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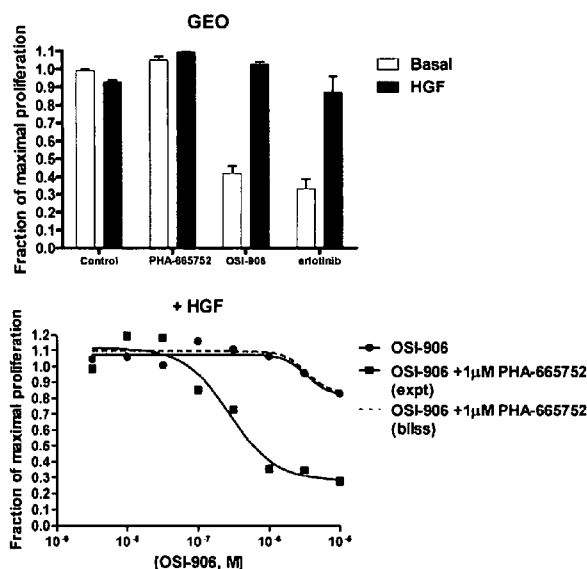
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[Continued on next page]

(54) Title: COMBINATION ANTI-CANCER THERAPY

Figure 3A



(57) Abstract: The present invention provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an inhibitor of MET kinase signaling (e.g. a small molecule MET kinase inhibitor, an anti-MET antibody, or an HGF binding protein) and an inhibitor of IGF-1R signaling (e.g. a small molecule IGF-1R kinase inhibitor (e.g. OSI-906), an anti-IGF-1R antibody, or one or more IGF binding proteins (e.g. IGFBP3)). The present invention also provides a pharmaceutical composition comprising a combination of an inhibitor of MET kinase signaling and an inhibitor of IGF-1R signaling, with a pharmaceutically acceptable carrier. The present invention also provides such methods or compositions where the inhibitory activities of MET kinase signaling and IGF-1R kinase signaling reside in the same molecule.

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TITLE OF THE INVENTION

COMBINATION ANTI-CANCER THERAPY**BACKGROUND OF THE INVENTION**

[1] The present invention is directed to compositions and methods for treating cancer patients. Cancer is a generic name for a wide range of cellular malignancies characterized by unregulated growth, lack of differentiation, and the ability to invade local tissues and metastasize. These neoplastic malignancies affect, with various degrees of prevalence, every tissue and organ in the body.

[2] A multitude of therapeutic agents have been developed over the past few decades for the treatment of various types of cancer. The most commonly used types of anticancer agents include: DNA-alkylating agents (e.g., cyclophosphamide, ifosfamide), antimetabolites (e.g., methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disrupters (e.g., vincristine, vinblastine, paclitaxel), DNA intercalators (e.g., doxorubicin, daunomycin, cisplatin), and hormone therapy (e.g., tamoxifen, flutamide). More recently, gene targeted therapies, such as protein-tyrosine kinase inhibitors (e.g. imatinib; the EGFR kinase inhibitor, erlotinib) have increasingly been used in cancer therapy.

[3] An anti-neoplastic drug would ideally kill cancer cells selectively, with a wide therapeutic index relative to its toxicity towards non-malignant cells. It would also retain its efficacy against malignant cells, even after prolonged exposure to the drug. Unfortunately, none of the current chemotherapies possess such an ideal profile. Instead, most possess very narrow therapeutic indexes. Furthermore, cancerous cells exposed to slightly sub-lethal concentrations of a chemotherapeutic agent will very often develop resistance to such an agent, and quite often cross-resistance to several other antineoplastic agents as well. Additionally, for any given cancer type one frequently cannot predict which patient is likely to respond to a particular treatment, even with newer gene-targeted therapies, such as EGFR kinase inhibitors, thus necessitating considerable trial and error, often at considerable risk and discomfort to

the patient, in order to find the most effective therapy.

[4] Thus, there is a need for more efficacious treatment for neoplasia and other proliferative disorders, and for more effective means for determining which tumors will respond to which treatment. Strategies for enhancing the therapeutic efficacy of existing drugs have involved changes in the schedule for their administration, and also their use in combination with other anticancer or biochemical modulating agents. Combination therapy is well known as a method that can result in greater efficacy and diminished side effects relative to the use of the therapeutically relevant dose of each agent alone. In some cases, the efficacy of the drug combination is additive (the efficacy of the combination is approximately equal to the sum of the effects of each drug alone), but in other cases the effect is synergistic (the efficacy of the combination is greater than the sum of the effects of each drug given alone).

[5] IGF-1R is a transmembrane RTK that binds primarily to IGF-1 but also to IGF-II and insulin with lower affinity. Binding of IGF-1 to its receptor results activation of receptor tyrosine kinase activity, intermolecular receptor autophosphorylation and phosphorylation of cellular substrates (major substrates are IRS1 and Shc). The ligand-activated IGF-1R induces mitogenic activity in normal cells and plays an important role in abnormal growth. A major physiological role of the IGF-1 system is the promotion of normal growth and regeneration. Overexpressed IGF-1R (type 1 insulin-like growth factor receptor) can initiate mitogenesis and promote ligand-dependent neoplastic transformation. Furthermore, IGF-1R plays an important role in the establishment and maintenance of the malignant phenotype. Unlike the epidermal growth factor (EGF) receptor, no mutant oncogenic forms of the IGF-1R have been identified. However, several oncogenes have been demonstrated to affect IGF-1 and IGF-1R expression. The correlation between a reduction of IGF-1R expression and resistance to transformation has been seen. Exposure of cells to the mRNA antisense to IGF-1R RNA prevents soft agar growth of several human tumor cell lines. IGF-1R abrogates progression into apoptosis, both *in vivo* and *in vitro*. It has also been shown that a decrease in the level of IGF-1R below wild-type levels causes apoptosis of tumor cells *in vivo*. The ability of IGF-1R disruption to cause apoptosis appears to be diminished in normal, non-tumorigenic cells.

[6] The IGF-1 pathway in human tumor development has an important role. IGF-1R overexpression is frequently found in various tumors (breast, colon, lung, sarcoma) and is often associated with an aggressive phenotype. High circulating IGF1 concentrations are strongly correlated with prostate, lung and breast cancer risk. Furthermore, IGF-1R is required for establishment and maintenance of the transformed phenotype *in vitro* and *in vivo* (Baserga R. *Exp. Cell. Res.*, 1999, 253, 1-6). The kinase activity of IGF-1R is essential for the transforming activity of several oncogenes: EGFR, PDGFR, SV40 T antigen, activated Ras, Raf, and v-Src. The expression of IGF-1R in normal fibroblasts induces neoplastic phenotypes. IGF-1R expression plays an important role in anchorage-independent growth. IGF-1R has also been shown to protect cells from chemotherapy-, radiation-, and cytokine-induced apoptosis. Conversely, inhibition of endogenous IGF-1R by dominant negative IGF-1R, triple helix formation or antisense expression vector has been shown to repress transforming activity *in vitro* and tumor growth in animal models.

[7] It has been recognized that inhibitors of protein-tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, Gleevec™ (also known as imatinib mesylate), a 2-phenylpyrimidine tyrosine kinase inhibitor that inhibits the kinase activity of the BCR-ABL fusion gene product, has been approved by the U.S. Food and Drug Administration for the treatment of CML. The 4-anilinoquinazoline compound Tarceva™ (erlotinib HCl) has also been recently approved by the FDA, and selectively inhibits EGF receptor kinase with high potency. The development for use as anti-tumor agents of compounds that directly inhibit the kinase activity of IGF-1R, as well as antibodies that reduce IGF-1R kinase activity by blocking IGF-1R activation or antisense oligonucleotides that block IGF-1R expression, are areas of intense research effort (e.g. see Larsson, O. et al (2005) *Brit. J. Cancer* 92:2097-2101; Ibrahim, Y.H. and Yee, D. (2005) *Clin. Cancer Res.* 11:944s-950s; Mitsiades, C.S. et al. (2004) *Cancer Cell* 5:221-230; Camirand, A. et al. (2005) *Breast Cancer Research* 7:R570-R579 (DOI 10.1186/bcr1028); Camirand, A. and Pollak, M. (2004) *Brit. J. Cancer* 90:1825-1829; Garcia-Echeverria, C. et al. (2004) *Cancer Cell* 5:231-239).

[8] Human IGFBP-3 is expressed in multiple tissues (e.g. liver) as a 291 amino acid precursor protein with a putative 27 amino acid signal peptide that is processed to

generate a 264 amino acid mature protein with three potential N-linked and two potential O-linked glycosylation sites. Human IGFBP-3 is the major IGF binding protein in plasma where it exists in a ternary complex with IGF-I or IGF-II and the acid-labile subunit (Jones, J.I. and D.R. Clemmons (1995), *Endocrine Rev.* 16:3; Kelley, K.M. et al., 1996, *Int. J. Biochem. Cell Biol.* 28:619; Spagnoli, A. and R.G. Rosenfeld (1997) *Curr. Op. Endocrinology and Diabetes* 4:1).

[9] MET (i.e. c-Met) was first discovered in the 1980s as an activated oncogene (Cooper, C. S. et al. (1984). *Nature* 311, 29-33) and is the prototype member of a sub-family of RTKs, including Ron, that are structurally distinct from other RTK families. MET is the only known high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor (Birchmeier, C. et al. (2003). *Nat Rev Mol Cell Biol* 4, 915-925). In vitro and in vivo experiments have shown that this receptor-growth factor pair is involved in multiple physiologic cellular responses including embryogenesis, cell proliferation, survival, differentiation, motility, and invasion (Birchmeier, C. et al. (2003). *Nat Rev Mol Cell Biol* 4, 915-925). Subsequently, HGF and/or MET have been found to be frequently over-expressed in many types of human solid tumors. The various cancers in which MET overexpression is implicated include sarcomas and carcinomas, and their associated metastases, where the degree of MET expression often correlates with poor patient prognosis (Birchmeier, C. et al. (2003). *Nat Rev Mol Cell Biol* 4, 915-925). Such cancers include, but are not limited to, gastric adenocarcinoma, renal cancer, small cell lung carcinoma, colorectal cancer, prostate cancer, brain cancer, liver cancer, pancreatic cancer, and breast cancer.

[10] Activating MET mutations have been described in both sporadic and inherited forms of human renal papillary carcinomas (Danilkovitch-Miagkova, A., and Zbar, B. (2002). *J Clin Invest* 109, 863-867), while genomic amplification of met has been found associated with gastric carcinoma (Nakajima, M. et al. *Cancer* 85, 1894-1902). Ectopic HGF and/or MET overexpression can drive tumorigenesis and metastasis in both human xenograft tumor bearing mice and transgenic mouse models (Takayama, H. et al. (1997). *Proc Natl Acad Sci USA* 94, 701-706). Taken together, these data provide compelling evidence for the functional relevance of MET activated networks in tumorigenesis and metastatic progression, thus MET is an attractive cancer therapeutic target.

[11] Hepatocyte growth factor (HGF), also known as scatter factor, is a paracrine cellular growth, motility and morphogenic factor. It is secreted by mesenchymal cells and acts on epithelial cells, endothelial cells, and haemopoietic progenitor cells. It plays a major role in embryonic organ development, adult organ regeneration, and wound healing. It also promotes transformation, tumor development and metastasis by stimulating mitogenesis, cell motility and invasion via various signaling pathways. In order to produce cellular effects, HGF must bind to the MET receptor (i.e. MET), a receptor tyrosine kinase. This is a widely expressed heterodimeric protein comprising a 50 kilodalton (kDa) α -subunit and 145 kDa subunit β -subunit (Maggiore et al., J. Cell Physiol., 173:183-186, 1997). The MET receptor is initially produced as a single-chain precursor, that is proteolytically cleaved at a furin site to yield the highly glycosylated extracellular α -subunit and the transmembrane β -subunit, which are linked together by a disulfide bridge.

[12] EGFR, MET, IGF-1R, and IR are each sufficient for oncogenic transformation *in vitro* and *in vivo* (1-9). Inhibitors targeting each of these RTKs individually have shown efficacy in a wide range of preclinical models, and this has spurred their evaluation as anti-tumor therapeutics in the clinic (2, 4, 10-12). Antibody or small molecule inhibitors of EGFR are clinically approved for the treatment of a number of tumor types including NSCLC (erlotinib), SCCHN (cetuximab), CRC (cetuximab / panitumumab), and pancreatic cancer (erlotinib) (13-16). Drug candidates targeting IGF-1R, IR, and MET are currently in advanced clinical development (17).

[13] Over the past several years there has been a growing appreciation for the plasticity that can exist between RTK signaling nodes. Acquired resistance to agents targeting an individual RTK may be associated with increased activity of an alternate RTK, manifesting in compensatory adaptation to maintain cellular proliferation and survival. Compensatory crosstalk may occur within an RTK family. For example, there is evidence for bidirectional crosstalk between IGF-1R and IR, where blockade of either receptor is associated with a compensatory increase in activity through the reciprocal receptor (18). Compensatory crosstalk can also extend between different RTK families. NSCLC tumor cells harboring primary activating mutations in EGFR exhibit elevated sensitivity to the EGFR tyrosine kinase inhibitors erlotinib and

gefitinib, however, acquired resistance following prolonged exposure to an EGFR TKI can be associated with increased dependence on MET (19-22). This mode of resistance to EGFR inhibitors is especially prominent for tumors exhibiting genetic amplification of the MET loci (23, 24). In tumors expressing wild-type (WT) EGFR, IGF-1R/IR signaling can confer acquired resistance, where prolonged exposure to agents targeting either EGFR or IGF-1R/IR may be associated with an increased dependence on signaling through the reciprocal receptor (25, 26). For a number of tumor types, including NSCLC, dependence on either EGFR or IGF-1R/IR appears to be greater in epithelial tumor cell lines compared to those that have undergone an epithelial-mesenchymal-transition (EMT), and crosstalk between EGFR and IGF-1R/IR is commonly observed in tumor cells with an epithelial EMT status (25, 27-29). In preclinical models the combination of an EGFR inhibitor with either an IGF-1R/IR or MET inhibitor achieves a synergistic inhibition of cell proliferation and survival as well as increased anti-tumor efficacy *in vivo*. Currently, the combination of EGFR inhibitors with either IGF-1R/IR or MET inhibitors is being evaluated in clinical trials. The results from a recently reported phase 2 study showed significantly prolonged progression free survival for advanced, 2nd line, NSCLC patients treated with the combination of EGFR and MET TKIs compared to those who received erlotinib alone, and this combination is being further evaluated in advanced clinical development (30).

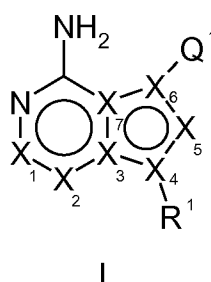
[14] Although crosstalk between the EGF axis and either the IGF or HGF axis has been described, the potential for compensatory crosstalk between the IGF and HGF axes has thus far not been reported. The data described herein demonstrates that such crosstalk exists in tumor cells, and has lead to the invention described herein that provides new anti-cancer combination therapies that utilize a combination of an IGF-1R kinase inhibitor with a MET kinase inhibitor, that unexpectedly has been found to act together synergistically to inhibit cancer cell growth. Preferred IGF-1R kinase inhibitors for use such combinations include a new class of relatively specific, orally-available, small-molecule IGF-1R kinase inhibitors that also inhibit IR kinase (e.g. OSI-906, (a.k.a. linsitinib)), or alternatively, small-molecule IGF-1R kinase inhibitors that also inhibit MET kinase may be used, thus precluding the need for a separate MET kinase inhibitor.

SUMMARY OF THE INVENTION

[15] The present invention provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of a MET kinase inhibitor and an IGF-1R kinase inhibitor. The IGF-1R kinase inhibitor may be a small-molecule IGF-1R kinase inhibitor, such as those of Formula (I) (e.g. OSI-906), an anti-IGF-1R antibody or antibody fragment, or one or more IGF binding proteins that antagonizes activation of IGF-1R. Alternatively, the combined IGF-1R kinase and MET kinase inhibitory activities may reside in the same molecule, e.g. a small-molecule IGF-1R kinase inhibitor that also has inhibitory activity on MET kinase (i.e. a dual IGF-1R kinase/MET kinase inhibitor), thus precluding the need for a separate MET kinase inhibitor.

[16] In any of the methods, compositions or kits of the invention described herein, the IGF-1R kinase inhibitor of Formula (I) can be any IGF-1R kinase inhibitor compound encompassed by Formula (I) that inhibits IGF-1R kinase upon administration to a patient. Specific examples of such inhibitors have been published in US Published Patent Application US 2006/0235031, which is incorporated herein in its entirety, and includes OSI-906 as used in the experiments described herein.

[17] An IGF-1R kinase inhibitor of Formula (I) is represented by the formula:



[18] or a pharmaceutically acceptable salt thereof, wherein:

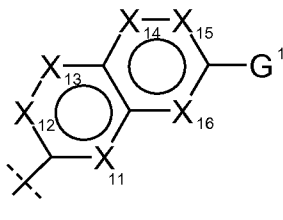
[19] X_1 , and X_2 are each independently N or $C-(E^1)_{aa}$;

[20] X_5 is N, $C-(E^1)_{aa}$, or $N-(E^1)_{aa}$;

[21] X_3 , X_4 , X_6 , and X_7 are each independently N or C;

[22] wherein at least one of X_3 , X_4 , X_5 , X_6 , and X_7 is independently N or $N-(E^1)_{aa}$;

[23] Q^1 is



[24] X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , and X_{16} are each independently N, $C-(E^{11})_{bb}$, or N^+-O^- ; wherein at least one of X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , and X_{16} is N or N^+-O^- ;

[25] R^1 is absent, C_{0-10} alkyl, cyclo C_{3-10} alkyl, bicyclo C_{5-10} alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo C_{5-10} alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

[26] E^1 , E^{11} , G^1 , and G^{41} are each independently halo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{2a})_{j1}$, $-C(=O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, $-CN$, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $-NR^2C(=O)R^3$, $-NR^2C(=O)OR^3$, $-NR^2C(=O)NR^3R^{2a}$, $-NR^2S(O)_{j1}R^3$, $-C(=S)OR^2$, $-C(=O)SR^2$, $-NR^2C(=NR^3)NR^{2a}R^{3a}$, $-NR^2C(=NR^3)OR^{2a}$, $-NR^2C(=NR^3)SR^{2a}$, $-OC(=O)OR^2$, $-OC(=O)NR^2R^3$, $-OC(=O)SR^2$, $-SC(=O)OR^2$, $-SC(=O)NR^2R^3$, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{222a})_{j1a}$, $-C(=O)R^{222}$, $-CO_2R^{222}$, $-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(=O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j1a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents;

[27] or E^1 , E^{11} , or G^1 optionally is $-(W^1)_n-(Y^1)_m-R^4$;

[28] or E^{11} , E^{11} , G^1 , or G^{41} optionally independently is aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{222a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j2a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents;

[29] G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, $-NO_2$, $-CN$, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}C(=O)OR^{31}$, $NR^{21}C(=O)NR^{31}R^{2a1}$, $NR^{21}S(O)_{j4}R^{31}$, $-C(=S)OR^{21}$, $-C(=O)SR^{21}$, $-NR^{21}C(=NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}C(=NR^{31})OR^{2a1}$, $-NR^{21}C(=NR^{31})SR^{2a1}$, $-OC(=O)OR^{21}$, $-OC(=O)NR^{21}R^{31}$, $-OC(=O)SR^{21}$, $-SC(=O)OR^{21}$, $-SC(=O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{1-10} alkylidene, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j4a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

[30] or G^{11} is aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$,

$-\text{NR}^{2221}\text{C}(=\text{O})\text{NR}^{3331}\text{R}^{222a1}$, $-\text{NR}^{2221}\text{S}(\text{O})_{j5a}\text{R}^{3331}$, $-\text{C}(=\text{S})\text{OR}^{2221}$, $-\text{C}(=\text{O})\text{SR}^{2221}$,
 $-\text{NR}^{2221}\text{C}(=\text{NR}^{3331})\text{NR}^{222a1}\text{R}^{333a1}$, $-\text{NR}^{2221}\text{C}(=\text{NR}^{3331})\text{OR}^{222a1}$,
 $-\text{NR}^{2221}\text{C}(=\text{NR}^{3331})\text{SR}^{222a1}$, $-\text{OC}(=\text{O})\text{OR}^{2221}$, $-\text{OC}(=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $-\text{OC}(=\text{O})\text{SR}^{2221}$,
 $-\text{SC}(=\text{O})\text{OR}^{2221}$, $-\text{P}(\text{O})\text{OR}^{2221}\text{OR}^{3331}$, or $-\text{SC}(=\text{O})\text{NR}^{2221}\text{R}^{3331}$ substituents;

[31] or G^{11} is C, taken together with the carbon to which it is attached forms a $\text{C}=\text{C}$ double bond which is substituted with R^5 and G^{111} ;

[32] R^2 , R^{2a} , R^3 , R^{3a} , R^{222} , R^{222a} , R^{333} , R^{333a} , R^{21} , R^{2a1} , R^{31} , R^{3a1} , R^{2221} , R^{222a1} , R^{3331} , and R^{333a1} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, heterocyclyl- C_{2-10} alkynyl, aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, or aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted by one or more independent G^{111} substituents;

[33] or in the case of $-\text{NR}^2\text{R}^3(\text{R}^{2a})_{j1}$ or $-\text{NR}^{222}\text{R}^{333}(\text{R}^{222a})_{j1a}$ or $-\text{NR}^{222}\text{R}^{333}(\text{R}^{222a})_{j2a}$ or $-\text{NR}^{21}\text{R}^{31}(\text{R}^{2a1})_{j4}$ or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{222a1})_{j4a}$ or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{222a1})_{j5a}$, then R^2 and R^3 , or R^{222} and R^{333} , or R^{2221} and R^{3331} , respectfully, are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted by one or more independent G^{111} substituents and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^2 and R^3 , or R^{222} and R^{333} , or R^{2221} and R^{3331} are attached;

[34] W^1 and Y^1 are each independently $-\text{O}-$, $-\text{NR}^7-$, $-\text{S}(\text{O})_{j7}-$, $-\text{CR}^5\text{R}^6-$, $-\text{N}(\text{C}(\text{O})\text{OR}^7)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{NR}^7)-$, $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{OR}^7)-$, $-\text{CH}_2\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}(\text{NHR}^7)-$, $-\text{CH}(\text{NHC}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{NHSO}_2\text{R}^7)-$, $-\text{CH}(\text{NHC}(\text{O})\text{OR}^7)-$, $-\text{CH}(\text{OC}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{OC}(\text{O})\text{NHR}^7)-$, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(=\text{NOR}^7)-$, $-\text{C}(\text{O})-$, $-\text{CH}(\text{OR}^7)-$, $-\text{C}(\text{O})\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^8)-$, $-\text{NR}^7\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})\text{N}(\text{R}^7)-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^8)-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^8)-$, $-\text{C}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$,

$-\text{S}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{OS}(\text{O})\text{N}(\text{R}^7)-$, $-\text{OS}(\text{O})_2\text{N}(\text{R}^7)-$,
 $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{O}-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{C}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{C}(\text{O})-$,
 $-\text{SON}(\text{C}(\text{O})\text{R}^7)-$, $-\text{SO}_2\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{SON}(\text{R}^8)-$, $-\text{N}(\text{R}^7)\text{SO}_2\text{N}(\text{R}^8)-$, $-\text{C}(\text{O})\text{O}-$,
 $-\text{N}(\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{N}(\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$, $-\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)-$,
 $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$,
 $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{OR}^8)-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{SO}_2\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{O}-$, $-\text{CH}(\text{R}^7)\text{S}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{SO}_2\text{R}^8)-$,
 $-\text{CH}(\text{R}^7)\text{C}(=\text{NOR}^8)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{CH}(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^8)-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})_2-$,
 $-\text{CH}(\text{R}^7)\text{OC}(\text{O})\text{N}(\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{7a})-$, $-\text{CH}(\text{R}^7)\text{NR}^8\text{C}(\text{O})\text{O}-$,
 $-\text{CH}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{S}(\text{O})-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})\text{N}(\text{R}^{7a})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})_2\text{N}(\text{R}^{7a})-$,
 $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^8)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^8)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^8)\text{C}(\text{O})-$,
 $-\text{CH}(\text{R}^7)\text{OS}(\text{O})\text{N}(\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{OS}(\text{O})_2\text{N}(\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})\text{O}-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})_2\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{S}(\text{O})_2\text{C}(\text{O})-$,
 $-\text{CH}(\text{R}^7)\text{SON}(\text{C}(\text{O})\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{SO}_2\text{N}(\text{C}(\text{O})\text{R}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{SON}(\text{R}^{7a})-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{SO}_2\text{N}(\text{R}^{7a})-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{P}(\text{OR}^{7a})\text{O}-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{P}(\text{OR}^{7a})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{P}(\text{O})(\text{OR}^{7a})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^8)\text{P}(\text{O})(\text{OR}^{7a})-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{O})(\text{OR}^{7a})\text{O}-$, or $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})-$;

[35] R^5 , R^6 , G^{111} , and G^{1111} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, heterocyclyl- C_{2-10} alkynyl, aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{77}$, $-\text{NR}^{77}\text{R}^{87}$, $-\text{C}(\text{O})\text{R}^{77}$, $-\text{CO}_2\text{R}^{77}$, $-\text{CONR}^{77}\text{R}^{87}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j5a}\text{R}^{77}$, $-\text{SO}_2\text{NR}^{77}\text{R}^{87}$, $-\text{NR}^{77}\text{C}(=\text{O})\text{R}^{87}$, $-\text{NR}^{77}\text{C}(=\text{O})\text{OR}^{87}$, $-\text{NR}^{77}\text{C}(=\text{O})\text{NR}^{78}\text{R}^{87}$, $-\text{NR}^{77}\text{S}(\text{O})_{j5a}\text{R}^{87}$,

$-\text{C}(=\text{S})\text{OR}^{77}$, $-\text{C}(=\text{O})\text{SR}^{77}$, $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{NR}^{78}\text{R}^{88}$, $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{OR}^{78}$,
 $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{SR}^{78}$, $-\text{OC}(=\text{O})\text{OR}^{77}$, $-\text{OC}(=\text{O})\text{NR}^{77}\text{R}^{87}$, $-\text{OC}(=\text{O})\text{SR}^{77}$,
 $-\text{SC}(=\text{O})\text{OR}^{77}$, $-\text{P}(\text{O})\text{OR}^{77}\text{OR}^{87}$, or $-\text{SC}(=\text{O})\text{NR}^{77}\text{R}^{87}$ substituents;

[36] or R^5 with R^6 are optionally taken together with the carbon atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent R^{69} substituents and wherein said ring optionally includes one or more heteroatoms;

[37] R^7 , R^{7a} , and R^8 are each independently acyl, C_{0-10} alkyl, C_{2-10} alkenyl, aryl, heteroaryl, heterocyclyl or cyclo C_{3-10} alkyl, any of which is optionally substituted by one or more independent G^{111} substituents;

[38] R^4 is C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, cyclo C_{3-10} alkyl, heterocyclyl, cyclo C_{3-8} alkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more independent G^{41} substituents;

[39] R^{69} is halo, $-\text{OR}^{78}$, $-\text{SH}$, $-\text{NR}^{78}\text{R}^{88}$, $-\text{CO}_2\text{R}^{78}$, $-\text{C}(=\text{O})\text{NR}^{78}\text{R}^{88}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_j\text{R}^{78}$, $-\text{SO}_2\text{NR}^{78}\text{R}^{88}$, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-\text{OR}^{778}$, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$ substituents;

[40] or R^{69} is aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, hetaryl- C_{2-10} alkynyl, mono(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono(aryl)amino C_{1-6} alkyl, di(aryl)amino C_{1-6} alkyl, or $-\text{N}(\text{C}_{1-6}\text{alkyl})-\text{C}_{1-6}\text{alkyl}-\text{aryl}$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-\text{OR}^{778}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-\text{COOH}$, C_{1-4} alkoxycarbonyl, $-\text{C}(=\text{O})\text{NR}^{778}\text{R}^{888}$, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$ substituents;

[41] or in the case of $-\text{NR}^{78}\text{R}^{88}$, R^{78} and R^{88} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10} alkoxy, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$

substituents, and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R⁷⁸ and R⁸⁸ are attached;

[42] R⁷⁷, R⁷⁸, R⁸⁷, R⁸⁸, R⁷⁷⁸, and R⁸⁸⁸ are each independently C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, heterocyclyl-C₂₋₁₀alkynyl, C₁₋₁₀alkylcarbonyl, C₂₋₁₀alkenylcarbonyl, C₂₋₁₀alkynylcarbonyl, C₁₋₁₀alkoxycarbonyl, C₁₋₁₀alkoxycarbonylC₁₋₁₀alkyl, monoC₁₋₆alkylaminocarbonyl, diC₁₋₆alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C₁₋₁₀alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C₁₋₁₀alkoxy, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents;

[43] or R⁷⁷, R⁷⁸, R⁸⁷, R⁸⁸, R⁷⁷⁸, and R⁸⁸⁸ are each independently aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, aryl-C₂₋₁₀alkynyl, hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, hetaryl-C₂₋₁₀alkynyl, mono(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, mono(aryl)aminoC₁₋₆alkyl, di(aryl)aminoC₁₋₆alkyl, or -N(C₁₋₆alkyl)-C₁₋₆alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C₀₋₄alkyl), C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CON(C₀₋₄alkyl)(C₀₋₁₀alkyl), -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents;

[44] n, m, j1, j1a, j2a, j4, j4a, j5a, j7, and j8 are each independently 0, 1, or 2; and aa and bb are each independently 0 or 1.

