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(54) Title: METHODS COMPRISING FIXED INTERMITTENT DOSING OF CEDIRANIB
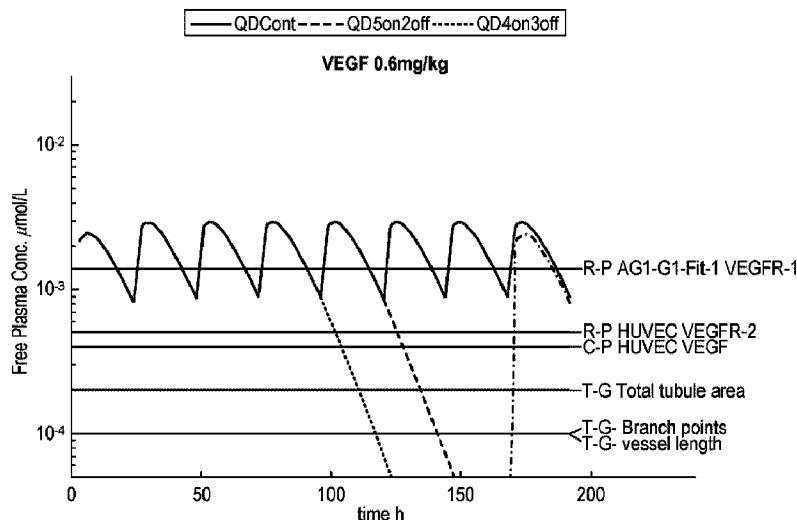
(57) Abrégé/Abstract:
Methods comprising repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen comprising administration of an effective amount of the composition comprising cediranib on one or more

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(57) **Abrégé(suite)/Abstract(continued):**

consecutive days of a cycle followed by one or more consecutive days of rest on which said composition is not administered are disclosed herein, and may be used as monotherapy or may comprise administration of one or more partner drugs or therapies and may be used in combination therapy. Such methods may produce an antiangiogenic and/or vascular permeability reducing effect, treat at least one disease state associated with angiogenesis, reduce the total dose of cediranib required to provide effective VEGF inhibition, reduce adverse events and toxicity due to cediranib administration, maintain cover on the VEGF pathway despite reduction of total doses of cediranib, and/or increase repair of healthy, non-cancerous tissue during treatment of cancer using combination therapies.

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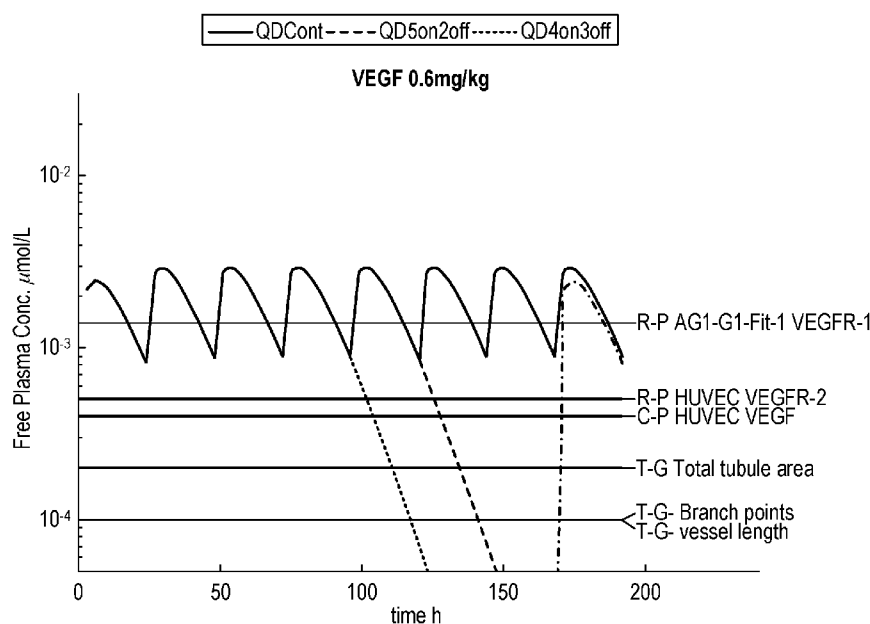

Figure 1A

(57) **Abstract:** Methods comprising repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen comprising administration of an effective amount of the composition comprising cediranib on one or more consecutive days of a cycle followed by one or more consecutive days of rest on which said composition is not administered are disclosed herein, and may be used as monotherapy or may comprise administration of one or more partner drugs or therapies and may be used in combination therapy. Such methods may produce an antiangiogenic and/or vascular permeability reducing effect, treat at least one disease state associated with angiogenesis, reduce the total dose of cediranib required to provide effective VEGF inhibition, reduce adverse events and toxicity due to cediranib administration, maintain cover on the VEGF pathway despite reduction of total doses of cediranib, and/or increase repair of healthy, non-cancerous tissue during treatment of cancer using combination therapies.

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METHODS COMPRISING FIXED INTERMITTENT DOSING OF CEDIRANIB

Methods for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need thereof are disclosed herein and comprise repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. Also disclosed herein are methods of treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, in need thereof which methods comprise repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. The fixed intermittent dosing regimens comprise administration of an effective amount of the composition comprising cediranib on one or more consecutive days of a cycle followed by one or more consecutive days of rest on which said composition is not administered. These methods comprise only the use of compositions comprising cediranib and thus may be used in monotherapy or may further comprise the administration of one or more partner drugs and thus may be used in combination therapy.

New methods of reducing the total dose of cediranib required to provide effective VEGF inhibition are disclosed herein as well as methods of reducing adverse events and toxicity due to cediranib administration, the methods comprising repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen.

The disclosed methods may maintain cover on the VEGF pathway despite reduction of total doses of cediranib, and thus also may provide methods for improving the overall therapeutic index of cediranib. Furthermore, these disclosures provide new methods of increasing repair of healthy, non-cancerous tissue during treatment of cancer using combination therapies.

Angiogenesis, the process of new blood vessel formation, plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995,

Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, *Nature Medicine* 1: 27-31). Indeed, angiogenesis is essential to tumor growth and metastasis. (Folkman J. Tumor angiogenesis: therapeutic implications. *N. Engl. J. Med.* 1971;285:1182-6; Cullinan-Bove et al, 1993, *Endocrinology* 133: 829-837; Senger et al, 1993, *Cancer and Metastasis Reviews*, 12: 303-324).

The inhibition of angiogenesis is therefore a possibility for the treatment of cancer. Disruption of blood vessel formation may be possible at several stages in the angiogenic process. Since vascular endothelial growth factor (VEGF) is known to be an important proangiogenic factor (Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J. Mol. Med.* 1999;77:527-43; Ferrara N. VEGF and the quest for tumor angiogenesis factors. *Nature Reviews Cancer* 2002;2:795-803.), VEGF and its receptor (VEGFR) are targets for inhibition of angiogenesis (Kim et al, 1993, *Nature* 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, *Biochem. Biophys. Res. Comm.* 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Compounds which inhibit the effects of VEGF are of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as

cancer (including leukemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, lymphoedema, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including macular degeneration.

Two high-affinity receptors for VEGF with associated tyrosine kinase activity have been identified on human vascular endothelium: VEGFR-1 and VEGFR-2. VEGFR-3, a third member of the VEGFR gene family, plays a key role in the regulation of endothelial tip cells that initiate the formation of new blood vessels and is thought to be important for lymphangiogenesis. VEGFR-3 is activated by the ligands VEGF-C and VEGF-D and has potential to cross talk to VEGFR-2. Although their relative contributions in mediating tumor progression have not been resolved, some studies suggest VEGFR-2 may have a predominant role (Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J. Mol. Med.* 1999;77:527-43).

Cediranib, as used herein, refers to a compound having IUPAC name of 4-[(4-fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline maleate, also referred to as AZD2171 maleate and has the following structure:
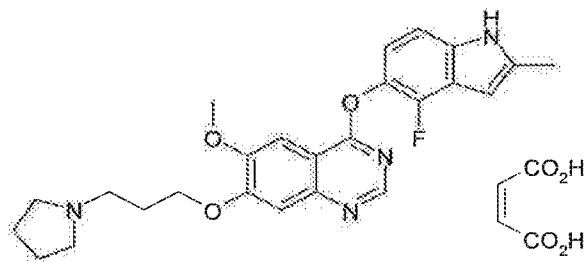
As used herein, cediranib includes its salts, esters, prodrugs, hydrates, and solvates.

The free base 4-[(4-fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline is exemplified in WO 00/47212 (and U.S. Patent No. 7,074,800) for example as Example 240. Its maleate salt, cediranib, is disclosed and exemplified in U.S. Patent No. 8,859,570.

Cediranib is an orally active VEGF receptor tyrosine kinase (RTK) inhibitor of all three VEGF receptors (VEGFR-1,-2,-3), which act as receptors for VEGF-A, B, C, and D.

Targeting all three VEGFRs results in comprehensive inhibition of the VEGF signaling pathway. Inhibition of signalling through VEGFR-2 reduces angiogenesis, neovascular survival, and vascular permeability. Inhibition of signaling through VEGFR-3 additionally reduces lymphangiogenesis, contributing to a reduction in metastatic spread. Cediranib has been reported to inhibit the growth of tumors in a dose-dependent manner in a range of preclinical models, associated with reduction in microvessel density and metastasis. Collectively, these changes indicate that cediranib inhibits tumor growth, metastases, and vascular permeability through inhibition of the VEGFR family (Brave et al. Assessing the activity of cediranib, a VEGFR-2/3 tyrosine kinase inhibitor, against VEGFR-1 and members of the structurally related PDGFR family. *Mol. Cancer Ther.* 2011;10(5):861-73; Heckman et al. The tyrosine kinase inhibitor cediranib blocks ligand-induced vascular endothelial growth factor receptor-3 activity and lymphangiogenesis. *Cancer Res.* 2008;68(12):4754-62; Smith et al. Acute pharmacodynamic and antivascular effects of the vascular endothelial growth factor signaling inhibitor AZD2171 in Calu-6 human lung tumor xenografts. *Mol. Cancer Ther.* 2007;6(8):2198-208; Wedge et al. AZD2171: A Highly Potent, Orally Bioavailable, Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor for the Treatment of Cancer. *Cancer Res.* 2005; 65:4389-400.)

Cediranib has been evaluated in a broad clinical program that includes both monotherapy and combination therapy studies, in multiple tumor types, including for example colorectal cancer, glioblastoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), renal cell carcinoma (RCC), alveolar soft part sarcoma (ASPS), and ovarian cancer, as well as a large number of signal searching studies in a range of other tumor types. The feasibility, activity, and pharmacokinetics (PK) of cediranib have been explored in combination with carboplatin and paclitaxel (Laurie et al. Phase I pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer: the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 2008;26(11):1871-78) and cisplatin and gemcitabine (Goss et al. Phase I pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: a study of the National Cancer Institute of Canada Clinical Trials Group. *Eur. J. Cancer* 2009;45(5):782-8).

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Methods for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need thereof are disclosed herein and comprise repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. In another aspect, there is

5   disclosed methods for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need thereof and which methods comprise at least two cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. Also disclosed herein are methods of treating at least one disease state associated with angiogenesis in a warm-

10   blooded animal, such as a human being, in need thereof which methods comprise repeating cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. Also disclosed herein are methods of treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, in need thereof which methods comprise at least two cycles of administration of a

15   composition comprising cediranib according to a fixed intermittent dosing regimen. The fixed intermittent dosing regimens comprise administration of an effective amount of the composition comprising cediranib on one or more consecutive days of a cycle, such as at least two consecutive days, followed by one or more consecutive days of rest, such as at least two consecutive days, on which said composition is not administered. These methods

20   comprise only the use of compositions comprising cediranib and thus may be used in monotherapy or may further comprise the administration of one or more partner drugs and thus may be used in combination therapy.

New methods of reducing the total dose of cediranib required to provide effective VEGF inhibition are disclosed herein as well as methods of reducing adverse events and/or

25   toxicity due to cediranib administration, the methods comprising repeating cycles, such as at least two cycles, of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen. Non-limiting examples of adverse events and toxicity identified risks for cediranib include diarrhea, severe fatigue, severe neutropenia and febrile neutropenia, hypertension, GI perforation, fistulae, arterial thromboembolism and

30   posterior reversible encephalopathy syndrome (PRES).

The disclosed methods may maintain cover on the VEGF pathway despite reduction of total doses of cediranib, and thus also may provide methods for improving the overall therapeutic index of cediranib. Furthermore, these disclosures provide new methods of increasing repair of healthy, non-cancerous tissue during treatment of cancer using combination therapies.

5 The new methods comprising administration of a composition comprising cediranib according to a fixed intermittent dosing regimen may surprisingly result in maintenance of tumor control, unlike dosing schedules involving 7 days off from cediranib and also unlike previous studies involving unscheduled dose holidays from a continuous dosing regimen necessitated by adverse events in patients. The new methods thereby allow administration of a reduced total dose

10 of cediranib required to provide effective VEGF inhibition. Accordingly, the use of the new dosing regimen also provides a method of reducing adverse events and/or toxicity due to cediranib administration while maintaining cover on the VEGF pathway. Furthermore, this presents a method of increasing repair of healthy, non-cancerous tissue during treatment of cancer using combination therapies.

