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(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEDGE, Stephen, Robert** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **RYAN, Anderson, Joseph** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Sodertalje (SE).

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(54) Title: USE OF THE QUINAZOLINE DERIVATIVE ZD6474 COMBINED WITH PLATINUM COMPOUNDS AND OPTIONALLY IONISING RADIATION IN THE TREATMENT OF DISEASES ASSOCIATED WITH ANGIOGENESIS AND/OR INCREASED VASCULAR PERMEABILITY

(57) Abstract: The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of ZD6474 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising ZD6474 and a platinum anti-tumour agent; to a combination product comprising ZD6474 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising ZD6474 and a platinum anti-tumour agent; to the use of ZD6474 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

USE OF THE QUINAZOLINE DERIVATIVE ZD6474 COMBINED WITH PLATINUM COMPOUNDS AND OPTIONALLY IONISING RADIATION IN THE TREATMENT OF DISEASES ASSOCIATED WITH ANGIOGENESIS AND/OR INCREASED VASCULAR PERMEABILITY

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of ZD6474 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising ZD6474 and a platinum anti-tumour agent; to a combination product comprising ZD6474 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising ZD6474 and a platinum anti-tumour agent; to the use of ZD6474 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis 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). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (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

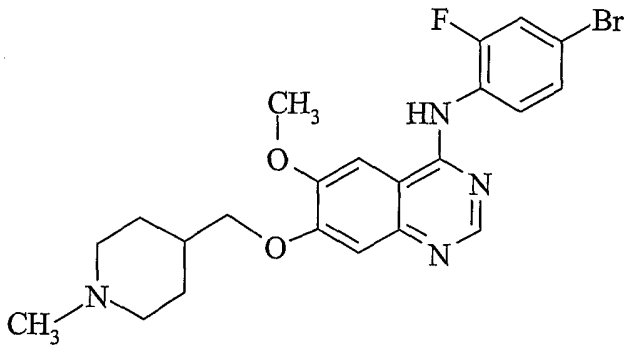
characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation 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 (also referred to as VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as VEGFR-2 or 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.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., Science (Washington DC), *246*: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., Microvasc. Res., *55*: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., Enzyme Protein, *49*: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (Int. Arch. Allergy Immunol., *107*: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. Physiol. (Lond.), *533*: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C., EMBO J., *18*: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., J. Biol. Chem., *276*: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., *276*: 3222-3230, 2001).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Applications Publication Nos. WO 98/13354 and WO 01/32651. In WO 98/13354 and WO 01/32651 compounds are described which possess activity against VEGF receptor tyrosine kinase (VEGF RTK) whilst possessing some activity against epidermal growth factor (EGF) receptor tyrosine kinase (EGF RTK).

ZD6474 is 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline:



ZD6474

ZD6474 falls within the broad general disclosure of WO 98/13354 and is exemplified in WO 01/32651. ZD6474 is a potent inhibitor of VEGF RTK and also has some activity against EGF RTK. ZD6474 has been shown to elicit broad-spectrum anti-tumour activity in a range of models following once-daily oral administration (Wedge S.R., Ogilvie D.J., Dukes M. et al, Proc. Am. Assoc. Canc. Res. 2001; 42: abstract 3126).

In WO 98/13354 and WO 01/32651 it is stated that compounds of their inventions: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

WO 98/13354 and WO 01/32651 then go on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent.

Nowhere in WO 98/13354 and WO 01/32651 is the specific combination of ZD6474 and a platinum anti-tumour agent suggested.

Nowhere in WO 98/13354 and WO 01/32651 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection from the broad description of combination therapies listed in WO 98/13354 and WO 01/32651, namely with a platinum anti-tumour agent, produces significantly better effects than any one of ZD6474 and a platinum anti-tumour agent used alone. In particular, ZD6474 used in combination with a platinum anti-tumour agent produces significantly better effects on solid tumours than any one of ZD6474 and a platinum anti-tumour agent used alone.

A platinum anti-tumour agent is any anti-tumour agent containing platinum. Platinum anti-tumour agents include cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, satraplatin and AMD473.

Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, with or without a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises ZD6474 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit comprising ZD6474 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a kit comprising:

a) ZD6474 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) a platinum anti-tumour agent in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) ZD6474 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;

b) a platinum anti-tumour agent together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of a platinum anti-tumour agent, wherein a platinum anti-tumour agent may optionally be administered together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment. Such therapeutic treatment includes an antiangiogenic and/or vascular permeability effect, an anti-cancer effect and an anti-tumour effect.

A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention.

Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with ZD6474 described herein.

Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 01/32651 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents including vascular targeting agents;

(ii) cytostatic agents;

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology; and other categories of agent are:

(vi) antisense therapies;

(vii) gene therapy approaches; and

(ix) immunotherapy approaches.

Particular examples of chemotherapeutic agents for use with a combination treatment of the present invention are raltitrexed, etoposide, vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan (CPT-11) and 5-fluorouracil (5-FU); such combinations are expected to be particularly useful for the treatment of cancer of the lung, head and neck, colon, rectum, oesophagus, stomach, cervix, ovary, skin, breast, bladder and pancreas.

The administration of a triple combination of ZD6474, a platinum anti-tumour agent and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with any of ZD6474, a platinum anti-tumour agent and ionising radiation used alone, greater than those achieved with the combination of ZD6474 and a platinum anti-tumour agent, greater than those achieved with the combination of ZD6474 and ionising radiation, greater than those achieved with the combination of a platinum anti-tumour agent and ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as

a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of a platinum anti-tumour agent, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the ZD6474, a platinum anti-tumour agent and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament or combination treatment comprising ZD6474 and a platinum anti-tumour agent. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before to a week after the administration of a medicament or combination

treatment comprising ZD6474 and a platinum anti-tumour agent. This means that ZD6474, a platinum anti-tumour agent and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of ZD6474, a platinum anti-tumour agent and radiation simultaneously.

According to one aspect of the present invention the ionising radiation is administered before one of ZD6474 and a platinum anti-tumour agent or after one of ZD6474 and a platinum anti-tumour agent.

According to one aspect of the present invention the ionising radiation is administered before both ZD6474 and a platinum anti-tumour agent or after both ZD6474 and a platinum anti-tumour agent.

According to one aspect of the present invention ZD6474 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of ZD6474 and a platinum anti-tumour agent used alone or of each of ZD6474, a platinum anti-tumour agent and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of ZD6474 and a platinum anti-tumour agent used alone or of each of ZD6474, a platinum anti-tumour agent and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with ZD6474 or a platinum anti-tumour agent or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not

respond (or responds poorly) to ZD6474 or a platinum anti-tumour agent or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of ZD6474 or a platinum anti-tumour agent or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or an increase in vascular permeability is present in a wide range of disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration. Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma. In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, pancreas, bladder, breast, prostate, lungs and skin. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours in colorectal cancer and in lung cancer, for example mesothelioma and non-small cell lung cancer (NSCLC). More particularly such combination treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, mulitple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon (including rectum), pancreas, bladder, breast, prostate, lung, vulva, skin and particularly NSCLC.

In another aspect of the present invention ZD6474 and a platinum anti-tumour agent, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF especially those tumours which are significantly dependent on VEGF for their growth and spread.

In another aspect of the present invention ZD6474 and a platinum anti-tumour agent, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with both VEGF and EGF especially those tumours which are significantly dependent on VEGF and EGF for their growth and spread.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the ZD6474 of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. Preferably ZD6474 is administered orally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

ZD6474 will normally be administered to a warm-blooded animal at a unit dose within the range 10-500mg per square metre body area of the animal, for example approximately 0.3-15mg/kg in a human. A unit dose in the range, for example, 0.3-15mg/kg, preferably 0.5-5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually contain, for example 25-500mg of active ingredient. Preferably a daily dose in the range of 0.5-5mg/kg is employed.

Platinum anti-tumour agents may be dosed according to known routes of administration and dosages.

For example cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 40-120mg/m^2 every 3-4 weeks. Alternatively for example cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 15-20mg/m^2 daily for up to 5 days every 3-4 weeks.

For example carboplatin may be administered as a single short-term intravenous infusion over a period of 15-60 minutes at a dose of 250-400mg/m^2 every 4 weeks.

For example oxaliplatin may be administered by intravenous infusion over a period of 2-6 hours at a dose of about 85mg/m^2 every 2 weeks.

The dosages and schedules may vary according to the particular disease state and the overall condition of the patient. Dosages and schedules may also vary if, in addition to a combination treatment of the present invention, one or more additional chemotherapeutic agents is/are used. Scheduling can be determined by the practitioner who is treating any particular patient.

Radiotherapy may be administered according to the known practices in clinical radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ-rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

As stated above the size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

The present invention relates to combinations of a platinum anti-tumour agent with ZD6474 or with a salt of ZD6474.

Salts of ZD6474 for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of ZD6474 and its pharmaceutically acceptable salts. Such salts may be formed with an inorganic or organic

base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

ZD6474 may be synthesised according to any of the known processes for making ZD6474. For example ZD6474 may be made according to any of the processes described in WO 01/32651; for example those described in Examples 2(a), 2(b) and 2(c) of WO 01/32651.