[45] The present invention also provides a pharmaceutical composition comprising an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)), in a pharmaceutically acceptable carrier.

[46] The present invention also provides a kit comprising one or more containers, comprising an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)), and an MET kinase inhibitor.

[47] The present invention also provides a pharmaceutical composition comprising a MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)), in a pharmaceutically acceptable carrier.

[48] The present invention also provides a kit comprising one or more containers, comprising a MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)).

[49] In any of the methods of treatment of the invention described herein the patient may be a patient in need of treatment for cancer. In embodiments of any of the methods of treatment of the invention described herein, the cells of the tumors or tumor metastases may be relatively insensitive or refractory to treatment with one of the anti-cancer agents (i.e. the MET kinase inhibitor or the IGF-1R kinase inhibitor) as a single agent.

BRIEF DESCRIPTION OF THE FIGURES

[50] **Figure 1. Coordinated expression and phosphorylation of receptors within the EGF, HGF, and IGF axes.** A. Heat map showing correlative expression of mRNAs for 18 RTKs within a human tumor database comprised of NSCLC, CRC, SCCHN, and OvCa tumors (left panel). Heat map showing co-correlative expression of mRNA for IR, MET, and EGFR within the human tumor database, anchored on INSR expression (right panel). Pearson correlation coefficients which reached significance are shown. B. RTK arrays for a select group of human tumor cell lines showing the phosphorylation pattern for EGFR, MET, IR, and IGF-1R (left panel). Within a group of 35 tumor cell lines, seven exhibit concurrent expression of phospho-EGFR, phospho-IGF-1R/IR, and phospho-MET and are all sensitive to OSI-906 (right panel).

[51] **Figure 2. Either EGF or HGF can rescue phospho-AKT/PRAS40, proliferation, and survival in tumor cells treated with OSI-906, alone or in combination with erlotinib.** A. Effect of OSI-906 (1 μ M), erlotinib (1 μ M), or the combination of OSI-906 and erlotinib on phospho-AKT/PRAS40 under either basal (10% FCS), EGF(50ng/ml), or HGF(100ng/ml) conditions. B. Effect of varying concentrations of OSI-906 on cellular proliferation under basal conditions or in the

presence of HGF (left panel). Effect of varying concentrations of OSI-906, alone or in combination with 1 μ M erlotinib, on caspase 3/7 activity under basal or HGF-treated conditions. Proliferation data were captured 72 hours after dosing, and caspase 3/7 activity was captured 48 hours after dosing.

[52] **Figure 3. The combination of a MET TKI and OSI-906, but not an IGF-1R specific antibody, results in synergistic inhibition of cell proliferation and AKT signaling.** A. Effect of PHA (1 μ M), OSI-906 (1 μ M), or erlotinib (1 μ M) on cell proliferation for GEO tumor cells under basal or HGF-treated conditions (top panel). Effect of varying concentrations of OSI-906, alone or in the presence of PHA, on cell proliferation for GEO tumor cells cultured in the presence of HGF (bottom panel). B. Effect of OSI-906, MAB391 (3 μ g/ml), PHA, and OSI-906 or MAB391 in combination with PHA on phospho-AKT/PRAS40, and phospho-ERK for GEO tumor cells under basal or HGF-treated conditions. C. Effect of PHA, OSI-906 (+/- PHA), erlotinib (+/- PHA) or the combination of OSI-906, erlotinib, and PHA on phospho-AKT/PRAS40, and phospho-ERK for GEO tumor cells under basal or HGF-treated conditions. D. HGF protein expression in media derived from GEO tumor cells or MRC5 or WI38 lung fibroblasts (left panel). Effect of OSI-906, PHA, or OSI-906 + PHA on phospho-AKT/PRAS40 and phospho-ERK for GEO tumor cells under basal conditions or upon treatment with conditioned media derived from MRC-5 or WI38 cells. Cells were treated with kinase inhibitors (1 μ M) for 2 hours prior to HGF treatment.

[53] **Figure 4. Bi-directional crosstalk between IGF-1R/IR and either EGFR or MET.** A. Effect of 2hr and 24hr treatment with OSI-906 on phospho-ATK/PRAS40 for GEO and MDA-1186 cells (upper panel). Effect of 24hour OSI-906 treatment on the phosphorylation of IR, IGF-1R, EGFR, and MET (bottom panel). B. Effect of OSI-906, PHA, and OSI-906 + PHA on IP:p85/IB:IR, phospho-MET, and phospho-RTK array profile for GEO tumor cells. Cells were treated with 1 μ M each kinase inhibitor for 24 hours.

Figure 5. Knockdown of MET is associated with increased sensitivity to erlotinib, OSI-906, and the combination of erlotinib and OSI-906. A. Effect of OSI-906, erlotinib, OSI-906 + erlotinib, or MAB391 on IP:p85/IB: IR, IP:p85/IB:p85, and

phospho-MET for control EV or MET KD GEO cells. Cells were treated with kinase inhibitors (1 μ M) for 24 hours prior to harvest. B. Effect of varying concentrations of erlotinib (top panel) or OSI-906 (bottom panel) on induction of caspase 3/7 activity for EV control or MET KD GEO cells. C. Effect of varying concentrations of OSI-906, alone or in combination with erlotinib, on cellular proliferation (top panel) and caspase 3/7 activity (bottom panel) for EV control and MET KD cells. D. Effect of OSI-906, erlotinib, OSI-906 + erlotinib, and MAB391 on MET, IR, and phospho-AKT expression in control EV or MET KD GEO cells. Quantitation of effect of treatments on phospho-AKT is shown.

[54] **Figure 6. Cartoon outlining hypotheses for crosstalk between the IGF, EGF, and HGF axes.**

[55] **Figure 7. Summary of 35 tumor cell lines, highlighting EMT status as epithelial (E) or mesenchymal (M), erlotinib and OSI-906 sensitivity (EC₅₀, μ M), and level of phosphorylation of EGFR, IR, IGF-1R, and MET.** Phosphorylation is highlighted when detected for a given tumor cell line. Also shown is the mutation status for KRAS, BRAF, PIK3CA, and PTEN as described by the Sanger Institute.

[56] **Figure 8. Neither FGF1/2 or PDGF α treatment is sufficient to rescue activation of AKT pathway signaling in GEO tumor cells treated with OSI-906 or erlotinib.** Effect of OSI-906, erlotinib, or the combination of OSI-906 and erlotinib on pAKT-S473 and pPRAS40 in GEO cells cultured under basal growing conditions or treated with FGF1/2 or PDGF α for 5 minutes prior to harvesting and analysis of phospho-proteins.

[57] **Figure 9. Treatment with OSI-906 results in enhanced phosphorylation of EGFR, ErbB3, and MET in GEO tumor cells.** Effect of OSI-906 treatment on phosphorylation for a panel of 42 RTKs in GEO tumor cells. RTK phosphorylation was assessed using the RTK array (ARY001) (R&D Systems).

[58] **Figure 10: Knockdown of MET using shRNA in GEO tumor cells is associated with a 91% reduction in mRNA expression and loss of detectable MET phosphorylation.**

[59] **Figure 11. Knockdown of MET expression using shRNA in GEO tumor cells is not associated with a significant change in overall proliferation, assessed over a period of 48 hours using the Cell Titer Glo assay (Promega).**

DETAILED DESCRIPTION OF THE INVENTION

[60] The term "cancer" in an animal refers to the presence of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, and certain characteristic morphological features. Often, cancer cells will be in the form of a tumor, but such cells may exist alone within an animal, or may circulate in the blood stream as independent cells, such as leukemic cells.

[61] "Cell growth", as used herein, for example in the context of "tumor cell growth", unless otherwise indicated, is used as commonly used in oncology, where the term is principally associated with growth in cell numbers, which occurs by means of cell reproduction (i.e. proliferation) when the rate of the latter is greater than the rate of cell death (e.g. by apoptosis or necrosis), to produce an increase in the size of a population of cells, although a small component of that growth may in certain circumstances be due also to an increase in cell size or cytoplasmic volume of individual cells. An agent that inhibits cell growth can thus do so by either inhibiting proliferation or stimulating cell death, or both, such that the equilibrium between these two opposing processes is altered.

[62] "Tumor growth" or "tumor metastases growth", as used herein, unless otherwise indicated, is used as commonly used in oncology, where the term is principally associated with an increased mass or volume of the tumor or tumor metastases, primarily as a result of tumor cell growth.

[63] "Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or over-expression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (4) any tumors that proliferate by receptor tyrosine kinases; (5) any tumors that proliferate by aberrant serine/threonine kinase activation; and (6) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

[64] The term "treating" as used herein, unless otherwise indicated, means to give medical aid to counteract a disease or condition. The phrase "a method of treating" or its equivalent, when applied to cancer refers to a procedure or course of action that is designed to reduce or eliminate the number of cancer cells in a patient, or to alleviate the symptoms of a cancer. "A method of treating" cancer or another proliferative disorder does not necessarily mean that the cancer cells or other disorder will, in fact, be eliminated, that the number of cells or disorder will, in fact, be reduced, or that the symptoms of a cancer or other disorder will, in fact, be alleviated. Often, a method of treating cancer will be performed even with a low likelihood of success, but which, given the medical history and estimated survival expectancy of a patient, is nevertheless deemed an overall beneficial course of action.

[65] The term "therapeutically effective agent" means a composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[66] The term "therapeutically effective amount" or "effective amount" means the amount of the subject compound or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[67] The terms "responsive" or "responsiveness" when used herein in referring to a patient's reaction to administration of an IGF-1R kinase inhibitor, refers to a response that is positive or effective, from which the patient is likely to benefit.

[68] The term “method for manufacturing a medicament” or “use of for manufacturing a medicament” relates to the manufacturing of a medicament for use in the indication as specified herein, and in particular for use in tumors, tumor metastases, or cancer in general.

[69] The term “antibody molecule” as used herein refers to a protein of the immunoglobulin (Ig) superfamily that binds noncovalently to certain substances (e.g. antigens and immunogens) to form an antibody – antigen complex, including but not limited to antibodies produced by hybridoma cell lines, by immunization to elicit a polyclonal antibody response, by chemical synthesis, and by recombinant host cells that have been transformed with an expression vector that encodes the antibody. In humans, the immunoglobulin antibodies are classified as IgA, IgD, IgE, IgG, and IgM and members of each class are said to have the same isotype. Human IgA and IgG isotypes are further subdivided into subtypes IgA₁, and IgA₂, and IgG₁, IgG₂, IgG₃, and IgG₄. Mice have generally the same isotypes as humans, but the IgG isotype is subdivided into IgG₁, IgG_{2a}, IgG_{2b}, and IgG₃ subtypes. Thus, it will be understood that the term “antibody molecule” as used herein includes within its scope (a) any of the various classes or sub-classes of immunoglobulin, e.g., IgG, IgM, IgE derived from any of the animals conventionally used and (b) polyclonal and monoclonal antibodies, such as murine, chimeric, or humanized antibodies. Antibody molecules have regions of amino acid sequences that can act as an antigenic determinant, e.g. the Fc region, the kappa light chain, the lambda light chain, the hinge region, etc. An antibody that is generated against a selected region is designated anti-[region], e.g. anti-Fc, anti-kappa light chain, anti-lambda light chain, etc. An antibody is typically generated against an antigen by immunizing an organism with a macromolecule to initiate lymphocyte activation to express the immunoglobulin protein. The term antibody molecule, as used herein, also covers any polypeptide or protein having a binding domain that is, or is homologous to, an antibody binding domain, including, without limitation, single-chain Fv molecules (scFv), wherein a VH domain and a VL domain are linked by a peptide linker that allows the two domains to associate to form an antigen binding site (Bird et al., Science 242, 423 (1988) and Huston et al., Proc. Natl. Acad. Sci. USA 85, 5879 (1988)). These

can be derived from natural sources, or they may be partly or wholly synthetically produced.

[70] The term “antibody fragments” as used herein refers to fragments of antibody molecules that retain the principal selective binding characteristics of the whole antibody molecule. Particular fragments are well-known in the art, for example, Fab, Fab', and F(ab')₂, which are obtained by digestion with various proteases and which lack the Fc fragment of an intact antibody or the so-called "half-molecule" fragments obtained by reductive cleavage of the disulfide bonds connecting the heavy chain components in the intact antibody. Such fragments also include isolated fragments consisting of the light-chain-variable region, "Fv" fragments consisting of the variable regions of the heavy and light chains, and recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker. Other examples of binding fragments include (i) the Fd fragment, consisting of the VH and CH1 domains; (ii) the dAb fragment (Ward, et al., *Nature* 341, 544 (1989)), which consists of a VH domain; (iii) isolated CDR regions; and (iv) single-chain Fv molecules (scFv) described above. In addition, arbitrary fragments can be made using recombinant technology that retains antigen-recognition characteristics.

[71] The data presented in the Examples herein below demonstrate that in tumor cells the inhibition of both IGF-1R signaling and MET receptor signaling will lead to a greater anti-proliferative effect than inhibition of just one of these pathways. Thus combination therapies that utilize combinations of IGF-1R kinase inhibitors with MET kinase inhibitors will be more effective than either agent as single agent treatments, and unexpectedly such agents in combination have also been found to act together synergistically to inhibit tumor cell growth. Inhibitors of IGF-1R kinase may be small molecule IGF-1R kinase inhibitors, anti-IGF-1R antibodies, or agents that antagonize activation of IGF-1R, such as IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody). Similarly, inhibitors of MET kinase may be small molecule MET kinase inhibitors, anti-MET antibodies, or agents that antagonize activation of MET receptor, such as HGF binding proteins (e.g. an anti-HGF antibody). Preferred small molecule IGF-1R kinase inhibitors for use in these combinations are a new class of relatively specific, orally-available, small-molecule compounds as described, for example, in US Published Patent Application US 2006/0235031, such as

the compound OSI-906, a molecule that also has inhibitory activity on IR kinase. Another preferred molecule is a small molecule kinase inhibitor that inhibits both IGF-1R kinase and MET kinase, and preferably also IR kinase, e.g. BMS754807 (see Carboni, J.M. et al. (2009) Mol Cancer Ther 8(12):3341-3349, including Supplemental Figures and Tables). The latter compound demonstrates that it is possible to design kinase inhibitors that have dual specificity for IGF-1R kinase and MET kinase.

[72] Thus the anti-tumor effects of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) with an MET kinase inhibitor, are superior to the anti-tumor effects of either agent by itself, and co-administration of these agents can be effective for treatment of patients with advanced cancers such as NSCL, pancreatic, head and neck, colon, ovarian and breast cancers. This combination was found to produce a synergistic effect in inhibiting the growth of tumor cells, apparently at least in part by the MET kinase inhibitor increasing the potency of the IGF-1R kinase inhibitor to inhibit tumor cell growth.

[73] Accordingly, the present invention provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of a MET kinase inhibitor (e.g. a small molecule MET kinase inhibitor or an anti-MET antibody) and an IGF-1R kinase inhibitor (e.g. a small molecule IGF-1R kinase inhibitor such as that of Formula (I) described herein (e.g. OSI-906); or an anti-IGF-1R antibody). The MET kinase inhibitor and the IGF-1R kinase inhibitor may be activities associated with separate molecules, or they may reside in the same molecule. The present invention also provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor. In one embodiment of any of these methods the patient is a human that is in need of treatment for cancer. In different embodiments, the combination of two inhibitors are co-administered to the patient in the same formulation; are co-administered to the patient in different formulations; are co-administered to the patient by the same route; or are

co-administered to the patient by different routes. In another embodiment one or more other anti-cancer agents can additionally be administered to said patient.

[74] Reference to an "antibody" in the methods, compositions or kits of this invention optionally includes "antibody molecules", "antibody fragments", or mixtures of such antibody molecules or fragments. In any of the methods, compositions or kits of the invention described herein, an "anti-IGF-1R antibody" includes any anti-IGF-1R antibody or antibody fragment that can partially or completely block IGF-1R activation by its natural ligands IGF-1 and IGF-2. Non-limiting examples of antibody-based IGF-1R kinase inhibitors include those described in Larsson, O. et al (2005) Brit. J. Cancer 92:2097-2101 and Ibrahim, Y.H. and Yee, D. (2005) Clin. Cancer Res. 11:944s-950s; or being developed by Imclone (e.g. IMC-A12), or AMG-479, an anti-IGF-1R antibody (Amgen); R1507, an anti-IGF-1R antibody (Genmab/Roche); AVE-1642, an anti-IGF-1R antibody (Immunogen/Sanofi-Aventis); CP-751871 (Pfizer Inc.); anti-IGF-1R antibodies disclosed in US Patent Nos. 7,037,487 or 7,371,378, or US Published Patent Application No. US 2004/0202651; MK 0646, an anti-IGF-1R antibody (Merck); or h7C10 (Centre de Recherche Pierre Fabre); EM-164 (ImmunoGen Inc.), an IGF-1R modulator; or antibodies being developed by Schering-Plough Research Institute (e.g. SCH 717454 or 19D12; or as described in US Patent Application Publication Nos. US 2005/0136063 A1 and US 2004/0018191 A1). Additional examples include IGF-1R neutralizing antibodies that are in pre-clinical (e.g. h10H5, Genentech) or clinical (e.g. CP-751,871, Pfizer; IMC-A12, Imclone; MK0646, Merck; AMG479, Amgen; SCH717454, Schering; R1507, Roche; AVE-1642, Aventis; and BIIB022, Biogen) development (see Rodon et al. (2008) Mol. Cancer Ther. 7(9): 2575-2588). Thus, the IGF-1R kinase inhibitor of this invention can be a monoclonal antibody, or an antibody or antibody fragment having the binding specificity thereof. In a preferred example the anti-IGF-1R antibody is a humanized monoclonal antibody.

[75] In any of the methods, compositions or kits of the invention described herein, an "IGF binding protein" includes any protein that binds to IGF-1 and/or IGF-2 and can partially or completely block IGF-1R activation by these ligands. Non-limiting examples of such IGF binding proteins include insulin-like growth factor binding proteins (Rajaram S, et al. (1998) "Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions." *Endocr. Rev.* 18(6): 801-31;

Ferry RJ, et al. (1999) "Insulin-like growth factor binding proteins: new proteins, new functions." *Horm. Res.* 51(2): 53–67), or protein fragments or fusion proteins comprising an IGF-binding domain from such proteins; IGFBP3 (insulin-like growth factor binding protein 3; GeneID: 3486; GenBank Database Accession numbers of precursor protein isoforms a and b, NP_001013416, NP_000589), an IGF-binding fragment thereof, or a protein comprising such a fragment, including recombinant fusion proteins comprising an IGF-binding fragment of IGFBP3; an IGFBP3 protein comprising amino acid residues 2-265 of SEQ ID No. 1 herein below; a recombinant human IGFBP3 (rhIGFBP3) being developed by Insmed Inc. (Richmond, VA) as a means to block the IGF-1R axis (see reference 26 below); an IGFBP-3 fusion protein (e.g. see US Patent 7,192,738); IGFBP1 (insulin-like growth factor binding protein 1; GeneID: 3484; GenBank Database Accession number of precursor protein, NP_000587); IGFBP2 (insulin-like growth factor binding protein 2; GeneID: 3485; GenBank Database Accession number of precursor protein, NP_000588); IGFBP4 (insulin-like growth factor binding protein 4; GeneID: 3487; GenBank Database Accession number of precursor protein, NP_001543); IGFBP5 (insulin-like growth factor binding protein 5; GeneID: 3488; GenBank Database Accession number of precursor protein, NP_000590); IGFBP6 (insulin-like growth factor binding protein 6; GeneID: 3489; GenBank Database Accession number of precursor protein, NP_002169); IGFBP7 (insulin-like growth factor binding protein 7; GeneID: 3490; GenBank Database Accession number of precursor protein, NP_001544); or an anti-IGF-1 or anti-IGF-2 antibody or antibody fragment that can partially or completely block IGF-1R activation by IGF-1 and/or IGF-2 (e.g. MEDI-573; or see Miyamoto, S. et al. (2005) *Clinical Cancer Research* 11:3494-3502; anti-IGF2 antibodies in development by Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan); and soluble extracellular domains of IGF-1R that can bind to and partially or completely block IGF-1R activation by IGF-1 and/or IGF-2. Human versions of the above binding proteins are preferred. In an alternative embodiment of any of the methods, compositions or kits of the instant invention the "IGF binding protein" may be replaced by an "IGF binding aptamer" that can partially or completely block IGF-1R activation by IGF-1 and/or IGF-2.

[76] Additional examples of IGF binding proteins that may be used in the instant invention include those described in: U.S. Pat. No. 6,417,330, WO 99/63086, and U.S.

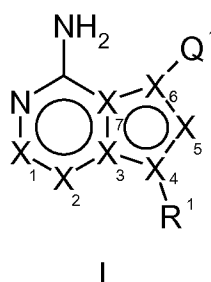
application No. 2002/0072589, that disclose IGFBP-3 variants modified to be resistant to hydrolysis, and variant IGFBP-3s where the nuclear localization signal (NLS) in native IGFBP-3 is altered; McCaig et al., Br. J. Cancer, 86: 1963 1969 (2002), and Perks et al., Biochim. Biophys. Res. Comm. 294: 988 994 (2002), that disclose peptides derived from the mid-region of IGFBP-3 that were found to be active on breast cancer cells; WO 02/098914, that discloses IGF binding polypeptides consisting of the amino acids 39-91 of IGFBP-1, the amino acids 55-107 of IGFBP-2, the amino acids 47-99 of IGFBP-3, the amino acids 39-91 of IGFBP4, the amino acids 40-92 of IGFBP-5, or the amino acids 40-92 of IGFBP-6, fragments thereof, and IGFBP mutants with enhanced binding affinity for IGF-I and/or IGF-II; WO 00/23469, that discloses IGFBP fragments that account for IGF-IGFBP binding, and provides an isolated IGF binding domain of an IGFBP or modifications thereof, which binds IGF with at least about the same binding affinity as the full-length IGFBP, including isolated IGF binding domains of IGFBP1, IGFBP3, IGFBP4, IGFBP5, and IGFBP6; and WO 99/32620, that discloses IGFBP fragments and utilization thereof, including for IGFBP-3.

[77] The NCBI GeneID numbers listed herein are unique identifiers of the gene from the NCBI Entrez Gene database record (National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine, 8600 Rockville Pike, Building 38A, Bethesda, MD 20894; Internet address www.ncbi.nlm.nih.gov). IGF binding proteins expressed by genes thus identified represent proteins that may be used in the methods of this invention, and the sequences of these proteins, including different isoforms, as disclosed in NCBI database records are herein incorporated by reference.

[78] In any of the methods, compositions or kits of the invention described herein, the term “small molecule inhibitor” (e.g. “small molecule IGF-1R kinase inhibitor,” “small molecule MET kinase inhibitor”) refers to a low molecular weight (i.e. less than 5000 Daltons; preferably less than 1000, and more preferably between 300 and 700 Daltons) organic compound that inhibits a target protein, e.g. IGF-1R kinase or MET kinase, by for example binding to the kinase domain of the enzyme. Examples of such compounds include IGF-1R kinase inhibitors of Formula (I) as described herein. The IGF-1R kinase inhibitor of Formula (I) can be any IGF-1R kinase inhibitor compound encompassed by Formula (I) that inhibits IGF-1R kinase upon administration to a patient. Examples of such inhibitors have been published in US Published Patent

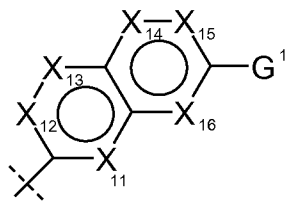
Application US 2006/0235031, which is incorporated herein in its entirety, and include OSI-906 (*cis*-3-[8-amino-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-*a*]pyrazin-3-yl]-1-methyl-cyclobutanol), as used in the experiments described herein.

