates (ORR; RECIST v1.1) were evaluated.

The starting dose of avelumab 10 mg/kg (1h IV infusion) Q2W + axitinib 5 mg PO BID met MTD criteria. By 05 April 2016, 6 pts (median age 59.5 [range, 45-73]) have been treated with avelumab for a median of 17.0 wks (range, 11.9-21.7) and with axitinib for 16.3 wks (range, 12.7-22.7). One DLT of grade 3 proteinuria occurred. The most common treatment-related (TR) AEs of any grade were dysphonia (n=4), hypertension (n=4), fatigue (n=3), and headache (n=3). Grade 3-4 TRAEs were hypertension (n=2), hand-foot syndrome (n=1), elevated lipase (n=1), and proteinuria (n=1). Confirmed ORR is 83.3% (95% CI: 35.9, 99.6) based on 5 PRs and stable disease in 1 pt.

The MTD/RP2D for this expansion phase and further studies in aRCC has been confirmed as avelumab 10 mg/kg IV Q2W + axitinib 5 mg PO BID continuously. The regimen has shown preliminary antitumour activity in treatment-naïve pts with aRCC. Enrollment is ongoing in the expansion cohort. These results demonstrate the efficacy and safety of avelumab + axitinib vs current monotherapies for aRCC.

Although the disclosed teachings have been described with reference to various applications, methods, kits, and compositions, it will be appreciated that various changes and modifications can be made without departing from the teachings herein and the claimed invention below. The foregoing examples are provided to better illustrate the disclosed teachings and are not intended to limit the scope of the teachings presented herein. While the present teachings have been described in terms of these exemplary embodiments, the skilled artisan will readily understand that numerous variations and modifications of these exemplary embodiments are possible without undue experimentation. All such variations and modifications are within the scope of the current teachings.

All references cited herein, including patents, patent applications, papers, text books, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated by reference in their entirety. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this

application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

The foregoing description and Examples detail certain specific embodiments of the invention and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

Claims

1. An antagonist of a Programmed Death Ligand 1 protein (PD-L1) and a VEGFR inhibitor for use as a medicament in the treatment of a cancer in a subject; or
a PD-L1 antagonist for use as a medicament in the treatment of a cancer in a subject, wherein the PD-L1 antagonist is for use in combination with a VEGFR inhibitor in the form of a medicament; or
a VEGFR inhibitor for use as a medicament in the treatment of a cancer in a subject, wherein the VEGFR inhibitor is for use in combination with a PD-L1 antagonist in the form of a medicament;

wherein the PD-L1 antagonist is an anti-PD-L1 monoclonal antibody comprising three CDRs from a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 8, and three CDRs from a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 9, and further wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]benzamide or a pharmaceutically acceptable salt thereof.

2. Use of:
a) an antagonist of a Programmed Death Ligand 1 protein (PD-L1) and a VEGFR inhibitor in the manufacture of a medicament for the treatment of a cancer in a subject; or
b) an antagonist of a Programmed Death Ligand 1 protein (PD-L1) in the manufacture of a medicament for the treatment of a cancer in a subject, wherein the medicament is for use in combination with a VEGFR inhibitor in the form of a medicament; or
c) a VEGFR inhibitor in the manufacture of a medicament for the treatment of a cancer in a subject, wherein the medicament is for use in combination with a PD-L1 antagonist in the form of a medicament;

and wherein the PD-L1 antagonist is an anti-PD-L1 monoclonal antibody comprising three CDRs from a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 8, and three CDRs from a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 9, and further wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]benzamide or a pharmaceutically acceptable salt thereof.

3. The use of claim 2, wherein the subject is a human.

4. The use of claim 2 or claim 3, wherein the cancer is a solid tumor.

5. The use of claim 4, wherein the tumor tests positive for PD-L1 expression by an immune-histochemical (IHC) assay.

6. The use of claim 2 or claim 3, wherein the cancer is renal cell carcinoma.

7. The use of any one of claims 2 to 6, wherein the PD-L1 antagonist is avelumab and the VEGFR inhibitor is axitinib.

8. The use of any one of claims 2 to 7, wherein the PD-L1 antagonist is to be administered as an initial dose of at least about 5 mg/kg, or about 10 mg/kg; and the VEGFR inhibitor is to be administered as an initial dose of at least 3 mg/kg or 5 mg/kg.

9. The use of any one of claims 2 to 8, wherein the PD-L1 antagonist is to be administered about once a week, or about once every two, three, four, or five weeks; and the VEGFR inhibitor is to be administered twice daily.

10. The use of claim 9, wherein the PD-L1 antagonist is to be administered about once every two weeks; and the VEGFR inhibitor is to be administered twice daily.

11. The use of claim 7, wherein the avelumab is formulated as a liquid medicament and axitinib is formulated as a 1 mg tablet, a 3 mg tablet, or a 5 mg tablet.

12. Use of a kit including:
i) a first container comprising at least one dose of a medicament comprising an antagonist of a Programmed Death 1 protein (PD-L1);
ii) a second container comprising at least one dose of a medicament comprising a VEGFR inhibitor; and
iii) a package insert comprising instructions to treat a subject for cancer using the medicaments;

in the manufacture of a medicament for the treatment of cancer in a subject,

wherein the PD-L1 antagonist is an anti-PD-L1 monoclonal antibody comprising three CDRs from a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 8 and three CDRs from a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 9, and further wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-inda-zol-6-ylsulfanyl]benzamide or a pharmaceutically acceptable salt thereof.

13. The use of claim 12, wherein the instructions state that the medicaments are intended for use in treating a subject having a cancer that tests positive for PD-L1 expression by an immunehistochemical (IHC) assay.

14. The use of any one of claims 12 or claim 13, wherein the PD-L1 antagonist is avelumab formulated as a liquid medicament and the VEGFR inhibitor is axitinib formulated as a 1 mg tablet or a 5 mg tablet.

15. The use of any one of claims 2-14, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B- cell lymphoma (DLBCL), follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), Squamous Cell Carcinoma of the Head and Neck (SCCHN), or small lymphocytic lymphoma (SLL).

16. The use of any one of claims 1 to 14, wherein the cancer is advanced renal cell carcinoma.

17. The use of claim 16, wherein the renal cell carcinoma is previously untreated advanced renal cell carcinoma.