COMBINATION OF MOTESANIB, A TAXANE AND A PLATINUM-CONTAINING ANTI-CANCER DRUG FOR USE IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER IN A POPULATION SUBSET

FIELD

The present invention provides a method of improving survival associated with cancer in a unique subset of the general population. The invention provides a method of improving survival associated with cancer in patients of Asian ethnic/racial background. In addition, the present application relates to the treatment of angiogenesis related disease in an Asian patient with kinase inhibitors. In addition the present application relates to the treatment of non-small cell lung cancer in an Asian patient with motesanib.

BACKGROUND

Certain diseases are known to be associated with deregulated angiogenesis, for example ocular neovascularization, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases, for example, so-called solid tumors.

For instance, angiogenesis plays a crucial role in tumor progression. Nascent and small tumors can obtain sufficient oxygen and nutrients to sustain their growth by simple diffusion. Beyond a diameter of 1 to 2 mm, however, diffusion cannot provide these elements in the amounts required for further growth. For growth beyond that size, all tumors require a vasculature, whatever their cause, origin, type, age, or location. Thus, tumor growth beyond a diameter of 1 to 2 mm requires angiogenesis. Angiogenesis, accordingly, has been seen as a promising target for developing an effective general treatment for tumors.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: (i) inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved between cell death and proliferation; (ii) prevention of the migration of tumor cells owing to the absence of blood flow to and from tumors; and (iii) inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels. See Exp. Opin. Ther. Patents, 11:77-114 (2001).

Efforts to develop therapeutically effective inhibitors of angiogenesis have targeted all three of these principal mechanisms. As a result of these efforts, a variety of promising anti-angiogenic agents have been identified.

At the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth, and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as Vascular Endothelial Growth Factor" (VEGF; originally termed 'Vascular Permeability Factor", VPF), along with its cellular receptors (see Trends in Cell Biology, 6:454-456 (1996)).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein related to "Platelet-Derived Growth Factor" (PDGF); it is produced by normal cell lines and tumor cell lines; is an endothelial cell-specific mitogen; shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea); is chemotactic for endothelial cells and monocytes; and induces plasminogen activators in endothelial cells, which are involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placental Growth Factor" (PlGF) and VEGF-C.

VEGF receptors (VEGFR) are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, e.g. VEGFR-1 (also known as flt-1), VEGFR-2 (also known as KDR), and VEGFR-3.

Lung cancer is the most common cancer worldwide, responsible for about 18% of cancer deaths. Most patients present with advanced disease, and >80% have non–small-cell lung cancer (NSCLC). Among patients receiving a standard two-drug chemotherapy regimen as first-line treatment, median survival time is approximately 8 months.

The proangiogenic cytokine vascular endothelial growth factor (VEGF) and its receptors are important targets for NSCLC therapy. In the E4599 study, treatment with the anti-VEGF-A monoclonal antibody bevacizumab plus carboplatin/paclitaxel resulted in improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) compared with carboplatin/paclitaxel plus placebo among patients with stage IIIB or IV NSCLC of nonsquamous histology. Bevacizumab plus carboplatin/paclitaxel is the only antiangiogenic therapy currently approved in the United States for treatment of NSCLC. Addition of bevacizumab to cisplatin/gemcitabine has been shown to improve PFS in NSCLC but did not have a statistically significant effect on overall survival. Other antiangiogenic agents have failed to demonstrate improved clinical outcomes when combined with chemotherapy as first-line treatments for advanced disease.

Motesanib, an orally administered small-molecule antagonist of VEGF receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor and Kit, has shown promising antitumor activity in solid tumors as monotherapy and in combination with chemotherapy. A phase I, dose-finding study evaluated the safety, pharmacokinetics, and pharmacodynamics of AMG 706 in patients with refractory advanced solid tumors. Journal of Clinical Oncology (2007), 25(17), 2369-2376 In a phase 1b study in NSCLC, treatment with motesanib plus carboplatin/paclitaxel was tolerable at doses up to 125 mg once daily (QD), with pharmacokinetics supporting that dosing regimen as combination therapy. Clinical Cancer Research (2010), 16(1), 279-290.Purpose: This phase II study investigated the efficacy and tolerability of motesanib, an investigational, highly selective inhibitor of vascular endothelial growth factor receptors 1, 2, and 3; platelet-derived growth factor receptor; and Kit in advanced medullary thyroid cancer (MTC). Patients and Methods: Patients with locally advanced or metastatic, progressive or symptomatic MTC received motesanib 125 mg/d orally for up to 48 wk or until unacceptable toxicity or disease progression. New England Journal Medicine 2008 359:31-42. The results of an open label phase 2 study of motesanib in combination with paclitaxel and carboplatin for advanced nonsquamous non-smallcell lung cancer was reported at ASCO. Journal of Clinical Oncology, 28, 15s, 2010 (Abstract 7528). Results of a Phase II, multicenter, open-label randomized study of motesanib or bevacizumab in combination with paclitaxel and carboplatin for advanced nonsquamous non-small-cell lung cancer were reported in Annals of Oncology, 22, 2057-2067 (2011). A Phase 1 study investigated the safety and pharmacokinetics of motesanib (AMG 706), in Japanese patients with advanced solid tumors. Cancer Chemotherapy and Pharmacology (2010), 66(5), 935-943. A phase II clinical study assessed the efficacy and safety of single-agent motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate. Cancer Chemotherapy and Pharmacology (2010), 65(5), 961-967.