[79] An IGF-1R kinase inhibitor of Formula (I) is represented by the formula:



or a pharmaceutically acceptable salt thereof, wherein:

X_1 , and X_2 are each independently N or C-(E^1)_{aa}; X_5 is N, C-(E^1)_{aa}, or N-(E^1)_{aa};
 X_3 , X_4 , X_6 , and X_7 are each independently N or C; wherein at least one of X_3 , X_4 , X_5 , X_6 , and X_7 is independently N or N-(E^1)_{aa};
 Q^1 is



X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , and X_{16} are each independently N, C-(E^{11})_{bb}, or N⁺-O⁻;
 wherein at least one of X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , and X_{16} is N or N⁺-O⁻;
 R^1 is absent, C₀₋₁₀alkyl, cycloC₃₋₁₀alkyl, bicycloC₅₋₁₀alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicycloC₅₋₁₀alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G¹¹ substituents;
 E^1 , E^{11} , G^1 , and G^{41} are each independently halo, -CF₃, -OCF₃, -OR², -NR²R³(R^{2a})_{j1}, -C(=O)R², -CO₂R², -CONR²R³, -NO₂, -CN, -S(O)_{j1}R², -SO₂NR²R³, -NR²C(=O)R³, -NR²C(=O)OR³, -NR²C(=O)NR³R^{2a}, -NR²S(O)_{j1}R³, -C(=S)OR², -C(=O)SR², -NR²C(=NR³)NR^{2a}R^{3a}, -NR²C(=NR³)OR^{2a}, -NR²C(=NR³)SR^{2a}, -OC(=O)OR², -OC(=O)NR²R³, -OC(=O)SR², -SC(=O)OR², -SC(=O)NR²R³, C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋

$_{10}$ alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{222a})_{j1a}$, $-C(=O)R^{222}$, $-CO_2R^{222}$, $-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(=O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j1a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents;

or E^1 , E^{11} , or G^1 optionally is $-(W^1)_n-(Y^1)_m-R^4$;

or E^1 , E^{11} , G^1 , or G^{41} optionally independently is aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{222a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j2a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, $-NO_2$, $-CN$, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}C(=O)R^{31}$, $NR^{21}C(=O)OR^{31}$, $NR^{21}C(=O)NR^{31}R^{2a1}$, $NR^{21}S(O)_{j4}R^{31}$, $-C(=S)OR^{21}$, $-C(=O)SR^{21}$, $-NR^{21}C(=NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}C(=NR^{31})OR^{2a1}$, $-NR^{21}C(=NR^{31})SR^{2a1}$, $-OC(=O)OR^{21}$, $-OC(=O)NR^{21}R^{31}$, $-OC(=O)SR^{21}$, $-SC(=O)OR^{21}$, $-SC(=O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{1-10} alkylidene, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl,

heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, oxo, -CF₃, -OCF₃, -OR²²²¹, -NR²²²¹R³³³¹(R^{222a1})_{j4a}, -C(O)R²²²¹, -CO₂R²²²¹, -C(=O)NR²²²¹R³³³¹, -NO₂, -CN, -S(O)_{j4a}R²²²¹, -SO₂NR²²²¹R³³³¹, -NR²²²¹C(=O)R³³³¹, -NR²²²¹C(=O)OR³³³¹, -NR²²²¹C(=O)NR³³³¹R^{222a1}, -NR²²²¹S(O)_{j4a}R³³³¹, -C(=S)OR²²²¹, -C(=O)SR²²²¹, -NR²²²¹C(=NR³³³¹)NR^{222a1}R^{333a1}, -NR²²²¹C(=NR³³³¹)OR^{222a1}, -NR²²²¹C(=NR³³³¹)SR^{222a1}, -OC(=O)OR²²²¹, -OC(=O)NR²²²¹R³³³¹, -OC(=O)SR²²²¹, -SC(=O)OR²²²¹, -P(O)OR²²²¹OR³³³¹, or -SC(=O)NR²²²¹R³³³¹ substituents;

or G¹¹ is aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, aryl-C₂₋₁₀alkynyl, hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR²²²¹, -NR²²²¹R³³³¹(R^{222a1})_{j5a}, -C(O)R²²²¹, -CO₂R²²²¹, -C(=O)NR²²²¹R³³³¹, -NO₂, -CN, -S(O)_{j5a}R²²²¹, -SO₂NR²²²¹R³³³¹, -NR²²²¹C(=O)R³³³¹, -NR²²²¹C(=O)OR³³³¹, -NR²²²¹C(=O)NR³³³¹R^{222a1}, -NR²²²¹S(O)_{j5a}R³³³¹, -C(=S)OR²²²¹, -C(=O)SR²²²¹, -NR²²²¹C(=NR³³³¹)NR^{222a1}R^{333a1}, -NR²²²¹C(=NR³³³¹)OR^{222a1}, -NR²²²¹C(=NR³³³¹)SR^{222a1}, -OC(=O)OR²²²¹, -OC(=O)NR²²²¹R³³³¹, -OC(=O)SR²²²¹, -SC(=O)OR²²²¹, -P(O)OR²²²¹OR³³³¹, or -SC(=O)NR²²²¹R³³³¹ substituents;

or G¹¹ is C, taken together with the carbon to which it is attached forms a C=C double bond which is substituted with R⁵ and G¹¹¹;

R², R^{2a}, R³, R^{3a}, R²²², R^{222a}, R³³³, R^{333a}, R²¹, R^{2a1}, R³¹, R^{3a1}, R²²²¹, R^{222a1}, R³³³¹, and R^{333a1} are each independently C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, heterocyclyl-C₂₋₁₀alkynyl, aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted by one or more independent G¹¹¹ substituents;

or in the case of -NR²R³(R^{2a})_{j1} or -NR²²²R³³³(R^{222a})_{j1a} or -NR²²²R³³³(R^{222a})_{j2a} or -NR²¹R³¹(R^{2a1})_{j4} or -NR²²²¹R³³³¹(R^{222a1})_{j4a} or -NR²²²¹R³³³¹(R^{222a1})_{j5a}, then R² and R³, or R²²² and R³³³, or R²²²¹ and R³³³¹, respectfully, are optionally taken together with the

nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted by one or more independent G^{1111} substituents and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^2 and R^3 , or R^{222} and R^{333} , or R^{2221} and R^{3331} are attached;

W^1 and Y^1 are each independently $-O-$, $-NR^7-$, $-S(O)_j-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$, $-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, $-CH=CH-$, $-C\equiv C-$, $-C(=NOR^7)-$, $-C(O)-$, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^8)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^8)-$, $-N(R^7)S(O)_2N(R^8)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^8)-$, $-N(R^7)SO_2N(R^8)-$, $-C(O)O-$, $-N(R^7)P(OR^8)O-$, $-N(R^7)P(OR^8)-$, $-N(R^7)P(O)(OR^8)O-$, $-N(R^7)P(O)(OR^8)-$, $-N(C(O)R^7)P(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, $-N(C(O)R^7)P(O)(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, $-CH(R^7)S(O)-$, $-CH(R^7)S(O)_2-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)O-$, $-CH(R^7)S-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)C(=NOR^8)-$, $-CH(R^7)C(O)-$, $-CH(R^7)CH(OR^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, $-CH(R^7)N(R^8)S(O)_2-$, $-CH(R^7)OC(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)N(R^{7a})-$, $-CH(R^7)NR^8C(O)O-$, $-CH(R^7)S(O)N(R^8)-$, $-CH(R^7)S(O)_2N(R^8)-$, $-CH(R^7)N(C(O)R^8)S(O)-$, $-CH(R^7)N(C(O)R^8)S(O)-$, $-CH(R^7)N(R^8)S(O)N(R^{7a})-$, $-CH(R^7)N(R^8)S(O)_2N(R^{7a})-$, $-CH(R^7)C(O)N(R^8)C(O)-$, $-CH(R^7)S(O)N(R^8)C(O)-$, $-CH(R^7)S(O)_2N(R^8)C(O)-$, $-CH(R^7)OS(O)N(R^8)-$, $-CH(R^7)OS(O)_2N(R^8)-$, $-CH(R^7)N(R^8)S(O)O-$, $-CH(R^7)N(R^8)S(O)_2O-$, $-CH(R^7)N(R^8)S(O)C(O)-$, $-CH(R^7)N(R^8)S(O)_2C(O)-$, $-CH(R^7)SON(C(O)R^8)-$, $-CH(R^7)SO_2N(C(O)R^8)-$, $-CH(R^7)N(R^8)SON(R^{7a})-$, $-CH(R^7)N(R^8)SO_2N(R^{7a})-$, $-CH(R^7)C(O)O-$, $-CH(R^7)N(R^8)P(OR^{7a})O-$, $-CH(R^7)N(R^8)P(OR^{7a})-$, $-CH(R^7)N(R^8)P(O)(OR^{7a})O-$, $-CH(R^7)N(R^8)P(O)(OR^{7a})-$,

$-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})-$,
 $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{O})(\text{OR}^{7a})\text{O}-$, or $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^8)\text{P}(\text{OR}^{7a})-$;
 R^5 , R^6 , G^{111} , and G^{1111} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl,
 C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl,
cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl,
cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl,
heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl,
heterocyclyl- C_{2-10} alkynyl, aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl,
hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is
optionally substituted with one or more independent halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{77}$,
 $-\text{NR}^{77}\text{R}^{87}$, $-\text{C}(\text{O})\text{R}^{77}$, $-\text{CO}_2\text{R}^{77}$, $-\text{CONR}^{77}\text{R}^{87}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j5a}\text{R}^{77}$, $-\text{SO}_2\text{NR}^{77}\text{R}^{87}$,
 $-\text{NR}^{77}\text{C}(=\text{O})\text{R}^{87}$, $-\text{NR}^{77}\text{C}(=\text{O})\text{OR}^{87}$, $-\text{NR}^{77}\text{C}(=\text{O})\text{NR}^{78}\text{R}^{87}$, $-\text{NR}^{77}\text{S}(\text{O})_{j5a}\text{R}^{87}$,
 $-\text{C}(=\text{S})\text{OR}^{77}$, $-\text{C}(=\text{O})\text{SR}^{77}$, $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{NR}^{78}\text{R}^{88}$, $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{OR}^{78}$,
 $-\text{NR}^{77}\text{C}(=\text{NR}^{87})\text{SR}^{78}$, $-\text{OC}(=\text{O})\text{OR}^{77}$, $-\text{OC}(=\text{O})\text{NR}^{77}\text{R}^{87}$, $-\text{OC}(=\text{O})\text{SR}^{77}$,
 $-\text{SC}(=\text{O})\text{OR}^{77}$, $-\text{P}(\text{O})\text{OR}^{77}\text{OR}^{87}$, or $-\text{SC}(=\text{O})\text{NR}^{77}\text{R}^{87}$ substituents;
or R^5 with R^6 are optionally taken together with the carbon atom to which they are
attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is
optionally substituted with one or more independent R^{69} substituents and wherein said
ring optionally includes one or more heteroatoms;
 R^7 , R^{7a} , and R^8 are each independently acyl, C_{0-10} alkyl, C_{2-10} alkenyl, aryl, heteroaryl,
heterocyclyl or cyclo C_{3-10} alkyl, any of which is optionally substituted by one or more
independent G^{111} substituents;
 R^4 is C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, cyclo C_{3-10} alkyl,
heterocyclyl, cyclo C_{3-8} alkenyl, or heterocycloalkenyl, any of which is optionally
substituted by one or more independent G^{41} substituents;
 R^{69} is halo, $-\text{OR}^{78}$, $-\text{SH}$, $-\text{NR}^{78}\text{R}^{88}$, $-\text{CO}_2\text{R}^{78}$, $-\text{C}(=\text{O})\text{NR}^{78}\text{R}^{88}$, $-\text{NO}_2$, $-\text{CN}$,
 $-\text{S}(\text{O})_{j8}\text{R}^{78}$, $-\text{SO}_2\text{NR}^{78}\text{R}^{88}$, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl,
 C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl,
 C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl,
cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl,
cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl,
heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of

which is optionally substituted with one or more independent halo, cyano, nitro, $-\text{OR}^{778}$, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$ substituents;

or R^{69} is aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, hetaryl- C_{2-10} alkynyl, mono(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono(aryl)amino C_{1-6} alkyl, di(aryl)amino C_{1-6} alkyl, or $-\text{N}(\text{C}_{1-6}\text{alkyl})-\text{C}_{1-6}\text{alkyl}-\text{aryl}$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-\text{OR}^{778}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-\text{COOH}$, C_{1-4} alkoxycarbonyl, $-\text{C}(=\text{O})\text{NR}^{778}\text{R}^{888}$, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$ substituents;

or in the case of $-\text{NR}^{78}\text{R}^{88}$, R^{78} and R^{88} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10} alkoxy, $-\text{SO}_2\text{NR}^{778}\text{R}^{888}$, or $-\text{NR}^{778}\text{R}^{888}$ substituents, and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^{78} and R^{88} are attached;

R^{77} , R^{78} , R^{87} , R^{88} , R^{778} , and R^{888} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, heterocyclyl- C_{2-10} alkynyl, C_{1-10} alkylcarbonyl, C_{2-10} alkenylcarbonyl, C_{2-10} alkynylcarbonyl, C_{1-10} alkoxycarbonyl, C_{1-10} alkoxycarbonyl C_{1-10} alkyl, mono C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10} alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10} alkoxy, $-\text{SO}_2\text{N}(\text{C}_{0-4}\text{alkyl})(\text{C}_{0-4}\text{alkyl})$, or $-\text{N}(\text{C}_{0-4}\text{alkyl})(\text{C}_{0-4}\text{alkyl})$ substituents;

or R^{77} , R^{78} , R^{87} , R^{88} , R^{778} , and R^{888} are each independently aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, aryl- C_{2-10} alkynyl, hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, hetaryl- C_{2-10} alkynyl, mono(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono(aryl)amino C_{1-6} alkyl, di(aryl)amino C_{1-6} alkyl, or $-\text{N}(\text{C}_{1-6}\text{alkyl})-\text{C}_{1-6}\text{alkyl}-\text{aryl}$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-\text{O}(\text{C}_{0-4}\text{alkyl})$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl,

haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CON(C₀₋₄alkyl)(C₀₋₁₀alkyl), -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents; n, m, j1, j1a, j2a, j4, j4a, j5a, j7, and j8 are each independently 0, 1, or 2; and aa and bb are each independently 0 or 1.

[80] IGF-1R kinase inhibitor compounds of Formula (I), such as OSI-906 (a.k.a. linsitinib), have a number of important advantages over other compounds that inhibit the IGF-1R signaling pathway. These include: (a) They are small molecule inhibitors and therefore, should be easier to dose in combination with other inhibitors (e.g. antibody inhibitors) because of the ease of scheduling. (b) Small molecule compounds (e.g. OSI-906) also produce inhibition of IR in both in vitro and in vivo models. Such inhibition of IR is thought to contribute to the anti-cancer efficacy of these molecules. Antibodies, which are typically more highly selective for IGF-1R, do not possess such an advantage. (c) Certain other small molecule IGF-1R kinase inhibitors (e.g. BMS754807, BMS-536924 (both Bristol-Myers Squibb) inhibit both IGF-1R and IR in addition to a number of other kinases and are therefore less selective than IGF-1R kinase inhibitor compounds of Formula (I). This may contribute to the enhanced toxicity of these agents compared with IGF-1R kinase inhibitor compounds of Formula (I) (e.g. OSI-906).

[81] In an alternative embodiment of any of the methods, compositions or kits of the invention described herein, the IGF-1R kinase inhibitor may be an IGF-1R kinase inhibitor as described in the following publications: Buck, E. and Mulvihill, M. (2011) Expert Opin. Investig. Drugs 20(4):605-621, and Rodon et al. (2008) Mol. Cancer Ther. 7(9): 2575-2588), that both describe IGF-1R kinase inhibitors in development by pharmaceutical companies; International Patent Publication No. WO 05/037836, that describes imidazopyrazine IGF-1R kinase inhibitors, International Patent Publication Nos. WO 03/018021 and WO 03/018022, that describe pyrimidines for treating IGF-1R related disorders, International Patent Publication Nos. WO 02/102804 and WO 02/102805, that describe cyclolignans and cyclolignans as IGF-1R inhibitors, International Patent Publication No. WO 02/092599, that describes pyrrolopyrimidines for the treatment of a disease which responds to an inhibition of the IGF-1R tyrosine kinase, International Patent Publication No. WO 01/72751, that describes

pyrrolopyrimidines as tyrosine kinase inhibitors, and in International Patent Publication No. WO 00/71129, that describes pyrrolotriazine inhibitors of kinases, and in International Patent Publication No. WO 97/28161, that describes pyrrolo [2,3-d]pyrimidines and their use as tyrosine kinase inhibitors, Parrizas, et al., which describes tyrphostins with *in vitro* and *in vivo* IGF-1R inhibitory activity (Endocrinology, 138:1427-1433 (1997)), International Patent Publication No. WO 00/35455, that describes heteroaryl-aryl ureas as IGF-1R inhibitors, International Patent Publication No. WO 03/048133, that describes pyrimidine derivatives as modulators of IGF-1R, International Patent Publication No. WO 03/024967, WO 03/035614, WO 03/035615, WO 03/035616, and WO 03/035619, that describe chemical compounds with inhibitory effects towards kinase proteins, International Patent Publication No. WO 03/068265, that describes methods and compositions for treating hyperproliferative conditions, International Patent Publication No. WO 00/17203, that describes pyrrolopyrimidines as protein kinase inhibitors, Japanese Patent Publication No. JP 07/133280, that describes a cephem compound, its production and antimicrobial composition, Albert, A. et al., *Journal of the Chemical Society*, 11: 1540-1547 (1970), which describes pteridine studies and pteridines unsubstituted in the 4-position, and A. Albert et al., *Chem. Biol. Pteridines Proc. Int. Symp.*, 4th, 4: 1-5 (1969) which describes a synthesis of pteridines (unsubstituted in the 4-position) from pyrazines, via 3-4-dihydropteridines.; or an IGF-1R kinase inhibitor selected from the following compounds: IGF-1R kinase inhibitors in development by Novartis (e.g. NVP-AEW541, Garcia-Echeverria, C. et al. (2004) Cancer Cell 5:231-239; or NVP-ADW742, Mitsiades, C.S. et al. (2004) Cancer Cell 5:221-230); IGF-1R protein-tyrosine kinase inhibitors (Ontogen Corp); AG-1024 (Camirand, A. et al. (2005) Breast Cancer Research 7:R570-R579 (DOI 10.1186/bcr1028); Camirand, A. and Pollak, M. (2004) Brit. J. Cancer 90:1825-1829; Pfizer Inc.), an IGF-1 antagonist; the tyrphostins AG-538 and I-OMe-AG 538; BMS-536924, a small molecule inhibitor of IGF-1R; PNU-145156E (Pharmacia & Upjohn SpA), an IGF-1 antagonist; BMS 536924, a dual IGF-1R and IR kinase inhibitor (Bristol-Myers Squibb); AEW541 (Novartis); GSK621659A (Glaxo Smith-Kline); INSM-18 (a.k.a. NDGA, i.e. nordihydroguaiaretic acid) (Insmed); XL-228 (Exelixis), INSM-18 (Insmed), XL-228 (Exelixis), BMS754807 (Bristol Myers), BMS536924 (Bristol Myers), XL228 (Exelixis), or AXL-1717 (PPP) (Axelar AB).

[82] Additional small molecule IGF-1R kinase inhibitors that may be useful in alternative embodiments of any of the methods, compositions or kits of the invention described herein include, for example imidazopyrazine IGF-1R kinase inhibitors, quinazoline IGF-1R kinase inhibitors, pyrido-pyrimidine IGF-1R kinase inhibitors, pyrimido-pyrimidine IGF-1R kinase inhibitors, pyrrolo-pyrimidine IGF-1R kinase inhibitors, pyrazolo-pyrimidine IGF-1R kinase inhibitors, phenylamino-pyrimidine IGF-1R kinase inhibitors, oxindole IGF-1R kinase inhibitors, indolocarbazole IGF-1R kinase inhibitors, phthalazine IGF-1R kinase inhibitors, isoflavone IGF-1R kinase inhibitors, quinalone IGF-1R kinase inhibitors, and tyrphostin IGF-1R kinase inhibitors, and all pharmaceutically acceptable salts and solvates of such IGF-1R kinase inhibitors.

[83] IGF-1R kinase inhibitors include inhibitors that act by binding directly to the intracellular domain of the receptor and inhibiting its kinase activity; inhibitors that act by occupying the ligand binding site or a portion thereof of the IGF-1 receptor, thereby making the receptor inaccessible to its natural ligand so that its normal biological activity is prevented or reduced; and inhibitors that act by inhibiting the dimerization of IGF-1R polypeptides, or interaction of IGF-1R polypeptide with other proteins, or enhance ubiquitination and endocytotic degradation of IGF-1R. An IGF-1R kinase inhibitor can also act by reducing the amount of IGF-1 available to activate IGF-1R, by for example antagonizing the binding of IGF-1 to its receptor, by reducing the level of IGF-1, or by promoting the association of IGF-1 with proteins other than IGF-1R such as IGF binding proteins (e.g. IGFBP3). IGF-1R kinase inhibitors include but are not limited to low molecular weight inhibitors, aptamers, antibodies or antibody fragments, antisense constructs, small inhibitory RNAs (i.e. RNA interference by dsRNA; RNAi), and ribozymes.

[84] In any of the methods, compositions or kits of the invention described herein, the MET kinase inhibitor may be a small molecule MET kinase inhibitor, an anti-MET antibody or antibody fragment, an agent that antagonize activation of MET receptor, such as an HGF binding protein or anti-HGF antibody or antibody fragment, or any other MET kinase inhibitor or MET antagonist. MET antagonists useful in this invention include polypeptides that specifically bind to MET, anti-MET antibodies, MET small molecule inhibitors, receptor molecules and derivatives which bind

specifically to MET, and fusions proteins. MET antagonists also include antagonistic variants of MET polypeptides, RNA aptamers and peptibodies against MET and HGF. Also included as MET antagonists useful in the methods of the invention are anti-HGF antibodies, anti-HGF polypeptides, MET receptor molecules and derivatives which bind specifically to HGF. Examples of each of these are described herein below.

[85] Anti-MET antibodies that are useful in the methods of the invention include any antibody that binds with sufficient affinity and specificity to MET and can reduce or inhibit MET activity. The antibody selected will normally have a sufficiently strong binding affinity for MET, for example, the antibody may bind human MET with a K_d value of between 100 nM-1 pM. Antibody affinities may be determined by a surface plasmon resonance based assay (such as the BIAcore assay as described in PCT Application Publication No. WO2005/012359); enzyme-linked immunoabsorbent assay (ELISA); and competition assays (e.g. RIA's), for example. Preferably, the anti-MET antibody of the invention can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein MET/HGF activity is involved. Also, the antibody may be subjected to other biological activity assays, e.g., in order to evaluate its effectiveness as a therapeutic. Such assays are known in the art and depend on the target antigen and intended use for the antibody. Anti-MET antibodies are known in the art (see, e.g. MetMAb (Genentech/Roche), Martens, T, et al (2006) Clin Cancer Res 12(20 Pt 1):6144; U.S. Pat. No. 6,468,529; WO2006/015371; WO2007/063816; U.S. Pat. No. 7,408,043; WO2009/007427; WO2005/016382; WO2007/126799; or US Patent Application 2009/0226443).

[86] Anti-HGF antibodies are well known in the art. See, e.g., Kim K J, et al. Clin Cancer Res. (2006) 12(4):1292-8; WO2007/115049; WO2009/002521; WO2007/143098; WO2007/017107; WO2005/017107; L2G7; TAK-701 (a.k.a. HuL2G7: Takeda), AV-299 (a.k.a. SCH900105; Aveo/Merck) and AMG-102 (Amgen). MET receptor molecules or fragments thereof that specifically bind to HGF can be used in the methods of the invention, e.g., to bind to and sequester the HGF protein, thereby preventing it from signaling. Preferably, the MET receptor molecule, or HGF binding fragment thereof, is a soluble form. In some embodiments, a soluble form of the receptor exerts an inhibitory effect on the biological activity of the MET protein by binding to HGF, thereby preventing it from binding to its natural receptors present on

the surface of target cells. Also included are MET receptor fusion proteins, examples of which are described below. A soluble MET receptor protein or chimeric MET receptor proteins of the present invention includes MET receptor proteins which are not fixed to the surface of cells via a transmembrane domain. As such, soluble forms of the MET receptor, including chimeric receptor proteins, while capable of binding to and inactivating HGF, do not comprise a transmembrane domain and thus generally do not become associated with the cell membrane of cells in which the molecule is expressed. See, e.g., Kong-Beltran, M et al Cancer Cell (2004) 6(1): 75-84. HGF molecules or fragments thereof that specifically bind to MET and block or reduce activation of MET, thereby preventing it from signaling, can be used in the methods of the invention. Aptamers are nucleic acid molecules that form tertiary structures that specifically bind to a target molecule, such as a HGF polypeptide.

[87] The generation and therapeutic use of aptamers are well established in the art. See, e.g., U.S. Pat. No. 5,475,096. A HGF aptamer is a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular HGF. Additional information on aptamers can be found in U.S. Patent Application Publication No. 20060148748. A peptibody is a peptide sequence linked to an amino acid sequence encoding a fragment or portion of an immunoglobulin molecule. Polypeptides may be derived from randomized sequences selected by any method for specific binding, including but not limited to, phage display technology. In a preferred embodiment, the selected polypeptide may be linked to an amino acid sequence encoding the Fc portion of an immunoglobulin. Peptibodies that specifically bind to and antagonize HGF or MET are also useful in the methods of the invention.

[88] MET kinase antagonists include small molecules such as compounds described in U.S. Pat. No. 5,792,783; U.S. Pat. No. 5,834,504; U.S. Pat. No. 5,880,141; U.S. Pat. No. 6,297,238; U.S. Pat. No. 6,599,902; U.S. Pat. No. 6,790,852; US 2003/0125370; US 2004/0242603; US 2004/0198750; US 2004/0110758; US 2005/0009845; US 2005/0009840; US 2005/0245547; US 2005/0148574; US 2005/0101650; US 2005/0075340; US 2006/0009453; US 2006/0009493; WO 98/007695; WO 2003/000660; WO 2003/087026; WO 2003/097641; WO 2004/076412; WO 2005/004808; WO 2005/121 125; WO 2005/030140; WO 2005/070891; WO 2005/080393; WO 2006/014325; WO 2006/021886; WO 2006/021881, WO

2007/103308, WO 2009/099982, WO 2011/109593, WO 2010 059771, WO 2011/143645 and WO 2009/100282.

[89] Other MET kinase inhibitors, many at various stages of clinical development, include OSI-296 (OSI Pharmaceuticals), PHA-665752 ((2*R*)-1-[[5-[(*Z*)-[5-[(2,6-Dichlorophenyl)methyl] sulfonyl]-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene]methyl]-2,4-dimethyl-1*H*-pyrrol-3-yl]carbonyl]-2-(1-pyrrolidinylmethyl)pyrrolidine; Pharmacia), a small molecule, ATP-competitive, active-site inhibitor of the catalytic activity of MET (Ma et al (2005) Clin. Cancer Res. 11:2312-2319; Christensen et al (2003) Cancer Res. 63:7345-7355), MP470 (SuperGen), XL184 (Exelixis), E-7050 (Eisai), GSK 1363089/XL880 (N-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; Exelixis), EMD-1214063 (EMD Serono), I8060NCB02 (Incyte /Novartis), PF-02341066 (a.k.a. crizotinib or VGH; 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-yl-1*H*-pyrazol-4-yl)pyridin-2-amine; Pfizer), MP470 (SuperGen), DFQ ((2*E*)-3-{6-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]quinolin-3-yl}-N-methylprop-2-enamide; Chugai), JNJ-38877605 (Johnson and Johnson), PF-04217903 (Pfizer), SGX523 (6-{[6-(1-methyl-1*H*-pyrazol-4-yl)[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl]sulfanyl}quinoline; SGX Pharmaceuticals), LKG (4-[(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl]phenol; Amgen), AMG-208 (Amgen), MT3 (2-benzyl-5-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]-3-fluorophenyl}-3-methylpyrimidin-4(3*H*)-one; Amgen), MT4 (5-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]-3-fluorophenyl}-2-[(4-fluorophenyl)amino]-3-methylpyrimidin-4(3*H*)-one; Amgen), AM7 (2-benzyl-5-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-3-methylpyrimidin-4(3*H*)-one; Amgen), L5G (7-methoxy-4-[(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methoxy]quinoline; Amgen), ARQ197 (1-[(3*R*,4*R*)-4-(1*H*-indol-3-yl)-2,5-dioxopyrrolidin-3-yl]pyrrolo[3,2,1-*ij*]quinolinium; ArQule), K-252A (Pharmacia), SU11274 AM8 (N-(3-chlorophenyl)-N-methyl-2-oxo-3-[(3,4,5-trimethyl-1*H*-pyrrol-2-yl)methyl]-2*H*-indole-5-sulfonamide; Amgen), B2D (7-methoxy-N-[(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl]-1,5-naphthyridin-4-amine; Amgen), MGCD265 (Methylgene), ZZY (1-[(2-Nitrophenyl)Sulfonyl]-1*H*-Pyrrolo[3,2-*B*]Pyridine-6-Carboxamide; UCB-Celltech), IHX (3-[3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinoxalin-5-yl]phenol; UCB-Celltech),

BMS-777607 (Bristol-Myers-Squibb), 3QT (6-{[6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]methyl}quinoline; Novartis), CKK (N-{[4-({5-[(4-aminopiperidin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl}oxy)-3-fluorophenyl]carbamoyl}-2-(4-fluorophenyl)acetamide; Bristol-Myers-Squibb), 319 (N-({4-[(2-aminopyridin-4-yl)oxy]-3-fluorophenyl}carbamoyl)-2-(4-fluorophenyl)acetamide 1FN (1-(4-fluorophenyl)-N-[3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxamide; Bristol-Myers-Squibb); Bristol-Myers-Squibb), BMS-777607 353 (N-{4-[(2-amino-3-chloropyridin-4-yl)oxy]-3-fluorophenyl}-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide; BMS-777607), LY2801653 (Eli Lilly), L8V (2-({4-[(2-aminopyridin-4-yl)oxy]-3-fluorophenyl}amino)-N-(2,4-difluorophenyl)pyridine-3-carboxamide; Bristol-Myers-Squibb), MK-2461 (Merck), MK-8033 (Merck), Q6W (3-{5-oxo-3-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl}-N-(pyridin-2-ylmethyl)propanamide; Merck) MetMAb (a.k.a. One-armed 5D5, OA5D5 or Onartuzumab; a humanized, monovalent, antagonistic anti-MET antibody; Genentech), and AMG102 (a fully human IgG₂ monoclonal antibody; Amgen). Details of these and additional MET inhibitors can be found in Eder J.P. et al., Clin Cancer Res 2009;2209 15(7) April 1, 2009; Cui, J.J. (2007) Expert Opin. Ther. Patents 17(9):1035-1045; and Gherardi, E. et al. (2012) Nature Reviews, Cancer 12:89-103.