15 Also disclosed herein is use of cediranib for treating at least one disease state associated with angiogenesis in a human, wherein: the cediranib is for administration for at least two cycles according to a fixed intermittent dosing regimen, the fixed intermittent dosing regimen is 7 days, and an effective amount of the cediranib is for administration on 5 consecutive days followed by 2 days of rest, and the at least one disease state associated with angiogenesis is chosen from lung

20 cancers; digestive and gastrointestinal cancers; esophageal cancers; gallbladder cancers; liver cancers; pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

25 Further disclosed herein is use of cediranib for the manufacture of a medicament for treating at least one disease state associated with angiogenesis in a human, wherein: the medicament is for administration for at least two cycles according to a fixed intermittent dosing regimen, the fixed intermittent dosing regimen is 7 days, and an effective amount of the medicament is for administration on 5 consecutive days followed by 2 days of rest, and the at

30 least one disease state associated with angiogenesis is chosen from lung cancers; digestive and gastrointestinal cancers; esophageal cancers; gallbladder cancers; liver cancers;

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pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

5   Still further disclosed herein is cediranib for use in treating at least one disease state associated with angiogenesis in a human, wherein: the cediranib is for administration for at least two cycles according to a fixed intermittent dosing regimen, the fixed intermittent dosing regimen is 7 days, and an effective amount of the cediranib is for administration on 5 consecutive days followed by 2 days of rest, and the at least one disease state associated with angiogenesis is chosen from lung cancers; digestive and gastrointestinal cancers; esophageal

10 cancers; gallbladder cancers; liver cancers; pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Figures 1(A)-(P) show modelled mean free plasma concentrations of cediranib over time in pre-clinical models dosed at a). 0.6 mg/kg (Figures 1A-1D), b). 1.2 mg/kg (Figures 1E-1H), c). 2.4 mg/kg (Figures 1I-L), or d). 4.8 mg/kg (Figures 1M-1P), respectively, following dosing regimens of once daily continuous (QDCont), once daily 5 days on 2 days off (QD5on2off), or once daily 4 days (QD4on3off), with horizontal lines showing the cellular IC_{50} values generated in vitro for

20 inhibition of pVEGFR, pKit, pPDGFRα, and pPDGFRβ as indicated. For the plots exemplifying VEGFR and Kit cover, R-P stands for receptor phosphorylation in a cell based assay; C-P stands for cell proliferation; for VEGFR plots, T-G stands for tubule growth in an endothelial-fibroblast co-culture assay. The relevant cell lines are indicated. For the graphs depicting PDGFRα and β cover, inhibition of PDGFRα and PDGFRβ phosphorylation and PDGFBB or PDGFAA driven

25 proliferation are shown together with the relevant cell lines.

        Figure 2 shows modelled mean the free drug exposure in humans for cediranib (black line) versus time for 20 mg and 15 mg doses of cediranib.

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Figure 3 shows mean tumor volume versus time from three efficacy studies (performed in Calu6, A498, and SW620 tumor xenografts) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 6 (three 7-day cycles of 1.5 mg/kg cediranib once daily for 5 days followed by vehicle once daily for 2 days). Data are shown as the mean (+/- standard error of the mean). n shows the number of animals that were terminated at the relevant day.

Figure 4 shows mean tumor volume versus time from three efficacy studies (in Calu6, A498, and SW620 tumor xenografts) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 7 (three 7-day cycles of 3 mg/kg cediranib once daily for 5 days followed by vehicle once daily for 2 days). Data are shown as the mean (+/- standard error of the mean). n shows the number of animals that were terminated at the relevant day.

Figure 5 shows mean tumor volume versus time from three efficacy studies (Calu6, A498, and SW620) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 8 (three 7-day cycles of 1.5 mg/kg cediranib once daily for 3 days followed by vehicle once daily for 4 days). Data are shown as the mean (+/- standard error of the mean). n shows the number of animals that were terminated at the relevant day.

Figure 6 shows mean tumor volume versus time from three efficacy studies (Calu6, A498, and SW620) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 9 (three 7-day cycles of 3 mg/kg cediranib once daily for 3 days followed by vehicle once daily for 4 days). Data are shown as the mean (+/- standard error of the mean). n shows the number of animals that were terminated at the relevant day.

Figure 7 shows mean tumour volume versus time from an efficacy study performed in the OV2022 (ovarian cancer) patient derived tumour xenograft model. This study compared cediranib and olaparib combinations where cediranib was administered once

daily or once daily on a 5 days on 2 days off schedule. Group 1 - control, Group 2 - cediranib 3mg/kg once daily, Group 3 - cediranib 3mg/kg once daily 5 days on 2 days off, Group 4 - olaparib 100mg/kg once daily, Group 5 - cediranib 3mg/kg once daily plus olaparib 100mg/kg once daily, Group 6 - cediranib 3mg/kg once daily 5 days on 2 days off plus olaparib 100mg/kg once daily.

Figure 8 shows the body weight change for each group of tumour bearing animals in the study. This study compared cediranib and olaparib combinations where cediranib was administered once daily or once daily on a 5 days on 2 days off schedule. Group 1 – control, Group 2 - cediranib 3mg/kg once daily, Group 3 - cediranib 3mg/kg once daily 5 days on 2 days off, Group 4 – olaparib 100mg/kg once daily, Group 5 - cediranib 3mg/kg once daily plus olaparib 100mg/kg once daily, Group 6 - cediranib 3mg/kg once daily 5 days on 2 days off plus olaparib 100mg/kg once daily.

Figure 9 shows the largest response in the tumor size (from baseline) observed during the trial (i.e., the largest response observed may have been observed at any time point during the trial) for each patient in the different dosing regimen cohorts (DL1, DL2 and DL3 as described in Example 5). The black crosses indicate the patients receiving treatment according at data lock.

Figure 10 show the changes from baseline in the patient's tumor size over time for each patient in the different dosing regimen cohorts (DL1, DL2 and DL3 as described in Example 5).

As used herein, "treating" and "treatment" refer to the reduction or amelioration of the progression, severity and/or duration of a disease state, disorder, angiogenesis and/or vascular permeability effect or the amelioration of at least one symptom of any of the foregoing. In some embodiments, "treating" refers to an increase in progression-free survival.

In some embodiments, the methods disclosed herein result in maintenance of tumor control. In some embodiments, the methods disclosed herein allow administration of a reduced total dose of cediranib required to provide effective VEGF inhibition. In some embodiments, the methods disclosed herein are methods of reducing adverse events and/or toxicity due to cediranib administration while maintaining cover on the VEGF pathway. In

some embodiments, the methods disclosed herein treat a warm blooded animal with platinum sensitive relapsed ovarian cancer. In some embodiments, the methods disclosed herein improve the progression-free survival of patients. In some embodiments, the improvement in the progression-free survival of patients is statistically significant. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.05$. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.01$.

In some embodiments, the methods disclosed herein improve the overall survival of patients. In some embodiments, the improvement in the overall survival of patients is statistically significant. In some embodiments, a statistically significant improvement in the overall survival of patients is when $p < 0.05$. In some embodiments, a statistically significant improvement in the overall survival of patients is when $p < 0.01$.

In another embodiment, there is disclosed a composition comprising cediranib for use in producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed intermittent dosing regimen. In another embodiment, there is disclosed a composition comprising cediranib for use in producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed intermittent dosing regimen.

In another embodiment, there is disclosed herein a composition comprising cediranib for use in treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is a composition comprising cediranib for use in treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed a composition comprising cediranib for use in reducing the total dose of cediranib required to provide effective VEGF inhibition in a warm-blooded animal, such as a human being, wherein the composition comprising

cediranib is administered according to a fixed dosing regimen. Also disclosed herein is a composition comprising cediranib for use in reducing the total dose of cediranib required to provide effective VEGF inhibition in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed a composition comprising cediranib for use in reducing adverse events and/or toxicity due to cediranib administration in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is a composition comprising cediranib for use in reducing adverse events and/or toxicity due to cediranib administration in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed a composition comprising cediranib for use in increasing repair of healthy, non-cancerous tissue during combination therapy treatment of cancer in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein, is a composition comprising cediranib for use in increasing repair of healthy, non-cancerous tissue during combination therapy treatment of cancer in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed a composition comprising cediranib for use in treating a warm-blooded animal, such as a human being, with platinum sensitive relapsed cancer wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is a composition comprising cediranib for use in treating a warm-blooded animal, such as a human being, with platinum sensitive relapsed cancer wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed a composition comprising cediranib for use in the maintenance of tumor control. In another embodiment, there is disclosed a composition comprising cediranib for use in reducing the total dose of cediranib required

to provide effective VEGF inhibition. In another embodiment, there is disclosed a composition comprising cediranib for use in reducing adverse events and/or toxicity due to cediranib administration while maintaining cover on the VEGF pathway. In another embodiment, the compositions disclosed herein improve the progression-free survival of patients. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.05$. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.01$.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed intermittent dosing regimen. In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed intermittent dosing regimen.

In another embodiment, there is disclosed herein the use of a composition comprising cediranib for the manufacture of a medicament for treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is the use of a composition comprising cediranib for the manufacture of a medicament for treating at least one disease state associated with angiogenesis in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for reducing the total dose of cediranib required to provide effective VEGF inhibition in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. In one embodiment, cover on the VEGF pathway is maintained. Also disclosed herein is the use of a composition comprising cediranib for the manufacture of a

medicament for reducing the total dose of cediranib required to provide effective VEGF inhibition in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for reducing adverse events and/or toxicity due to cediranib administration in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is the use of a composition comprising cediranib for the manufacture of a medicament for reducing adverse events and/or toxicity due to cediranib administration in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for increasing repair of healthy, non-cancerous tissue during combination therapy treatment of cancer in a warm-blooded animal, such as a human being, wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein, is the use of a composition comprising cediranib for the manufacture of a medicament for increasing repair of healthy, non-cancerous tissue during combination therapy treatment of cancer in a warm-blooded animal, such as a human being, wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for treating a warm-blooded animal, such as a human being, with platinum sensitive relapsed cancer wherein the composition comprising cediranib is administered according to a fixed dosing regimen. Also disclosed herein is the use of a composition comprising cediranib for the manufacture of a medicament for treating a warm-blooded animal, such as a human being, with platinum sensitive relapsed cancer wherein at least two cycles of the composition comprising cediranib is administered according to a fixed dosing regimen.

In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for maintenance of tumor control. In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for reducing the total dose of cediranib required to provide effective VEGF inhibition. In another embodiment, there is disclosed the use of a composition comprising cediranib for the manufacture of a medicament for reducing adverse events and/or toxicity due to cediranib administration while maintaining cover on the VEGF pathway. In another embodiment, the compositions disclosed herein improve the progression-free survival of patients. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.05$. In some embodiments, a statistically significant improvement in the progression-free survival of patients is when $p < 0.01$.

As used herein, "effective amount" means an amount sufficient to elicit a desired biological response. As will be recognized by a person of ordinary skill in the art, the effective amount of cediranib may vary depending on various factors, such as the disease state being treated, the severity of disease state being treated, the desired effect of treatment, the warm-blooded animal in need of treatment, and the route of administration.

As used herein, "at least one disease state associated with angiogenesis" includes the following non-limiting examples: cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration.

As used herein, the term "cancer" includes any member of a class of diseases characterized by uncontrolled growth of aberrant cells. Cancer as used herein may affect any tissue, including soft tissue or solid, and includes leukemia, multiple myeloma, and lymphoma. The term includes all known cancers and neoplastic conditions, whether characterized as malignant or benign, whether primary or recurrent, any stage or grade, and regardless of clinical pathology, morphology, and/or sensitivity to chemotherapy. Non-limiting examples of cancer include lung cancers (e.g., non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)); digestive and gastrointestinal cancers such

as colorectal cancer, gastrointestinal stromal tumors, gastrointestinal carcinoid tumors, colon cancer, rectal cancer, anal cancer, bile duct cancer, small intestine cancer, and stomach (gastric) cancer; esophageal cancer; gallbladder cancer; liver cancer; pancreatic cancer; appendix cancer; breast cancer; ovarian cancer; renal cancer (e.g., renal cell carcinoma); prostate cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; mesotheliomas; choriocarcinomas; cholangiocarcinomas; alveolar soft part sarcoma (ASPS); head and neck cancers (including thyroid cancers); osteogenic sarcomas; and blood cancers. Non-limiting examples of ovarian cancer include platinum sensitive ovarian cancers, platinum sensitive relapsed ovarian cancers, platinum insensitive ovarian cancers (resistant and refractory), high grade serous ovarian cancers, high grade endometrial ovarian cancer, clear cell ovarian cancers, mucinous ovarian cancers, and others. As used herein, ovarian cancer includes fallopian tube and peritoneal cancers, including primary peritoneal cancers.

As used herein, "an antiangiogenic and/or vascular permeability reducing effect" can be assessed by a variety of assays and tests known to one of ordinary skill in the art including, for example, those measuring inhibition of tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR. These properties may be assessed, for example, by one or more of: (a) In Vitro Receptor Tyrosine Kinase Inhibition Test, (b) In Vitro HUVEC Proliferation Assay, (c) In Vivo Solid Tumor Disease Model. Non-limiting examples of such assays are set out below but one of ordinary skill will recognize that other procedures are equally suitable.