Platinum anti-tumour agents are commercially available.

The following tests may be used to demonstrate the activity of ZD6474 in combination with a platinum anti-tumour agent.

Calu 6 lung cancer xenograft model

A human lung cancer (NSCLC) xenograft model is used. Athymic nude mice are injected subcutaneously (s.c.) with Calu 6 human tumour cells. Treatment begins after 7-10 days (in a particular experiment 13 days) when tumours are established (tumour volume 100-300mm^3, in a particular experiment = 200 mm^3). Groups of animals (n = 8 per group in a particular experiment but could be 10-12 per group) are randomized to receive a single treatment with cisplatin (4 mg/kg intraperitoneally (i.p.)) on day of randomization, or treatment with ZD6474 (25 - 75 mg/m^2 orally (p.o.) daily, or 6.25 - 25mg/kg p.o. daily, in a particular experiment 25mg/kg) for the duration of the experiment, or drug vehicles only. An additional group of animals (n = 8 in a particular experiment but could be 10-12) receives a combination of cisplatin and ZD6474, using the same doses and schedules as used for single agent treatment. On days where animals received both ZD6474 and cisplatin the cisplatin was administered 2 hours after oral dosing with ZD6474.

Animals in all groups are sacrificed when the control tumours reach approximately 2.0 cm^3 or alternatively on the basis of a certain number of doses of treatment received. Tumour size is assessed throughout the experiment by using caliper measurements. Antitumour effects are determined by comparing tumour growth in the drug-treated groups with tumour growth in the vehicle treated groups. Additionally, the effects of combination treatment are assessed by comparing tumour growth in the group of animals receiving cisplatin plus ZD6474 with the tumour growth in the groups where animals received single agent therapy alone.

Statistical significance was evaluated using a one-tailed two-sample t-test.

The results using cisplatin (4mg/kg) and ZD6474 (25mg/kg) are shown in Figure 1.

The growth of the tumours was inhibited significantly more by the combination of the two agents ZD6474 (25mg/kg) and cisplatin (4mg/kg) than by cisplatin alone. The effect of the combination was also greater than that of ZD6474 alone.

An analogous experiment may be used to look at the combination of ZD6474 and a platinum anti-tumour agent with ionising radiation.

CLAIMS

1. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

2. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

3. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

4. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

5. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

6. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

7. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is cisplatin.

8. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is carboplatin.

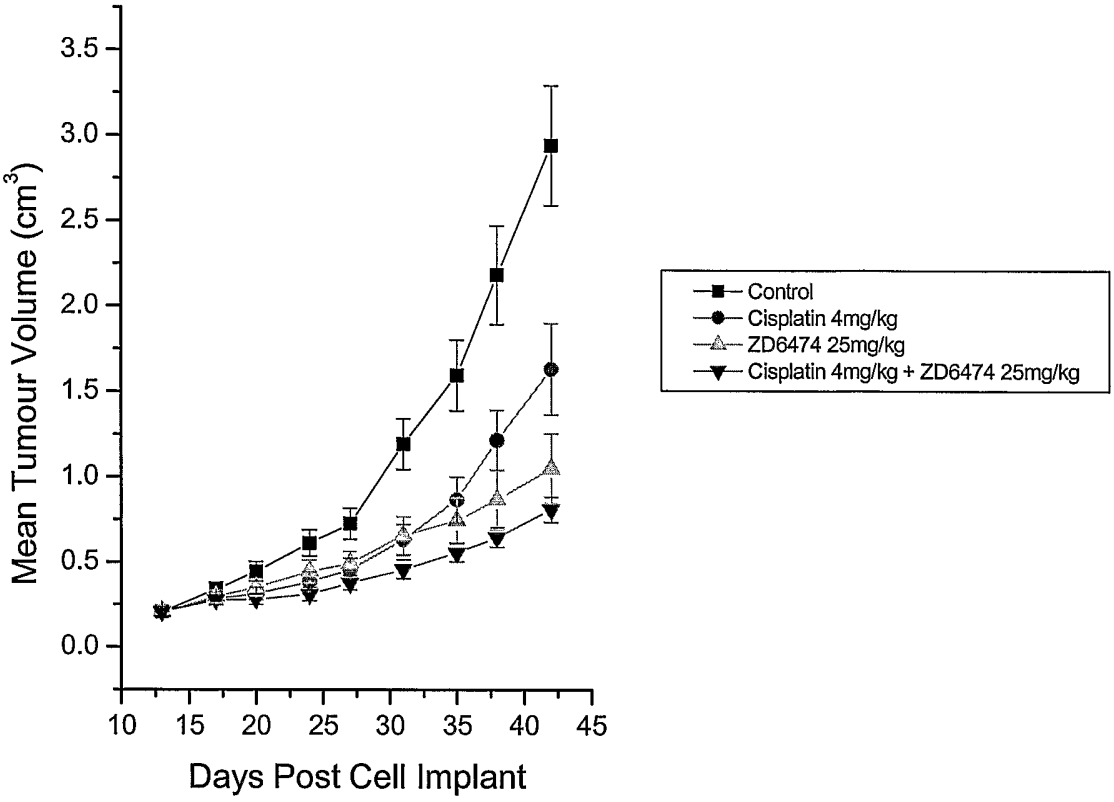
9. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is oxaliplatin.