[90] The MET kinase inhibitor and IGF-1R kinase inhibitor of this invention may also be activities that reside in the same molecule, and thus one molecule provides the combined inhibition of MET and IGF-1R signaling pathways. Furthermore, in embodiments with two molecules, the MET kinase inhibitor of this invention may also possess IGF-1R kinase inhibitory activity, and/or the IGF-1R kinase inhibitor of this invention may also possess MET kinase inhibitory activity. Inhibitors with IGF-1R kinase inhibitory activity may also possess IR kinase inhibitory activity. An example of a molecule that is MET kinase inhibitor and an IGF-1R kinase inhibitor is the compound BMS754807 (e.g. see Carboni, J.M. et al. (2009) Mol Cancer Ther 8(12):3341-3349, including Supplemental Figures and Tables). The latter compound teaches a design for a kinase inhibitor that has dual specificity for IGF-1R kinase and MET kinase, that may be further modified if one wishes to enhance either activity over the other for applications where that may be desirable.

[91] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment an amount of a MET kinase inhibitor and an amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)). In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[92] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment a therapeutically effective amount of a MET kinase inhibitor and a therapeutically effective amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)). In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[93] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment an amount of an MET kinase inhibitor and an amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); wherein at least one of the amounts is administered as a sub-therapeutic amount. In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[94] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment an amount of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and; and an amount of MET kinase inhibitor. In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[95] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment a therapeutically effective amount of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a therapeutically effective amount of a MET kinase inhibitor. In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[96] The present invention also provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment an amount of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and an amount of an MET kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); wherein at least one of the amounts is administered as a sub-therapeutic amount. In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[97] The present invention also provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a synergistically effective therapeutic amount of a combination of an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)). In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[98] The present invention also provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a synergistically effective therapeutic amount of a combination of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor. In one embodiment, one or more other anti-cancer agents can additionally be administered to said patient.

[99] In embodiments of any of the methods of treatment of the invention described herein, the cells of the tumors or tumor metastases may be relatively insensitive or refractory to treatment with either of the anti-cancer agents or treatments used in the combination when used as a single agent/treatment.

[100] The present invention also provides a pharmaceutical composition comprising an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)), in a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition can additionally comprise one or more other anti-cancer agents.

[101] The present invention also provides a pharmaceutical composition comprising one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor, in a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition can additionally comprise one or more other anti-cancer agents.

[102] The present invention also provides a kit comprising one or more containers, comprising an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)). In a preferred embodiment, the kit containers may further include a pharmaceutically acceptable carrier. The kit may further include a sterile diluent, which is preferably stored in a separate additional container. In another embodiment, the kit further comprising a package insert comprising printed instructions directing the use of a combined treatment of an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) to a patient as a method for treating tumors, tumor metastases, or other cancers in a patient. The kit may also comprise additional containers comprising additional anti-cancer agents, agents that enhances the effect of such agents, or other compounds that improve the efficacy or tolerability of the treatment.

[103] The present invention also provides a kit comprising one or more containers, comprising one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor. In a preferred embodiment, the kit containers may further include a pharmaceutically acceptable carrier. The kit may further include a sterile diluent, which is preferably stored in a separate additional container. In another embodiment, the kit further comprising a package insert comprising printed instructions directing the use of a combined treatment of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor to a patient as a method for treating tumors, tumor metastases, or other cancers in a patient. The kit may also comprise additional containers comprising additional anti-cancer agents, agents that enhances the effect of such agents, or other compounds that improve the efficacy or tolerability of the treatment.

[104] In any of the methods of treatment of the invention described herein the patient may be a patient in need of treatment for cancer, including, for example, NSCL, pancreatic, head and neck, colon, ovarian or breast cancers.

[105] This invention also provides a method for treating abnormal cell growth of cells in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an MET kinase inhibitor and an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)).

[106] This invention also provides a method for treating abnormal cell growth of cells in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of one or more IGF binding proteins (e.g. IGFBP3; IGFBP1; an anti-IGF-1 antibody; an anti-IGF-2 antibody) and a MET kinase inhibitor.

[107] In one embodiment of the methods of this invention, the MET kinase inhibitor is administered at the same time as the IGF-1R kinase inhibitor. In another embodiment of the methods of this invention, MET kinase inhibitor is administered prior to the IGF-1R kinase inhibitor. In another embodiment of the methods of this invention, the MET kinase inhibitor is administered after the IGF-1R kinase inhibitor. In another embodiment of the methods of this invention, the IGF-1R kinase inhibitor is pre-administered prior to administration of a combination of an IGF-1R kinase inhibitor and the MET kinase inhibitor .

[108] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, and in addition, one or more other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds that enhance the effects of such agents.

[109] In the context of this invention, additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds that enhance the effects of such agents, include, for example: alkylating agents or agents with an alkylating action, such as

cyclophosphamide (CTX; e.g. CYTOXAN®), chlorambucil (CHL; e.g. LEUKERAN®), cisplatin (CisP; e.g. PLATINOL®) busulfan (e.g. MYLERAN®), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; e.g. VEPESID®), 6-mercaptopurine (6MP), 6-thioguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5-FU), capecitabine (e.g. XELODA®), dacarbazine (DTIC), and the like; antibiotics, such as actinomycin D, doxorubicin (DXR; e.g. ADRIAMYCIN®), daunorubicin (daunomycin), bleomycin, mithramycin and the like; alkaloids, such as vinca alkaloids such as vincristine (VCR), vinblastine, and the like; and other antitumor agents, such as paclitaxel (e.g. TAXOL®) and pacticetaxel derivatives, the cytostatic agents, glucocorticoids such as dexamethasone (DEX; e.g. DECADRON®) and corticosteroids such as prednisone, nucleoside enzyme inhibitors such as hydroxyurea, amino acid depleting enzymes such as asparaginase, leucovorin and other folic acid derivatives, and similar, diverse antitumor agents. The following agents may also be used as additional agents: arnifostine (e.g. ETHYOL®), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, lomustine (CCNU), doxorubicin lipo (e.g. DOXIL®), gemcitabine (e.g. GEMZAR®), daunorubicin lipo (e.g. DAUNOXOME®), procarbazine, mitomycin, docetaxel (e.g. TAXOTERE®), aldesleukin, carboplatin, oxaliplatin, cladribine, camptothecin, CPT 11 (irinotecan), 10-hydroxy 7-ethyl-camptothecin (SN38), floxuridine, fludarabine, ifosfamide, idarubicin, mesna, interferon beta, interferon alpha, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171,

batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR, KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, CG-781, CG-1521, SB-556629, chlamydocin, JNJ-16241199, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide (optionally further including irinotecan; e.g., in a method to treat glioblastoma multiforme, for example, comprising administering the antibody or fragment, temozolomide and radiation therapy; or administering the antibody or fragment, temozolomide and irinotecan), ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-, disodium salt, heptahydrate, camptothecin, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES (diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258, 3-[5-(methylsulfonylpiperadinemethyl)indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, goserelin acetate (i.e. acetate salt of [D-Ser(But)₆,Azgly¹⁰]LHRH), leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, lonafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, amsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deoxyuridine, cytosine arabinoside, 6-mercaptopurine, deoxycoformycin, calcitriol,

valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3 (metastat), neovastat, BMS-275291, squalamine, endostatin, SU5416 (semaxinib), SU6668 ([*(Z)*-3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid), EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxifene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox, gefitinib, bortezomib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS-247550 (ixabepilone), BMS-310705, droloxifene, 4-hydroxytamoxifen, pibendoxifene, ERA-923 (2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol hydrochloride), arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424 (bazedoxifene acetate), HMR-3339 (4-chloro-11b-[4-(2-[diethylamino]ethoxy)phenyl]-estra-1,3,5(10)-triene-3-,17b-diol), ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, filgrastim, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zoledronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, and darbepoetin alfa. The structures of these agents, and how to make and use them, is well known in the art (e.g. see US Published Patent Application No. 2011/0262525, Schering Corporation).

[110] Additional chemotherapeutic agents that may be added to the combinations or treatments of this invention include therapeutic antibodies such as alemtuzumab (Campath), cetuximab (ERBITUX[®], Imclone), panitumumab (VECTIBIX[®], Amgen),

pertuzumab (OMNITARG[®], 2C4, Genentech), tositumomab (Bexxar, Corixa), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG[®], Wyeth).

Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG₁λ antibody genetically modified to recognize interleukin-12 p40 protein.

[111] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, one or more anti-hormonal agents. As used herein, the term "anti-hormonal agent" includes natural or synthetic organic or peptidic compounds that act to regulate or inhibit hormone action on tumors.

[112] Antihormonal agents include, for example: steroid receptor antagonists, anti-estrogens such as tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, other aromatase inhibitors, 42-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (e.g. FARESTON[®]); anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above; agonists and/or antagonists of glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating

hormone (TSH), and luteinizing hormone (LH) and LHRH (leuteinizing hormone-releasing hormone); the LHRH agonist goserelin acetate, commercially available as ZOLADEX[®] (AstraZeneca); the LHRH antagonist D-alaninamide N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N6-(3-pyridinylcarbonyl)-L-lysyl-N6-(3-pyridinylcarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl -L-proline (e.g ANTIDE[®], Ares-Serono); the LHRH antagonist ganirelix acetate; the steroidal anti-androgens cyproterone acetate (CPA) and megestrol acetate, commercially available as MEGACE[®] (Bristol-Myers Oncology); the nonsteroidal anti-androgen flutamide (2-methyl-N-[4, 20-nitro-3-(trifluoromethyl) phenylpropanamide), commercially available as EULEXIN[®] (Schering Corp.); the non-steroidal anti-androgen nilutamide, (5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-imidazolidine-dione); and antagonists for other non-permissive receptors, such as antagonists for RAR, RXR, TR, VDR, and the like.

[113] The use of the cytotoxic and other anticancer agents described above in chemotherapeutic regimens is generally well characterized in the cancer therapy arts, and their use herein falls under the same considerations for monitoring tolerance and effectiveness and for controlling administration routes and dosages, with some adjustments. For example, the actual dosages of the cytotoxic agents may vary depending upon the patient's cultured cell response determined by using histoculture methods. Generally, the dosage will be reduced compared to the amount used in the absence of additional other agents.

[114] Typical dosages of an effective cytotoxic agent can be in the ranges recommended by the manufacturer, and where indicated by in vitro responses or responses in animal models, can be reduced by up to about one order of magnitude concentration or amount. Thus, the actual dosage will depend upon the judgment of the physician, the condition of the patient, and the effectiveness of the therapeutic method based on the in vitro responsiveness of the primary cultured malignant cells or histocultured tissue sample, or the responses observed in the appropriate animal models.

[115] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or

sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, one or more angiogenesis inhibitors.

[116] Anti-angiogenic agents include, for example: VEGFR inhibitors, such as SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, Calif., USA), or as described in, for example International Application Nos. WO 99/24440, WO 99/62890, WO 95/21613, WO 99/61422, WO 98/50356, WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438, WO 99/16755, and WO 98/02437, and U.S. Patent Nos. 5,883,113, 5,886,020, 5,792,783, 5,834,504 and 6,235,764; VEGF inhibitors such as IM862 (Cytran Inc. of Kirkland, Wash., USA); angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colo.) and Chiron (Emeryville, Calif.); OSI-930 (OSI Pharmaceuticals, Melville, USA); and antibodies to VEGF, such as bevacizumab (e.g. AVASTIN™, Genentech, South San Francisco, CA), a recombinant humanized antibody to VEGF; integrin receptor antagonists and integrin antagonists, such as to $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_v\beta_6$ integrins, and subtypes thereof, e.g. cilengitide (EMD 121974), or the anti-integrin antibodies, such as for example $\alpha_v\beta_3$ specific humanized antibodies (e.g. VITAXIN®); factors such as IFN-alpha (U.S. Patent Nos. 4,153,901, 4,503,035, and 5,231,176); angiostatin and plasminogen fragments (e.g. kringle 1-4, kringle 5, kringle 1-3 (O'Reilly, M. S. et al. (1994) Cell 79:315-328; Cao et al. (1996) J. Biol. Chem. 271: 29461-29467; Cao et al. (1997) J. Biol. Chem. 272:22924-22928); endostatin (O'Reilly, M. S. et al. (1997) Cell 88:277; and International Patent Publication No. WO 97/15666); thrombospondin (TSP-1; Frazier, (1991) Curr. Opin. Cell Biol. 3:792); platelet factor 4 (PF4); plasminogen activator/urokinase inhibitors; urokinase receptor antagonists; heparinases; fumagillin analogs such as TNP-4701; suramin and suramin analogs; angiostatic steroids; bFGF antagonists; flk-1 and flt-1 antagonists; anti-angiogenesis agents such as MMP-2 (matrix-metalloproteinase 2) inhibitors and MMP-9 (matrix-metalloproteinase 9) inhibitors. Examples of useful matrix metalloproteinase inhibitors are described in International Patent Publication Nos. WO 96/33172, WO 96/27583, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, and WO 99/07675, European Patent Publication Nos. 818,442, 780,386, 1,004,578, 606,046, and 931,788; Great Britain Patent Publication No. 9912961, and U.S. patent Nos. 5,863,949 and 5,861,510. Preferred MMP-2 and MMP-9 inhibitors are

those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

[117] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, one or more other tumor cell pro-apoptotic or apoptosis-stimulating agents.

[118] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, one or more other signal transduction inhibitors.

[119] Signal transduction inhibitors include, for example: erbB2 receptor inhibitors, such as organic molecules, or antibodies that bind to the erbB2 receptor, for example, trastuzumab (e.g. HERCEPTIN[®]); inhibitors of other protein tyrosine-kinases, e.g. imitinib (e.g. GLEEVEC[®]); EGFR kinase inhibitors (see herein below); ras inhibitors; raf inhibitors; MEK inhibitors; mTOR inhibitors, including mTOR inhibitors that bind to and directly inhibits both mTORC1 and mTORC2 kinases; mTOR inhibitors that are dual PI3K/mTOR kinase inhibitors, such as for example the compound PI-103 as described in Fan, Q-W et al (2006) Cancer Cell 9:341-349 and Knight, Z.A. et al. (2006) Cell 125:733-747; mTOR inhibitors that are dual inhibitors of mTOR kinase and one or more other PIKK (or PIK-related) kinase family members. Such members include MEC1, TEL1, RAD3, MEI-41, DNA-PK, ATM, ATR, TRRAP, PI3K, and PI4K kinases; cyclin dependent kinase inhibitors; protein kinase C inhibitors; PI-3 kinase inhibitors; and PDK-1 inhibitors (see Dancey, J. and Sausville, E.A. (2003) Nature Rev. Drug Discovery 2:92-313, for a description of several examples of such inhibitors, and their use in clinical trials for the treatment of cancer).

[120] The data presented in the Examples herein below demonstrate that in tumor cells the inhibition of IGF-1R signaling, EGFR signaling, and MET receptor signaling will lead to a greater anti-proliferative effect than inhibition of just one or two of these signaling pathways. Thus combination therapies that utilize a combination of an IGF-1R kinase inhibitor, an EGFR kinase inhibitor and a MET kinase inhibitor will be more effective than single agent or dual agent treatments. Unexpectedly such a three agent combination has also been found to be more efficacious with respect to inhibiting tumor cell growth than erlotinib, OSI-906, or erlotinib plus OSI-906 treatments, i.e. treatments without inhibition of MET signaling. Since OSI-906 was used in these studies, and this compound inhibits both IGF-1R signaling and IR signaling, such a three agent combination will also be inhibiting IR signaling. This also implies that a four agent combination, where each of the agents inhibits only one of the IGF-1R signaling, IR signaling, EGFR signaling, or MET receptor signaling may be just as effective as this three agent combination. In such an embodiment, the two agents inhibiting IGF-1R signaling and IR signaling may for example be antibodies specific to each of the two receptor proteins. A selective inhibitor of IR signaling may inhibit IR alone, IR-A alone, or both.

[121] ErbB2 receptor inhibitors include, for example: ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), monoclonal antibodies such as AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Tex., USA) and 2B-1 (Chiron), and erbB2 inhibitors such as those described in International Publication Nos. WO 98/02434, WO 99/35146, WO 99/35132, WO 98/02437, WO 97/13760, and WO 95/19970, and U.S. Patent Nos. 5,587,458, 5,877,305, 6,465,449 and 6,541,481.

[122] As used herein, the term “mTOR inhibitor that binds to and directly inhibits both mTORC1 and mTORC2 kinases” refers to any mTOR inhibitor that binds to and directly inhibits both mTORC1 and mTORC2 kinases that is currently known in the art, or will be identified in the future, and includes any chemical entity that, upon administration to a patient, binds to and results in direct inhibition of both mTORC1 and mTORC2 kinases in the patient. Examples of mTOR inhibitors useful in the invention described herein include those disclosed and claimed in US Patent Application 11/599,663, filed November 15, 2006, a series of compounds that inhibit mTOR by binding to and directly inhibiting both mTORC1 and mTORC2 kinases.

[123] As used herein, the term "EGFR kinase inhibitor" refers to any EGFR kinase inhibitor that is currently known in the art or that will be identified in the future, and includes any chemical entity that, upon administration to a patient, results in inhibition of a biological activity associated with activation of the EGF receptor in the patient, including any of the downstream biological effects otherwise resulting from the binding to EGFR of its natural ligand. Such EGFR kinase inhibitors include any agent that can block EGFR activation or any of the downstream biological effects of EGFR activation that are relevant to treating cancer in a patient. Such an inhibitor can act by binding directly to the intracellular domain of the receptor and inhibiting its kinase activity. Alternatively, such an inhibitor can act by occupying the ligand binding site or a portion thereof of the EGF receptor, thereby making the receptor inaccessible to its natural ligand so that its normal biological activity is prevented or reduced. Alternatively, such an inhibitor can act by modulating the dimerization of EGFR polypeptides, or interaction of EGFR polypeptide with other proteins, or enhance ubiquitination and endocytotic degradation of EGFR. EGFR kinase inhibitors include but are not limited to small molecule inhibitors, antibodies or antibody fragments, peptide or RNA aptamers, antisense constructs, small inhibitory RNAs (i.e. RNA interference by dsRNA; RNAi), and ribozymes. In a preferred embodiment, the EGFR kinase inhibitor is a small organic molecule or an antibody that binds specifically to the human EGFR.

[124] EGFR kinase inhibitors include, for example quinazoline EGFR kinase inhibitors, pyrido-pyrimidine EGFR kinase inhibitors, pyrimido-pyrimidine EGFR kinase inhibitors, pyrrolo-pyrimidine EGFR kinase inhibitors, pyrazolo-pyrimidine EGFR kinase inhibitors, phenylamino-pyrimidine EGFR kinase inhibitors, oxindole EGFR kinase inhibitors, indolocarbazole EGFR kinase inhibitors, phthalazine EGFR kinase inhibitors, isoflavone EGFR kinase inhibitors, quinalone EGFR kinase inhibitors, and tyrphostin EGFR kinase inhibitors, such as those described in the following patent publications, and all pharmaceutically acceptable salts and solvates of said EGFR kinase inhibitors: International Patent Publication Nos. WO 96/33980, WO 96/30347, WO 97/30034, WO 97/30044, WO 97/38994, WO 97/49688, WO 98/02434, WO 97/38983, WO 95/19774, WO 95/19970, WO 97/13771, WO 98/02437, WO 98/02438, WO 97/32881, WO 98/33798, WO 97/32880, WO 97/3288, WO 97/02266,

WO 97/27199, WO 98/07726, WO 97/34895, WO 96/31510, WO 98/14449, WO 98/14450, WO 98/14451, WO 95/09847, WO 97/19065, WO 98/17662, WO 99/35146, WO 99/35132, WO 99/07701, and WO 92/20642; European Patent Application Nos. EP 520722, EP 566226, EP 787772, EP 837063, and EP 682027; U.S. Patent Nos. 5,747,498, 5,789,427, 5,650,415, and 5,656,643; and German Patent Application No. DE 19629652. Additional non-limiting examples of small molecule EGFR kinase inhibitors include any of the EGFR kinase inhibitors described in Traxler, P., 1998, *Exp. Opin. Ther. Patents* 8(12):1599-1625.

[125] Specific preferred examples of small molecule EGFR kinase inhibitors that can be used according to the present invention include [6,7-bis(2-methoxyethoxy)-4-quinazolin-4-yl]-(3-ethynylphenyl) amine (also known as OSI-774, erlotinib, or TARCEVA[®] (erlotinib HCl); OSI Pharmaceuticals/Genentech/ Roche) (U.S. Pat. No. 5,747,498; International Patent Publication No. WO 01/34574, and Moyer, J.D. et al. (1997) *Cancer Res.* 57:4838-4848); CI-1033 (formerly known as PD183805; Pfizer) (Sherwood et al., 1999, *Proc. Am. Assoc. Cancer Res.* 40:723); PD-158780 (Pfizer); AG-1478 (University of California); CGP-59326 (Novartis); PKI-166 (Novartis); EKB-569 (Wyeth); GW-2016 (also known as GW-572016 or lapatinib ditosylate; GSK); and gefitinib (also known as ZD1839 or IRESSA[™]; Astrazeneca) (Woodburn et al., 1997, *Proc. Am. Assoc. Cancer Res.* 38:633). A particularly preferred small molecule EGFR kinase inhibitor that can be used according to the present invention is [6,7-bis(2-methoxyethoxy)-4-quinazolin-4-yl]-(3-ethynylphenyl) amine (i.e. erlotinib), its hydrochloride salt (i.e. erlotinib HCl, TARCEVA[®]), or other salt forms (e.g. erlotinib mesylate).

[126] EGFR kinase inhibitors also include, for example multi-kinase inhibitors that have activity on EGFR kinase, i.e. inhibitors that inhibit EGFR kinase and one or more additional kinases. Examples of such compounds include the EGFR and HER2 inhibitor CI-1033 (formerly known as PD183805; Pfizer); the EGFR and HER2 inhibitor GW-2016 (also known as GW-572016 or lapatinib ditosylate; GSK); the EGFR and JAK 2/3 inhibitor AG490 (a tyrphostin); the EGFR and HER2 inhibitor ARRY-334543 (Array BioPharma); BIBW-2992, an irreversible dual EGFR/HER2 kinase inhibitor (Boehringer Ingelheim Corp.); the EGFR and HER2 inhibitor EKB-569 (Wyeth); the VEGF-R2 and EGFR inhibitor ZD6474 (also known as

ZACTIMA™; AstraZeneca Pharmaceuticals), and the EGFR and HER2 inhibitor BMS-599626 (Bristol-Myers Squibb).

[127] Antibody-based EGFR kinase inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR kinase inhibitors include those described in Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al., 1995, Clin. Cancer Res. 1:1311-1318; Huang, S. M., et al., 1999, Cancer Res. 59:1935-40; and Yang, X., et al., 1999, Cancer Res. 59:1236-1243. Thus, the EGFR kinase inhibitor can be the monoclonal antibody Mab E7.6.3 (Yang, X.D. et al. (1999) Cancer Res. 59:1236-43), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof. Suitable monoclonal antibody EGFR kinase inhibitors include, but are not limited to, IMC-C225 (also known as cetuximab or ERBITUX™; Imclone Systems), ABX-EGF (Abgenix), EMD 72000 (Merck KGaA, Darmstadt), RH3 (York Medical Bioscience Inc.), and MDX-447 (Medarex/ Merck KGaA).

[128] EGFR kinase inhibitors for use in the present invention can alternatively be peptide or RNA aptamers. Such aptamers can for example interact with the extracellular or intracellular domains of EGFR to inhibit EGFR kinase activity in cells. An aptamer that interacts with the extracellular domain is preferred as it would not be necessary for such an aptamer to cross the plasma membrane of the target cell. An aptamer could also interact with the ligand for EGFR (e.g. EGF, TGF- α), such that its ability to activate EGFR is inhibited. Methods for selecting an appropriate aptamer are well known in the art. Such methods have been used to select both peptide and RNA aptamers that interact with and inhibit EGFR family members (e.g. see Buerger, C. et al. et al. (2003) J. Biol. Chem. 278:37610-37621; Chen, C-H. B. et al. (2003) Proc. Natl. Acad. Sci. 100:9226-9231; Buerger, C. and Groner, B. (2003) J. Cancer Res. Clin. Oncol. 129(12):669-675. Epub 2003 Sep 11.).

[129] EGFR kinase inhibitors for use in the present invention can alternatively be based on antisense oligonucleotide constructs. Anti-sense oligonucleotides, including anti-sense RNA molecules and anti-sense DNA molecules, would act to directly block the translation of EGFR mRNA by binding thereto and thus preventing protein

translation or increasing mRNA degradation, thus decreasing the level of EGFR kinase protein, and thus activity, in a cell. For example, antisense oligonucleotides of at least about 15 bases and complementary to unique regions of the mRNA transcript sequence encoding EGFR can be synthesized, e.g., by conventional phosphodiester techniques and administered by e.g., intravenous injection or infusion. Methods for using antisense techniques for specifically inhibiting gene expression of genes whose sequence is known are well known in the art (e.g. see U.S. Patent Nos. 6,566,135; 6,566,131; 6,365,354; 6,410,323; 6,107,091; 6,046,321; and 5,981,732).

[130] Small inhibitory RNAs (siRNAs) can also function as EGFR kinase inhibitors for use in the present invention. EGFR gene expression can be reduced by contacting the tumor, subject or cell with a small double stranded RNA (dsRNA), or a vector or construct causing the production of a small double stranded RNA, such that expression of EGFR is specifically inhibited (i.e. RNA interference or RNAi). Methods for selecting an appropriate dsRNA or dsRNA-encoding vector are well known in the art for genes whose sequence is known (e.g. see Tuschli, T., et al. (1999) *Genes Dev.* 13(24):3191-3197; Elbashir, S.M. et al. (2001) *Nature* 411:494-498; Hannon, G.J. (2002) *Nature* 418:244-251; McManus, M.T. and Sharp, P. A. (2002) *Nature Reviews Genetics* 3:737-747; Bremmelkamp, T.R. et al. (2002) *Science* 296:550-553; U.S. Patent Nos. 6,573,099 and 6,506,559; and International Patent Publication Nos. WO 01/36646, WO 99/32619, and WO 01/68836).

[131] Ribozymes can also function as EGFR kinase inhibitors for use in the present invention. Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Engineered hairpin or hammerhead motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of *EGFR* mRNA sequences are thereby useful within the scope of the present invention. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, which typically include the following sequences, GUA, GUU, and GUC. Once identified, short RNA sequences of between about 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site can be evaluated for predicted structural features, such as

secondary structure, that can render the oligonucleotide sequence unsuitable. The suitability of candidate targets can also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using, e.g., ribonuclease protection assays.

[132] Both antisense oligonucleotides and ribozymes useful as EGFR kinase inhibitors can be prepared by known methods. These include techniques for chemical synthesis such as, e.g., by solid phase phosphoramidite chemical synthesis. Alternatively, anti-sense RNA molecules can be generated by in vitro or in vivo transcription of DNA sequences encoding the RNA molecule. Such DNA sequences can be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Various modifications to the oligonucleotides of the invention can be introduced as a means of increasing intracellular stability and half-life. Possible modifications include but are not limited to the addition of flanking sequences of ribonucleotides or deoxyribonucleotides to the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2'-O-methyl rather than phosphodiesterase linkages within the oligonucleotide backbone.

[133] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, an anti-HER2 antibody or an immunotherapeutically active fragment thereof.

[134] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition, one or more additional anti-proliferative agents.

[135] Additional antiproliferative agents include, for example: Inhibitors of the enzyme farnesyl protein transferase, PDGFR kinase inhibitors, including the

compounds disclosed and claimed in U.S. patent Nos. 6,080,769, 6,194,438, 6,258,824, 6,586,447, 6,071,935, 6,495,564, 6,150,377, 6,596,735 and 6,479,513, and International Patent Publication WO 01/40217, and FGFR kinase inhibitors.