However, as the incidence of lung cancer is increasing in Asian countries, there is a need in the art for methods for new and more effective treatments for cancer in Asian patients.

DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the overall survival of the motesanib treated patients in the NSCLC Phase 3 study.

Fig. 2 shows the median progression-free survival for the full analysis set.

Fig. 3 shows the overall survival of the motesanib treated patients from Japan, Republic of Korea, Taiwan, China (Hong Kong), Philippines, and Singapore in the NSCLC Phase 3 study.

Fig. 4 shows the median progression-free survival for the Asian patient analysis subset.

Fig. 5 shows the overall survival of the motesanib treated non-Asian patient analysis subset in the NSCLC Phase 3 study.

Fig. 6 shows the median progression-free survival for the non-Asian patient analysis subset.

Fig. 7 shows the updated overall survival of the motesanib treated Japanese patient analysis subset in the NSCLC Phase 3 study.

Fig. 8 shows the updated median progression-free survival for the Japanese patient analysis subset.

Fig. 9 shows the updated median progression-free survival for the Asian patient analysis subset.

Fig. 10 shows the updated overall survival of the motesanib treated patients from Japan, Republic of Korea, Taiwan, China (Hong Kong), Philippines, and Singapore in the NSCLC Phase 3 study.

DESRIPTION OF THE INVENTION

In the present invention, the results of the MONET1 phase 3 clinical trial involving the overall survival of patients administered motesanib were reexamined and reevaluated for subset populations. The response of motesanib treatment with patients in Japan, Korea, Hong Kong, Singapore Taiwan and the Philippines provided unexpected survival benefits when compared to Non-Asian patients.

The present application relates to methods and kits for treatment of cancer in Asian patients.

The present application relates to the treatment of cancer in Asian patients with kinase inhibitors.

The invention also relates to treatment of neoplasia including cancer and metastasis, including, but not limited to lung cancer. The invention also relates to the treatment of non-small cell lung cancer. The invention also relates to the treatment of non-squamous non-small cell lung cancer. The invention also relates to treatment of adenocarcinoma.

The present application relates to a method of first line treatment of nonsquamous non-small cell lung cancer in an Asian patient comprising administering motesanib.

The present application relates to a method of improving survival associated with non squamous non-small cell lung cancer in an Asian patient comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

The present application relates to a method of increasing overall survival of an Asian patient diagnosed with non squamous non-small cell lung cancer comprising treating the Asian patient with a combination comprising motesanib and a taxane.

The present application relates to a method wherein the combination comprises a platinum-containing anti-cancer drug.

The present application relates to a method of increasing overall survival of an Asian patient diagnosed with non squamous non-small cell lung cancer comprising treating the Asian patient with a combination comprising motesanib, and a platinum-containing anti-cancer drug.

The present application relates to a method wherein the combination comprises a taxane.

The present application relates to a method wherein the motesanib is administered in combination with one or more chemotherapeutic agents.

The present application relates to a method wherein the chemotherapeutic agent is paclitaxel or carboplatin.

The present application relates to a method wherein the taxane is paclitaxel and the platinum-containing anti-cancer drug is carboplatin.

The present application relates to a method wherein the paclitaxel is administered at 200 mg/m^2 .

The present application relates to a method wherein the carboplatin is administered at a AUC 6 mg/mL•min.

The present application relates to a method wherein the non-small cell lung cancer is adenocarcinoma.

The present application relates to a method wherein the non-small cell lung cancer is nonsquamous.

The present application relates to a method wherein the treatment is first line treatment.

The present application relates to a method wherein the motesanib is administered at a daily dose of 100 mg or 125 mg.

The present application relates to a method wherein the motesanib is administered at a daily dose of 125 mg.

The present application relates to a method wherein the Asian patient is of Japan, Republic of Korea, Taiwan, China (Hong Kong), Philippines, or Singapore origin/ethnicity. This determination is similar to that described in a US census description. For further

clarification, such race/ethnicity determination would include someone with at least one parent of that race/ethnicity.

The present application relates to a method wherein the Asian patient is Japanese.

The present application relates to a method of increasing progression free survival associated with non squamous non-small cell lung cancer in an Asian patient comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

The present application relates to a method of increasing progression free survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

The present application relates to a method of increasing overall survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments as a medicament.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments in the manufacture of a medicament for the treatment of cancer.

Another aspect of the invention relates to the following 19 specific uses and corresponding methods:

1. A use of motesanib in the manufacture of a medicament for effectively increasing overall survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

2. The use of Claim 1 wherein the medicament increases overall survival when compared with treatment with paclitaxel and carboplatin.

3. The use of Claim 1 wherein the nonsquamous non-small cell lung cancer is advanced.

4. The use of Claim 1 wherein the nonsquamous non-small cell lung cancer is Stage IIIB, Stage IV or recurrent.

5. A use of motesanib in the manufacture of a medicament for effectively increasing progression free survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug

alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

6. The use of Claim 5 wherein the medicament increases progression free survival when compared with treatment with paclitaxel and carboplatin.

7. A use of motesanib in the manufacture of a medicament for effectively improving overall survival associated with nonsquamous non-small cell lung cancer in an Asian patient comprising treating the Asian patient with motesanib, a taxane and a platinum-containing anti-cancer drug.