As used herein, the term "fixed intermittent dosing regimen" refers to repeating cycles of preplanned drug administration in which the drug is administered on one or more consecutive days ("days on") followed by one or more consecutive days of rest on which the drug is not administered ("days off").

In some embodiments, the cycles are regular, in that the pattern of days on and days off is the same in each cycle. In some embodiments, the cycles are irregular, in that the pattern of days on and days off differs from one cycle to the next cycle. In some embodiments, each of the repeating cycles, however, is preplanned in that it is not determined solely in response to the appearance of one or more adverse events.

In some embodiments, administration of the composition comprising cediranib is repeated for one to ten cycles, such as for example one cycle, two cycles, three cycles, four cycles, five cycles, six cycles, seven cycles, eight cycles, nine cycles or ten cycles.

In some embodiments, a cycle comprises 3 days to 60 days. In some embodiments, a cycle comprises 7 to 50 days, such as 7 to 30 days, 7 to 21 days, or 7 to 14 days. In some embodiments, a cycle consists of 7 days.

In some embodiments, the fixed intermittent dosing regimen comprises a repeating cycle of administration of an effective amount of said composition comprising cediranib on 1 to 5 consecutive days, such as 2 to 5 consecutive days, followed by 6 to 2 days of rest, such as 5 to 2 days of rest. In some embodiments, the fixed intermittent dosing regimen comprises a repeating cycle of administration of an effective amount of said composition comprising cediranib on 5 consecutive days followed by 2 days of rest. In some embodiments, the fixed intermittent dosing regimen comprises a repeating cycle of administration of an effective amount of said composition comprising cediranib on 4 consecutive days followed by 3 days of rest. In some embodiments, the fixed intermittent dosing regimen comprises a repeating cycle of administration of an effective amount of said composition comprising cediranib on 3 consecutive days followed by 4 days of rest.

In some embodiments, the fixed intermittent dosing regimen comprises a repeating cycle of administration of an effective amount of said composition comprising cediranib on 1 to 5 consecutive days, such as 2 to 5 consecutive days, followed by 6 to 2 days of rest, such as 5 to 2 days of rest. In some embodiments, placebo is administered on said days of rest.

In some embodiments, the fixed intermittent dosing regimen comprises administering cediranib orally at a dose of 20 mg once daily for five days of a seven day cycle followed by two days of placebo doses. In some embodiments, the fixed intermittent dosing regimen comprises administering cediranib orally at a dose of 20 mg once daily for four days of a seven day cycle followed by three days of placebo doses. In some embodiments, the fixed intermittent dosing regimen comprises administering cediranib orally at a dose of 30 mg once daily for five days of a seven day cycle followed by two days of placebo doses. In some embodiments, the fixed intermittent dosing regimen comprises administering cediranib orally at a dose of 30 mg once daily for four days of a

seven day cycle followed by three days of placebo doses. In some embodiments, the selection of cycles of administration followed by cycles of rest may be determined by the needs of the warm-blooded animals to be treated. For instance, any iteration of number of days of administration followed by number of days of rest may be selected for one to ten cycles, wherein each cycle comprises 3-60 days.

Compositions comprising cediranib suitable for use in the presently disclosed methods may be in a form suitable for oral administration (for example, as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for administration by inhalation (for example, as a finely divided powder or a liquid aerosol), for administration by insufflation (for example, as a finely divided powder), for parenteral injection (for example, as a sterile solution, suspension or emulsion for intravenous, subcutaneous, intramuscular, intravascular or infusion dosing), for topical administration (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), or for rectal administration (for example as a suppository). In some embodiments, compositions comprising cediranib are administered orally.

In some embodiments, compositions comprising cediranib may be prepared in a conventional manner using at least one conventional excipient. In some embodiments, compositions comprising cediranib consist of cediranib. In some embodiments, compositions comprising cediranib further comprise at least one pharmaceutically acceptable excipient or carrier. In some embodiments, compositions comprising cediranib comprise cediranib as the sole pharmaceutically active ingredient. In some embodiments, compositions comprising cediranib further comprise at least one additional pharmaceutically active ingredient.

Doses of cediranib may vary according to therapeutic requirements. In some embodiments, the compositions comprising cediranib are in unit dosage form. In some embodiments, the compositions comprising cediranib are administered to a warm-blooded animal at a unit dose within a range of 1-50 mg per square meter body area of the animal, for example approximately 0.03 mg/kg to 1.5 mg/kg in a human. In some embodiments, unit doses range, for example, from 0.01 mg/kg to 1.5 mg/kg, further for example from 0.05 mg/kg to 0.75 mg/kg, and further for example from 0.03 mg/kg to 0.5 mg/kg.

In some embodiments, the compositions comprising cediranib are administered at dose of 0.6 mg/kg. In some embodiments, the compositions comprising cediranib are administered at dose of 1.2 mg/kg. In some embodiments, the compositions comprising cediranib are administered at dose of 2.4 mg/kg. In some embodiments, the compositions comprising cediranib are administered at dose of 4.8 mg/kg.

In some embodiments, a solid dosage form comprises cediranib in an amount ranging from 0.5 mg to 90 mg as measured by weight of the free base of cediranib. In some embodiments, a solid dosage form comprises cediranib in an amount ranging from 1 mg to 50 mg as measured by weight of the free base of cediranib. In some embodiments, the solid dosage form comprises cediranib in an amount ranging from 5 mg to 50 mg, such as from 10 mg to 40 mg, a such as from 15 mg to 35 mg, and further such as from 20 mg to 30 mg as measured by weight of the free base of cediranib. In some embodiments, the solid dosage form comprises cediranib in an amount of 30 mg as measured by weight of the free base of cediranib. In some embodiments, the solid dosage form comprises cediranib in an amount of 20 mg as measured by weight of the free base of cediranib. In some embodiments, the solid dosage form comprises cediranib in an amount of 15 mg as measured by weight of the free base of cediranib.

In some embodiments, the daily dose of cediranib ranges from 5 mg to 50 mg, such as from 15 mg to 35 mg, and further such as from 20 mg to 30 mg as measured by weight of the free base of cediranib. In some embodiments, the daily dose of cediranib is 30 mg as measured by weight of the free base of cediranib. In some embodiments, the daily dose of cediranib is 20 mg as measured by weight of the free base of cediranib. In some embodiments, the daily dose of cediranib is 15 mg as measured by weight of the free base of cediranib. In some embodiments, the daily dose of cediranib is 10 mg as measured by weight of the free base of cediranib.

In some embodiments, cediranib is administered in a solid dosage form, such as a tablet, comprising the weight equivalent of 30 mg of the free base of cediranib, which is 37.8 mg of cediranib, the maleate salt. In some embodiments, cediranib is administered in a solid dosage form, such as a tablet, comprising the weight equivalent of 20 mg of the free base of cediranib, which is 25.2 mg of cediranib, the maleate salt. In some embodiments,

cediranib is administered in a solid dosage form comprising the weight equivalent of 15 mg of the free base of cediranib, which is 18.9 mg of cediranib, the maleate salt.

In some embodiments, cediranib is administered once daily. In some embodiments, cediranib is administered twice daily. In some embodiments, cediranib is administered three times daily. In some embodiments, cediranib is administered four times daily. In some embodiments, cediranib is administered five times daily.

In some embodiments, cediranib is administered to a warm-blooded animal, such as a human being, with an empty stomach, such as, for example, at least one 1 hour before or at least 2 hours after a meal.

In some embodiments, such as where the warm-blooded animal has difficulty swallowing tablets, cediranib tablets are dispersed in non- carbonated drinking water. In some embodiments, a cediranib dispersion is administered through nasogastric or gastrostomy tubes.

As disclosed above, the methods may use cediranib as a monotherapy or as part of a combination therapy that may involve, in addition to cediranib, at least one other component chosen from partner drugs and other treatments. Such combination therapy may be achieved by way of simultaneous, sequential, and/or separate administration of the individual components (cediranib compositions and at least one other component) of the treatment. In some embodiments, the individual components are administered simultaneously. In some embodiments, the individual components are administered separately. In some embodiments, the individual components are administered sequentially.

Angiogenesis and VEGR2-mediated maintenance of vascular function as well as control of hypertension is important for many normal tissues, and long term suppression of VEGFR signaling can lead to stress in normal tissues that can be manifested as clinical observations such as fatigue, modification in thyroid function, and diarrhea. When combined with at least one other component that also can have significant impact on normal tissues, for example in particular those that can cause damage that requires repair, then continuous dosing of cediranib may delay and/or prevent repair of normal tissues. Accordingly, administering cediranib using the fixed intermittent dosing regimen disclosed

herein with regular, short intermittent breaks (either as monotherapy or combination) in a schedule may allow repair of normal tissue but without allowing the tumor to recover. Moreover, the short breaks may ensure that there is no issue with co-medications such as, for example, anti-hypertensives.

In the field of medical oncology, it is common to use a combination of different forms of treatment to treat patients with cancer. In medical oncology, the at least one other component(s) of such combination therapy treatment in addition to administration of cediranib may be chosen from surgery, radiotherapy, and chemotherapy. Such chemotherapy may include at least one partner drug. For partner drugs that have greater impact on normal tissues, such as for example chemotherapies, the same strategy applies. Around times when the damage is greatest then slightly longer preplanned dose interruptions may be appropriate, for example, interruption of 4-5 days. Non-limiting examples of partner drugs include:

DNA damage response inhibitors (such as, for example, PARP inhibitors (such as, for example, olaparib (Lynparza)), Wee-1 inhibitors, ATR inhibitors, ATM inhibitors, and DNAPK inhibitors),

immune checkpoint modulators (such as, for example, anti-PD-1 antibodies, anti-PD-L1 antibodies (such as, for example, MEDI4736 (durvalumab)), anti-CTLA4 antibodies, TLR7 agonists, CD40 agonists, Lag-3 antagonists, and OX40 agonists),

tumor cell targeting therapy agents (such as, for example, EGFR, Her2, MAPK/raf, Met, Pi3K, mTOR, Akt, estrogen antagonists, androgen targeted therapeutics, FGFR, MCT-1 and MCT-4 inhibitors), and

chemotherapy agents (such as for example, platinum based chemotherapy, taxane based chemotherapy, and irotecan), including:

(i) other antiangiogenic agents such as alkylating agents (for example, cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, bendamustine, temozolamide, nitrosoureas, and thiotepa); antimetabolites (for example, gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and purine analogues such as fludarabine, and adenosine analogues); antitumor antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin,

idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example

vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine, taxoids like taxol

and taxotere, and polokinase inhibitors); and topoisomerase inhibitors (for example

epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, camptothecin,

5   and irinotecan); enzymes (for example asparaginase); and thymidylate synthase inhibitors

(for example raltitrexed);

        (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene,

raloxifene, droloxifene, and iodoxyfene,), androgen receptor down regulators (for example

fulvestrant), antagonists MDV3100 or ARN-509 which prevent nuclear translocation of the

10   androgen receptor and its binding to either DNA or coactivator proteins, inhibitors of

CYP17A1 such as abiraterone [ZYTIGA™], and mixed inhibitors of androgen receptor

function and CYP17A1 such as TOK-001 (galeterone), LHRH antagonists and LHRH

agonists (for example goserelin, goserelin acetate, luprolide, leuprorelin and buserelin),

progestogens (for example megestrol acetate), aromatase inhibitors (for example

15   anastrozole, letrozole, vorazole, and exemestane), antiprogestogens, antiandrogens (for

example flutamide, nilutamide, bicalutamide, and cyproterone acetate), and inhibitors of

5α-reductase (for example finasteride),

        (iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-

chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-

20   tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO

01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-

methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med.*

Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), metalloproteinase inhibitors like

marimastat, inhibitors of urokinase plasminogen activator receptor function, and antibodies

25   to Heparanase),

        (iv) inhibitors of growth factor function, such as inhibitors of platelet derived

growth factor and inhibitors of hepatocyte growth factor, such as growth factor antibodies

and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab

[Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab

30   [Erbitux, C225]) and inhibitors of any other growth factor antibodies or other growth factor

receptor antibodies, such as farnesyl transferase inhibitors (for example those disclosed by

Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, p. 11-29); such inhibitors also include tyrosine kinase inhibitors for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)) and serine/threonine kinase inhibitors), erbB2 tyrosine kinase inhibitors (such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinase inhibitors kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and AZD9291 (tagrisso); lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and /or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) other antiangiogenic agents such as those that work by different mechanisms from those defined hereinbefore (for example Ang-2 (such as MEDI-3617) and DLL4 (such as MEDI-0639)), and including vascular targeting agents (for example combretastatin phosphate (Combretastatin A4) and compounds disclosed in International Patent Application Publication Nos. WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213 and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 (for example N-acetylcolchinol-O-phosphate)); and

(vi) endothelin receptor antagonists (for example zibotentan (ZD4054) and atrasentan);

biological response modifiers (for example, interferon);

antibodies (for example edrecolomab);

antisense therapies (for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense);

gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

immunotherapy approaches, including for example ex-vivo and in vivo approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell energy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies, approaches for T-cell enhancement including CTLA4 antibodies, and antibodies directed toward CD137, PD-1 or B7-H1, toll-receptor agonists; agonistic antibodies to CD40 such as SGN-40 (Dacetuzumab) or to the Tweak receptor such as PDL-192; agonistic antibodies to FAS; approaches using antibodies to tumor associated antigens, and antibodies that deplete target cell types (e.g. unconjugated anti-CD20 antibodies such as Rituximab, ofatumumab, Obinutuzumab, anti-CD 19 antibodies such as MEDI-551, anti-CD52 antibodies such as Alemtuzumab, anti-CD37 antibodies such as TRU-016, anti-CD22 antibodies such as Inotuzumab, radiolabeled anti-CD20 antibodies Bexxar and Zevalin, and anti-CD54 antibody Campath; immunotoxins such as moxetumumab pasudotox), approaches using anti-idiotypic antibodies, approaches that enhance Natural Killer cell function, and approaches that utilize antibody-toxin conjugates (e.g. anti-CD33 antibody Mylotarg), and immune modifiers such as Revlimid (Lenalidomide).