As used herein, the term "PDGFR kinase inhibitor" refers to any PDGFR kinase inhibitor that is currently known in the art or that will be identified in the future, and includes any chemical entity that, upon administration to a patient, results in inhibition of a biological activity associated with activation of the PDGF receptor in the patient, including any of the downstream biological effects otherwise resulting from the binding to PDGFR of its natural ligand. Such PDGFR kinase inhibitors include any agent that can block PDGFR activation or any of the downstream biological effects of PDGFR activation that are relevant to treating cancer in a patient. Such an inhibitor can act by binding directly to the intracellular domain of the receptor and inhibiting its kinase activity. Alternatively, such an inhibitor can act by occupying the ligand binding site or a portion thereof of the PDGF receptor, thereby making the receptor inaccessible to its natural ligand so that its normal biological activity is prevented or reduced.

Alternatively, such an inhibitor can act by modulating the dimerization of PDGFR polypeptides, or interaction of PDGFR polypeptide with other proteins, or enhance ubiquitination and endocytotic degradation of PDGFR. PDGFR kinase inhibitors include but are not limited to small molecule inhibitors, antibodies or antibody fragments, antisense constructs, small inhibitory RNAs (i.e. RNA interference by dsRNA; RNAi), and ribozymes. PDGFR kinase inhibitors include anti-PDGF or anti-PDGFR aptamers, anti-PDGF or anti-PDGFR antibodies, or soluble PDGF receptor decoys that prevent binding of a PDGF to its cognate receptor. In a preferred embodiment, the PDGFR kinase inhibitor is a small organic molecule or an antibody that binds specifically to the human PDGFR. The ability of a compound or agent to serve as a PDGFR kinase inhibitor may be determined according to the methods known in art and, further, as set forth in, *e.g.*, Dai *et al.*, (2001) Genes & Dev. 15: 1913-25; Zippel, *et al.*, (1989) Eur. J. Cell Biol. 50(2):428-34; and Zwiller, *et al.*, (1991) Oncogene 6: 219-21.

[136] The invention includes PDGFR kinase inhibitors known in the art as well as those supported below and any and all equivalents that are within the scope of ordinary skill to create. For example, inhibitory antibodies directed against PDGF are known in

the art, *e.g.*, those described in U.S. Patent Nos. 5,976,534, 5,833,986, 5,817,310, 5,882,644, 5,662,904, 5,620,687, 5,468,468, and PCT WO 2003/025019, the contents of which are incorporated by reference in their entirety. In addition, the invention includes N-phenyl-2-pyrimidine-amine derivatives that are PDGFR kinase inhibitors, such as those disclosed in U. S. Patent No. 5,521,184, as well as WO2003/013541, WO2003/078404, WO2003/099771, WO2003/015282, and WO2004/05282 which are hereby incorporated in their entirety by reference.

[137] Small molecules that block the action of PDGF are known in the art, *e.g.*, those described in U.S. Patent or Published Application Nos. 6,528,526 (PDGFR tyrosine kinase inhibitors), 6,524,347 (PDGFR tyrosine kinase inhibitors), 6,482,834 (PDGFR tyrosine kinase inhibitors), 6,472,391 (PDGFR tyrosine kinase inhibitors), 6,949,563, 6,696,434, 6,331,555, 6,251,905, 6,245,760, 6,207,667, 5,990,141, 5,700,822, 5,618,837, 5,731,326, and 2005/0154014, and International Published Application Nos. WO 2005/021531, WO 2005/021544, and WO 2005/021537, the contents of which are incorporated by reference in their entirety.

[138] Proteins and polypeptides that block the action of PDGF are known in the art, *e.g.*, those described in U.S. Patent Nos. 6,350,731 (PDGF peptide analogs), 5,952,304, the contents of which are incorporated by reference in their entirety.

[139] Bis mono- and bicyclic aryl and heteroaryl compounds which inhibit EGF and/or PDGF receptor tyrosine kinase are known in the art, *e.g.*, those described in, *e.g.* U.S. Patent Nos. 5,476,851, 5,480,883, 5,656,643, 5,795,889, and 6,057,320, the contents of which are incorporated by reference in their entirety.

[140] Antisense oligonucleotides for the inhibition of PDGF are known in the art, *e.g.*, those described in U.S. Patent Nos. 5,869,462, and 5,821,234, the contents of each of which are incorporated by reference in their entirety.

[141] Aptamers (also known as nucleic acid ligands) for the inhibition of PDGF are known in the art, *e.g.*, those described in, *e.g.*, U.S. Patent Nos. 6,582,918, 6,229,002, 6,207,816, 5,668,264, 5,674,685, and 5,723,594, the contents of each of which are incorporated by reference in their entirety.

[142] Other compounds for inhibiting PDGF known in the art include those described in U.S. Patent Nos. 5,238,950, 5,418,135, 5,674,892, 5,693,610, 5,700,822, 5,700,823, 5,728,726, 5,795,910, 5,817,310, 5,872,218, 5,932,580, 5,932,602, 5,958,959, 5,990,141, 6,358,954, 6,537,988 and 6,673,798, the contents of each of which are incorporated by reference in their entirety.

[143] A number of types of tyrosine kinase inhibitors that are selective for tyrosine kinase receptor enzymes such as PDGFR are known (see, *e.g.*, Spada and Myers ((1995) Exp. Opin. Ther. Patents, 5: 805) and Bridges ((1995) Exp. Opin. Ther. Patents, 5: 1245). Additionally Law and Lydon have summarized the anticancer potential of tyrosine kinase inhibitors ((1996) Emerging Drugs: The Prospect For Improved Medicines, 241-260). For example, U.S. Patent No. 6,528,526 describes substituted quinoxaline compounds that selectively inhibit platelet-derived growth factor-receptor (PDGFR) tyrosine kinase activity. The known inhibitors of PDGFR tyrosine kinase activity includes quinoline-based inhibitors reported by Maguire *et al.*, ((1994) J. Med. Chem., 37: 2129), and by Dolle, *et al.*, ((1994) J. Med. Chem., 37: 2627). A class of phenylamino-pyrimidine-based inhibitors was recently reported by Traxler, *et al.*, in EP 564409 and by Zimmerman *et al.*, ((1996) Biorg. Med. Chem. Lett., 6: 1221-1226) and by Buchdunger, *et al.*, ((1995) Proc. Nat. Acad. Sci. (USA), 92: 2558). Quinazoline derivatives that are useful in inhibiting PDGF receptor tyrosine kinase activity include bismono- and bicyclic aryl compounds and heteroaryl compounds (see, *e.g.*, WO 92/20642), quinoxaline derivatives (see (1994) Cancer Res., 54: 6106-6114), pyrimidine derivatives (Japanese Published Patent Application No. 87834/94) and dimethoxyquinoline derivatives (see Abstracts of the 116th Annual Meeting of the Pharmaceutical Society of Japan (Kanazawa), (1996), 2, p. 275, 29(C2) 15-2).

[144] Specific preferred examples of small molecule PDGFR kinase inhibitors that can be used according to the present invention include Imatinib (GLEEVEC[®]; Novartis); SU-12248 (sunitib malate, SUTENT[®]; Pfizer); Dasatinib (SPRYCEL[®]; BMS; also known as BMS-354825); Sorafenib (NEXAVAR[®]; Bayer; also known as Bay-43-9006); AG-13736 (Axitinib; Pfizer); RPR127963 (Sanofi-Aventis); CP-868596 (Pfizer/OSI Pharmaceuticals); MLN-518 (tandutinib; Millennium Pharmaceuticals); AMG-706 (Motesanib; Amgen); ARAVA[®] (leflunomide; Sanofi-Aventis; also known

as SU101), and OSI-930 (OSI Pharmaceuticals); Additional preferred examples of small molecule PDGFR kinase inhibitors that are also FGFR kinase inhibitors that can be used according to the present invention include XL-999 (Exelixis); SU6668 (Pfizer); CHIR-258/TKI-258 (Chiron); RO4383596 (Hoffmann-La Roche) and BIBF-1120 (Boehringer Ingelheim).

[145] As used herein, the term "FGFR kinase inhibitor" refers to any FGFR kinase inhibitor that is currently known in the art or that will be identified in the future, and includes any chemical entity that, upon administration to a patient, results in inhibition of a biological activity associated with activation of the FGF receptor in the patient, including any of the downstream biological effects otherwise resulting from the binding to FGFR of its natural ligand. Such FGFR kinase inhibitors include any agent that can block FGFR activation or any of the downstream biological effects of FGFR activation that are relevant to treating cancer in a patient. Such an inhibitor can act by binding directly to the intracellular domain of the receptor and inhibiting its kinase activity. Alternatively, such an inhibitor can act by occupying the ligand binding site or a portion thereof of the FGF receptor, thereby making the receptor inaccessible to its natural ligand so that its normal biological activity is prevented or reduced. Alternatively, such an inhibitor can act by modulating the dimerization of FGFR polypeptides, or interaction of FGFR polypeptide with other proteins, or enhance ubiquitination and endocytotic degradation of FGFR. FGFR kinase inhibitors include but are not limited to small molecule inhibitors, antibodies or antibody fragments, antisense constructs, small inhibitory RNAs (i.e. RNA interference by dsRNA; RNAi), and ribozymes. FGFR kinase inhibitors include anti-FGF or anti-FGFR aptamers, anti-FGF or anti-FGFR antibodies, or soluble FGFR receptor decoys that prevent binding of a FGF to its cognate receptor. In a preferred embodiment, the FGFR kinase inhibitor is a small organic molecule or an antibody that binds specifically to the human FGFR. Anti-FGFR antibodies include FR1-H7 (FGFR-1) and FR3-D11 (FGFR-3) (Imclone Systems, Inc.).

[146] FGFR kinase inhibitors also include compounds that inhibit FGFR signal transduction by affecting the ability of heparan sulfate proteoglycans to modulate FGFR activity. Heparan sulfate proteoglycans in the extracellular matrix can mediate the actions of FGF, e.g., protection from proteolysis, localization, storage, and

internalization of growth factors (Faham, S. et al. (1998) Curr. Opin. Struct. Biol., 8:578-586), and may serve as low affinity FGF receptors that act to present FGF to its cognate FGFR, and/or to facilitate receptor oligomerization (Galzie, Z. et al. (1997) Biochem. Cell. Biol., 75:669-685).

[147] The invention includes FGFR kinase inhibitors known in the art (e.g. PD173074) as well as those supported below and any and all equivalents that are within the scope of ordinary skill to create.

[148] Examples of chemicals that may antagonize FGF action, and can thus be used as FGFR kinase inhibitors in the methods described herein, include suramin, structural analogs of suramin, pentosan polysulfate, scopolamine, angiostatin, sprouty, estradiol, carboxymethylbenzylamine dextran (CMDB7), suradista, insulin-like growth factor binding protein-3, ethanol, heparin (e.g., 6-O-desulfated heparin), small molecule heparin, protamine sulfate, cyclosporin A, or RNA ligands for bFGF.

[149] Other agents or compounds for inhibiting FGFR kinase known in the art include those described in U.S. Patent Nos. 7,151,176 (Bristol-Myers Squibb Company; Pyrrolotriazine compounds); 7,102,002 (Bristol-Myers Squibb Company; pyrrolotriazine compounds); 5,132,408 (Salk Institute; peptide FGF antagonists); and 5,945,422 (Warner-Lambert Company; 2-amino-substituted pyrido[2,3-d]pyrimidines); U.S. published Patent application Nos. 2005/0256154 (4-amino-thieno[3,2-c]pyridine-7-carboxylic acid amide compounds); and 2004/0204427 (pyrimidino compounds); and published International Patent Applications WO-2007019884 (Merck Patent GmbH; N-(3-pyrazolyl)-N'-4-(4-pyridinyloxy)phenylurea compounds); WO-2007009773 (Novartis AG; pyrazolo[1,5-a]pyrimidin-7-yl amine derivatives); WO-2007014123 (Five Prime Therapeutics, Inc.; FGFR fusion proteins); WO-2006134989 (Kyowa Hakko Kogyo Co., Ltd.; nitrogenous heterocycle compounds); WO-2006112479 (Kyowa Hakko Kogyo Co., Ltd.; azaheterocycles); WO-2006108482 (Merck Patent GmbH; 9-(4-ureidophenyl)purine compounds); WO-2006105844 (Merck Patent GmbH; N-(3-pyrazolyl)-N'-4-(4-pyridinyloxy)phenylurea compounds); WO-2006094600 (Merck Patent GmbH; tetrahydropyrroloquinoline derivatives); WO-2006050800 (Merck Patent GmbH; N,N'-diarylurea derivatives); WO-2006050779 (Merck Patent GmbH; N,N'-diarylurea derivatives); WO-2006042599

(Merck Patent GmbH; phenylurea derivatives); WO-2005066211 (Five Prime Therapeutics, Inc.; anti-FGFR antibodies); WO-2005054246 (Merck Patent GmbH; heterocyclyl amines); WO-2005028448 (Merck Patent GmbH; 2-amino-1-benzyl-substituted benzimidazole derivatives); WO-2005011597 (Irm Llc; substituted heterocyclic derivatives); WO-2004093812 (Irm Llc/Scripps; 6-phenyl-7H-pyrrolo[2,3-d]pyrimidine derivatives); WO-2004046152 (F. Hoffmann La Roche AG; pyrimido[4,5-e]oxadiazine derivatives); WO-2004041822 (F. Hoffmann La Roche AG; pyrimido[4,5-d]pyrimidine derivatives); WO-2004018472 (F. Hoffmann La Roche AG; pyrimido[4,5-d]pyrimidine derivatives); WO-2004013145 (Bristol-Myers Squibb Company; pyrrolotriazine derivatives); WO-2004009784 (Bristol-Myers Squibb Company; pyrrolo[2,1-f][1,2,4]triazin-6-yl compounds); WO-2004009601 (Bristol-Myers Squibb Company; azaindole compounds); WO-2004001059 (Bristol-Myers Squibb Company; heterocyclic derivatives); WO-02102972 (Prochon Biotech Ltd./Morphosys AG; anti-FGFR antibodies); WO-02102973 (Prochon Biotech Ltd.; anti-FGFR antibodies); WO-00212238 (Warner-Lambert Company; 2-(pyridin-4-ylamino)-6-dialkoxyphenyl-pyrido[2,3-d]pyrimidin-7-one derivatives); WO-00170977 (Amgen, Inc.; FGFR-L and derivatives); WO-00132653 (Cephalon, Inc.; pyrazolone derivatives); WO-00046380 (Chiron Corporation; FGFR-Ig fusion proteins); and WO-00015781 (Eli Lilly; polypeptides related to the human SPROUTY-1 protein).

[150] Specific preferred examples of small molecule FGFR kinase inhibitors that can be used according to the present invention include RO-4396686 (Hoffmann-La Roche); CHIR-258 (Chiron; also known as TKI-258); PD 173074 (Pfizer); PD 166866 (Pfizer); ENK-834 and ENK-835 (both Enkam Pharmaceuticals A/S); and SU5402 (Pfizer). Additional preferred examples of small molecule FGFR kinase inhibitors that are also PDGFR kinase inhibitors that can be used according to the present invention include XL-999 (Exelixis); SU6668 (Pfizer); CHIR-258/TKI-258 (Chiron); RO4383596 (Hoffmann-La Roche), and BIBF-1120 (Boehringer Ingelheim).

[151] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and a MET kinase inhibitor,

and in addition, a COX II (cyclooxygenase II) inhibitor. Examples of useful COX-II inhibitors include alecoxib (e.g. CELEBREX™) and valdecoxib (e.g. BEXTRA™).

[152] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition treatment with radiation or a radiopharmaceutical.

[153] The source of radiation can be either external or internal to the patient being treated. When the source is external to the patient, the therapy is known as external beam radiation therapy (EBRT). When the source of radiation is internal to the patient, the treatment is called brachytherapy (BT). Radioactive atoms for use in the context of this invention can be selected from the group including, but not limited to, radium, cesium-137, iridium-192, americium-241, gold-198, cobalt-57, copper-67, technetium-99, iodine-123, iodine-131, and indium-111.

[154] Radiation therapy is a standard treatment for controlling unresectable or inoperable tumors and/or tumor metastases. Improved results have been seen when radiation therapy has been combined with chemotherapy. Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (Gy), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various considerations, but the two most important are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. A typical course of treatment for a patient undergoing radiation therapy will be a treatment schedule over a 1 to 6 week period, with a total dose of between 10 and 80 Gy administered to the patient in a single daily fraction of about 1.8 to 2.0 Gy, 5 days a week. Parameters of adjuvant radiation therapies are, for example, contained in International Patent Publication WO 99/60023.

[155] The present invention further provides a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or

sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, and in addition treatment with one or more agents capable of enhancing antitumor immune responses.

[156] Agents capable of enhancing antitumor immune responses include, for example: CTLA4 (cytotoxic lymphocyte antigen 4) antibodies (e.g. MDX-CTLA4, ipilimumab (a.k.a. MDX-010, Bristol-Myers Squibb/Medarex), and other agents capable of blocking CTLA4. Specific CTLA4 antibodies that can be used in the present invention include those described in U.S. Patent No. 6,682,736.

[157] The present invention further provides a method for reducing the side effects caused by the treatment of tumors or tumor metastases in a patient with an IGF-1R kinase inhibitor or a MET kinase inhibitor, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) and an MET kinase inhibitor, in amounts that are effective to produce a superadditive or synergistic antitumor effect, and that are effective at inhibiting the growth of the tumor.

[158] The present invention further provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) an effective first amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); and (ii) an effective second amount of an agent that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor, wherein that agent is an MET kinase inhibitor.

[159] The present invention further provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) a sub-therapeutic first amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); and (ii) a sub-therapeutic second amount of an agent that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor, wherein that agent is an MET kinase inhibitor.

[160] The present invention further provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) an effective first

amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); and (ii) a sub-therapeutic second amount of an agent that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor, wherein that agent is an MET kinase inhibitor.

[161] The present invention further provides a method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) a sub-therapeutic first amount of an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)); and (ii) an effective second amount of an agent that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor, wherein that agent is an MET kinase inhibitor.

[162] In the preceding methods the order of administration of the first and second amounts can be simultaneous or sequential, i.e. the agent that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor can be administered before the IGF-1R kinase inhibitor, after the IGF-1R kinase inhibitor, or at the same time as the IGF-1R kinase inhibitor.

[163] In the context of this invention, an "effective amount" of an agent or therapy is as defined above. A "sub-therapeutic amount" of an agent or therapy is an amount less than the effective amount for that agent or therapy, but when combined with an effective or sub-therapeutic amount of another agent or therapy can produce a result desired by the physician, due to, for example, synergy in the resulting efficacious effects, or reduced side effects.

[164] As used herein, the term "patient" preferably refers to a human in need of treatment with an anti-cancer agent for any purpose, and more preferably a human in need of such a treatment to treat cancer, or a precancerous condition or lesion. However, the term "patient" can also refer to non-human animals, preferably mammals such as dogs, cats, horses, cows, pigs, sheep and non-human primates, among others, that are in need of treatment with an anti-cancer agent. In a preferred embodiment, the patient is a human in need of treatment for cancer, including tumors and tumor metastases, or a precancerous condition or lesion, wherein the cancer is for example NSCL, pancreatic, head and neck, colon, ovarian or breast cancers, or Ewing's sarcoma.

[165] Cancers that may be treated by any of the the methods described herein include lung cancer, NSCLC, SCLC (small-cell lung cancer), bronchioloalveolar cell lung cancer, bone cancer, skin cancer, cancer of the head and neck (e.g. SCCHN), cutaneous or intraocular melanoma, pancreatic cancer, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, colon or colorectal cancer, cancer of the small intestine, cancer of the endocrine system, colorectal cancer, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, Ewing's sarcoma, ACC (Adrenocortical Carcinoma), HCC (hepatocellular carcinoma), cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the ureter, cervical cancer, breast cancer, kidney or renal cancer, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, cancer of the kidney, renal cell carcinoma, chronic or acute leukemia, lymphocytic lymphomas, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwannomas, ependymomas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenomas, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. The precancerous condition or lesion includes, for example, the group consisting of oral leukoplakia, actinic keratosis (solar keratosis), precancerous polyps of the colon or rectum, gastric epithelial dysplasia, adenomatous dysplasia, hereditary nonpolyposis colon cancer syndrome (HNPCC), Barrett's esophagus, bladder dysplasia, and precancerous cervical conditions.

[166] The term "refractory" as used herein is used to define a cancer for which treatment (e.g. chemotherapy drugs, biological agents, and/or radiation therapy) has proven to be ineffective. A refractory cancer tumor may shrink, but not to the point where the treatment is determined to be effective. Typically however, the tumor stays the same size as it was before treatment (stable disease), or it grows (progressive disease). As used herein the term can apply to any of the treatments or agents described herein, when used as single agents or combinations.

[167] For purposes of the present invention, "co-administration of" and "co-administering" an IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)), and an MET kinase inhibitor, (both components referred to hereinafter as the "two active agents") refer to any administration of the two active agents, either separately or together, where the two active agents are administered as part of an appropriate dose regimen designed to obtain the benefit of the combination therapy. Thus, the two active agents can be administered either as part of the same pharmaceutical composition or in separate pharmaceutical compositions. The MET kinase inhibitor that sensitizes tumor cells to the effects of the small molecule IGF-1R kinase inhibitor (e.g. an IGF-1R kinase inhibitor of Formula (I)) can be administered prior to, at the same time as, or subsequent to administration of the IGF-1R kinase inhibitor, or in some combination thereof. Where the IGF-1R kinase inhibitor is administered to the patient at repeated intervals, e.g., during a standard course of treatment, the MET kinase inhibitor that sensitizes tumor cells to the effects of the IGF-1R kinase inhibitor can be administered prior to, at the same time as, or subsequent to, each administration of the IGF-1R kinase inhibitor, or some combination thereof, or at different intervals in relation to therapy with the IGF-1R kinase inhibitor, or in a single dose prior to, at any time during, or subsequent to the course of treatment with the IGF-1R kinase inhibitor.

[168] The IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, will typically be administered to the patient in a dose regimen that provides for the most effective treatment of the cancer (from both efficacy and safety perspectives) for which the patient is being treated, as known in the art. In conducting the treatment method of the present invention, the IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, can be administered in any effective manner known in the art, such as by oral, topical, intravenous, intra-peritoneal, intramuscular, intra-articular, subcutaneous, intranasal, intra-ocular, vaginal, rectal, or intradermal routes, depending upon the type of cancer being treated, the type of the IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, and the medical judgement of the prescribing physician as based, e.g., on the results of published clinical studies.

[169] The amount and the timing of inhibitor administration will depend on the type (species, gender, age, weight, etc.) and condition of the patient being treated, the

severity of the disease or condition being treated, and on the route of administration. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

[170] The IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, can be administered with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Administration of such dosage forms can be carried out in single or multiple doses. Carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Oral pharmaceutical compositions can be suitably sweetened and/or flavored.

[171] The IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, can be combined together with various pharmaceutically acceptable inert carriers in the form of sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, and the like. Administration of such dosage forms can be carried out in single or multiple doses. Carriers include solid diluents or fillers, sterile aqueous media, and various non-toxic organic solvents, etc.

[172] Methods of preparing pharmaceutical compositions comprising IGF-1R kinase inhibitors are known in the art (e.g. US Published Patent Application 2006/0235031). Methods of preparing pharmaceutical compositions comprising a MET kinase inhibitor are also known in the art. In view of the teaching of the present invention, methods of preparing pharmaceutical compositions comprising both an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, will be apparent from the art, from for example known standard references such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 18th edition (1990).

[173] For oral administration of an IGF-1R kinase inhibitor and/or MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, tablets containing one or both

of the active agents are combined with any of various excipients such as, for example, micro-crystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine, along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinyl pyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, active agents may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[174] For parenteral administration of either or both of the active agents, solutions in either sesame or peanut oil or in aqueous propylene glycol may be employed, as well as sterile aqueous solutions comprising the active agent or a corresponding water-soluble salt thereof. Such sterile aqueous solutions are preferably suitably buffered, and are also preferably rendered isotonic, e.g., with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. The oily solutions are suitable for intra-articular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

[175] Additionally, it is possible to topically administer the the IGF-1R kinase inhibitor and/or MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, by way of, for example, creams, lotions, jellies, gels, pastes, ointments, salves and the like, in accordance with standard pharmaceutical practice. For example, a topical formulation comprising the IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, in about 0.1% (w/v) to about 5% (w/v) concentration can be prepared.

[176] For veterinary purposes, the active agents can be administered separately or together to animals using any of the forms and by any of the routes described above. In a preferred embodiment, the IGF-1R kinase inhibitor and/or MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, is administered in the form of a capsule, bolus, tablet, liquid drench, by injection or as an implant. As an alternative the IGF-1R kinase inhibitor and MET kinase inhibitor, or dual IGF-1R kinase/MET kinase inhibitor, can be administered with the animal feedstuff, and for this purpose a concentrated feed additive or premix may be prepared for a normal animal feed. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice.

[177] The present invention also encompasses the use of a therapeutically effective amount of a combination of an IGF-1R kinase inhibitor and a MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, for the manufacture of a medicament for the treatment of tumors or tumor metastases in a patient in need thereof, wherein each inhibitor in the combination can be administered to the patient either simultaneously or sequentially. The present invention also encompasses the use of a synergistically effective combination of an IGF-1R kinase inhibitor and a MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, for the manufacture of a medicament for the treatment of tumors or tumor metastases in a patient in need thereof, wherein each inhibitor in the combination can be administered to the patient either simultaneously or sequentially. The present invention also encompasses the use of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, for the manufacture of a medicament for the treatment of abnormal cell growth in a patient in need thereof, wherein each inhibitor in the combination can be administered to the patient either simultaneously or sequentially. In an alternative embodiment of any of the above uses the present invention also encompasses the use of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, in combination with another anti-cancer agent or agent that enhances the effect of such an agent for the manufacture of a medicament for the treatment of tumors or tumor metastases in a patient in need thereof, wherein each inhibitor or agent in the combination can be administered to the patient either simultaneously or sequentially. In this context, the other anti-cancer agent or agent that enhances the effect of such an agent can be any of the agents listed herein that can be

added to the IGF-1R kinase inhibitor and MET kinase inhibitor combination, or a dual IGF-1R kinase/MET kinase inhibitor, when treating patients.

[178] The present invention further provides for any of the “methods of treatment” (or methods for reducing the side effects caused by treatment) described herein, a corresponding “method for manufacturing a medicament”, for administration with an IGF-1R kinase inhibitor, and use with the same indications and under identical conditions or modalities described for the method of treatment, characterized in that a MET kinase inhibitor is used, and such that where any additional agents, inhibitors or conditions are specified in alternative embodiments of the method of treatment they are also included in the corresponding alternative embodiment for the method for manufacturing a medicament. In an alternative embodiment, the present invention further provides for any of the “methods of treatment” (or methods for reducing the side effects caused by treatment) described herein, a corresponding “method for manufacturing a medicament” for use with the same indications and under identical conditions or modalities described for the method of treatment, characterized in that a combination an IGF-1R kinase inhibitor, and a MET kinase inhibitor, is used, such that where any additional agents, inhibitors or conditions are specified in alternative embodiments of the method of treatment they are also included in the corresponding alternative embodiment for the method for manufacturing a medicament.

[179] The present invention further provides, for any of the methods, compositions or kits of the invention described herein that include, e.g. in a step or ingredient, the phrase “comprising”..... a combination of IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, a corresponding method, composition or kit in which that phrase is substituted with the phrase “consisting essentially of” or “consisting of”..... a combination of IGF-1R kinase inhibitor and a MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor ”.

[180] The invention also encompasses a pharmaceutical composition that is comprised of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, in combination with a pharmaceutically acceptable carrier.

[181] Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof).

[182] Moreover, within this preferred embodiment, the invention encompasses a pharmaceutical composition for the treatment of disease, the use of which results in the inhibition of growth of neoplastic cells, benign or malignant tumors, or metastases, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof).

[183] The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When a compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (cupric and cuprous), ferric, ferrous, lithium, magnesium, manganese (manganic and manganous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[184] When a compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

[185] The pharmaceutical compositions of the present invention comprise a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof) as active ingredients, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Other therapeutic agents may include those cytotoxic, chemotherapeutic or anti-cancer agents, or agents which enhance the effects of such agents, as listed above. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[186] In practice, the compounds represented by the combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof) of this invention can be combined as the active ingredient(s) in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous

liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof) may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredients with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[187] Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof). A combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof), can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds. Other therapeutically active compounds may include those cytotoxic, chemotherapeutic or anti-cancer agents, or agents which enhance the effects of such agents, as listed herein.