8. The use of Claim 1 wherein the motesanib is administered in combination with one or more chemotherapeutic agents, provided the chemotherapeutic agent is not panitumumab.

9. The use of Claim 1 wherein the taxane is paclitaxel and the platinum-containing anti-cancer drug is carboplatin.

10. The use of 9 wherein the paclitaxel is administered at 200 mg/m^2 .

11. The use of 9 wherein the carboplatin is administered at a AUC 6 mg/mL•min.

12. The use of Claim 1, 5 or 7 wherein the nonsquamous non-small cell lung cancer is adenocarcinoma.

13. The use of Claim 1, 5 or 7 wherein the treatment is first line treatment.

14. The use of Claim 1, 5 or 7 wherein the motesanib is administered at a daily dose of 100 mg or 125 mg.

15. The use of Claim 1, 5 or 7 wherein the motesanib is administered at a daily dose of 125 mg.

16. The use of Claim 1, 5 or 7 wherein the Asian patient is of Japan, Republic of Korea, Taiwan, China, Hong Kong, Philippines, or Singapore ethnicity.

17. The use of Claim 1, 5 or 7 wherein the Asian patient is of Republic of Korea, Taiwan, China, Hong Kong, Philippines, or Singapore ethnicity.

18. The use of Claim 1, 5 or 7 wherein the Asian patient is Japanese.

19. A use of motesanib in the manufacture of a medicament for first line treatment of nonsquamous non-small cell lung cancer in a patient, wherein the patient is not of Non-Asian origin.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU, fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents which may be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group

consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-1, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α-carotene, α-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin

ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanlne derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim,

finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077

(Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

The taxanes are a group of drugs that includes paclitaxel (Taxol®) and docetaxel (Taxotere®).

A platinum-containing anti-cancer drug includes cisplatin (Platinol®, Bristol-Myers Squibb), carboplatin (Paraplatin®, Bristol-Myers Squibb), and oxaliplatin (Eloxatin®, Sanofi-Synthelabo).

Alternatively, motesanib is combined with pemetrexed and a platinum-containing anti-cancer drug.

Definitions

An "Asian patient" is a person having origins in any of the original peoples of the Far East, or Southeast Asia, including, for example, Cambodia, China, Japan, Korea, Malaysia, the Philippine Islands, Thailand, and Vietnam.

A "Caucasian patient" is a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

A "non-Asian patient" is a person having origins in any of the original peoples of North, Central, or South America and maintains tribal affiliation or community; a person having origins in any of the black racial groups of Africa; a person of Pacific Islander origin; or a person having origins in India.

A tyrosine kinase inhibitor is a small molecule inhibitor of a tyrosine kinase, including a VEGFR inhibitor.

A VEGFR inhibitor is a small molecule inhibitor of a VEGFR, including motesanib, and its pharmaceutically acceptable salts. Motesanib is also known as AMG706 and N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide.

The term "OS" is meant to include overall survival.

The term "PFS" is meant to include progression-free survival.

The term "PR" is defined as partial response.

The term "CR" is defined as complete response.

As used in relation to the invention, the term "treating" or "treatment" and the like should be taken broadly. They should not be taken to imply that an animal is treated to total recovery. Accordingly, these terms include amelioration of the symptoms or severity of a

particular condition or preventing or otherwise reducing the risk of further development of a particular condition.

The term "first line treatment" or "first line therapy" means that the patients have not previously received treatment for lung cancer, including chemotherapy.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

It should be appreciated that methods of the invention may be applicable to humans.

As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt and the like.

The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, thyroid cancer and head and neck cancer.

Lung cancer means non-small cell lung cancer, including nonsquamous non-small cell lung cancer and adenocarcinomas.

The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-

hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, aistidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of the invention. When a basic group and an acid group are present in the same molecule, a compound of the invention may also form internal salts.

FORMULATIONS

Also embraced within this invention is a class of pharmaceutical compositions comprising the active VEGFR inhibitors in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an

amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods. For example dosages from about 10 mg to about 150 mg, or about 25 to about 125 mg may be used. The therapeutically effective amount of VEGFR inhibitor in the composition can be chosen to be about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, or about 150 mg. The therapeutically effective amount of VEGFR inhibitor in the composition can be chosen to be about 50 mg dosed twice a day, or about 75 mg dosed twice a day, or about 100 mg dosed twice a day, or about 100 mg dosed once a day, or about 125 mg dosed once a day.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.01 and about 50 mg/kg, and more preferably about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable

carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

The invention will now be further described with reference to the following non-limiting examples.

Example 1 - NSCLC

Eligible patients (≥18 years) had histologically or cytologically confirmed advanced nonsquamous NSCLC (unresectable stage IIIB with malignant effusion or stage IV), Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), and life expectancy ≥3 months. Patients were excluded if they had central nervous system metastases; history of pulmonary hemorrhage or gross hemoptysis; bleeding diathesis or nonpulmonary bleeding within 6 months of randomization; uncontrolled hypertension (>150/90 mmHg); peripheral neuropathy grade >1; inadequate cardiac, hepatic, hematologic, or renal function; prior chemotherapy for advanced NSCLC or adjuvant chemotherapy within 52 weeks of randomization; prior targeted therapy; anticoagulant therapy within 7 days of randomization; prior chemoradiation for locally advanced stage III disease; central radiation therapy within 28 days of randomization; or other radiation therapy within 14 days of randomization. Study procedures were approved by the respective institutional ethics committee at each site. All patients provided written informed consent. This was a phase 3, international, multicenter, open-label, randomized study conducted at >200 centers.