In certain embodiments, "anti-PD-L1 antibody" means an antibody that selectively binds a PD-L1 polypeptide. Exemplary anti-PD-L1 antibodies are described for example at US 8,779,108 and US 9,493,565. MEDI4736 is an exemplary anti-PD-L1 antibody. Other anti-PD-L1 antibodies include BMS-936559 (Bristol-Myers Squibb) and MPDL3280A (Roche).

MEDI4736 VL (SEQ ID NO: 1)

EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFSGSG
SGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK

MEDI4736 VH (SEQ ID NO: 2)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYVDSVKGR
FTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSS

MEDI4736 VH CDR1 (SEQ ID NO: 3)

RYWMS

MEDI4736 VH CDR2 (SEQ ID NO: 4)

NIKQDGSEKYYVDSVKG

MEDI4736 VH CDR3 (SEQ ID NO: 5)

EGGWFGELAFDY

MEDI4736 VL CDR1 (SEQ ID NO: 6)

RASQRVSSSYLA

MEDI4736 VL CDR2 (SEQ ID NO: 7)

DASSRAT

MEDI4736 VL CDR3 (SEQ ID NO: 8)

QQYGSLPWT

The at least one partner drug may be administered at the recommended dose(s) and according to the recommended dose regimen(s). For example, MEDI4736 (durvalumab) may be administered at a dose of 3 mg/kg or 10 mg/kg IV every 2 weeks or as a fixed dose of 1500 mg every 4 weeks. Further for example, olaparib (Lynparza) may be administered orally in the form of a 150 mg or 200 mg or 300 mg tablet BID.

In some embodiments, the warm blooded animal is a human being with relapsed ovarian cancers, fallopian tube or primary peritoneal cancers. In some embodiments, to said human being is administered cediranib according to a fixed intermittent dosing regimen in combination with at least one partner drug chosen from (a) platinum-based chemotherapy, (b) olaparib (Lynparza) and (c) durvalumab, each optionally followed by maintenance cediranib monotherapy. In some embodiments, to said human being is administered cediranib according to a fixed intermittent dosing regimen in combination with at least two partner drug chosen from (a) platinum-based chemotherapy, (b) olaparib (Lynparza) and (c) durvalumab, each optionally followed by maintenance cediranib monotherapy. In some embodiments, to said human being is administered cediranib according to a fixed intermittent dosing regimen in combination with platinum-based

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chemotherapy, olaparib (Lynparza) and durvalumab, each optionally followed by maintenance cediranib monotherapy. In some embodiments, to said human being is administered cediranib according to a fixed intermittent dosing regimen in combination with olaparib (Lynparza) and durvalumab, each optionally followed by maintenance cediranib monotherapy.

In some embodiments, cediranib is administered according to a fixed intermittent dosing regimen in combination with platinum-based chemotherapy, and followed by maintenance monotherapy, for the treatment of adult patients with platinum sensitive relapsed (PSR) ovarian cancer (including fallopian tube, high grade endometrial, clear cell, high grade serous or primary peritoneal). In some embodiments, cediranib is administered according to a fixed intermittent dosing regimen in combination with platinum-based chemotherapy, and followed by maintenance monotherapy, for the treatment of adult patients with platinum sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal). In some embodiments, a method of treating a warm blooded animal with platinum sensitive relapsed ovarian cancer comprises at least two cycles of administration of a composition comprising cediranib according to a fixed intermittent dosing regimen, said fixed intermittent dosing regimen comprising administration of an effective amount of said composition on at least two consecutive days of a cycle followed by at least two consecutive days of a cycle on which said composition is not administered, and further comprising administering platinum-based chemotherapy. In some embodiments, platinum sensitive relapsed ovarian cancer is chosen from fallopian tube cancers, high grade endometrial, clear cell, high grade serous and primary peritoneal cancers. In some embodiments, platinum sensitive relapsed ovarian cancer is chosen from fallopian tube and primary peritoneal cancers. In some embodiments, the method further comprises maintenance monotherapy of cediranib. In some embodiments, the maintenance monotherapy of cediranib comprises administration of a composition comprising cediranib according to a fixed intermittent dosing regimen.

In some embodiments, cediranib is administered according to a continuous dosing regimen, and followed by cediranib being administered according to a fixed intermittent dosing regimen. The continuous dosing regimens comprise administration of an effective amount of a composition comprising cediranib on one or more consecutive days. The

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fixed intermittent dosing regimens comprise administration of an effective amount of a composition comprising cediranib on one or more consecutive days of a cycle, such as at least two consecutive days, followed by one or more consecutive days of rest, such as at least two consecutive days, on which said composition is not administered. These methods comprise only the use of compositions comprising cediranib and thus may be used in monotherapy or may further comprise the administration of one or more partner drugs and thus may be used in combination therapy.

Clinical trials using the methods disclosed herein are currently being planned.

For example, one planned clinical trial is a randomized, double-blind, parallel-group, international study to evaluate the safety, tolerability and efficacy of 2 regimens of cediranib in combination with platinum-based chemotherapy in patients with platinum sensitive relapsed epithelial ovarian cancer, primary peritoneal and/or fallopian tube cancer. The proposed protocol involves randomization of subjects to receive 1 of the 2 following treatment regimens during 2 phases, a combination chemotherapy phase (up to 6 cycles) and a maintenance phase (until progression): (1) cediranib 20 mg orally once daily ("continuous" regimen) or (2) cediranib 20 mg orally once daily to be administered on a fixed intermittent regimen for five consecutive days of a seven day cycle followed by 2 consecutive days of placebo doses. All subjects will also concurrently receive 6 cycles of platinum-based chemotherapy. Subjects will be treated during the combination chemotherapy phase with a carboplatin regimen. Non-limiting examples of the carboplatin regimen include:

- carboplatin area under the concentration time curve 5 (AUC 5; glomerular filtration rate [GFR] measured) over 30 to 60 minutes, in combination with paclitaxel 175 mg/m^2 over 3 hours, once every 3 weeks (1 cycle) for 6 cycles (q3w x 6),

- carboplatin AUC 5 (GFR measured) over 30 to 60 minutes, in combination with PLD 30 mg/m^2 over 3 hours, once every 4 weeks (1 cycle) for 6 cycles (q4w x 6), and

- carboplatin AUC 4 (GFR) over 30 to 60 minutes (on Day 1) in combination with gemcitabine 1000 mg/m2 (on Days 1 and 8) over 3 hours, once every 3 weeks (1 cycle) for 6 cycles.

Safety and tolerability of a fixed intermittent cediranib regimen as compared to a continuous regimen will be measured by cediranib discontinuation rate due to toxicity defined by any adverse event or subject decision leading to discontinuation of cediranib within 6 months of randomization. The primary endpoint for this study is the proportion of subjects who discontinue cediranib treatment due to adverse event or subject's decision within 6 months of randomization. Analysis will be carried out once all subjects reach 6 months of treatment or discontinue, using the full analysis set consisting of all randomized subjects. All subjects will have Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) tumor assessments at screening (within 28 days of randomization) and every 12 weeks (±1 week) after randomization until objective radiological disease progression.

In some embodiments, the fixed intermittent regimen decreases the rate of discontinuation due to toxicity compared to continuous regimen. Efficacy of a fixed intermittent cediranib regimen as compared to a continuous regimen may be measured using one or more of the following endpoints: progression-free survival, overall survival, time to treatment failure, and objective response rate.

Progression-free survival (PFS) is defined as time from randomization to first documentation of objective disease progression as determined by independent radiology review or to death on study due to any cause, whichever occurs first.

Overall survival (OS) is defined as the time from randomization to the date of death due to any cause. For subjects still alive at the time of analysis, the OS time will be censored on the last date the subjects were known to be alive.

Time to treatment failure (TTF) is defined as time from randomisation to treatment failure.

Objective response rate (ORR) is defined as the percentage of subjects with a complete response (CR) or partial response (PR) according to RECIST (as determined by independent radiology review), relative to the total population of all randomized subjects.

Another planned clinical trial is a Phase I/II study of the anti-programmed death ligand-1 antibody MEDI4736 (durvalumab) in combination with cediranib for advanced solid tumors and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers. Dose schedules are shown in Table 1 and Table 2.

Table 1: Durvalumab + Cediranib Daily Schedule Dose Escalation Table

Dose Level (DL)	Durvalumab (intravenously, for 12mo)	Cediranib (oral, once daily, continuous)
DL -2	3 mg/kg every 2 weeks	15 mg
DL -1	3 mg/kg every 2 weeks	20 mg
DL 1 (starting dose)	10 mg/kg every 2 weeks	20 mg
DL 2	10 mg/kg every 2 weeks	30 mg

Table 2: Durvalumab + Cediranib Intermittent Schedule Dose Escalation Table

Dose Level (DL)	Durvalumab (intravenously, for 12mo)	Cediranib (oral, 5 days on/2 days off)
DL -2	A fixed dose of 500 mg every 4 weeks	15 mg
DL -1	A fixed dose of 1500 mg every 4 weeks	15 mg
DL 1 (starting dose)	A fixed dose of 1500 mg every 4 weeks	20 mg

For the durvalumab + cediranib arm, eligible patients will have been diagnosed with advanced or recurrent Ovarian Cancer (Cohort 1), NSCLC (Cohort 2), or CRC (Cohort 3). In Phase I, which used a continuous dosing regimen for administration of cediranib, 2 patients on DL1 required early discontinuation of cediranib due to pulmonary thromboembolism and 1 patient on DL1 had dose reduction to cediranib 15 mg daily due to recurrent grade 2 fatigue on cycle 2. Three of 4 patients on DL2 also had cediranib dose reduction to 20 mg daily due to recurrent grade 2 fatigue, grade 2 abdominal pain and grade 2 diarrhea during cycles 2-3.

The inventor of the present disclosure discovered that preclinical *in vivo* data showed no difference in anti-tumor activity with intermittent cediranib schedules (5 days on/2 days off) compared to a daily cediranib schedule. Thus, new durvalumab + cediranib dose levels with an intermittent cediranib schedule (5 days on/2 days off) according to the present disclosure with durvalumab at a fixed dose of 1500 mg every 28 days will be used in the clinical trials to determine whether there is, for example, an improvement in tolerability. Specifically, an intermittent cediranib dose schedule according to the present disclosure was investigated and a Phase II study of durvalumab +cediranib in ovarian cancer, NSCLC, and CRC is currently opened.

EXAMPLES

Example 1: In Vivo Solid Tumor Disease Model Assay. This assay can measure the capacity of compounds to inhibit solid tumor growth.

The following is an example of a typical procedure that may be used.

CaLu-6 tumor xenografts may be established in the flank of female athymic Swiss nu/nu mice, by subcutaneous injection of 1x10 CaLu-6 cells/mouse in 100pu of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice may be allocated to groups of 8-10, so as to achieve comparable group mean volumes. Tumors may be measured using vernier calipers and volumes may be calculated as: (l x w) x i (l x w) x (z/6), where l is the longest diameter and w the diameter perpendicular to the longest. Test compounds may be administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumors may be measured twice weekly. The level of growth inhibition may be calculated by comparison of the mean tumor volume of the control group versus the treatment group using a Student T test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment may be considered significant when $p < 0.05$.

Example 2: Assessing target cover. To establish the target cover achieved with cediranib in pre-clinical models, the time dependent PK profile was determined at a range of compound doses. The mean free drug profile of cediranib modelled based on multiple dosing at 0.6, 1.2, 2.4 and 4.8 mg/kg was calculated and aligned against the IC_{50} for potency versus VEGFR-1, VEGFR-2, c-kit and PDGFR.