[188] Thus in one embodiment of this invention, a pharmaceutical composition can comprise a combination of IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, in combination with another anticancer agent, wherein said anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents.

[189] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are

sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[190] In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[191] A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably contains from about 0.05mg to about 5g of the active ingredient.

[192] For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material that may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

[193] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example,

hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[194] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[195] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof) of this invention, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

[196] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[197] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a combination of an IGF-1R kinase inhibitor and an MET kinase inhibitor, or a dual IGF-1R kinase/MET kinase inhibitor, (including pharmaceutically acceptable salts of each component thereof) may also be prepared in powder or liquid concentrate form.

[198] Dosage levels for the compounds of the combination of this invention will be approximately as described herein, or as described in the art for these compounds. It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[199] In further embodiments of any of the above methods, compositions or kits of this invention where an IGF-1R kinase inhibitor is used, an IGF-1R kinase inhibitor of Formula (I) as described herein may be used, and the IGF-1R kinase inhibitor may comprise any compound of Formula (I) as described in US Published Patent Application US 2006/0235031 (e.g. OSI-906). In further embodiments of any of the above methods, compositions or kits of this invention where a MET kinase inhibitor is used, the MET kinase inhibitor may comprise any compound as described in WIPO Published Patent Application WO 2009/099982, WO 2011/109593, WO 2010 059771, WO 2011/143645 or WO 2009/100282.

[200] This invention will be better understood from the Experimental Details that follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter, and are not to be considered in any way limited thereto.

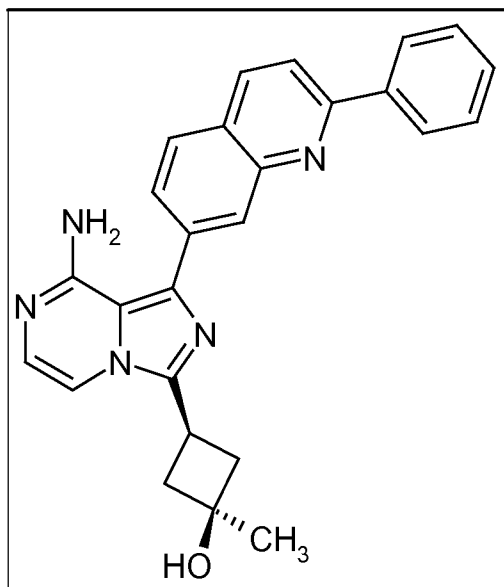
[201] **Experimental Details:**

[202] **Introduction**

[203] Although crosstalk between the EGF axis and either the IGF or HGF axis has been described, the potential for compensatory crosstalk between the IGF and HGF axes has thus far not been reported. In this study, it is shown that co-expression of IR, MET, and EGFR commonly occurs in human tumors. Elevated phospho-MET was detected in a subset of tumor cell lines that also exhibited elevated phosphorylation of both IGF-1R/IR and EGFR. Elevated phospho-MET was associated with an epithelial phenotype and sensitivity to the dual IGF-1R/IR inhibitor OSI-906. Treatment with HGF rescued cell proliferation and survival from the effects of OSI-906, alone or in combination with erlotinib. Under HGF-stimulated conditions OSI-906 synergized with a MET kinase inhibitor to inhibit signaling through the AKT pathway and cell proliferation. While neither OSI-906 nor erlotinib promoted apoptosis as single agents, both OSI-906 and erlotinib promoted apoptosis in tumor cells upon knockdown of MET by shRNA. These data support the hypothesis that receptors within the EGF, IGF, and HGF axes can be coordinately activated in epithelial tumor cells, where resistance to selective blockade of either the EGF or IGF axes may be mediated by elevated signaling through the HGF axis. This highlights the importance of considering combinatorial RTK targeting for the treatment of epithelial cancers, e.g. a combination of an IGF-1R kinase inhibitor with a MET kinase inhibitor.

[204] **Materials and Methods**

[205] *Pharmacologic inhibitors*:: IGF-1R kinase inhibitors useful in this invention include compounds represented by Formula (I) (see above), as described in US Published Patent Application US 2006/0235031, where their preparation is described in detail. OSI-906 represents an IGF-1R kinase inhibitor according to Formula (I), with the formula *cis*-3-[8-amino-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-*a*]pyrazin-3-yl]-1-methyl-cyclobutanol. OSI-906 and erlotinib were synthesized as previously described (31). PHA (a.k.a PHA-665752, i.e. (2*R*)-1-[[5-[(*Z*)-[5-[[2,6-Dichlorophenyl)methyl]sulfonyl]-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene]methyl]-2,4-dimethyl-1*H*-pyrrol-3-yl]carbonyl]-2-(1-pyrrolidinylmethyl)pyrrolidine) was obtained from Tocris Bioscience. MAB391 was from R&D Systems. OSI-906 has the structure as follows:



[206] *Cell lines*: Cell lines were obtained from the ATCC or other sources, banked after receipt, and propagated for fewer than 6 months before use. Cell viability was assayed at 72 hours after drug treatment using Cell Titer-Glo (Promega Corp., Madison, WI). Caspase 3/7 activity was assayed at 48 hours after drug treatment using Caspase-Glo (Promega Corp.)

[207] *Preparation of Protein Lysates and Western Blotting*: Lysates for Western blotting were prepared as previously described (32). Antibodies included: IGF-1R and IR (Santa Cruz, 1:200 dilution), phospho-p42/p44, phospho-Akt(S473) and phospho-Akt(T308), p-MET, and phospho-PRAS40 (Cell Signaling Technologies, 1:1000 dilution). Where indicated, 50ng/ml EGF or HGF ligands were added for 5 minutes prior to lysis. All other lysates were collected from cells growing under basal (10% FCS) growing conditions.

[208] *P85 immunoprecipitation*: 500µg of cell lysis (Cell Signaling Lysis Buffer 9803 + 10% glycerol + phosSTOP complete (Roche)) were incubated with 15µg anti-PI3K p85 agarose conjugated beads (Millipore) at 4 degrees C overnight. Beads were washed 1X in lysis buffer and 2X PBS. Resuspended beads were boiled prior to loading on gel.

[209] *Analysis of RTK phosphorylation via a proteome array:* RTK phosphorylation states were determined by Proteome Profiler arrays (R&D Systems, Minneapolis, MN) and processed according to manufacturer's protocol. RTKs included on the array are described in Supplementary Methods.

[210] *Taqman Assays:* Gene Expression Assay *MET* (Applied Biosystems, Foster City, CA) was conducted as described by the manufacturer using 50ng template.

[211] *MET shRNA*

[212] GEO and MDA-1186 tumor cells grown to 20% confluence were treated with shRNA lentiviral particles (TRCN, Sigma) at a MOI of 2. After 48 hours cells were transferred to media containing 10µg/ml puromycin for selection.

[213] Results

[214] *Receptors within the IGF, EGF, and HGF axes are coordinately expressed and activated*

[215] Previous reports have shown that EGFR can be jointly activated with MET in select human tumors, and that compensatory MET activity can mediate acquired resistance to EGFR inhibitors (19, 20). EGFR may also be co-activated with receptors within the IGF axis (IGF-1R and IR) in a subset of human tumor cell lines, where resistance to EGFR inhibitors including erlotinib is mediated by a compensatory increase in IGF-1R/IR activity. We sought to determine whether receptors within all three of these axes (IGF, EGF, and HGF) are coordinately expressed and concurrently activated in human tumors. We assessed the expression of mRNAs encoding a panel of 18 RTKs within a human tumor database comprised of non-small cell lung carcinomas (NSCLC), squamous cell carcinomas of the head and neck (SCCHN), pancreatic carcinomas (PaCa), and colorectal carcinomas (CRC). Consistent with prior reports we found that expression levels of *EGFR* and *MET* mRNA are positively correlated ($R=0.53$, Figure 1A). While correlated expression of *IGF1R* with *EGFR* and *MET* mRNA did not reach statistical significance, we did find that expression of *IR* mRNA is significantly positively correlated with *EGFR* and *MET* mRNA expression, and this correlation ranked highest compared with other RTKs evaluated, Figure 1A.

[216] We evaluated the phosphorylation of IGF-1R/IR, EGFR, and MET within a panel of 35 tumor cell lines representing CRC, NSCLC, SCCHN, and PaCa carcinomas, Figure 7. Tumor cell lines exhibited a range of sensitivities to the EGFR inhibitor erlotinib or the dual IGF-1R/IR inhibitor OSI-906 (33, 34). Phosphorylation levels for an RTK > 2-fold above the signal for IgG control were scored as detectable, Figure 7. Phosphorylation array data for a representative subset of four tumor cell lines is shown in Figure 1B. The majority of tumor cell lines (25/35) exhibited detectable levels of phospho-EGFR, which was positively correlated with sensitivity to erlotinib (Pearson correlation coefficient 0.4, p value 0.02), Table 1. 13/35 tumor cell lines showed detectable levels of phospho-IGF-1R/IR, Figure 7. Sensitivity to OSI-906 was positively correlated with phosphorylation of IR and IGF-1R, and the correlation between phospho-IR and OSI-906 sensitivity was statistically significant (Pearson correlation coefficient 0.35, p value 0.04), Table 1. 13/35 tumor cell lines also exhibited detectable levels of phospho-MET. MET-dependence has been previously shown to be related to *MET* amplification (23, 24). Copy number analysis for *MET* is available for 22/35 tumor cell lines within the panel (CONAN, Sanger Wellcome Trust), and none showed high level amplification for the MET locus, including ten tumor cell lines with detectable phospho-MET, Figure 7. Interestingly, there was a significant correlation between OSI-906 sensitivity and elevated phospho-MET (Pearson correlation coefficient 0.45, p value 0.01), Table 1. A subset of seven tumor cell lines that exhibited phosphorylation of EGFR and IGF-1R/IR also showed concurrent phosphorylation of MET (GEO, LS513, HT-29, Colo205, NCI-H358, NCI-H2009, and MDA-1186), Figure 1B. Within this group, each cell line was sensitive to OSI-906, and 5/7 (GEO, LS513, NCI-H358, NCI-H2122, and MDA-1186) were also sensitive to erlotinib. Since a subgroup of OSI-906 sensitive tumor cell lines exhibited elevated phospho-EGFR and phospho-MET this presents the potential for EGFR or MET signaling to limit long term sensitivity to OSI-906.

[217] **Table 1**

	pEGFR	pIR	pIGF-1R	pMET	EMT (E)	OSI-906 (EC ₅₀)	Erlotinib (EC ₅₀)
pEGFR							

pIR	0.37	1					
pIGF-1R	0.07	0.64	1				
pMET	0.21	0.15	-0.04	1			
EMT (E)	0.37	0.40	0.35	0.70	1		
OSI-906 (EC₅₀)	0.02	0.35	0.27	0.45	0.67	1	
erlotinib (EC₅₀)	0.40	0.29	0.03	0.21	0.60	0.12	1

[218] EMT status has been described for 19 tumor cell lines within the panel (27-29). Consistent with previous reports, sensitivity to either erlotinib or OSI-906 was significantly positively correlated with an epithelial phenotype (Pearson correlation coefficients 0.60 and 0.67, respectively) (25, 27-29, 35). Phospho-EGFR, phospho-IR, and phospho-IGF-1R each trended towards being positively correlated with epithelial status. Interestingly, phospho-MET was also positively correlated with epithelial status, and this association was statistically significant (Pearson correlation coefficient 0.7, p value <0.001), Table 1. Therefore, receptors within the EGF, IGF, and HGF axes are commonly co-expressed and phosphorylated in a subset of epithelial tumor cell lines (36). This supports the possibility for crosstalk between these three RTKs which could limit sensitivity to selective inhibition of an individual RTK or even to any paired combination of selective inhibitors.

[219] *Either EGF or HGF can promote desensitization to OSI-906*

[220] Compensatory crosstalk between IGF-1R/IR and EGFR has been well described. Inhibition of receptors in either axis is associated with an increase in the phosphorylation of receptors in the reciprocal axis, and the combination of a dual IGF-1R/IR and EGFR inhibitor results in more complete and sustained inhibition of the AKT pathway, synergistic inhibition of cellular proliferation and survival *in vitro*, and enhanced anti-tumor activity (25, 26). Since we observed phosphorylation of MET concurrently with phosphorylation of receptors within the EGF and IGF axes in select

tumor cell lines, we sought to determine if MET signaling can also affect sensitivity to inhibitors of these axes.

[221] While tumor cells frequently express the ligands for IGF-1R/IR and EGFR in an autocrine manner, intratumoral HGF is primarily derived from infiltrating stromal cells in a paracrine manner (37). Assessing the activity of OSI-906 under conditions where HGF was exogenously supplied allowed us to mimic this biology. We selected a group of three epithelial, OSI-906 sensitive, tumor cell lines (GEO, NCI-H358, and MDA-1186) which exhibited concomitant phosphorylation of RTKs within the IGF, EGF, and HGF axes. Treatment with OSI-906 for two hours resulted in inhibition of phospho-AKT/PRAS40, Figure 2A. Enhanced inhibition of phospho-AKT/PRAS40 was observed upon co-treatment with erlotinib. Consistent with crosstalk between IGF-1R/IR and EGFR, addition of EGF rescued AKT/PRAS40 phosphorylation in OSI-906-treated cells. In addition, HGF also rescued AKT/PRAS40 phosphorylation in cells either treated with OSI-906 alone or in combination with erlotinib. For GEO tumor cells neither treatment with FGF1/2 (i.e. FGF1 plus FGF2) nor PDGF α similarly rescued AKT/PRAS40 phosphorylation, indicating that not all RTKs are capable of functioning in a compensatory manner to promote acquired resistance, Figure 8. This highlights a unique aspect to the expression pattern and crosstalk between receptors within the EGF, IGF, and HGF RTK axes.

[222] By itself, exogenous addition of HGF to cell culture medium had a minimal effect on overall cell proliferation (<30% stimulation of proliferation, data not shown). However, HGF treatment resulted in diminished sensitivity to OSI-906 in all three cell lines evaluated, Figure 2B. Under basal growing conditions, the proliferation of GEO cells was inhibited approximately 80% by OSI-906, however in the presence of HGF, proliferation was maximally inhibited only 10-20% by OSI-906. Addition of HGF to culture medium also resulted in reduced proliferation (data not shown) and caspase 3/7 induction for the combination of OSI-906 and erlotinib, Figure 2B. Collectively, these data indicate that while HGF-MET signaling may not be a primary determinant of cell proliferation for these tumor cell lines, HGF-MET signaling can contribute to acquired resistance to IGF-1R/IR inhibition, alone or in conjunction with EGFR inhibition.

[223] *OSI-906 synergizes with a MET kinase inhibitor to block cellular proliferation*

[224] We evaluated the effect of combining OSI-906 with the MET kinase inhibitor, PHA-665752. While the anti-proliferative activities of either OSI-906 or erlotinib were significantly reduced by HGF treatment, PHA-665752 as a single agent had no effect on the proliferation of GEO tumor cells cultured under either basal or HGF-supplemented conditions. Therefore, while HGF-MET signaling may not be the primary determinant of cellular proliferation for these tumor cell lines, HGF-MET signaling can contribute to acquired resistance to either EGFR or IGF-1R/IR blockade, Figure 3A (top panel). Consistent with this hypothesis, under HGF-treated conditions, OSI-906 and PHA-665752 synergized to inhibit proliferation, Figure 3A (bottom panel). In the presence of HGF, only the combination of OSI-906 and PHA-665752, and not either agent individually, resulted in inhibition of phospho-AKT/PRAS40, Figure 3B. In addition, HGF treatment resulted in elevated phospho-ERK, which could be suppressed by PHA-665752.

[225] We have previously shown that OSI-906, as a dual IGF-1R/IR inhibitor, exhibits greater anti-tumor activity compared with a selective IGF-1R antibody in tumor models such as GEO that co-express both IGF-1R and IR. Herein we determined that under HGF-stimulated conditions, only OSI-906, and not the IGF-1R specific antibody MAB391, synergized with PHA-665752 to inhibit phospho-AKT/PRAS40 in GEO cells, Figure 3B. These data show that inhibition of both IGF-1R and IR may be required to maximize the inhibition of survival signaling pathways in combination with a MET TKI, although combination of a MET kinase inhibitor with an IGF-1R antibody may still prove to be superior to single agent treatment in certain circumstances. Similarly, the ability of erlotinib to suppress AKT and ERK signaling was reduced in the presence of HGF. Full inhibition of both pathways was achieved only upon treating GEO cells with the combination of OSI-906, erlotinib, and PHA-665752, Figure 3C.

[226] In these *in vitro* experiments, we had supplied exogenous recombinant HGF ligand. However, in human tumors *in situ*, HGF would likely be derived from infiltrating stromal cells such as fibroblasts. In order to more closely mimic this tumor microenvironment we assessed the activity of OSI-906, alone or in combination with PHA-665752, in the presence of conditioned media derived from two human lung

fibroblast cell lines (MRC-5 and WI-38). The conditioned media from both MRC-5 and WI-38 cells contained high concentrations of HGF ligand ($>7\text{ng/ml}$), whereas the conditioned media from GEO tumor cells did not (0.2ng/ml), Figure 3D. Phospho-MET was increased when GEO tumor cells were treated with conditioned media from either fibroblast cell line. Consistent with results obtained herein with recombinant HGF, treatment of GEO tumor cells with conditioned media from either HGF-expressing fibroblast cell line resulted in reduced ability of OSI-906 to inhibit AKT signaling. In the presence of the fibroblast medias, we saw more complete inhibition of phospho-AKT/PRAS40 when OSI-906 was combined with PHA compared to either inhibitor individually, Figure 3D. Treatment with the conditioned medias also resulted in increased phospho-ERK, which was suppressed by PHA. Collectively, these data indicate that sensitivity to OSI-906 might be mitigated by active MET, which could be stimulated by stromal derived HGF. The data indicate a rationale for combining OSI-906 with a MET inhibitor to achieve maximum sustained anti-proliferative activity.

[227] *Increased phosphorylation of EGFR, ErbB3, and MET can occur upon treatment with OSI-906*

[228] Short term (2 hour) treatment of MDA-1186 and GEO tumor cell lines with OSI-906 resulted in inhibition of phospho-AKT/PRAS40. However, the phosphorylation of both AKT and PRAS40 recovers upon prolonged exposure (24 hours or greater) to OSI-906, Figure 4A. Herein, we find that prolonged treatment (24 hours) with OSI-906 is associated with increased phosphorylation of both EGFR and MET, Figure 4A and Figure 9.

[229] We sought to determine if the crosstalk between IGF-1R/IR and MET was also bi-directional. The increased phospho-MET evoked by OSI-906 treatment was inhibited by PHA, Figure 4B. PHA treatment resulted in a modest increase in phospho-IR and phospho-IGF-1R. More striking, PHA treatment was associated with a significant increase in association between p85-PI3K and IR. These data indicate that similar to EGFR-IGF-1R/IR compensatory crosstalk, there is bi-directional crosstalk between IGF-1R/IR and MET, where blockade of either receptor axis results in increased phosphorylation for the reciprocal receptor and/or enhanced coupling of the reciprocal receptor to the PI3K-AKT pathway.

[230] *Knockdown of MET expression results in increased sensitivity to OSI-906 and erlotinib*

[231] In order to further test the hypothesis that signaling through MET modulates sensitivity to OSI-906, alone or in combination with erlotinib, we stably knocked down expression of MET in GEO cells using shRNA. Significant knockdown of MET (>75%) was achieved by shRNA (Figure 10), however this did not affect cell proliferation (Figure 11) indicating that ablation of MET expression is either not sufficient to affect cell growth by itself in these tumor cells or that they have adapted to loss of MET by relying on alternate pathways. In EV control cells treatment with erlotinib resulted in increased interactions between IR and p85-PI3K, and this was inhibited upon co-treatment with OSI-906, Figure 5A. Treatment with MAB391 also resulted in increased coupling of IR and p85-PI3K, consistent with IR compensatory signaling upon inhibition of IGF-1R. Consistent with observations using PHA, p85-PI3K interactions with IR were also significantly enhanced upon MET knockdown, and this was inhibited by OSI-906.

[232] For GEO tumor cells MET knockdown was associated with increased sensitivity to erlotinib and OSI-906, Figure 5B (left panel). While neither erlotinib or OSI-906 had any significant effect on caspase 3/7 activity for EV control GEO cells, both agents effectively activated caspase 3/7 activity in the context of MET knockdown. These data further support the hypothesis that MET signaling can mitigate sensitivity to an inhibitor of EGFR or IGF-1R/IR.

[233] We additionally assessed the impact of MET knockdown on the activity for OSI-906 in combination with erlotinib, Figure 5C. The combination of OSI-906 and erlotinib resulted in synergistic inhibition of cell proliferation and survival for parental GEO tumor cells, however the activity for this combination was enhanced in the context of MET knockdown. For example, the maximal inhibition of proliferation by OSI-906 combined with erlotinib was improved to >90% upon knockdown of MET, Figure 5C.

[234] We explored the impact of MET knockdown on downstream signaling in GEO cells, Figure 5D. In EV control cells 24 hour treatment with either OSI-906 or erlotinib resulted in a moderate inhibition of AKT/PRAS40 phosphorylation (~60%). Although the combination of OSI-906 and erlotinib resulted in greater inhibition of AKT/PRAS40 phosphorylation than either agent individually (~90%) it did not fully reduce phosphorylation to undetectable levels. In contrast, in MET KD GEO cells OSI-906 alone reduced AKT phosphorylation by ~95%, and the combination of OSI-906 and erlotinib resulted in inhibition of AKT/PRAS40 phosphorylation to undetectable levels. These data further highlight the improved activity of OSI-906, alone or in combination with erlotinib, in the context of reduced MET signaling. Collectively, these data support the hypothesis that EGFR and MET may both contribute to reduced sensitivity to an IGF-1R/IR inhibitor and that maximal anti-tumor activity might be achieved by the concomitant inhibition of EGFR, IGF-1R, IR, and MET, Figure 6.

[235] **Discussion**

[236] RTK signaling controls tumor cell proliferation and resistance to apoptosis (1, 2, 4). The tumorigenic properties of receptors within the EGF, HGF, and IGF axes are well established in preclinical models, and this understanding has spurred clinical evaluation of drugs targeting these RTKs. Over recent years there has been growing appreciation for plasticity among RTK signaling networks as a major mode of resistance to individual RTK inhibitors, wherein blockade of an individual receptor axis may be associated with increased signaling by an alternate RTK. Resistance to EGFR inhibitors can be mediated by a gain in signaling through either the IGF-1R/IR or MET axes, and combining EGFR inhibitors with other agents targeting IGF-1R/IR or MET results in enhanced sensitivity in a variety of preclinical models (19, 25, 26, 38-40). Evaluation of EGFR inhibitors with IGF-1R/IR and MET inhibitors is currently underway in clinical studies, and emerging clinical data show promise for enhanced efficacy of an EGFR tyrosine kinase inhibitor in combination with a MET tyrosine kinase inhibitor (30).

[237] In this report, we have demonstrated for the first time that MET signaling can contribute to reduced sensitivity to not only to EGFR inhibitors but also to IGF-1R/IR

inhibitors. EGFR, MET, and IGF-1R/IR are coordinately expressed and activated in several human tumor cell lines. Sensitivity to tyrosine kinase inhibitors of either EGFR (erlotinib) or IGF-1R/IR (OSI-906) was associated with an epithelial phenotype. Interestingly, we found that elevated phospho-MET is also associated with an epithelial phenotype, and phospho-MET was significantly higher in the subset of tumor cell lines that were sensitive to OSI-906.

[238] Dual inhibition of IGF-1R and IR upon treatment with OSI-906 resulted in enhanced phosphorylation of both EGFR and MET. EGF and HGF can both promote reduced sensitivity to IGF-1R/IR inhibition. Culture of tumor cells in media derived from HGF-expressing fibroblasts resulted in reduced sensitivity to OSI-906, indicating how a paracrine source of HGF may compromise IGF-1R/IR inhibitor sensitivity through activation of MET signaling. Under HGF-supplemented conditions the combination of an IGF-1R/IR TKI and a MET TKI resulted in synergistic inhibition of cellular proliferation and signaling through the AKT pathway. Crosstalk between IGF-1R/IR and EGFR or MET was bi-directional, where treatment of tumor cells with either erlotinib or the MET TKI resulted in increased interactions between p85-PI3K and IR.

[239] In order to further validate crosstalk between the IGF-1R/IR and MET signaling axes, we generated tumor cells with stable knockdown of MET expression using shRNA. MET KD was associated with enhanced sensitivity to either EGFR or IGF-1R/IR TKIs. In GEO tumor cells, while neither OSI-906 nor erlotinib treatment resulted in apoptosis in control cells, both agents could promote apoptosis in cells with ablated MET, and OSI-906 was more effective at inhibiting AKT signaling in GEO tumor cells upon ablation of MET. Furthermore, we showed that the combination of EGFR and IGF-1R/IR TKIs was more efficacious in the context of MET knockdown. Collectively these data support a model in which crosstalk between the IGF, EGF, and HGF axis may mediate adaptive resistance to inhibition of any individual RTK. This highlights the necessity of combinatorial RTK targeting for the treatment of cancer.

[240] **References**

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[281] **Abbreviations**

[282] IGF-1, Insulin-like growth factor 1 (also known as somatomedin C; human gene = GeneID 3479); IGF-2, Insulin-like growth factor 2 (also known as somatomedin A; human gene = GeneID 3481); IGF, Insulin-like growth factor (e.g. IGF-1, IGF-2); IGF-1R, Insulin-like growth factor 1 receptor (human gene = GeneID 3481); EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; NSCL, non-small cell lung; NSCLC, non-small cell lung cancer; HNSCC or SCCHN, head and neck squamous cell carcinoma; CRC, colorectal cancer; MBC, metastatic breast cancer; PaCa, pancreatic cancer; Brk, Breast tumor kinase (also known as protein tyrosine kinase 6 (PTK6)); FCS, fetal calf serum; LC, liquid chromatography; MS, mass spectrometry; IR or INSR, insulin receptor (human gene = GeneID 3643); TGF α , transforming growth factor alpha; HB-EGF, heparin-binding epidermal growth factor; LHRH, luteinizing hormone-releasing hormone; LPA,

lysophosphatidic acid; IC₅₀, half maximal inhibitory concentration; pY, phosphotyrosine; wt, wild-type; PI3K, phosphatidylinositol-3 kinase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MAPK, mitogen-activated protein kinase; PDK-1, 3-Phosphoinositide-Dependent Protein Kinase 1; Akt, also known as protein kinase B, is the cellular homologue of the viral oncogene v-Akt; pAkt, phosphorylated Akt; mTOR, mammalian target of rapamycin; 4EBP1, eukaryotic translation initiation factor-4E (mRNA cap-binding protein) Binding Protein-1, also known as PHAS-I; p70S6K, 70 kDa ribosomal protein-S6 kinase; eIF4E, eukaryotic translation initiation factor-4E (mRNA cap-binding protein); Raf, protein kinase product of Raf oncogene; MEK, ERK kinase, also known as mitogen-activated protein kinase kinase; ERK, Extracellular signal-regulated protein kinase, also known as mitogen-activated protein kinase; PTEN, “Phosphatase and Tensin homologue deleted on chromosome 10”, a phosphatidylinositol phosphate phosphatase; pPROTEIN, phospho-PROTEIN, “PROTEIN” can be any protein that can be phosphorylated, e.g. EGFR, Akt, IGF-1R, IR, ERK, S6 etc; PBS, phosphate-buffered saline; RTK, Receptor Tyrosine Kinase; TGI, tumor growth inhibition; WFI, Water for Injection; SDS, sodium dodecyl sulfate; ErbB2, “v-erb-b2 erythroblastic leukemia viral oncogene homolog 2”, also known as HER-2; ErbB3, “v-erb-b2 erythroblastic leukemia viral oncogene homolog 3”, also known as HER-3; ErbB4, “v-erb-b2 erythroblastic leukemia viral oncogene homolog 4”, also known as HER-4; FGFR, Fibroblast Growth Factor Receptor; MET, met proto-oncogene (a.k.a. c-met, or hepatocyte growth factor receptor; human gene = GeneID 4233); DMSO, dimethyl sulfoxide; “Taxol”, paclitaxel; PHA, PHA-665752; FCS, fetal calf serum; FGF, fibroblast growth factor; HGF, hepatocyte growth factor. PRAS40, AKT1 substrate 1 (proline-rich) (a.k.a. AKT1S1; human gene = GeneID 84335); IP, immunoprecipitation; IB, immunoblotting; IP:p85/IB:IR, immunoprecipitation with p85 antibodies followed with immunoblotting with IR antibodies.