The study evaluated whether motesanib plus carboplatin/paclitaxel improved overall survival (OS) compared with placebo and carboplatin/paclitaxel in patients with advanced nonsquamous NSCLC and in a subset of patients with adenocarcinoma. Patients had stage IIIB/IV or recurrent nonsquamous NSCLC and no prior systemic therapy for advanced NSCLC. The study initially enrolled all histologies but was amended to exclude patients with squamous NSCLC owing to a high rate of hemoptysis. Patients were randomized 1:1 to receive up to six 3-week cycles of carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2) with either motesanib 125 mg QD (Arm A) or placebo QD (Arm B) orally continuously. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), adverse events (AEs), and association between placental growth factor (PLGF) change and OS. OS was evaluated using a stratified Cox model and 2-sided log-rank test (α=0.03 for nonsquamous patients and α=0.02 for the adenocarcinoma subset). Demographics and baseline characteristics were balanced among the two groups (Table 1). One thousand ninety patients with advanced nonsquamous NSCLC were randomized (Arm A n=541; Arm B

n=549); 890 patients had adenocarcinoma (n=448/442). 61% were men; median age was 60 years (range 21–87); 83% had stage IV disease.

At the time of the analysis, 753 patients had died (608 patients with adenocarcinoma). Median follow-up was 10.6 mo. OS and PFS were not significantly improved in motesanib Arm A compared with placebo Arm B (**Table 2**). The incidence of grade ≥3 AEs in Arms A/B was 73/59%. Grade ≥3 AEs occurring more frequently in Arm A than B included neutropenia (22% vs 15%), diarrhea (9% vs 1%), hypertension (7% vs 1%), and cholecystitis (3% vs 0%). The incidence of grade 5 AEs was 14%/9% in Arms A/B.

Response was not significantly improved in motesanib Arm A compared with placebo Arm B (**Table 3**).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of survival based indicates an increase of overall survival. [**Figure 1**]. Cox Proportional Hazards - $P = 0.137$; Hazard Ratio = 0.897; (95% CI: 0.776, 1.035).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of progression free survival indicates an increase of progression free survival. [**Figure 2**] Cox Proportional Hazards - $P = 0.0006$; Hazard Ratio = 0.785; (95% CI: 0.684, 0.901).

In patients with advanced nonsquamous NSCLC, treatment with motesanib and carboplatin/paclitaxel did not significantly improve OS compared with carboplatin/paclitaxel alone.

Table 1 Baseline Demographics All Patients Full Analysis Set

	Placebo (N = 549)	Motesanib (N = 541)	All Subjects (N = 1090)
Sex – n (%)			
Female	213 (39)	207 (38)	420 (39)
Male	336 (61)	334 (62)	670 (61)
Race – n (%)			
White or Caucasian	353 (64)	362 (67)	715 (66)
Asian	97 (18)	84 (16)	181 (17)
Japanese	51 (9)	55 (10)	106 (10)
Hispanic or Latino	38 (7)	28 (5)	66 (6)
Age			
Mean	59.7	60.2	60.0
Median	60.0	60.0	60.0
CRF Histology n (%)			
Adenocarcinoma	442 (81)	448 (83)	890 (82)
Bronchoalveolar carcinoma	15 (3)	14 (3)	29 (3)
Large cell carcinoma	35 (6)	26 (5)	61 (6)
ECOG performance status - n (%)			
0	207 (38)	188 (35)	395 (36)
1	341 (62)	351 (65)	692 (63)
Disease stage - n (%)			
Stage IIIB	74 (13)	68 (13)	142 (13)
Stage IV	452 (82)	448 (83)	900 (83)
Recurrent	21 (4)	24 (4)	45 (4)
Brain metastasis - n (%)			
Yes	41 (7)	39 (7)	80 (7)
No	507 (92)	502 (93)	1009 (93)
Actual follow-up time (weeks)			
Mean	52.9	54.0	53.4
Median	45.0	48.0	46.0
Reason for End of Study			
Death	384 (70)	347 (64)	731 (67)
Consent withdrawn	38 (7)	41 (8)	79 (7)
Lost to follow-up	15 (3)	14 (3)	29 (3)

Table 2

	Arm A	Arm B	Hazard Ratio (95% CI)	*P*
Median OS, mo	13.0	11.0	0.897 (0.776–1.035)	0.137
Adenocarcinoma	13.5	11.0	0.878 (0.748–1.031)	0.113
Median PFS, mo	5.6	5.4	0.785 (0.684–0.901)	0.0006*
Adenocarcinoma	5.6	5.4	0.781 (0.670–0.911)	0.0016*

*Descriptive analysis

Table 3 Best Tumor Response for Subjects with Measurable Disease at Baseline per Modified RECIST per Investigator Non-Squamous Full Analysis Set

	Placebo (N = 549)	Motesanib (N = 541)
Subject with measurable disease at baseline	527 (96)	523 (97)
Subject with non-measurable disease at baseline	22 (4)	18 (3)
Response assessment - n (%)		
Confirmed complete response (CR)	2 (<1)	5 (<1)
Confirmed partial response (PR)	133 (25)	204 (39)
Stable disease (SD) [a]	265 (50)	207 (40)
Progressive disease (PD)	80 (15)	35 (7)
Unevaluable [b]	2 (<1)	5 (<1)
Not done	45 (9)	67 (13)
Confirmed objective response (CR or PR)	135 (26)	209 (40)
Difference in rate (95% CI) (Motesanib - Placebo) [c]		14.3 (8.7, 20.0)
P-value [d]		<0.0001

[a] Subjects with a response assessment of PR or CR that is not subsequently confirmed at least 4 weeks later are included as stable disease.