Figures 1A-P show modelled mean free plasma concentrations of cediranib over time in pre-clinical models dosed at a). 0.6 mg/kg (Figures 1A-1D), b). 1.2 mg/kg (Figures 1E-1H), c). 2.4 mg/kg (Figures 1I-1L), or d). 4.8 mg/kg (Figures 1M-1P) following dosing regimens of once daily continuous (QDCont), once daily 5 days on 2 days off (QD5on2off), or once daily 4 days (QD4on3off). In addition, the PK of cediranib following a redose after a 2 or 3 day break is shown. The reduction in PK is shown following the last dose of drug (at either 4 or 5 days dosing), and overlaid on each plot (horizontal lines) are the cellular IC_{50} values generated *in vitro* for inhibition of pVEGFR-1,-2, pKit, pPDGFRα and pPDGFRβ, as indicated. For the plots exemplifying VEGFR

and Kit cover, R-P stands for receptor phosphorylation in a cell based assay; C-P stands for cell proliferation; for VEGFR plots, T-G stands for tubule growth in an endothelial-fibroblast co-culture assay. The relevant cell lines are indicated. For the graphs depicting PDGFRα and β cover, inhibition of PDGFRα and PDGFRβ phosphorylation and PDGFBB or PDGFAA driven proliferation are shown together with the relevant cell lines. The plots in Figure 1A-P exemplify the preclinical PK profile for cediranib at a range of doses and show that target cover can be lost rapidly following the last dose. This also established that at doses up to 2.4 mg/kg cediranib was achieving target cover versus VEGFRs and c-kit but was not giving sufficient cover versus PDGFR. It also demonstrated that, following the final dose in a given treatment cycle, the dose interruption can relieve suppression of the VEGFR signaling.

To establish the target cover achieved with cediranib in humans, the mean time dependent free drug PK profile from a population PK analysis was plotted, and similarly aligned versus the same IC_{50} values versus VEGFR-1,VEGFR-2, c-kit and PDGFRs. This analysis demonstrated that the 20 mg and 30 mg has a similar target cover to that achieved in the 1.2-2.4 mg/kg range pre-clinically. It also showed that, when drug dosing is interrupted, cover versus VEGFR and c-kit are lost with hours and that a 2 day (or more) break can relieve suppression of the VEGFR signaling.

Figure 2 shows modelled mean the free drug exposure in humans for cediranib (black line) versus time for 20 mg and 15 mg doses of cediranib. The 95% confidence intervals are represented by the grey ribbon. The PK curve shows the reduction in cediranib concentration following the final dose of compound. Overlaid on the plot (horizontal lines) are the cellular IC_{50} values generated in vitro for inhibition of pVEGFR, pKit, pPDGFRs. This data confirms that the free drug levels observed in the clinic are in the range of exposures observed when cediranib is dose at 1.2 – 2.4 mg/kg preclinically, and that the PK profile is similar to that observed pre-clinically.

Example 3: To assess maintenance of anti-tumor benefit. To determine whether intermittent dosing of cediranib is able to maintain anti-tumor benefit, a range of tumor xenograft models implanted sub-cutaneously into nude or scid mice representing differential sensitivity to cediranib were used. Tumors were selected and randomized into groups when tumor volume reached approximately 0.2 cm³. SW620 (CRC model), Calu6

(NSCLC model) and A498 (renal cancer model) tumors were dosed once daily orally with 1.2 mg/kg and 2.4 mg/kg (equivalent to 1.5 and 3 mg/kg cediranib maleate salt). To test the impact of the intermittent dosing, cediranib was dosed once daily orally for 7 days, 5 days or 4 days out of each 7 days cycle. Groups of 10 animals were used, however in the final cycle cohorts of 5 animals were removed in between dosing group to support assessment of pharmacodynamic biomarkers in the tumor. This data demonstrated that the 5 days on 2 days off schedule maintains anti-tumor effects as monotherapy despite relief of VEGFR suppression. Moreover the 4 days on 3 days off schedule also maintains anti-tumor effects albeit at not as effectively as the 5/2 schedule. This data established that a specific intermittent dosing strategy can maintain anti-tumor effects of cediranib. This presents the opportunity to give short structured breaks in cediranib treatment as either a monotherapy or a combination therapy with drugs targeting other mechanism (e.g., DNA damaging agents, immunotherapy, or tumor cell targeted therapy). (Figures 3–6).

Figure 3 shows mean tumor volume versus time from three efficacy studies (performed in Calu6, A498, and SW620 tumor xenografts) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 6 (three 7-day cycles of 1.5 mg/kg cediranib once daily for 5 days followed by vehicle once daily for 2 days. This data shows that intermittent dosing of cediranib at 1.5 mg/kg on a 5/2 schedule maintains efficacy.

Figure 4 shows mean tumor volume versus time from three efficacy studies (in Calu6, A498, and SW620 tumor xenografts) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 7 (three 7-day cycles of 3 mg/kg cediranib once daily for 5 days followed by vehicle once daily for 2 days. This data shows that intermittent dosing of cediranib at 3 mg/kg on a 5/2 schedule maintains efficacy.

Figure 5 shows mean tumor volume versus time from three efficacy studies (Calu6, A498, and SW620) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 8 (three 7-day cycles of 1.5 mg/kg

cediranib once daily for 3 days followed by vehicle once daily for 4 days. This data shows that in 2 out of the three models intermittent dosing of cediranib at 1.5 mg/kg on a 4/3 schedule maintains efficacy.

Figure 6 shows mean tumor volume versus time from three efficacy studies (Calu6, A498, and SW620) each using four oral dosing regimen groups (Group 1 (Vehicle once daily for 21 days), Group 2 (1.5 mg/kg cediranib once daily for 21 days), Group 3 (3 mg/kg cediranib once daily for 21 days), and Group 9 (three 7-day cycles of 3 mg/kg cediranib once daily for 3 days followed by vehicle once daily for 4 days)). This data shows that intermittent dosing of cediranib at 3 mg/kg on a 4/3 schedule maintains efficacy.

Example 4: To test the benefit of cediranib in combination with olaparib using an intermittent schedule, an intermittent (5 days on 2 days off) daily dose of cediranib combined with olaparib is as efficacious as a constant daily dose of cediranib combined with olaparib.

To establish that giving an intermittent dose of cediranib does not reduce anti-tumour efficacy of cediranib alone or in combination with olaparib, OV2022 tumour (ovarian cancer) xenografts were treated with 3 mg/kg cediranib daily or on a 5 days on, 2 days off schedule alone or in combination with 100 mg/kg olaparib. The intermittent schedule of cediranib gave equivalent efficacy to the constant dose of cediranib, thus showing that the intermittent dose of cediranib may be used effectively.

Figure 7 shows mean tumour volume versus time from an efficacy study performed in the OV2022 (ovarian cancer) patient derived tumour xenograft model. This study compared cediranib and olaparib combinations where cediranib was administered once daily or once daily on a 5 days on 2 days off schedule. Group 1 – control, Group 2 - cediranib 3mg/kg once daily, Group 3 – cediranib 3mg/kg once daily 5 days on 2 days off, Group 4 – olaparib 100mg/kg once daily, Group 5 - cediranib 3mg/kg once daily plus olaparib 100mg/kg once daily, Group 6 – cediranib 3mg/kg once daily 5 days on 2 days off plus olaparib 100mg/kg once daily.

Figure 8 shows the body weight change for each group of tumour bearing animals in the study. This study compared cediranib and olaparib combinations where cediranib

was administered once daily or once daily on a 5 days on 2 days off schedule. Group 1 --
control, Group 2 - cediranib 3mg/kg once daily, Group 3 -- cediranib 3mg/kg once daily 5
days on 2 days off, Group 4 -- olaparib 100mg/kg once daily, Group 5 - cediranib 3mg/kg
once daily plus olaparib 100mg/kg once daily, Group 6 -- cediranib 3mg/kg once daily 5
5   days on 2 days off plus olaparib 100mg/kg once daily.

Example 5: Phase 1 clinical trial results-intermittent dosing of cediranib in combination with MEDI4736 (durvalumab).

The benefit of the intermittent schedule was tested clinically in a combination trial
where the ability to combine cediranib with durvalumab was examined using a continuous
10   or an intermittent schedule of cediranib. This trial showed that, while the continuous dose
was poorly tolerated, the intermittent schedule was tolerated and resulted in observable
clinical benefit. The data are presented below.

Study Design and Patients

Eligible patients had recurrent or metastatic RECIST v1.1 measurable solid
15   malignancies without prior immune checkpoint inhibitor therapy, controlled hypertension
on no more than 3 anti-hypertensives, and good end-organ function; germline *BRCA*
mutation status was requested at entry. All patients provided written informed consent
before enrollment. The trial was approved by the Institutional Review Board of the Center
for Cancer Research, National Cancer Institute. ClinicalTrials.gov identifier:
20   NCT02484404.

Eligible patients received durvalumab+cediranib in a 3+3 dose escalation format
according to Table 3. Cohorts enrolled patients simultaneously. Patients were evaluated for
toxicity per CTCAEv4. Clinical response was assessed every two cycles by imaging using
RECISTv1.1 criteria. Study treatment was discontinued for progression of disease,
25   intercurrent illness, adverse events not recovering to $\leq$ grade 1 within 14 days, or patient
withdrawal of consent.

Table 3: Dose levels (DL)

	Durvalumab+cediranib		
	Cediranib tablets	Durvalumab (MEDI4736), IV	N*
DL 1	20mg once daily	10mg/kg every 2 weeks	4
DL 2	30mg once daily	10mg/kg every 2 weeks	4
DL 3	20mg (5 days on/ 2 days off)	1500mg every 4 weeks	6

* One patient on DL1 withdrew consent on cycle one, one patient on DL2 took cediranib 20mg instead of 30mg for a week during cycle one, and one patient on DL3 developed grade 4 hypertension and off-treatment on cycle one.

Definitions of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)

The primary endpoint of this phase 1 study was to determine recommended phase 2 dose (RP2D) of durvalumab+cediranib combination, defined by the MTD or the highest protocol-defined dose in the absence of DLT. DLT was defined as grade 3 or 4 nonhematologic and grade 4 hematologic adverse events (AEs) related to study medications occurring during the first cycle (28 days). The following were exceptions: grade 3 lymphopenia or leukopenia in the absence of grade 3 or higher neutropenia, grade 3 hypertension controlled with anti-hypertensive therapy, or grade 3 asymptomatic electrolytes imbalance with optimal repletion that downgrades to grade 1 or better within 3 days, grade 3 asymptomatic increase in amylase or lipase that downgrades to grade 1 or better within 7 days after onset of the event, or grade 3 asymptomatic endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy. The MTD was defined as the highest dose level at which one or fewer of six patients experienced a DLT. If the observed AE was specifically attributed to only one of the drugs, that drug was held while the patient continued to receive the drug not associated

with the observed AE. Treatment-related serious AEs occurring 90 days or more after the last dose of study drugs were reported.

RESULTS

Patient characteristics

14 women were enrolled. Table 4 shows baseline patient characteristics. Ovarian carcinoma was the most common tumor type (9/14 [64%]).

Table 4: Baseline characteristics

	MEDI4736 (durvalumab) +cediranib (n=14)
Age (years): median (range)	58.4 (44.4-73.8)
Tumor type	
Ovarian cancer	9 (64%)
platinum-sensitive/platinum-resistant disease	4/5
high-grade serous/clear cell histology	7/2
BRCA mutation status*	
germline/wild type/unknown	2/6/1
lines of prior therapy	
2-4	4
$\geq$5	5
prior PARPi	4
prior bevacizumab	6
ECOG performance status (0/1/2)	2/12/0
Cervical cancer, squamous cell histology	2
lines of prior therapy	1, 4 each
prior PARPi	0
prior bevacizumab	1
ECOG performance status (0/1/2)	0/2/0
Uterine cancer	3
endometrial/leiomyosarcoma	2/1
lines of prior therapy	1,2,3 each
prior PARPi	0
prior bevacizumab	0
ECOG performance status (0/1/2)	1/2/0

Data are number of patients (total %) or median (range). ECOG=Eastern Cooperative Oncology Group.

Dose optimization and toxicities

The recommended phase 2 dose (RP2D) was determined as cediranib 20mg 5 days on/2 days off with durvalumab 1500mg every 4 weeks. Daily cediranib with durvalumab was not well-tolerated, although it did not meet the formal mark of dose-limiting toxicity (DLT) during the first treatment cycle. Daily cediranib was discontinued or dose-reduced due to recurrent grade 2 or non-DLT grade 3 or 4 adverse events (AEs) in 7/8 patients; two patients on DL1 discontinued cediranib due to new pulmonary thromboembolism (PE) on study, and one patient on DL1 was dose reduced on cycle two, with four patients on DL2 dose reduced one level due to recurrent grade 2 abdominal pain, diarrhea, fatigue on later cycles (cycles two, three, and five). Two patients were removed from treatment due to treatment-emergent AE (TEAE) consisting of grade 3 colitis (cycle six) and grade 3 pulmonary hypertension (cycle five). Patients were treated with systemic corticosteroids with no symptom improvement. The patient with pulmonary hypertension also had a PE and expired approximately one month after discontinuation of treatment; autopsy findings revealed disease progression including pericardial effusion, and infiltration of lung, thyroid, lymph nodes, and other organs. A protocol amendment added a new dose level with cediranib 20 mg 5 days on/2 days off. One patient on the intermittent schedule had DLT of grade 4 hypertension on cycle one, and five other patients tolerated the treatment across all administered cycles. All patients had at least one any grade TEAE, summarized in Table 5.