[283] Incorporation by Reference

[284] All patents, published patent applications and other references disclosed herein are hereby expressly incorporated herein by reference.

[285] Equivalents

[286] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an MET kinase inhibitor and an IGF-1R kinase inhibitor.
2. The method of claim 1, wherein the IGF-1R kinase inhibitor comprises OSI-906.
3. The method of claim 1, wherein the IGF-1R kinase inhibitor comprises an anti-IGF-1R antibody, or fragments thereof.
4. The method of claim 1, wherein the IGF-1R kinase inhibitor comprises an IGF binding protein, or fragments thereof.
5. The method of claim 1, wherein the MET kinase inhibitor comprises a small molecule MET kinase inhibitor.
6. The method of claim 1, wherein the MET kinase inhibitor comprises an anti-MET antibody, or fragments thereof.
7. The method of claim 1, wherein the MET kinase inhibitor and the IGF-1R kinase inhibitor are the same molecule.
8. A pharmaceutical composition comprising an MET kinase inhibitor and an IGF-1R kinase inhibitor, in a pharmaceutically acceptable carrier.
9. The composition of claim 8, wherein the IGF-1R kinase inhibitor comprises OSI-906.
10. The composition of claim 8, wherein the MET kinase inhibitor comprises a small molecule MET kinase inhibitor.

11. The composition of claim 8, wherein one or both of the MET kinase inhibitor and IGF-1R kinase inhibitor is an antibody, or fragments thereof.
12. The composition of claim 8, wherein the IGF-1R kinase inhibitor comprises one or more IGF binding proteins.
13. A kit comprising one or more containers, comprising an MET kinase inhibitor and a an IGF-1R kinase inhibitor.
14. The kit of claim 13, wherein the IGF-1R kinase inhibitor comprises OSI-906.
15. The kit of claim 13, wherein the MET kinase inhibitor comprises a small molecule MET kinase inhibitor.
16. The kit of claim 13, wherein one or both of the MET kinase inhibitor and IGF-1R kinase inhibitor is an antibody, or fragments thereof.
17. The kit of claim 13, wherein the IGF-1R kinase inhibitor comprises one or more IGF binding proteins.
18. A method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an MET kinase inhibitor, an IGF-1R kinase inhibitor and an EGFR kinase inhibitor.
19. The method of claim 18, wherein the EGFR kinase inhibitor comprises erlotinib.
20. A method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of a combination of an MET kinase inhibitor, an IGF-1R kinase inhibitor, an IR kinase inhibitor and an EGFR kinase inhibitor.
21. The method of claim 20, wherein the EGFR kinase inhibitor comprises erlotinib.

Figure 1A

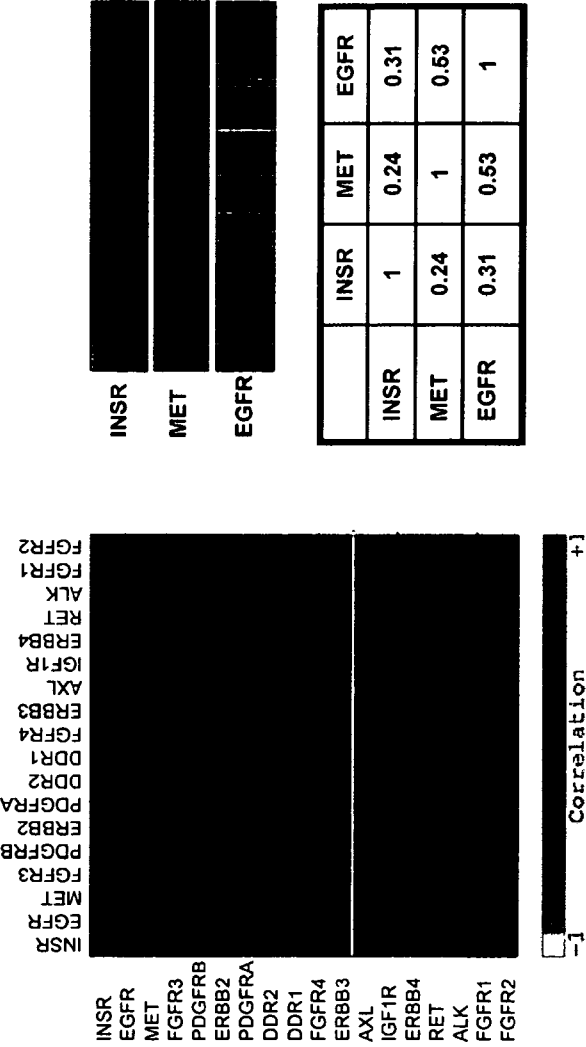


Figure 1B

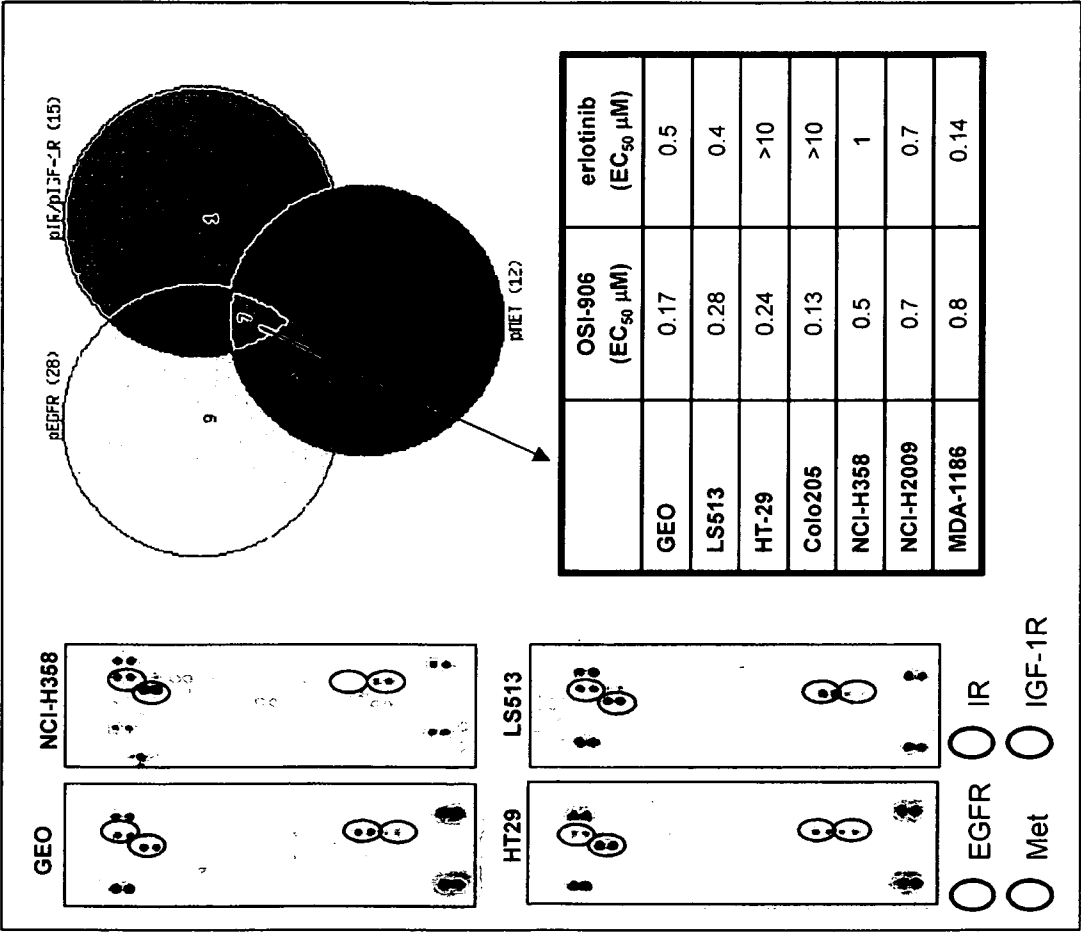


Figure 2A

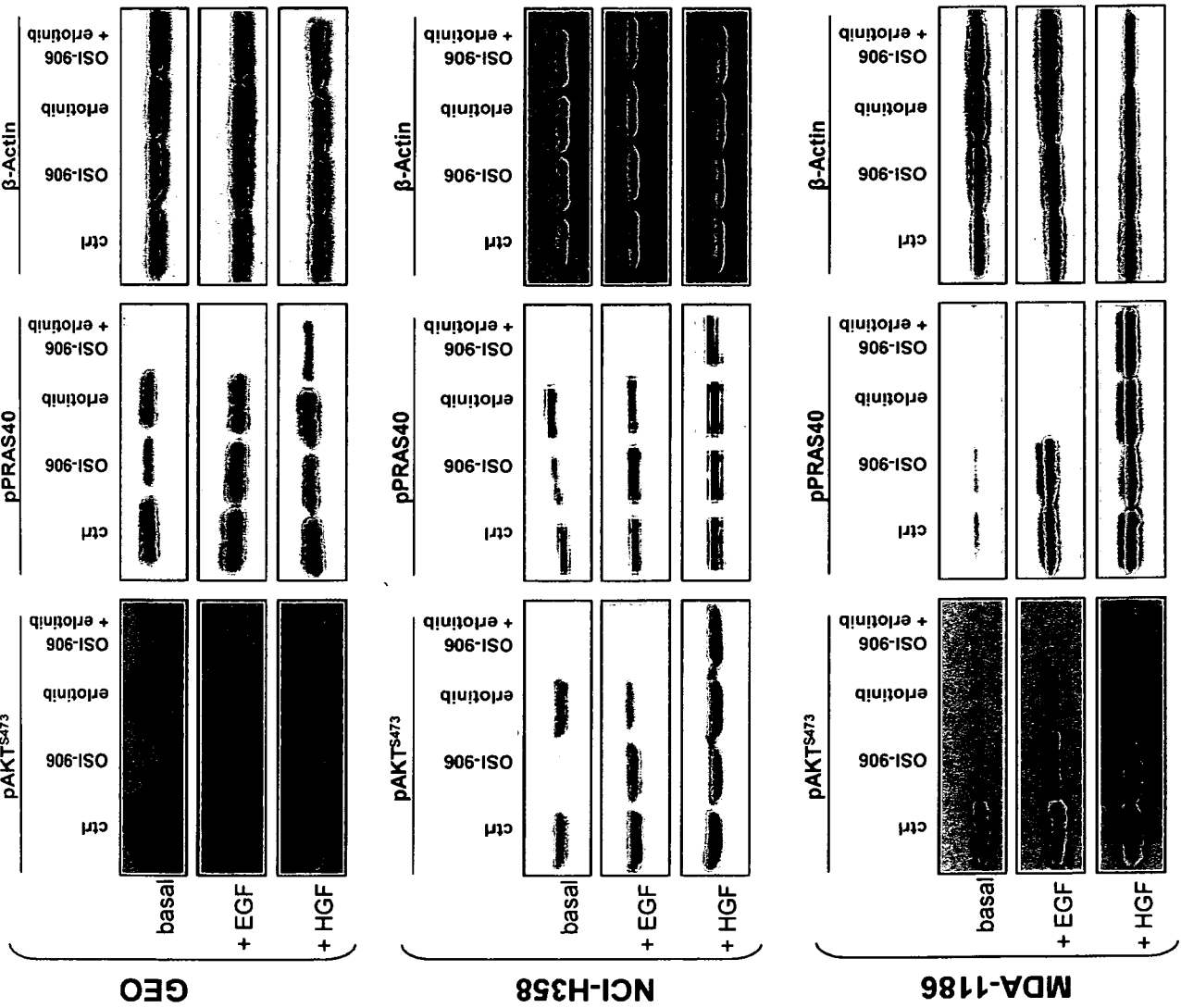


Figure 2B

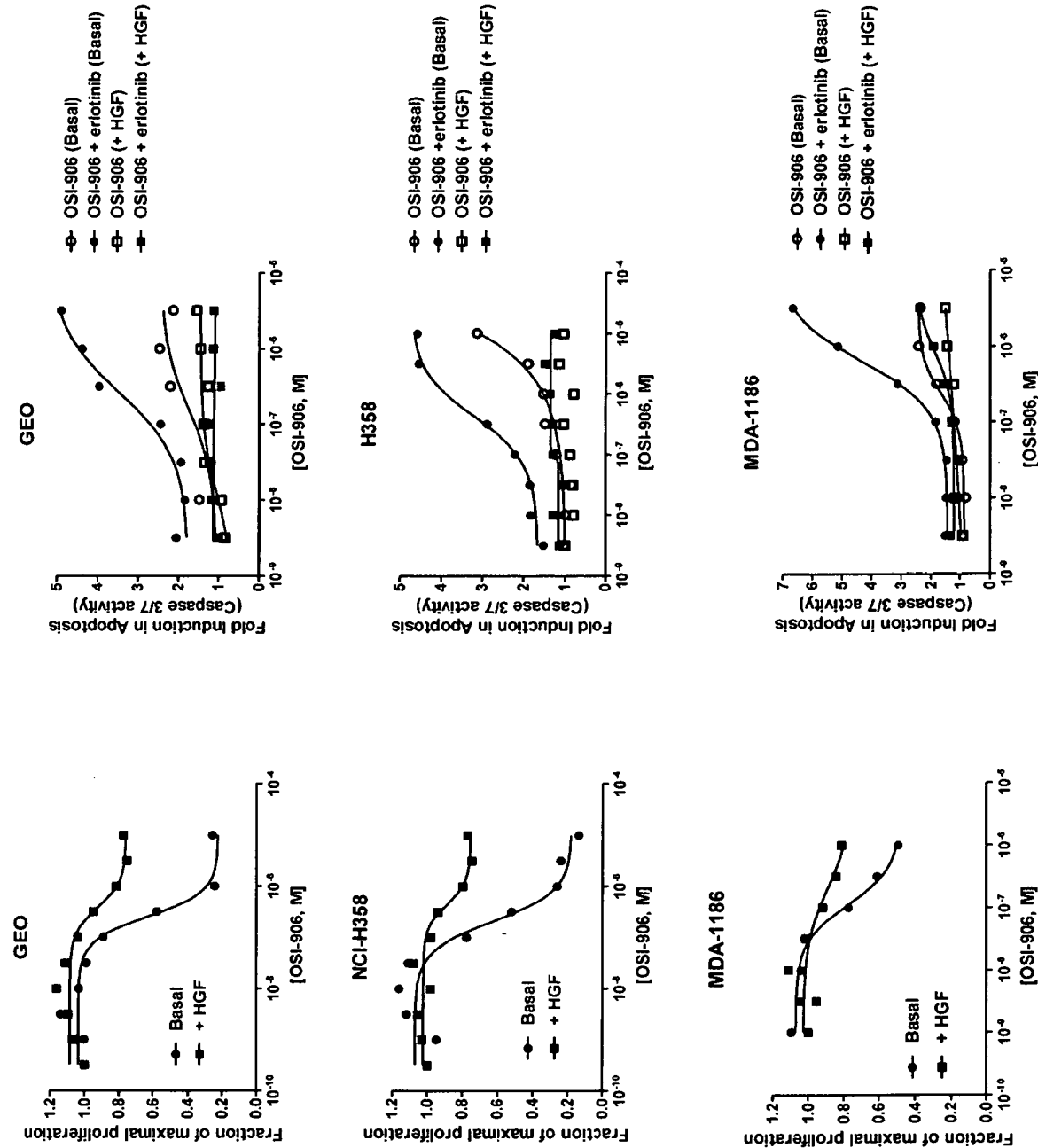


Figure 3A

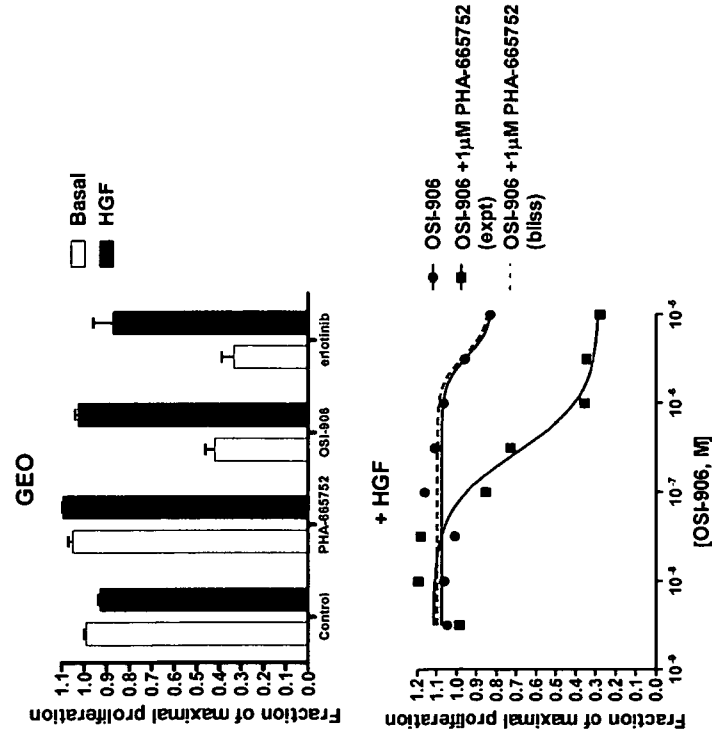


Figure 3B

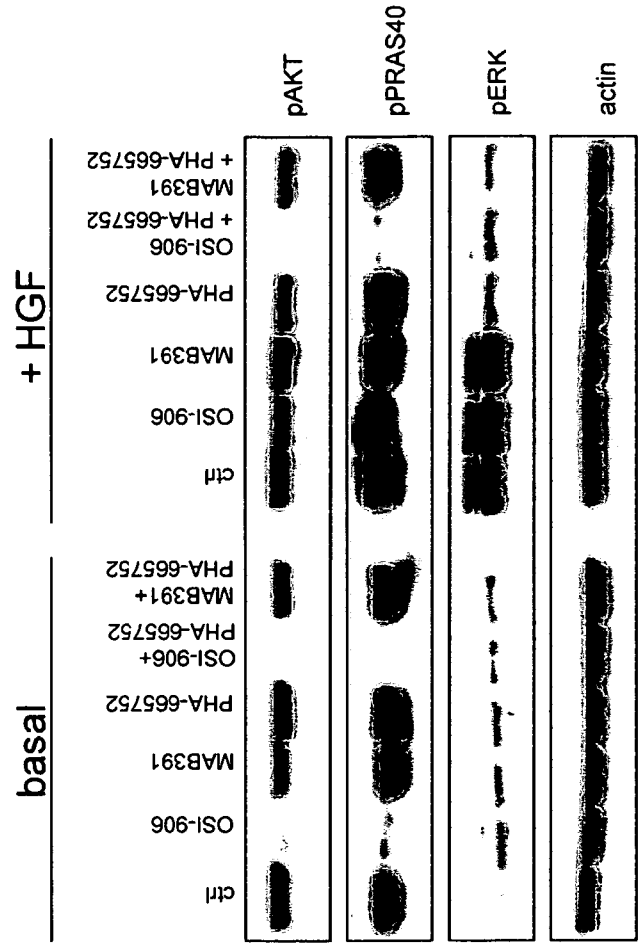
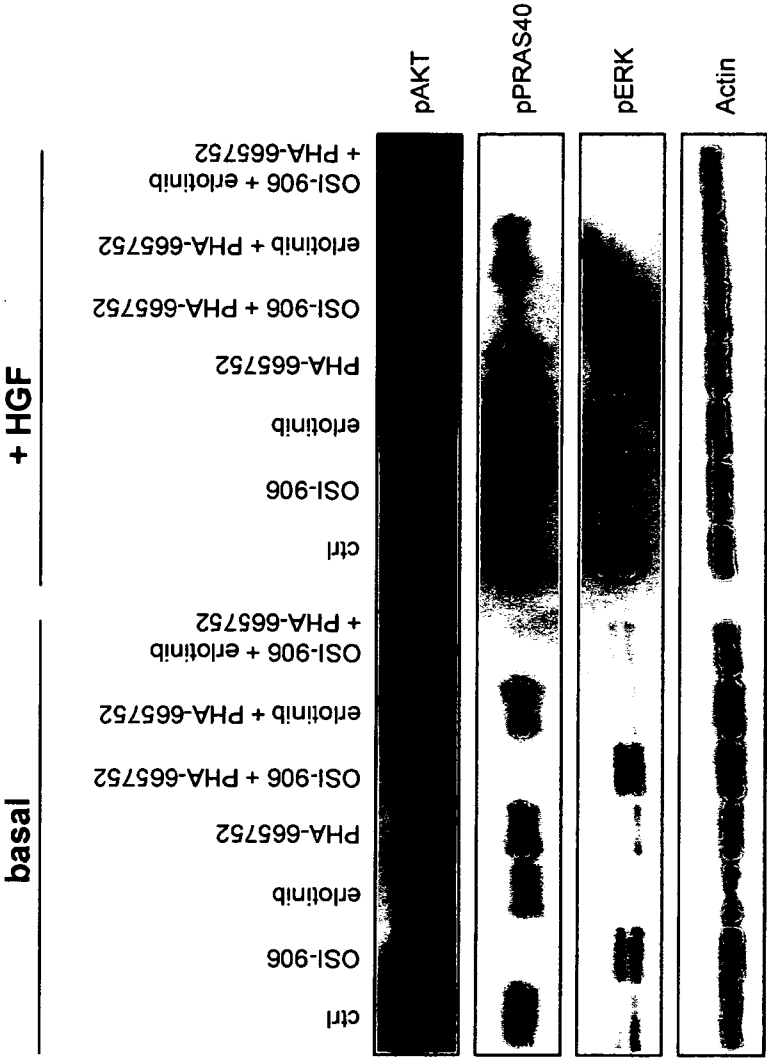


Figure 3C



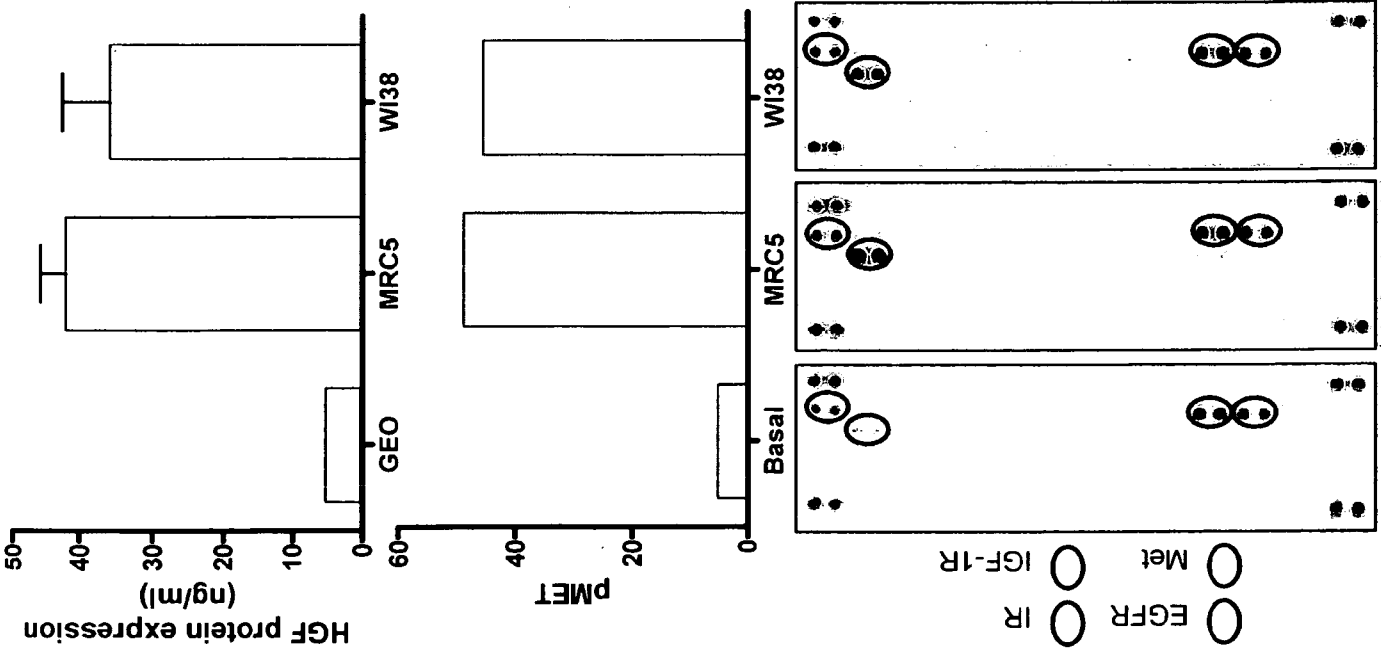


Figure 3D

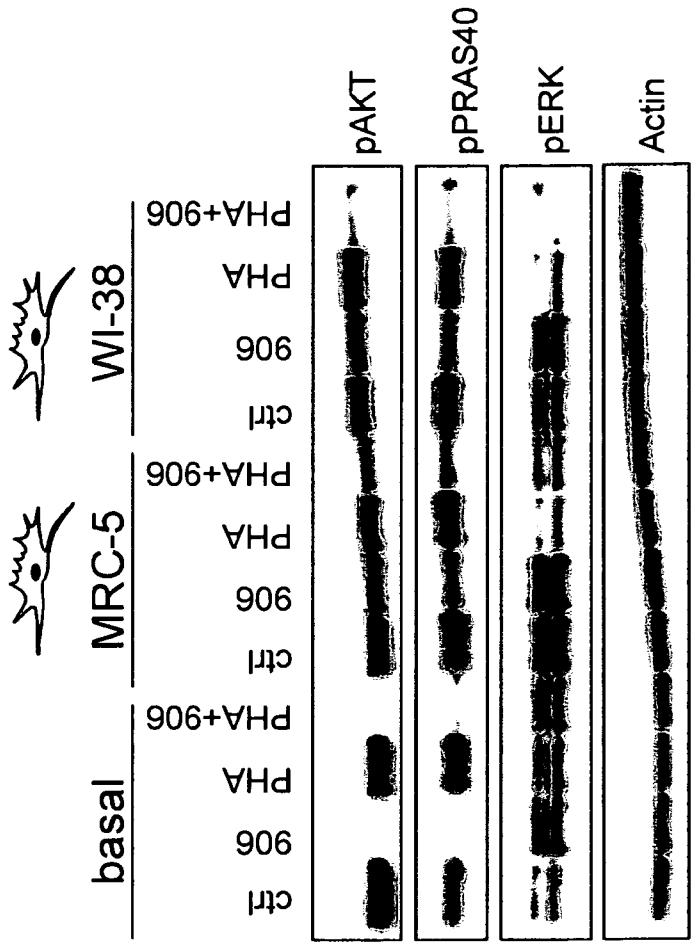
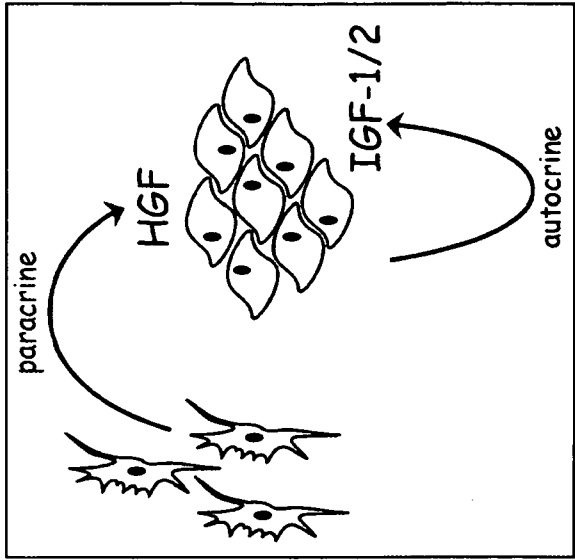
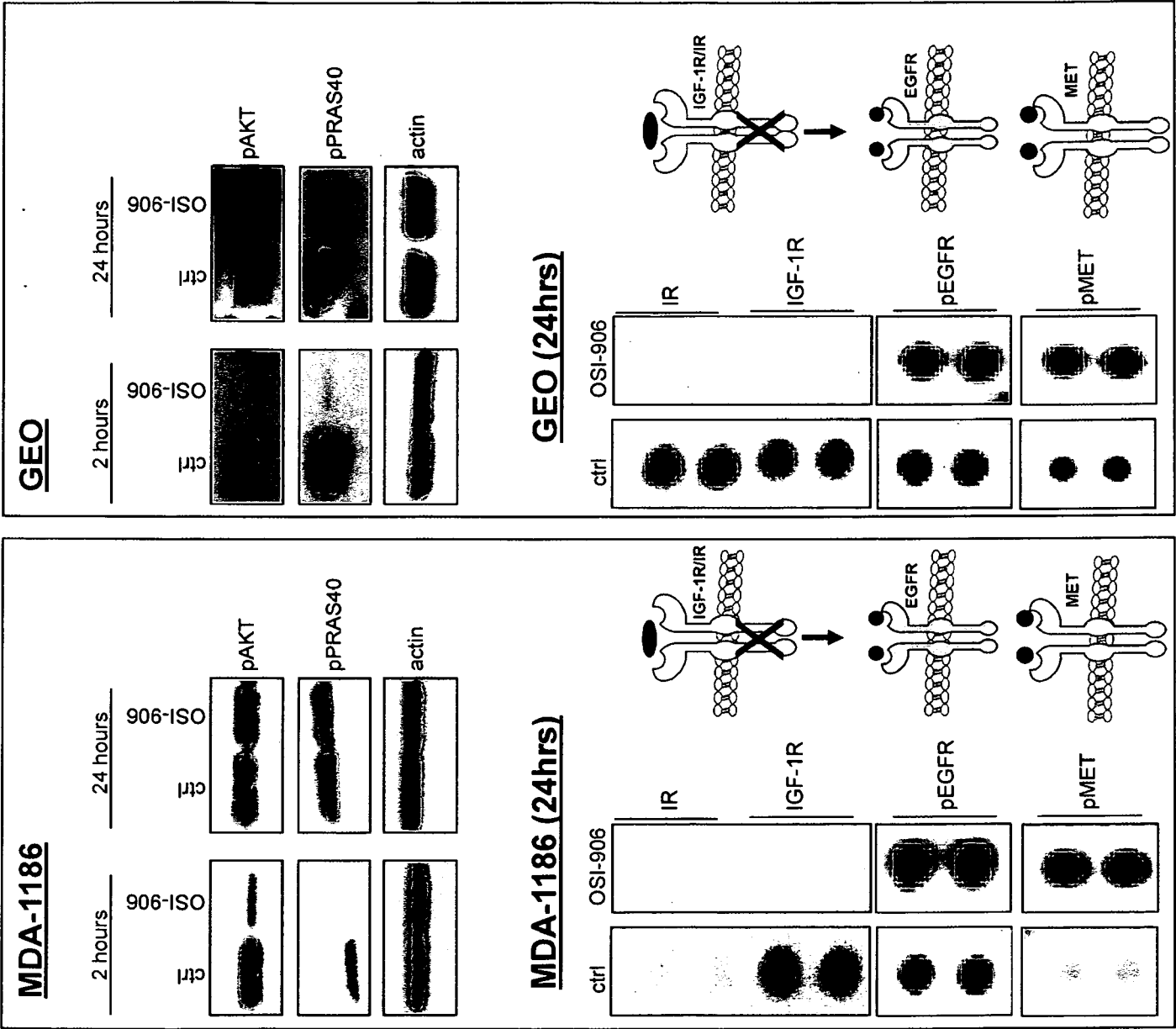