[b] Unevaluable includes subjects with a response assessment of CR, PR, or SD prior to the scheduled first assessment of response (35 days) without an additional assessment of response.

[c] 95% confidence interval (CI) for the difference in objective response calculated using the normal approximation to the binomial distribution.

[d] P-value based on Cochran-Mantel-Haenszel test stratified by the randomization stratification factors as recorded in the IVR system at time of randomization: stage (stage IIIB vs. stage IV or recurrent), weight loss (< 5% vs. 5% in the 6 months prior to randomization), sex (male vs. female) and prior adjuvant chemotherapy (yes vs. no).

The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous

histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.

EXAMPLE 2 – Efficacy results and baseline distributions for the Asian subgroup

The Asian subgroup (N=219) included patients from Japan, South Korea, Singapore, Philippine, Taiwan, and China (Hong Kong). Japan contributed 107 patients, and South Korea had 63 patients. Demographics and baseline characteristics were balanced among the two groups (Table 4).

Table 4 Baseline Demographics Asian Patients Only

	Placebo (N = 112)	Motesanib (N = 107)	All Subjects (N = 219)
Sex - n (%)			
Female	46 (41)	45 (42)	91 (42)
Male	66 (59)	62 (58)	128 (58)
Race - n (%)			
Asian excluding Japanese	61 (54)	52 (49)	113 (52)
Japanese	51 (46)	55 (51)	106 (48)
Age			
n	112	107	219
Mean	59.4	59.1	59.2
SD	9.8	10.0	9.9
Median	60.0	61.0	60.0
Q1, Q3	53.5, 66.0	54.0, 67.0	54.0, 66.0
Min, Max	30, 78	30, 77	30, 78

At the time of the analysis, 132 Asian patients had died. OS, PFS and Response were significantly improved in motesanib Arm A compared with placebo Arm B (**Tables 5-7**).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of survival based indicates an increase of overall survival. [**Figure 3**]. Medians were 20.9 months vs. 15.5 months for placebo. Cox Proportional Hazards - P = 0.017; Hazard Ratio = 0.657; (95% CI: 0.465, 0.929).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of progression free survival indicates an increase of progression free

survival. **[Figure 4]** Medians were 7 months vs. 4.5 months. Cox Proportional Hazards - P = 0.0003; Hazard Ratio = 0.58; (95% CI: 0.430, 0.782).

In the subset of Asian patients with advanced nonsquamous NSCLC, treatment with motesanib and carboplatin/paclitaxel significantly improved OS, PFS and Response compared with carboplatin/paclitaxel alone.

Table 5. Overall Survival Asian Patients Only

	Placebo (N = 112)	Motesanib (N = 107)
Censored [a] - n (%)	36 (32)	51 (48)
Deaths - n (%)	76 (68)	56 (52)
Overall survival [b] time (months)		
Median (K-M)	15.5	20.9
95% CI of median (K-M)	10.8, 19.3	15.4, 30.0
Q1, Q3 (K-M)	6.7, 31.6	11.0, NE
Min, Max	1.2, 35.1+	0.1, 35.0+
Kaplan-Meier estimate survival - % (95% CI)		
6 months	79 (70, 85)	93 (87, 97)
1 year	56 (47, 65)	73 (63, 80)
2 years	34 (24, 43)	45 (34, 55)
Hazard ratio (Motesanib/placebo) [c]		0.657
95% CI		(0.465, 0.929)
P-value based on the unadjusted log-rank test [d]		0.0166

[a] Subjects that have not been reported as dead are included as 'censored'.
[b] Overall survival time is calculated as the number of days from randomization to death or date of censoring.
[c] Hazard ratio estimated using an unadjusted Cox proportional hazards model.
[d] P-value is based on a 2-sided unadjusted log-rank test with no stratification factors.
The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.
K-M=Kaplan-Meier estimate; CI=Confidence Interval; + Indicates the value is a censoring time; NE=Not estimable

Table 6. Progression-Free Survival - Asian Patients

	Placebo (N = 112)	Motesanib (N = 107)
Censored [a] - n (%)	16 (14)	27 (25)
Subjects with events - n (%)	96 (86)	80 (75)
Disease Progression	88 (79)	73 (68)
Death, any cause	8 (7)	7 (7)
Progression-free survival [b] time (months)		
Median (K-M)	4.5	7.0
95% CI of median (K-M)	3.9, 5.7	5.8, 7.9
Q1, Q3 (K-M)	2.6, 7.0	4.2, 9.6
Min, Max	0.0+, 22.2	0.0+, 31.1+
Kaplan-Meier estimate progression-free survival - % (95% CI)		
3 months	65 (56, 74)	87 (79, 92)
6 months	35 (26, 45)	60 (50, 69)
9 months	16 (9, 24)	29 (19, 38)
1 year	8 (4, 15)	15 (9, 24)
Hazard ratio (Motesanib/placebo) [c]		0.580
95% CI		(0.430, 0.782)
P-value based on the unadjusted log-rank test [d]		0.0003

[a] Subjects who have not died and do not have an assessment of disease progression are 'censored'.