Table 5: Durvalumab+olaparib and durvalumab+cediranib treatment-related adverse events by maximum grade per patient

	Durvalumab+ daily cediranib (n=8)				Durvalumab+ intermittent cediranib (n=6)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Lymphopenia	2	2	1	1	0	0	0	0
Anemia	1	2	2	0	0	0	0	0
Thrombocytopenia	6	0	0	0	1	0	0	0
Nausea	0	1	1	0	0	0	0	0
Abdominal pain	1	2	0	0	0	0	0	0
Diarrhea	2	2	3	0	3	0	0	0
Anorexia	1	1	0	0	0	0	0	0
Vomiting	1	1	0	0	1	0	0	0
Oral mucositis	3	2	0	0	0	0	0	0
Colitis	0	0	1	0	0	0	0	0
Hypothyroidism	0	2	0	0	0	0	0	0
Hyperthyroidism	2	0	0	0	0	1	0	0
Alkaline phosphatase increased	2	0	0	0	0	0	0	0
AST increased	2	0	0	0	1	0	0	0
ALT increased	0	0	0	0	1	0	0	0
Fatigue	3	2	1	0	2	1	1	0
Headache	1	1	1	0	0	0	0	0
Skin rash	3	0	0	0	1	0	0	0
Pruritus	0	0	0	0	1	0	0	0
Hoarseness	0	0	0	0	1	0	0	0
Weight loss	1	2	0	0	0	0	0	0
Hypertension	0	4	3	0	0	4	0	1
Pulmonary thromboembolism †	0	0	1	1	0	0	0	0
Dyspnea on exertion	1	1	0	0	1	0	0	0
Pulmonary Hypertension†	0	0	1	0	0	0	0	0

Data are number. A patient could be counted under more than one preferred term. ALT=alanine
5   aminotransferase. AST=aspartate aminotransferase. One patient on DL1 of durvalumab+daily cediranib withdrew her consent on cycle one day 15 and did not report any AEs. One patient on durvalumab+daily cediranib DL1 had dose reduction to daily cediranib 15mg on cycle two, all four patients on durvalumab+daily cediranib DL2 had dose reduction to daily cediranib 20mg due to recurrent grade 2 abdominal pain, diarrhea, fatigue on cycle two (2 patients), cycle three (1 patient) and cycle five (1 patient).
10   *Two patients on durvalumab+daily cediranib received packed RBC transfusion on cycle one (DL1) and cycle five (DL2). †Daily cediranib was discontinued in two patients on DL1 due to pulmonary thromboembolism (PE) on cycle three and cycle five. One with PE developed pulmonary hypertension on cycle five. One patient discontinued daily cediranib and durvalumab due to grade 3 colitis on cycle six.

Clinical activity

Twelve of 14 patients on durvalumab+cediranib were assessed for tumor response; two were not evaluable due to drug toxicity or withdrawal of consent during cycle one, without demonstrated progression. Six of 12 patients attained a PR (5+-8+ months, 50% ORR), three of those were treated on DL3, suggesting response was not attenuated with the intermittent cediranib schedule. The largest response in the patient's tumor size (from baseline) observed during the trial is shown in Figure 9 (i.e., the largest response observed may have been observed at any time point during the trial). Figure 10 show the changes from baseline in tumor size over time for each patient.

The intermittent cediranib schedule results in improved tolerability and maintained the clinical benefit observed in the daily schedule.

Example 6: Phase 1 clinical trial-Intermittent dosing of Cediranib in combination with (MEDI4736) durvalumab and olaparib

The benefit of the intermittent schedule was further tested clinically in a combination trial where the ability to combine cediranib with durvalumab and olaparib was examined using an intermittent schedule of cediranib (5 days on/2 days off). The goal of the study was to determine recommended phase 2 dose (RP2D) of durvalumab + olaparib + intermittent cediranib (NCT02484404). This trial showed that intermittent dosing of Cediranib combined with durvalumab and olaparib is tolerable and active in recurrent women's cancers.

Study design:

Eligible patients with a Performance Status (PS) of 0 to 1 and good end organ function received durvalumab+olaparib+intermittent cediranib. Patients received 15 or 20 mg (5 days on/2 days off) of cediranib with 1500 mg IV every 28 days of durvalumab and with 300 mg tablets of olaparib BID. The dose-limiting toxicity period was one 28 day cycle. Safety was assessed by CTCAEv4.0 and response by RECISTv1.1. All patients provided written informed consent before enrolment.

Results:

9 women of median age 51 [range 44-73] and median 2 prior therapies [range 2-6] were treated with the durvalumab+olaparib+intermittent Cediranib. 7 patients had ovarian cancer, 1 patient had endometrial cancer and 1 patient had Triple Negative Breast Cancer

(TNBC). Two patients experienced grade 3/4 adverse events (lymphopenia). There was no toxicity-related dose reduction or discontinuation. Two partial responses (5^+, 2^+ months) and three stable disease (2^+-7^+ months) were seen in 5 evaluable patients.

CLAIMS:

1.   Use of cediranib for treating at least one disease state associated with angiogenesis in a human, wherein:

the cediranib is for administration for at least two cycles according to a fixed intermittent dosing regimen,

the fixed intermittent dosing regimen is 7 days, and an effective amount of the cediranib is for administration on 5 consecutive days followed by 2 days of rest, and

the at least one disease state associated with angiogenesis is chosen from lung cancers; digestive and gastrointestinal cancers; esophageal cancers; gallbladder cancers; liver cancers; pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

2.   The use according to claim 1, wherein the at least one disease state associated with angiogenesis is chosen from platinum sensitive relapsed ovarian cancers.

3.   The use according to claim 2, wherein the platinum sensitive relapsed ovarian cancers are chosen from fallopian tube cancers, high grade endometrial cancers, and primary peritoneal cancers.

4.   The use according to claim 1, wherein the cediranib is for administration in an amount of 30 mg or 20 mg as measured by weight of the free base of cediranib.

5.   The use according to claim 1, further comprising use of at least one other component chosen from partner drugs and other treatments.

6.   The use according to claim 5, wherein said partner drugs are chosen from DNA damage response inhibitors, immune checkpoint inhibitors, tumor cell targeting therapy agents, and chemotherapy agents.

7.   The use according to claim 6, wherein said partner drugs are chosen from PARP inhibitors.

8.   The use according to claim 7, wherein said PARP inhibitor is olaparib.

9.   The use according to claim 6, wherein said partner drugs are chosen from immune checkpoint inhibitors.

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10. The use according to claim 9, wherein said immune checkpoint inhibitor is MEDI4736 (durvalumab).

11. The use according to claim 6, wherein said partner drugs are chosen from chemotherapy agents.

12. The use according to claim 11, wherein said chemotherapy agents are chosen from platinum based chemotherapy agents, taxane based chemotherapy agents, and irotecan.
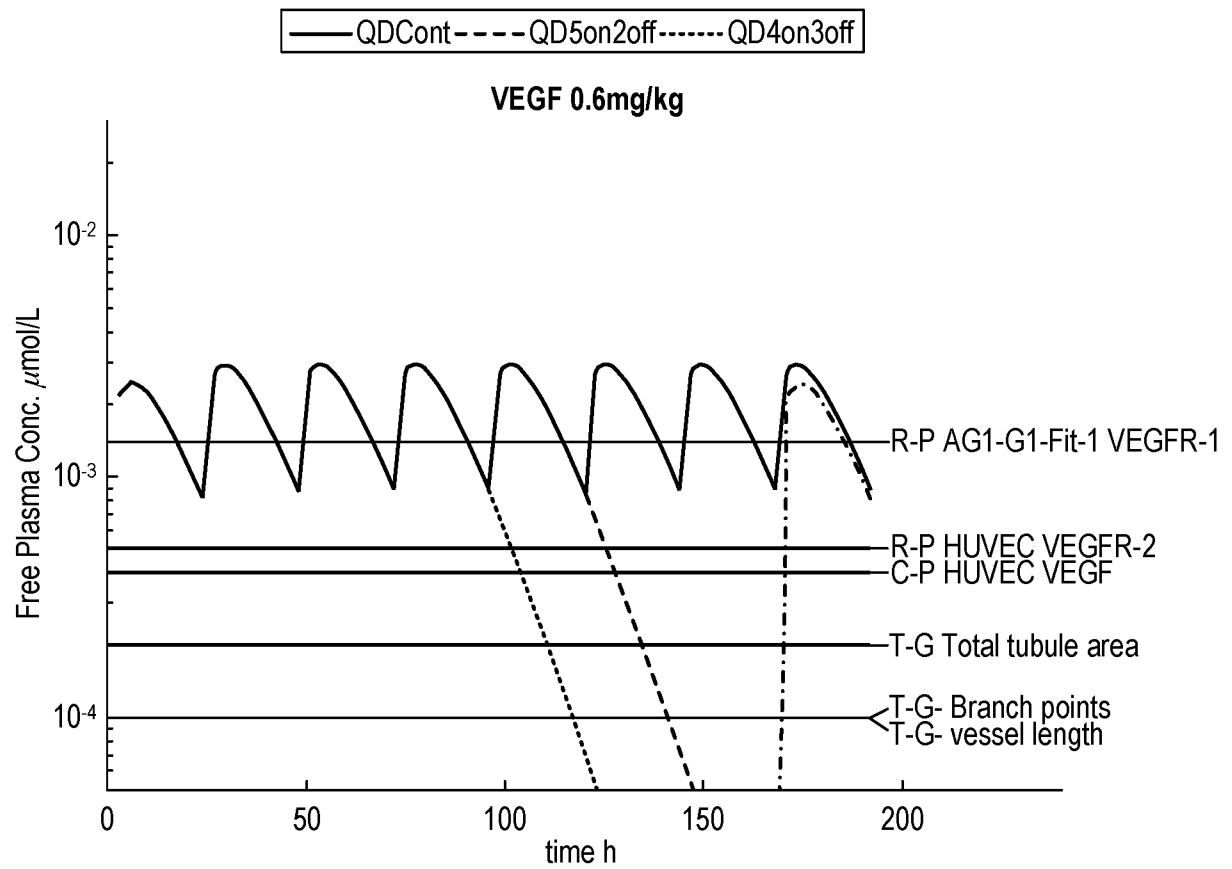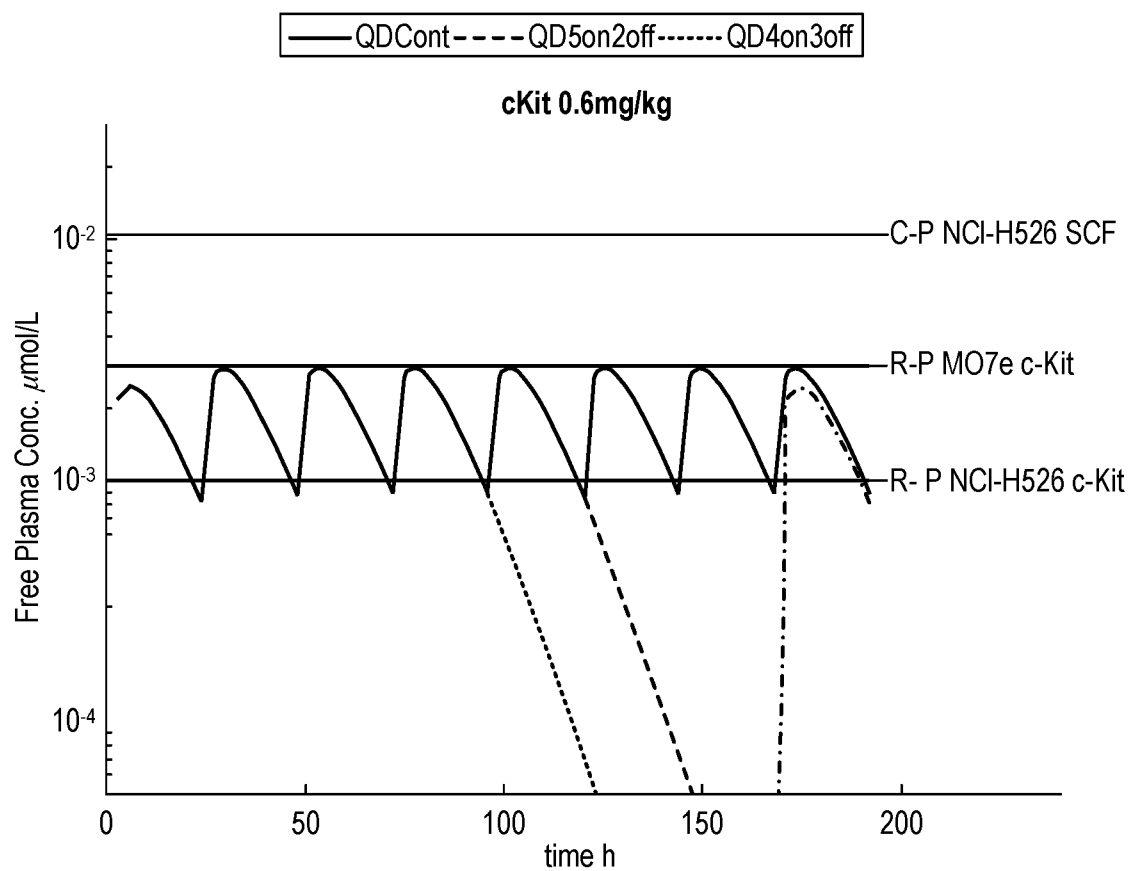
13. Use of cediranib for the manufacture of a medicament for treating at least one disease state associated with angiogenesis in a human, wherein:

the medicament is for administration for at least two cycles according to a fixed intermittent dosing regimen,

the fixed intermittent dosing regimen is 7 days, and an effective amount of the medicament is for administration on 5 consecutive days followed by 2 days of rest, and

the at least one disease state associated with angiogenesis is chosen from lung cancers; digestive and gastrointestinal cancers; esophageal cancers; gallbladder cancers; liver cancers; pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

14. The use according to claim 13, wherein the at least one disease state associated with angiogenesis is chosen from platinum sensitive relapsed ovarian cancers.