Figure 4A



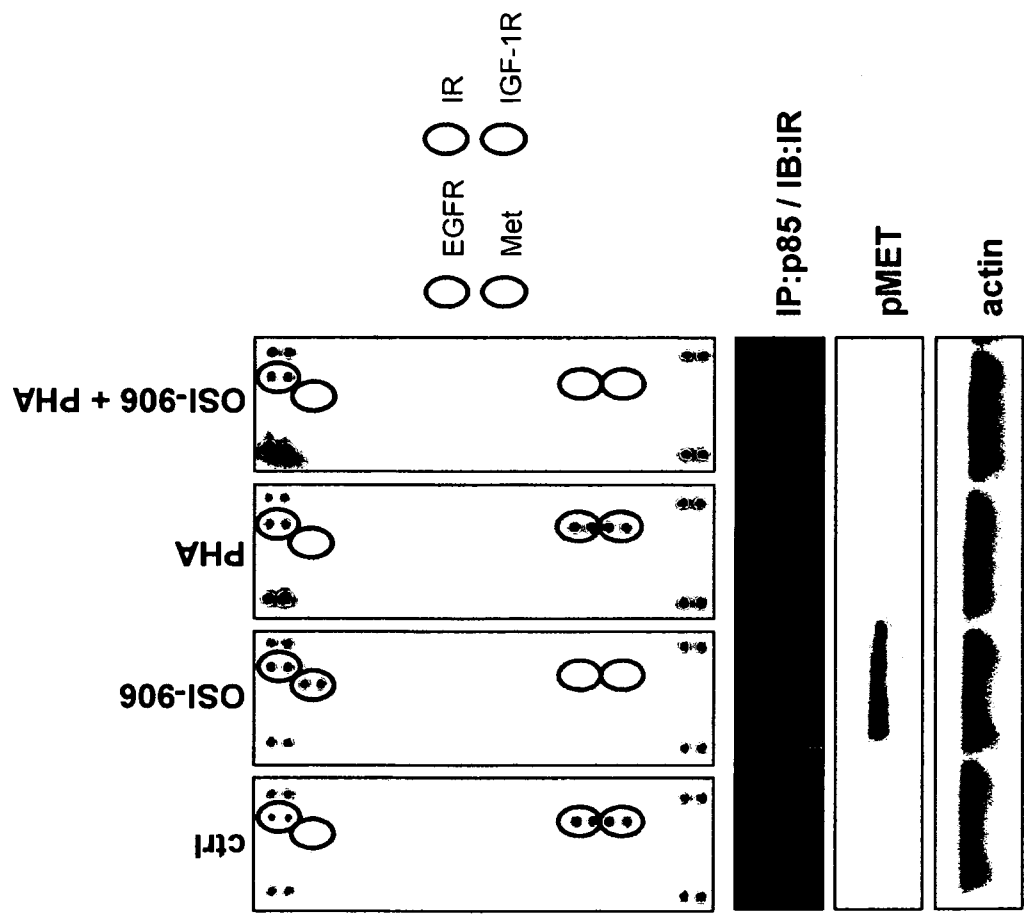


Figure 4B

Figure 5A

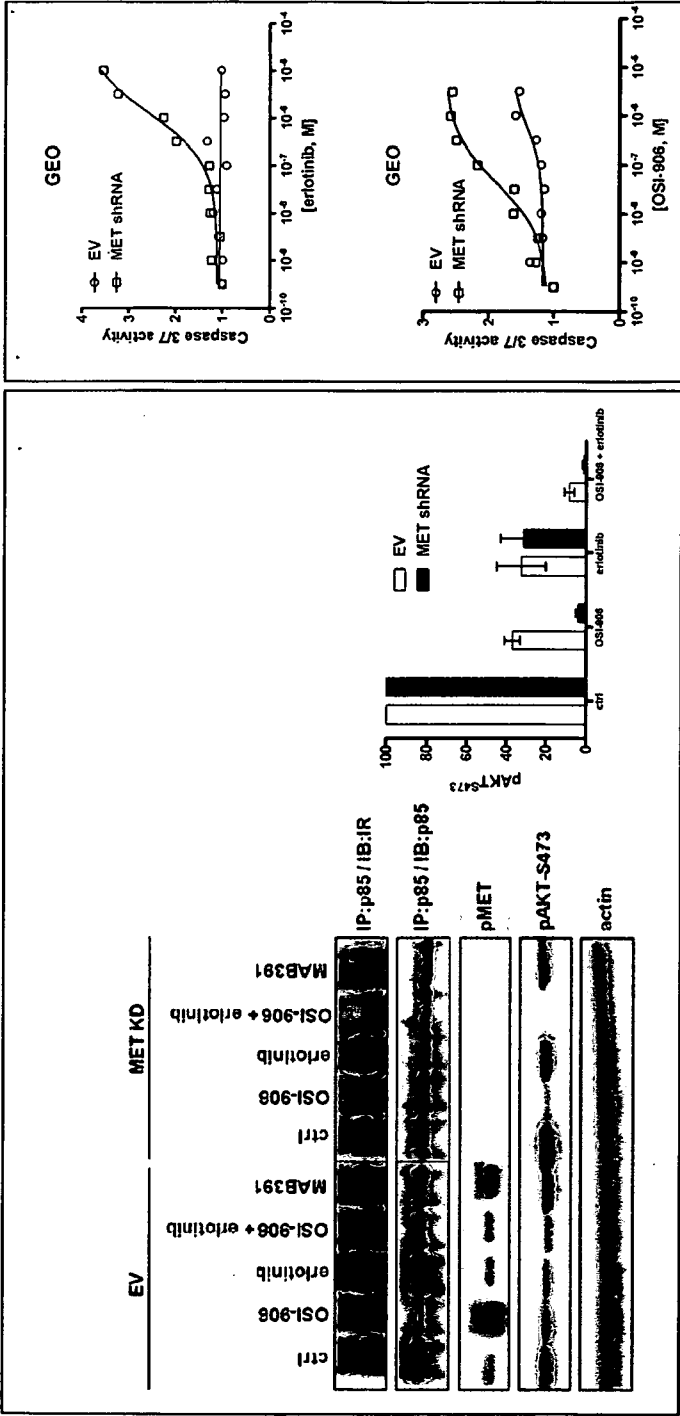


Figure 5B

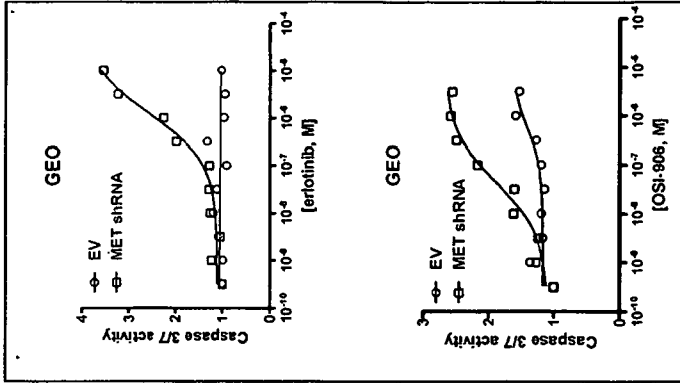
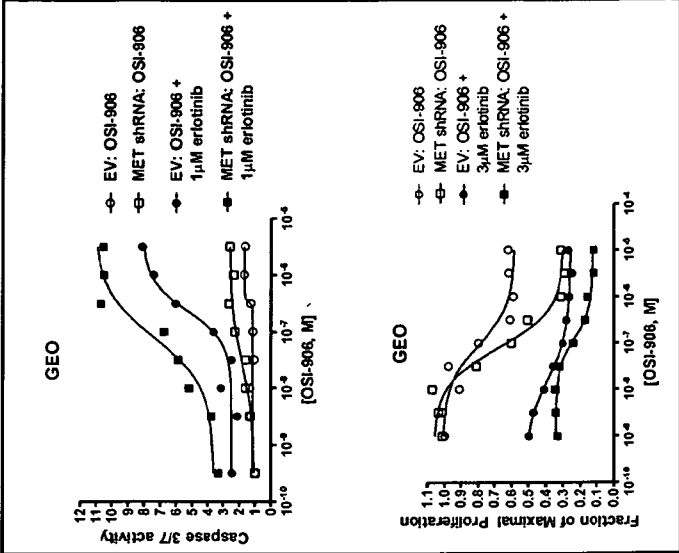


Figure 5C



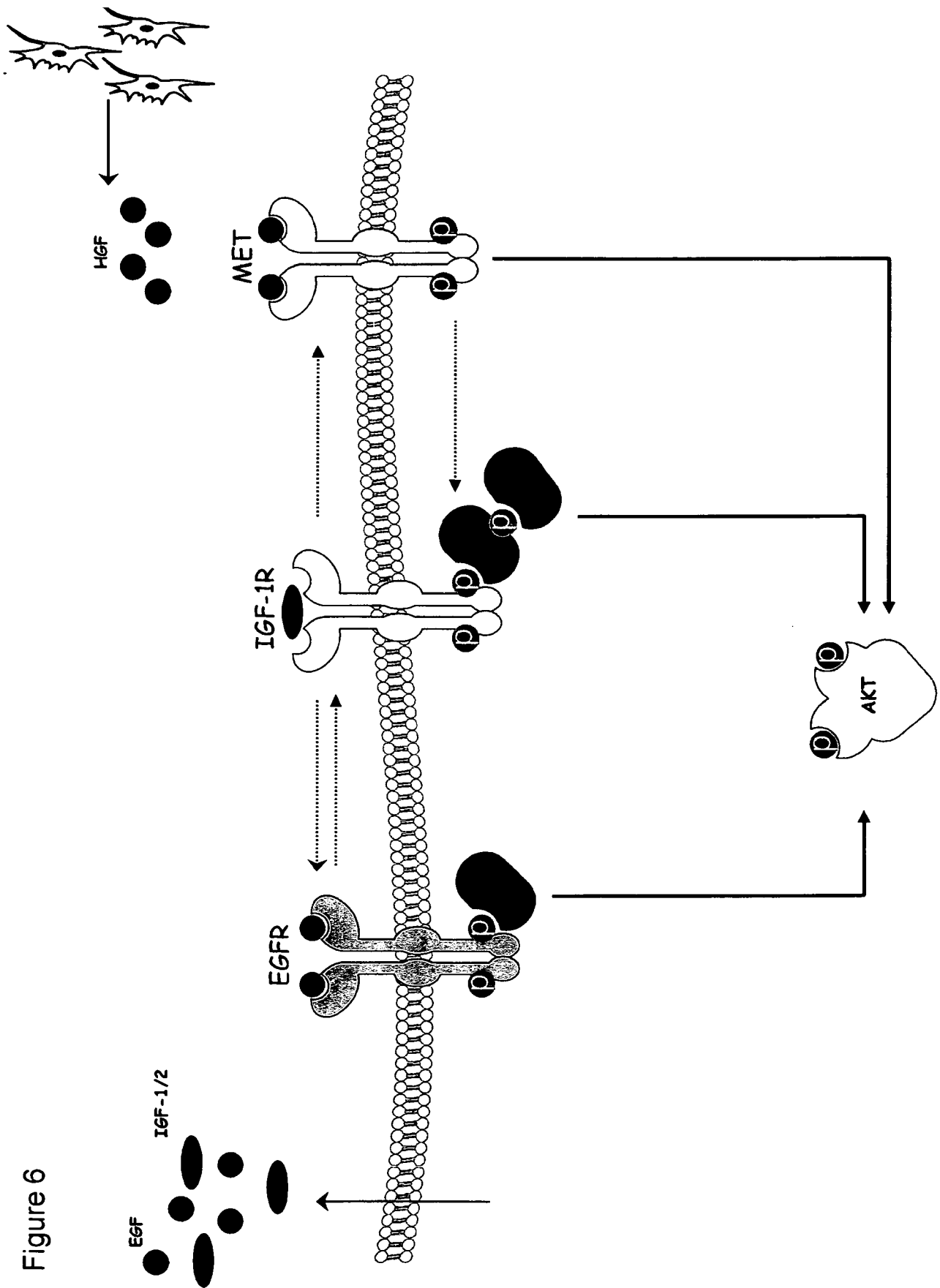


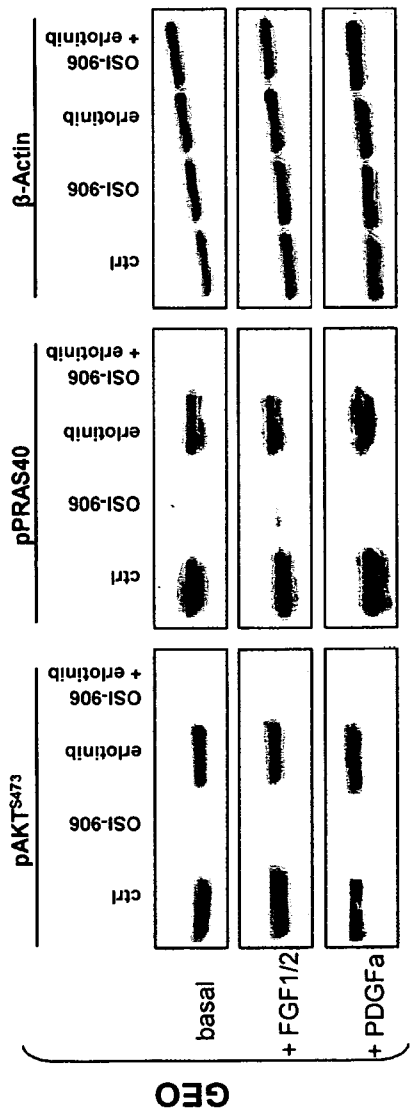
Figure 6

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Figure 7

	Tumor Type	pEGFR	pIR	pIGF-1R	pMET	EMT	KRAS	BRAF	PIK3CA	PTEV	OSI-906	erlotinib
CaCo2	CRC					ND					0.38	0.5
Colo205	CRC					E		M			0.13	>10
HCT-116	CRC					ND	M		M		>10	>10
HT-29	CRC					E		M			0.24	>10
GEO	CRC					E	M				0.17	0.50
LS174T	CRC					ND	M		M		1.45	0.74
LS180	CRC					ND	M				>10	0.62
LS513	CRC					ND	M				0.28	0.4
SW637	CRC					ND	M				0.08	0.1
Calu6	NSCLC					M	M				>10	>10
H358	NSCLC					E	M				0.5	1.0
H441	NSCLC					E	M				0.5	>10
H446	NSCLC					ND				M	>10	>10
H460	NSCLC					M	M		M		>10	>10
H1437	NSCLC					ND					0.10	>10
H2009	NSCLC					E	M				0.7	0.7
SW1573	NSCLC					M	M		M		1.0	>10
HCC827	NSCLC					ND	ND	ND	ND	ND	>10	0.01
HCC4006	NSCLC					ND	ND	ND	ND	ND	>10	0.03
HCC2935	NSCLC					ND	ND	ND	ND	ND	>10	0.07
LC2-AD	NSCLC					ND					0.4	2.7
H1703	NSCLC					M					>10	>10
A549	NSCLC					M	M				2.1	>10
Colo699	NSCLC					ND	ND	ND	ND	ND	0.09	>10
H23	NSCLC					M	M				0.17	>10
H522	NSCLC					M					0.3	1.5
MDA-1188	SCCHN					E	ND	ND	ND	ND	0.8	0.14
SCC4	SCCHN					ND					0.5	>10
1386	SCCHN					M	ND	ND	ND	ND	>10	>10
Cal27	SCCHN					ND					>10	0.09
2650	SCCHN					ND					0.4	>10
CFPAC	PaCa					E	M				1.2	0.68
BxPC3	PaCa					E					0.12	1.3
MiaPaca-2	PaCa					M	M				>10	>10
A1165	PaCa					M	M				>10	>10

Figure 8



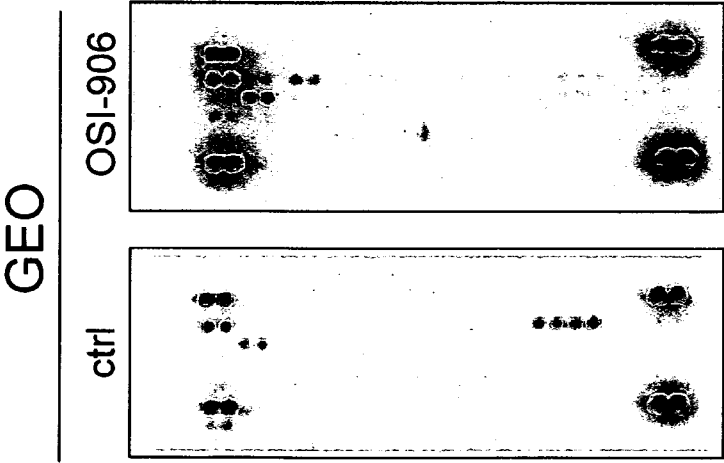
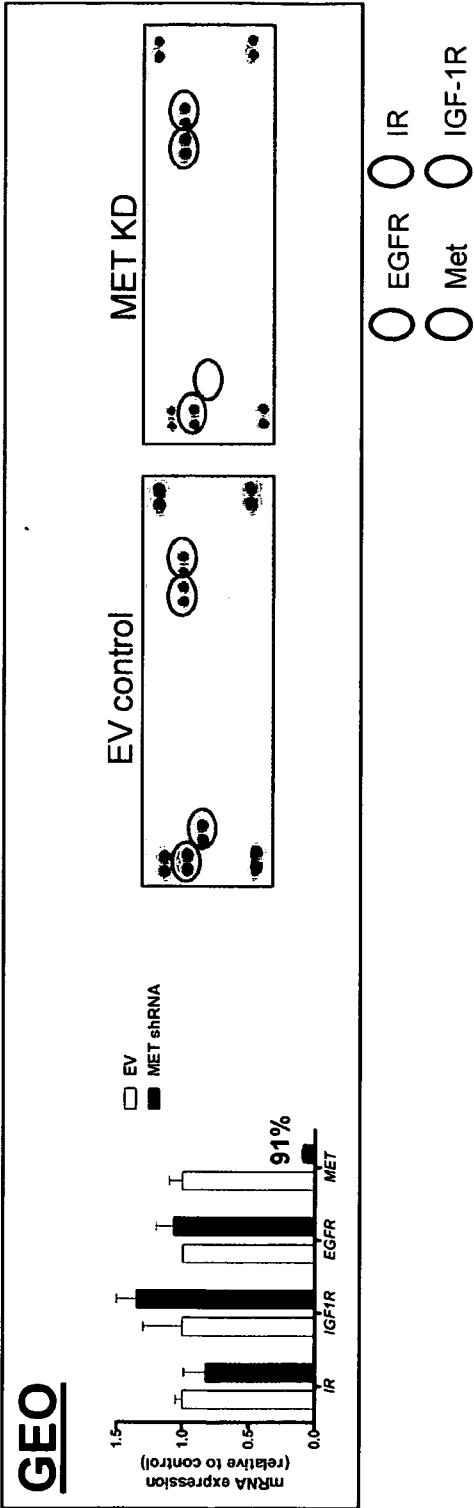
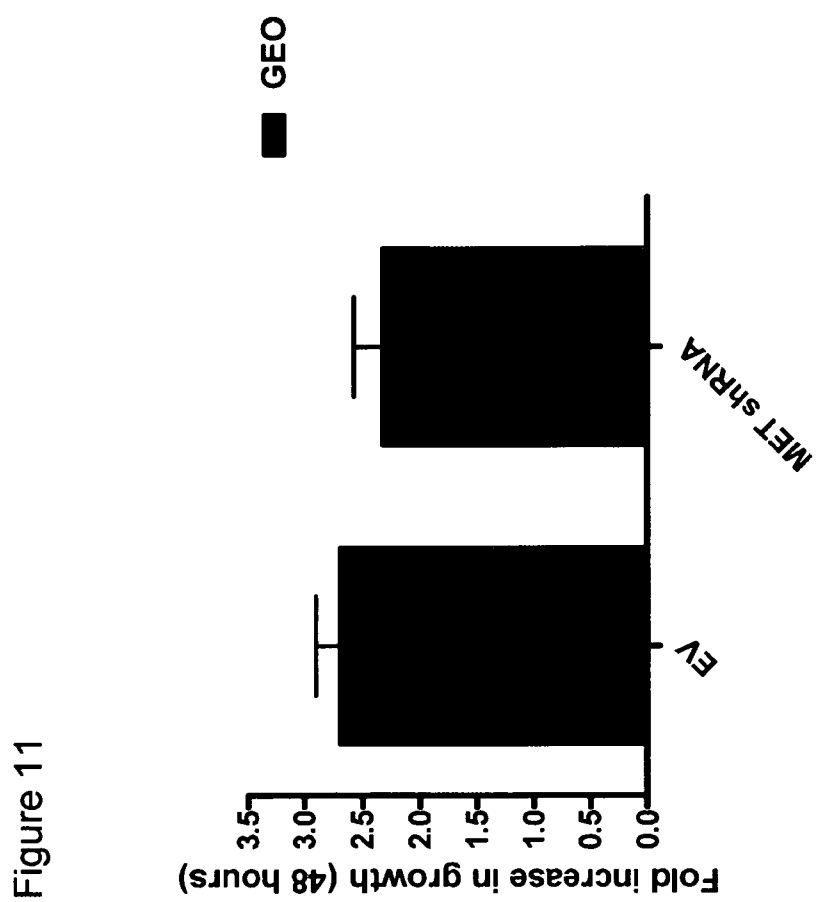


Figure 9

Figure 10





INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/035358

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K38/00	A61K39/00
	A61K31/517	A61K31/713
		A61P35/00
		A61K45/06
		A61K31/404
		A61K31/4985
		A61P35/04
		A61K31/53
ADD.		
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)		
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 practicable, search terms used)		
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/068110 A1 (SHANG YONGLEI [US] ET AL) 12 March 2009 (2009-03-12) paragraphs [0092], [0107], [0600]; claims -----	1,3-6,8, 10-13, 15-17
X	US 2011/224191 A1 (CHEN XIN [US] ET AL) 15 September 2011 (2011-09-15) paragraph [0310]; claims 1,14,20,21,24 ----- -/--	1,5,8, 10,13, 15,18
☒ Further documents are listed in the continuation of Box C. ☒ See patent family 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 application or patent 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
20 June 2013		01/07/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gradassi, Giulia

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/035358

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	KUHN DEBORAH J ET AL: "Blockade of IGF-1R with OSI-906 Overcomes Bortezomib-Resistance in Multiple Myeloma", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 118, no. 21 1 November 2011 (2011-11-01), page 421, XP008162884, ISSN: 0006-4971 Retrieved from the Internet: URL:http://www.bloodjournal.org/ the whole document -----	1,2,5, 8-10, 13-15, 18,20
A,P	WANG X ET AL: "Bortezomib inhibits the angiogenesis mediated by mesenchymal stem cells", CANCER INVESTIGATION, MARCEL DEKKER INC, US, vol. 30, no. 9, 1 November 2012 (2012-11-01), pages 657-662, XP008162883, ISSN: 0735-7907, DOI: DOI:10.3109/07357907.2012.725442 abstract figure 5 page 660, right-hand column, paragraph 1 ----- -/--	1-21

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/035358

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	BROWN ERIC ET AL: "Combination treatment strategy of an IGF-1R kinase inhibitor, OSI-906, in models of progressive disease following initial response to EGFR tyrosine kinase inhibitor therapy", AMERICAN ASSOCIATION FOR CANCER RESEARCH. PROCEEDINGS OF THE ANNUAL MEETING; 100TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH; DENVER, CA, USA; APRIL 18 -22, 2009, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 50, 1 April 2009 (2009-04-01), page 419, XP001539735, ISSN: 0197-016X the whole document -----	1-21
Y	BREVET M ET AL: "Coactivation of receptor tyrosine kinases in malignant mesothelioma as a rationale for combination targeted therapy", JOURNAL OF THORACIC ONCOLOGY, LIPPINCOTT WILLIAMS & WILKINS, PHILADELPHIA, PA, US, vol. 6, no. 5, 1 May 2011 (2011-05-01), pages 864-874, XP008162890, ISSN: 1556-0864, DOI: 10.1097/JTO.0B013E318215A07D abstract figure 7 page 868, right-hand column, paragraph 2 -----	1-21

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Information on patent family members

International application No

PCT/US2013/035358

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			WO 2010059771 A1 27-05-2010