[b] Progression-free survival is calculated as the number of days from randomization to the date of radiological evidence of disease progression/death or date of censoring. Subjects who are alive without a response assessment of progressive disease are censored at the last disease assessment date. In the case where there are two or more missing tumor assessment followed by disease progression or death at the next assessment, censoring will be done at the last complete tumor date prior to missing assessments.

[c] Hazard ratio estimated using an unadjusted Cox proportional hazards model.

[d] P-value is based on a 2-sided unadjusted log-rank test with no stratification.

The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.

K-M = Kaplan-Meier estimate; CI=Confidence Interval; + Indicates the value is a censoring time.

Table 7 Best Tumor Response for Asian Patients with Measurable Disease at Baseline per Modified RECIST per Investigator

	Placebo (N = 112)	Motesanib (N = 107)
Subject with measurable disease at baseline	109 (97)	104 (97)
Subject with non-measurable disease at baseline	3 (3)	3 (3)
Response assessment - n (%)		
Confirmed complete response (CR)	0 (0)	1 (<1)
Confirmed partial response (PR)	29 (27)	64 (62)
Stable disease (SD) [a]	54 (50)	29 (28)
Progressive disease (PD)	18 (17)	2 (2)
Unevaluable [b]	1 (<1)	2 (2)
Not done	7 (6)	6 (6)
Confirmed objective response (CR or PR)	29 (27)	65 (63)
Difference in rate (95% CI) (Motesanib - Placebo) [c]		35.9 (23.4, 48.4)
P-value [d]		<0.0001

[a] Subjects with a response assessment of PR or CR that is not subsequently confirmed at least 4 weeks later are included as stable disease

[b] Unevaluable includes subjects with a response assessment of CR, PR, or SD prior to the scheduled first assessment of response (35 days) without an additional assessment of response.

[c] 95% confidence interval (CI) for the difference in objective response calculated using the normal approximation to the binomial distribution.

[d] P-value based on Cochran-Mantel-Haenszel test stratified by the randomization stratification factors as recorded in the IVR system at time of randomization: stage (stage IIIB vs. stage IV or recurrent), weight loss (< 5% vs. 5% in the 6 months prior to randomization), sex (male vs. female) and prior adjuvant chemotherapy (yes vs. no).

The number of subjects with measurable disease at baseline is used as the denominator for all response categories. The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.

EXAMPLE 3 – Efficacy results and baseline distributions for the non-Asian subgroup

The non-Asian subgroup (N=871) included patients not with ethnicity from Japan, Korea, Singapore, Philippine, Taiwan, and China (Hong Kong). At the time of the analysis,

621 non-Asian patients had died. OS, PFS and Response were improved in motesanib Arm A compared with placebo Arm B (**Tables 8-10**).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of survival based indicates an increase of overall survival. **[Figure 5]**. Medians were 10.9 months vs. 10.7 months for placebo. Cox Proportional Hazards - P = 0.774; Hazard Ratio = 0.977; (95% CI: 0.835, 1.144).

A Kaplan Meier Plot made with the fraction of patients surviving with treatment with motesanib and the days of progression free survival indicates an increase of progression free survival. **[Figure 6]** Medians were 5.5 months vs. 5.4 months. Cox Proportional Hazards - P = 0.03; Hazard Ratio = 0.847; (95% CI: 0.727, 0.987).

In non-Asian patients with advanced nonsquamous NSCLC, treatment with motesanib and carboplatin/paclitaxel did not significantly improve OS, PFS or Response compared with carboplatin/paclitaxel alone.

Table 8 Overall Survival for Non-Asian Patients

	Placebo (N = 437)	Motesanib (N = 434)
Censored [a] - n (%)	119 (27)	131 (30)
Deaths - n (%)	318 (73)	303 (70)
Overall survival [b] time (months)		
Median (K-M)	10.7	10.9
95% CI of median (K-M)	9.6, 11.9	9.2, 12.7
Q1, Q3 (K-M)	5.6, 20.6	5.2, 20.9
Min, Max	0.0+, 37.9+	0.1+, 40.7+
Kaplan-Meier estimate survival - % (95% CI)		
6 months	74 (69, 77)	71 (67, 75)
1 year	45 (40, 50)	47 (42, 52)
2 years	19 (15, 24)	21 (17, 26)
Hazard ratio (Motesanib/placebo) [c]		0.977
95% CI		(0.835, 1.144)
P-value based on the unadjusted log-rank test [d]		0.7740

[a] Subjects that have not been reported as dead are included as 'censored'.

[b] Overall survival time is calculated as the number of days from randomization to death or date of censoring.

[c] Hazard ratio estimated using an unadjusted Cox proportional hazards model.

[d] P-value is based on a 2-sided unadjusted log-rank test with no stratification factors.

The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.

K-M=Kaplan-Meier estimate; CI=Confidence Interval; + Indicates the value is a censoring time.