15. The use according to claim 14, wherein the platinum sensitive relapsed ovarian cancers are chosen from fallopian tube cancers, high grade endometrial cancers, and primary peritoneal cancers.

16. The use according to claim 13, wherein the medicament comprises cediranib in an amount of 30 mg or 20 mg as measured by weight of the free base of cediranib.

17. The use according to claim 13, wherein the medicament is for use in combination with at least one other component chosen from partner drugs and other treatments.

18. The use according to claim 17, wherein said partner drugs are chosen from DNA damage response inhibitors, immune checkpoint inhibitors, tumor cell targeting therapy agents, and chemotherapy agents.

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19.   The use according to claim 18, wherein said partner drugs are chosen from PARP inhibitors.

20.   The use according to claim 19, wherein said PARP inhibitor is olaparib.

21.   The use according to claim 18, wherein said partner drugs are chosen from immune checkpoint inhibitors.

22.   The use according to claim 21, wherein said immune checkpoint inhibitor is MEDI4736 (durvalumab).

23.   The use according to claim 18, wherein said partner drugs are chosen from chemotherapy agents.

24.   The use according to claim 23, wherein said chemotherapy agents are chosen from platinum based chemotherapy agents, taxane based chemotherapy agents, and irotecan.
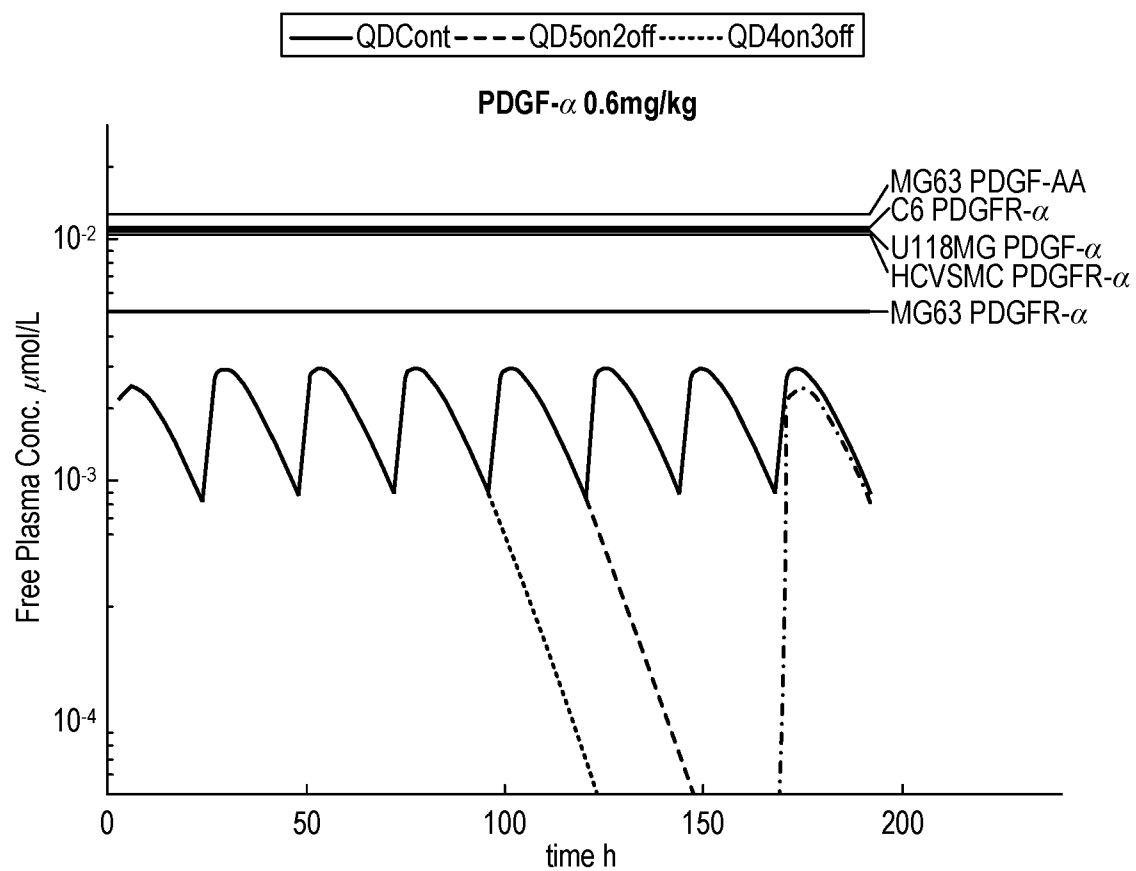
25.   Cediranib for use in treating at least one disease state associated with angiogenesis in a human, wherein:

the cediranib is for administration for at least two cycles according to a fixed intermittent dosing regimen,

the fixed intermittent dosing regimen is 7 days, and an effective amount of the cediranib is for administration on 5 consecutive days followed by 2 days of rest, and

the at least one disease state associated with angiogenesis is chosen from lung cancers; digestive and gastrointestinal cancers; esophageal cancers; gallbladder cancers; liver cancers; pancreatic cancers; appendix cancers; breast cancers; ovarian cancers; renal cancers; cancers of the central nervous system; skin cancers; lymphomas; glioblastomas; choriocarcinomas; alveolar soft part sarcomas; head and neck cancers; osteogenic sarcomas; and blood cancers.

26.   The cediranib for use according to claim 25, wherein the at least one disease state associated with angiogenesis is chosen from platinum sensitive relapsed ovarian cancers.

27.   The cediranib for use according to claim 26, wherein the platinum sensitive relapsed ovarian cancers are chosen from fallopian tube cancers, high grade endometrial cancers, and primary peritoneal cancers.

28.   The cediranib for use according to claim 25, wherein the cediranib is for administration in an amount of 30 mg or 20 mg as measured by weight of the free base of cediranib.

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29.   The cediranib for use according to claim 25, wherein the cediranib is for use in combination with at least one other component chosen from partner drugs and other treatments.

30.   The cediranib for use according to claim 29, wherein said partner drugs are chosen from DNA damage response inhibitors, immune checkpoint inhibitors, tumor cell targeting therapy agents, and chemotherapy agents.

31.   The cediranib for use according to claim 30, wherein said partner drugs are chosen from PARP inhibitors.

32.   The cediranib for use according to claim 31, wherein said PARP inhibitor is olaparib.

33.   The cediranib for use according to claim 30, wherein said partner drugs are chosen from immune checkpoint inhibitors.

34.   The cediranib for use according to claim 33, wherein said immune checkpoint inhibitor is MEDI4736 (durvalumab).

35.   The cediranib for use according to claim 30, wherein said partner drugs are chosen from chemotherapy agents.

36.   The cediranib for use according to claim 35, wherein said chemotherapy agents are chosen from platinum based chemotherapy agents, taxane based chemotherapy agents, and irotecan.

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Figure 1A

VEGF 0.6mg/kg

Figure 1B

| ——QDCont - - - - QD5on2off ······ QD4on3off |

cKit 0.6mg/kg

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Figure 1C

Figure 1D

| ——QDCont - - - QD5on2off ······ QD4on3off |

PDGF-β 0.6mg/kg

MG63 PDGF-BB
hAoVSMC PDGF-BB
U118MG PDGFR-β
HAoVSMC PDGFR-β
NIH3T3 PDGFR-β
MG63 PDGFR-β

Figure 1E

| QDCont - - - - QD5on2off ······ QD4on3off |

VEGF 1.2mg/kg

R-P AG1-G1-Fit-1 VEGFR-1

R-P HUVEC VEGFR-2
C-P HUVEC VEGF

T-G Total tubule area

T-G- Branch points
T-G- vessel length

Figure 1F

| QDCont - - - QD5on2off ------ QD4on3off |

cKit 1.2mg/kg

Figure 1G

Figure 1H

| QDCont - - - - QD5on2off ------ QD4on3off |

PDGF-β 1.2mg/kg

Figure 1I

| ——QDCont - - - - QD5on2off ······ QD4on3off |

VEGF 2.4mg/kg

Figure 1J

Legend: —— QDCont - - - QD5on2off ······ QD4on3off

cKit 2.4mg/kg

Figure 1K

PDGF-α 2.4mg/kg

Figure 1L

QDCont ---- QD5on2off ······ QD4on3off

PDGF-β 2.4mg/kg

Figure 1M

Figure 1N

cKit 4.8mg/kg

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Figure 1O

PDGF-α 4.8mg/kg

Legend: QDCont — — QD5on2off ······ QD4on3off

Y-axis: Free Plasma Conc. μmol/L (10^{-2}, 10^{-3}, 10^{-4})

X-axis: time h (0, 50, 100, 150, 200)