10. A pharmaceutical composition which comprises ZD6474 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

11. A kit comprising ZD6474 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent.

12. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

13. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.



Cisplatin 4mg/kg vs Cisplatin 4mg/kg + ZD6474 25mg/kg	p=0.009
ZD6474 25mg/kg vs Cisplatin 4mg/kg + ZD6474 25mg/kg	p=0.147

Figure 1

INTERNATIONAL SEARCH REPORT

GB2004/002932

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/517 A61K31/282 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/32651 A (HENNEQUIN LAURENT FRANCOIS AND ; THOMAS ANDREW PETER (GB); ASTRAZENECA) 10 May 2001 (2001-05-10) claims 1-9,11-13 page 26, line 22 - line 30 page 27, line 24 - line 25	1-3,7-12
X	WO 98/13354 A (LOHMANN JEAN JACQUES MARCEL ; HENNEQUIN LAURENT FRANCOIS AND (FR); ZEN) 2 April 1998 (1998-04-02) claims 1-16 page 47, line 14 - line 15	1-3,7-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 2004	05/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Siatou, E

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GORSKI D H ET AL: "Blockade of the Vascular Endothelial Growth Factor Stress Response Increases the Antitumor Effects of Ionizing Radiation" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 59, 15 July 1999 (1999-07-15), pages 3374-3378, XP002256383 ISSN: 0008-5472 the whole document	4-6,13

INTERNATIONAL SEARCH REPORT

PCT/GB2004/002932

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

GB2004/002932

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132651 A	10-05-2001	AU 769222 B2	22-01-2004
		AU 1288601 A	14-05-2001
		BG 106659 A	31-03-2003
		BR 0015203 A	16-07-2002
		CA 2389767 A1	10-05-2001
		CN 1387527 T	25-12-2002
		CZ 20021526 A3	17-07-2002
		EE 200200237 A	16-06-2003
		EP 1244647 A1	02-10-2002
		WO 0132651 A1	10-05-2001
		HU 0203453 A2	28-05-2003
		JP 3522727 B2	26-04-2004
		JP 2003513089 T	08-04-2003
		NO 20022139 A	03-05-2002
		NZ 518028 A	26-03-2004
		PL 355942 A1	31-05-2004
		SK 6122002 A3	09-01-2003
		ZA 200202775 A	03-12-2003
WO 9813354 A	02-04-1998	AT 228114 T	15-12-2002
		AU 729968 B2	15-02-2001
		AU 4561397 A	17-04-1998
		BR 9711302 A	17-08-1999
		CA 2263319 A1	02-04-1998
		CN 1231662 A ,C	13-10-1999
		CZ 9901039 A3	16-06-1999
		DE 69717294 D1	02-01-2003
		DE 69717294 T2	04-09-2003
		DK 929530 T3	24-02-2003
		EP 0929530 A1	21-07-1999
		ES 2185999 T3	01-05-2003
		WO 9813354 A1	02-04-1998
		HK 1019332 A1	05-09-2003
		IL 129038 A	10-11-2002
		JP 3438818 B2	18-08-2003
		JP 2001500891 T	23-01-2001
		JP 2003238539 A	27-08-2003
		JP 2004002406 A	08-01-2004
		KR 2000048572 A	25-07-2000
		NO 991422 A	24-03-1999
		NZ 334014 A	27-10-2000
		PL 332385 A1	13-09-1999
		PT 929530 T	31-03-2003
		RU 2198879 C2	20-02-2003
		SI 929530 T1	30-04-2003
		SK 38999 A3	08-10-1999
		TR 9900674 T2	21-07-1999
		TW 520364 B	11-02-2003
		US 2002173646 A1	21-11-2002
		US 6414148 B1	02-07-2002
		ZA 9708553 A	25-03-1998
		HU 9902850 A2	28-04-2000