Table 9 Progression-Free Survival per Investigator
Non-Asian Patients

	Placebo (N = 437)	Motesanib (N = 434)
Censored [a] - n (%)	82 (19)	125 (29)
Subjects with events - n (%)	355 (81)	309 (71)
Disease Progression	296 (68)	227 (52)
Death, any cause	59 (14)	82 (19)
Progression-free survival [b] time (months)		
Median (K-M)	5.4	5.5
95% CI of median (K-M)	4.8, 5.6	4.8, 5.7
Q1, Q3 (K-M)	2.7, 7.0	2.9, 8.4
Min, Max	0.0+, 30.4+	0.0+, 35.9
Kaplan-Meier estimate progression-free survival - % (95% CI)		
3 months	70 (65, 74)	73 (69, 78)
6 months	36 (31, 41)	42 (37, 48)
9 months	16 (12, 20)	20 (16, 25)
1 year	8 (6, 12)	13 (10, 18)
Hazard ratio (Motesanib/placebo) [c]		0.847
95% CI		(0.727, 0.987)
P-value based on the unadjusted log-rank test [d]		0.0335

[a] Subjects who have not died and do not have an assessment of disease progression are 'censored'.

[b] Progression-free survival is calculated as the number of days from randomization to the date of radiological evidence of disease progression/death or date of censoring. Subjects who are alive without a response assessment of progressive disease are censored at the last disease assessment date. In the case where there are two or more missing tumor assessment followed by disease progression or death at the next assessment, censoring will be done at the last complete tumor date prior to missing assessments.

[c] Hazard ratio estimated using an unadjusted Cox proportional hazards model.

[d] P-value is based on a 2-sided unadjusted log-rank test with no stratification.

The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.

K-M = Kaplan-Meier estimate; CI=Confidence Interval; + Indicates the value is a censoring time.

Table 10 Best Tumor Response for Non-Asian Patients with Measurable Disease at Baseline per Modified RECIST per Investigator

	Placebo (N = 437)	Motesanib (N = 434)
Subject with measurable disease at baseline	418 (96)	419 (97)
Subject with non-measurable disease at baseline	19 (4)	15 (3)
Response assessment - n (%)		
Confirmed complete response (CR)	2 (<1)	4 (<1)
Confirmed partial response (PR)	104 (25)	140 (33)
Stable disease (SD) [a]	211 (50)	178 (42)
Progressive disease (PD)	62 (15)	33 (8)
Unevaluable [b]	1 (<1)	3 (<1)
Not done	38 (9)	61 (15)
Confirmed objective response (CR or PR)	106 (25)	144 (34)
Difference in rate (95% CI) (Motesanib - Placebo) [c]		9.0 (2.8, 15.2)
P-value [d]		0.0040

[a] Subjects with a response assessment of PR or CR that is not subsequently confirmed at least 4 weeks later are included as stable disease.

[b] Unevaluable includes subjects with a response assessment of CR, PR, or SD prior to the scheduled first assessment of response (35 days) without an additional assessment of response.

[c] 95% confidence interval (CI) for the difference in objective response calculated using,the normal approximation to the binomial distribution.

[d] P-value based on Cochran-Mantel-Haenszel test stratified by the randomization stratification factors as recorded in the IVR system at time of randomization: stage (stage IIIB vs. stage IV or recurrent), weight loss (< 5% vs. 5% in the 6 months prior to randomization), sex (male vs. female) and prior adjuvant chemotherapy (yes vs. no).

The number of subjects with measurable disease at baseline is used as the denominator for all response categories. The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received

Example 4 – Corrected clinical data

During subsequent review of the initial clinical data it was discovered that eight patients were incorrectly classified. All analysis were regenerated and the corrected outcomes are provided below and in Figures 7-10.

Table 11 Baseline Demographics Asian Patients Full Analysis Set

	Placebo (N = 117)	Motesanib (N = 110)	All Subjects (N = 227)
Sex - n (%)			
Female	49 (42)	47 (43)	96 (42)
Male	68 (58)	63 (57)	131 (58)
Race - n (%)			
Asian	66 (56)	55 (50)	121 (53)
Japanese	51 (44)	55 (50)	106 (47)
Age			
n	117	110	227
Mean	58.9	59.1	59.0
SD	9.9	10.0	9.9
Median	60.0	60.5	60.0
Q1, Q3	52.0, 65.0	54.0, 67.0	53.0, 66.0
Min, Max	30, 78	30, 77	30, 78

Table 12 Overall Survival Asian Patients Full Analysis Set

	Placebo (N = 117)	Motesanib (N = 110)
Censored [a] - n (%)	25 (21)	39 (35)
Deaths - n (%)	92 (79)	71 (65)
Overall survival [b] time (months)		
Median (K-M)	14.9	21.1
95% CI of median (K-M)	10.8, 18.9	15.4, 30.0
Q1, Q3 (K-M)	6.7, 28.6	11.0, 42.5
Min, Max	1.2, 43.1+	0.1, 44.5+
Kaplan-Meier estimate survival - % (95% CI)		
6 months	79 (71, 86)	93 (86, 96)
1 year	56 (47, 65)	72 (62, 79)
2 years	34 (26, 43)	46 (37, 55)
Hazard ratio (Motesanib/placebo) [c]		0.702
95% CI		(0.507, 0.970)
P-value based on the stratified log-rank test [d]		0.0314
Hazard ratio (Motesanib/placebo) [e]		0.674
95% CI		(0.494, 0.919)
P-value based on the unadjusted log-rank test [f]		0.0121