Right labels:
MG63 PDGF-AA
C6 PDGFR-α
U118MG PDGF-α
HCVSMC PDGFR-α
MG63 PDGFR-α

Figure 1P

Figure 2

Figure 3

Calu-6
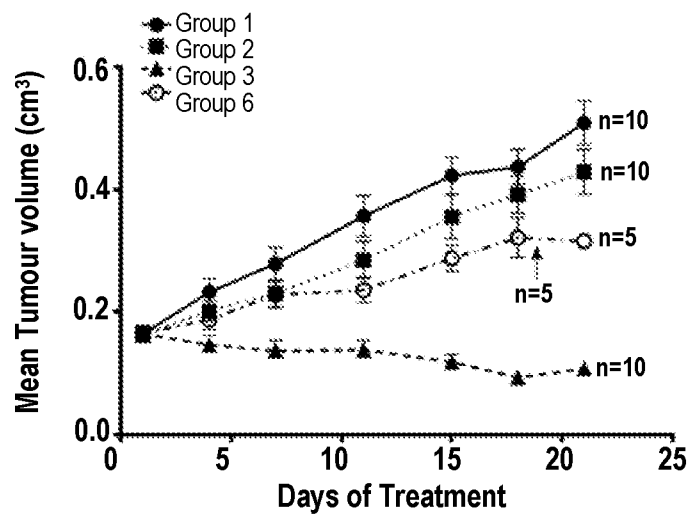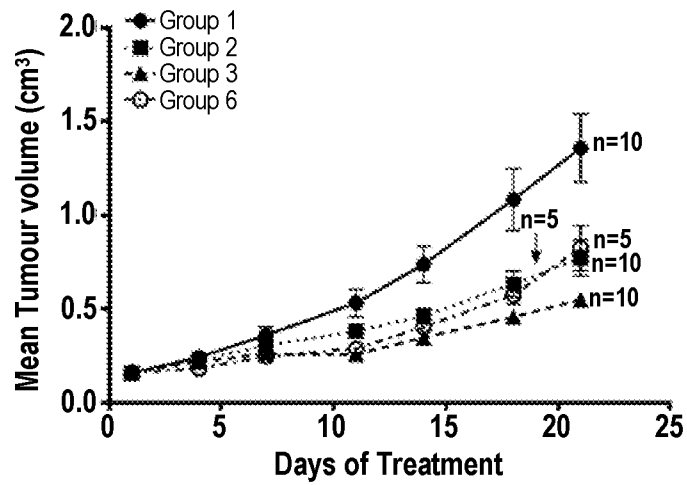
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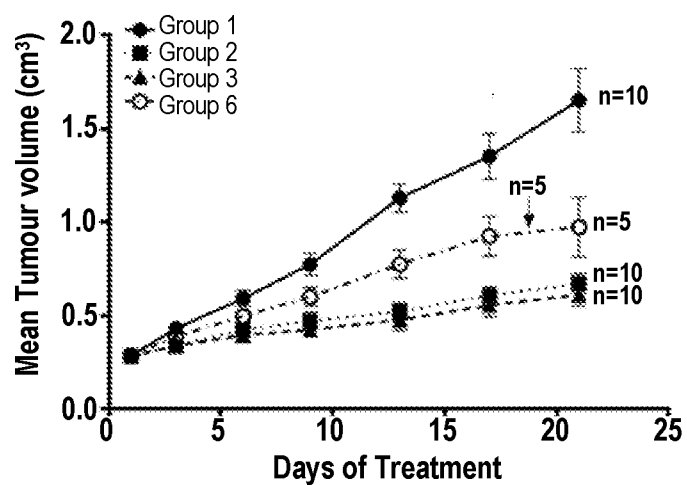
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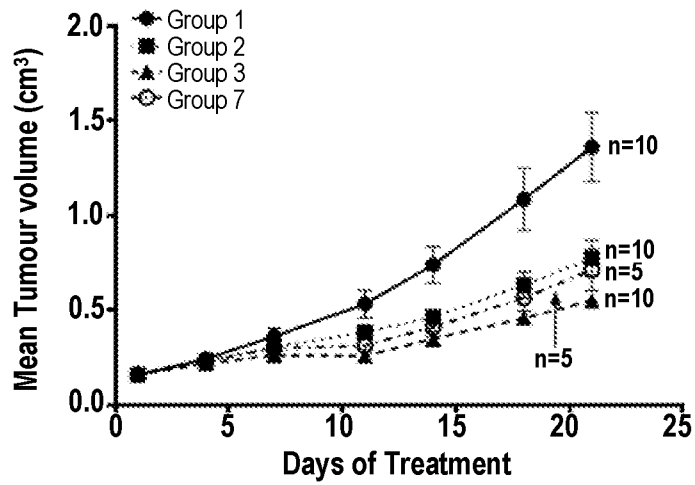
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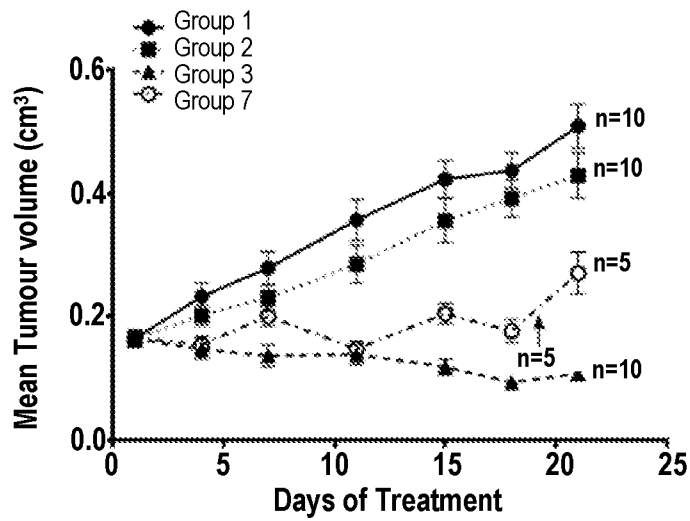
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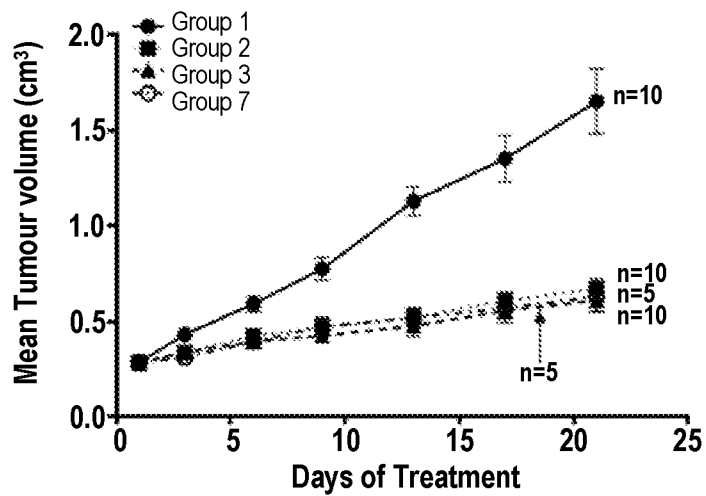
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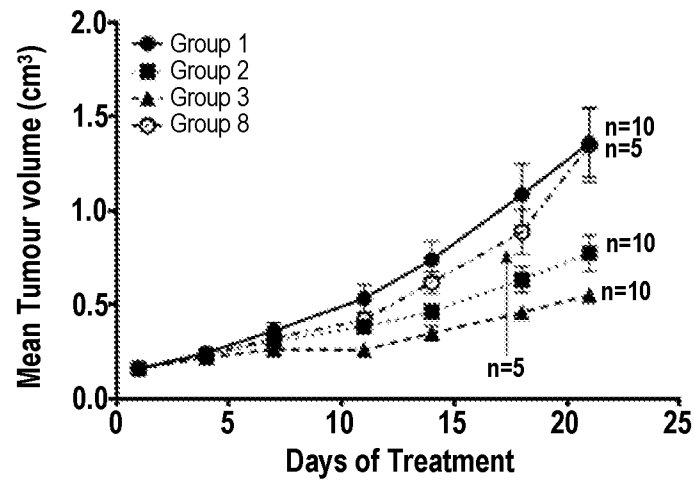
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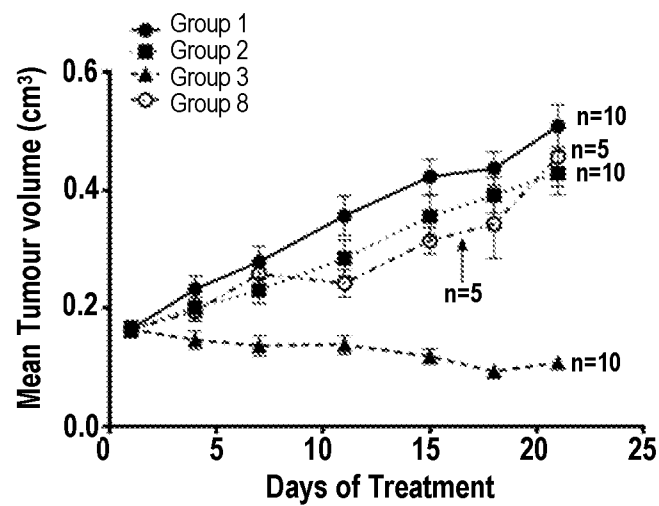
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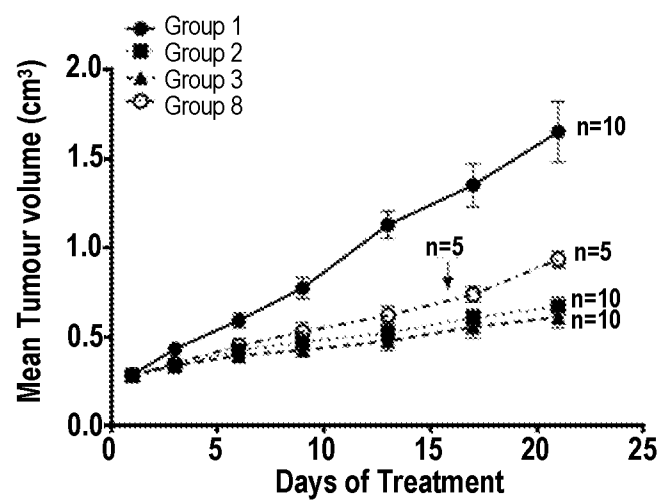
Figure 6

Calu-6
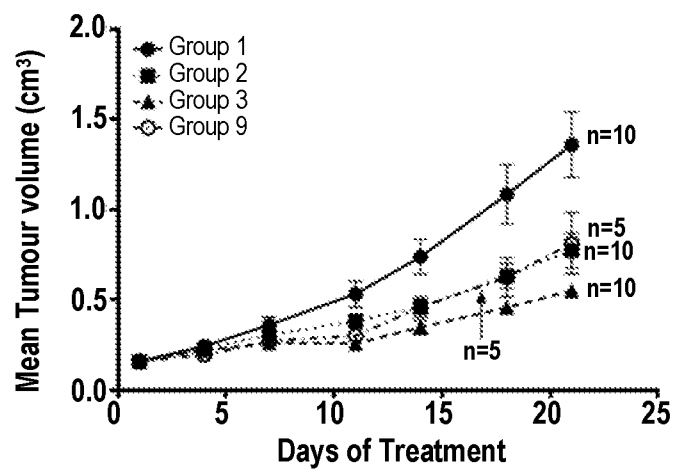
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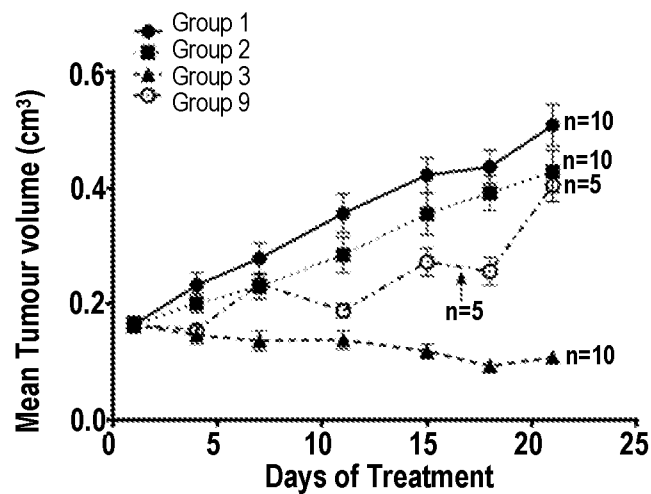
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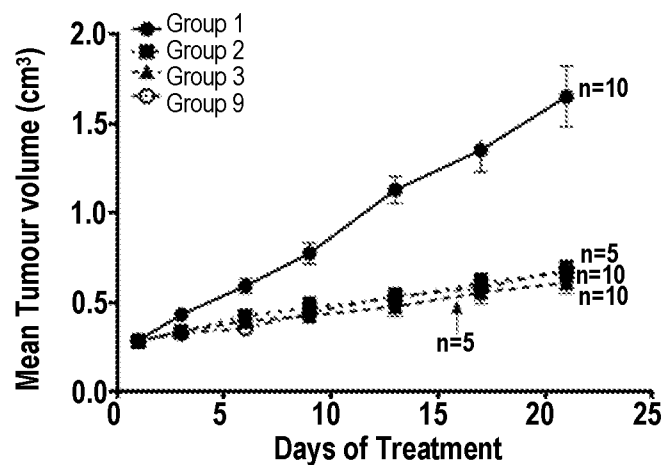
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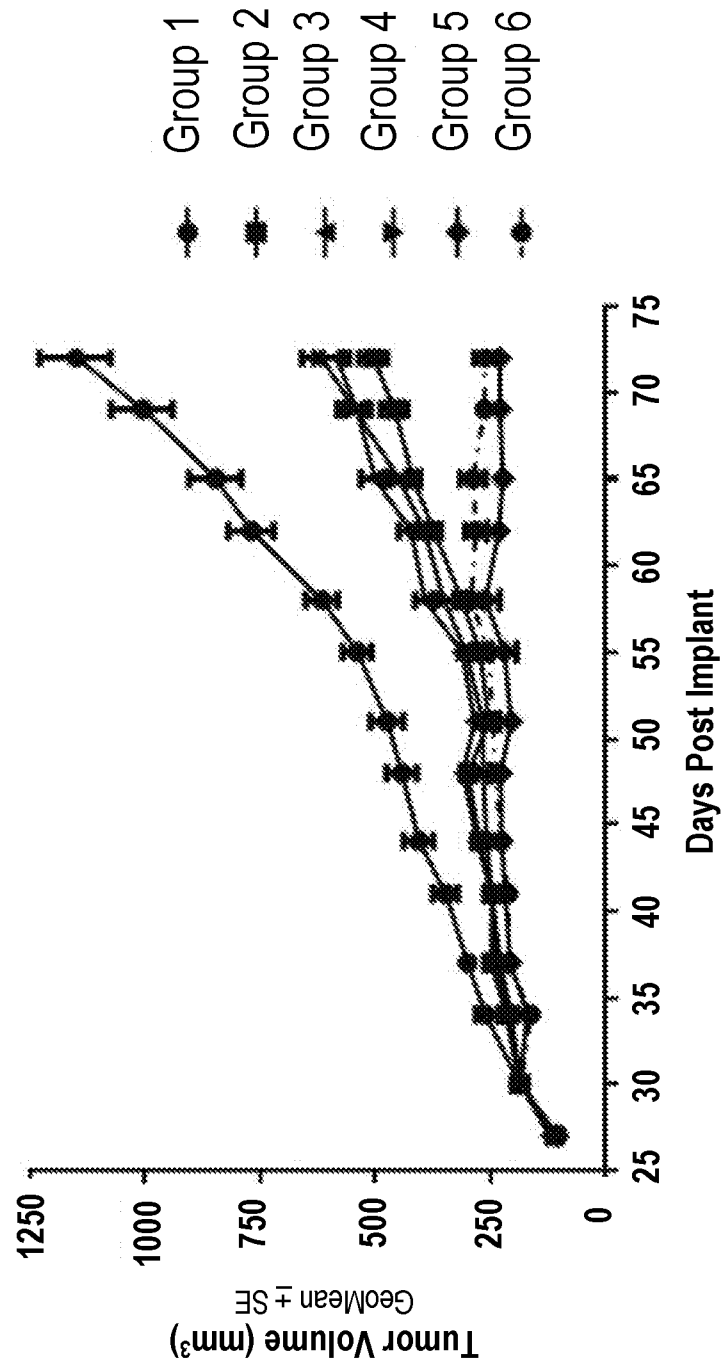
Figure 8

Figure 9

Figure 10

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VEGF 0.6mg/kg

Legend: QDCont — — — QD5on2off ········· QD4on3off

Y-axis: Free Plasma Conc. μmol/L

Y-axis values: 10^{-2}, 10^{-3}, 10^{-4}

X-axis: time h

X-axis values: 0, 50, 100, 150, 200

R-P AG1-G1-Fit-1 VEGFR-1

R-P HUVEC VEGFR-2
C-P HUVEC VEGF

T-G Total tubule area

T-G- Branch points
T-G- vessel length