Table 13 Progression-Free Survival –Asian Patients Full Analysis Set

	Placebo (N = 117)	Motesanib (N = 110)
Censored [a] - n (%)	16 (14)	26 (24)
Subjects with events - n (%)	101 (86)	84 (76)
Disease Progression	93 (79)	77 (70)
Death, any cause	8 (7)	7 (6)
Progression-free survival [b] time (months)		
Median (K-M)	5.3	7.0
95% CI of median (K-M)	4.0, 5.7	5.8, 7.9
Q1, Q3 (K-M)	2.7, 7.0	4.2, 9.7
Min, Max	0.0+, 22.2	0.0+, 38.3+
Kaplan-Meier estimate progression-free survival - % (95% CI)		
3 months	67 (57, 75)	87 (79, 92)
6 months	36 (27, 45)	59 (49, 68)
9 months	17 (10, 25)	29 (20, 38)
1 year	8 (4, 14)	16 (9, 25)
Hazard ratio (Motesanib/placebo) [c]		0.577
95% CI		(0.423, 0.786)
P-value based on the stratified log-rank test [d]		0.0004
Hazard ratio (Motesanib/placebo) [e]		0.590
95% CI		(0.440, 0.790)
P-value based on the unadjusted log-rank test [f]		0.0003

Table 14 Comparison

Outcome	Previous – March 2011		Updated – December 2011	
	Motesanib (n=110)	Placebo (n=117)	Motesanib (n=110)	Placebo (n=117)
Overall Survival – Asia				
Median (mos)	*20.9*	*14.5*	*21.1*	*14.9*
Hazard Ratio (95% CI)	*0.669 (0.473, 0.946)*		*0.702 (0.507, 0.970)*	
P-value	*0.0223*		*0.0314*	
Overall Survival – Japan Only				
Median (mos)	*26.7*	*19.3*	*26.7*	*20.7*
Hazard Ratio (95% CI)	*0.707 (0.404, 1.237)*		*0.859 (0.541, 1.433)*	
P-value	*0.2219*		*0.5588*	

The ethnicity of the patients was based upon the location of the clinical sites. There might be more patients that are of Asian ethnicity in other countries (e.g. USA) but they are not captured in this analysis.

The unexpected finding is that Asian patients (as herein defined) responded more favorably than non-Asian patients to the treatment with motesanib. An ethnicity difference in the effect of motesanib on overall survival of cancer patients is confirmed with this study. No clear evidence of an ethnicity difference was observed with treatment with carboplatin/paclitaxel.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

What is claimed is:

1. A use of motesanib in the manufacture of a medicament for effectively increasing overall survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

2. The use of Claim 1 wherein the medicament increases overall survival when compared with treatment with paclitaxel and carboplatin.

3. The use of Claim 1 wherein the nonsquamous non-small cell lung cancer is advanced.

4. The use of Claim 1 wherein the nonsquamous non-small cell lung cancer is Stage IIIB, Stage IV or recurrent.

5. A use of motesanib in the manufacture of a medicament for effectively increasing progression free survival associated with nonsquamous non-small cell lung cancer in an Asian patient greater than that observed with a taxane and a platinum-containing anti-cancer drug alone, comprising treating the Asian patient with a combination of motesanib, a taxane and a platinum-containing anti-cancer drug.

6. The use of Claim 5 wherein the medicament increases progression free survival when compared with treatment with paclitaxel and carboplatin.

7. A use of motesanib in the manufacture of a medicament for effectively improving overall survival associated with nonsquamous non-small cell lung cancer in an Asian patient comprising treating the Asian patient with motesanib, a taxane and a platinum-containing anti-cancer drug.

8. The use of Claim 1 wherein the motesanib is administered in combination with one or more chemotherapeutic agents, provided the chemotherapeutic agent is not panitumumab.

9. The use of Claim 1 wherein the taxane is paclitaxel and the platinum-containing anti-cancer drug is carboplatin.

10. The use of 9 wherein the paclitaxel is administered at 200 mg/m^2 .

11. The use of 9 wherein the carboplatin is administered at a AUC 6 mg/mL•min.

12. The use of Claim 1, 5 or 7 wherein the nonsquamous non-small cell lung cancer is adenocarcinoma.

13. The use of Claim 1, 5 or 7 wherein the treatment is first line treatment.

14. The use of Claim 1, 5 or 7 wherein the motesanib is administered at a daily dose of 100 mg or 125 mg.

15. The use of Claim 1, 5 or 7 wherein the motesanib is administered at a daily dose of 125 mg.

16. The use of Claim 1, 5 or 7 wherein the Asian patient is of Japan, Republic of Korea, Taiwan, China, Hong Kong, Philippines, or Singapore ethnicity.

17. The use of Claim 1, 5 or 7 wherein the Asian patient is of Republic of Korea, Taiwan, China, Hong Kong, Philippines, or Singapore ethnicity.

18. The use of Claim 1, 5 or 7 wherein the Asian patient is Japanese.

19. A use of motesanib in the manufacture of a medicament for first line treatment of nonsquamous non-small cell lung cancer in a patient, wherein the patient is not of Non-Asian origin.