[0005] Despite the significant advancement in the treatment of cancer, improved therapies are still being sought.

[0006] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY ~~OF THE INVENTION~~

[0007] Uses of a c-met antagonist for effectively treating cancer patients are provided. This application also provides better methods for diagnosing disease for use in treating the disease optionally with c-met antagonist in combination with a B-raf antagonist. In particular, results are described demonstrating that combination treatment using B-raf antagonist vemurafenib (PLX-4032) and c-met antagonist resulted in a statistically significant improvement in tumor regression, including a striking improved in partial responses, compared to treatment with vemurafenib alone. C-met expression was inversely correlated with sensitivity to vemurafenib treatment. In addition, patients with B-raf mutant melanoma who had higher levels of circulating hepatocyte growth factor (HGF) showed substantially reduced progression free survival and overall survival when treated with B-raf antagonist, relative to patients with lower circulating HGF levels treated with B-raf antagonist.

[0008] The present ~~invention~~disclosure provides combination therapies for treating a pathological condition, such as cancer, wherein a c-met antagonist is combined with a B-raf antagonist, thereby providing significant anti-tumor activity.

[0008a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for treating a patient with cancer wherein the medicament is to be administered with a c-met antagonist.

[0009] In one ~~aspect~~embodiment, provided are methods for treating a cancer patient who has increased likelihood of developing resistance to B-raf antagonist comprising administering an effective amount (in combination) of B-raf antagonist and c-met antagonist.

[0009a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for treating a cancer patient who has increased likelihood of developing resistance to B-raf antagonist wherein the medicament is to be administered with a c-met antagonist.

[0010] In one ~~aspect~~embodiment, provided are methods for increasing and/or restoring sensitivity to B-raf antagonist comprising administering to a cancer patient an effective amount of B-raf antagonist and c-met antagonist.

[0010a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for increasing and/or restoring sensitivity to B-raf antagonist in a cancer patient wherein the medicament is to be administered with a c-met antagonist.

[0011] In one ~~aspect~~embodiment, provided are methods for extending period of B-raf antagonist sensitivity comprising administering to a cancer patient an effective amount of B-raf antagonist and c-met antagonist.

[0011a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for extending period of B-raf antagonist sensitivity in a cancer patient wherein the medicament is to be administered with a c-met antagonist.

[0012] In one ~~aspect~~embodiment, provided are methods for treating a patient with B-raf resistant (B-raf antagonist resistant) cancer comprising administering an effective amount of B-raf antagonist and c-met antagonist.

[0012a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for treating a patient with B-raf antagonist resistant cancer wherein the medicament is to be administered with a c-met antagonist.

[0013] In one ~~aspect~~embodiment, provided are methods for extending duration of response to B-raf antagonist comprising administering an effect amount of B-raf antagonist and c-met antagonist.

[0013a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for extending duration of response to B-raf antagonist wherein the medicament is to be administered with a c-met antagonist.

[0014] In one ~~aspect~~embodiment, provided are methods for delaying or preventing development of HGF-mediated B-raf resistant cancer comprising administering an effective amount of B-raf antagonist and c-met antagonist.

[0014a] In one aspect, there is provided a use of a B-raf antagonist for the manufacture of a medicament for delaying or preventing development of HGF-mediated B-raf antagonist resistant cancer in a patient wherein the medicament is to be administered with a c-met antagonist.

[0015] In one ~~aspect~~embodiment, methods are provided for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is likely to have B-raf antagonist resistant cancer. In some embodiments, the patient's cancer has been shown to express B-raf biomarker. In some embodiments, c-met biomarker expression is protein expression and is determined in a sample from the patient using IHC. In some embodiments, high amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or IHC) indicates that the patient is likely to have B-raf antagonist resistant cancer. As used herein, "elevated" or "high" c-met refers to an amount of c-met associated with patient responsiveness to a treatment. In some embodiments, low amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or IHC) indicates that the patient is unlikely to have B-raf antagonist resistant cancer. In some embodiments, high c-met is low, moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, high c-met is moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. As used herein, a "low" amount of c-met refers to an amount of c-met associated with lack of response to a treatment, or, in some embodiments, an amount of c-met associated with worse response to a treatment (e.g. decreased clinical benefit compared to no treatment). In some embodiments, "low" c-met is low or no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met expression is no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein.

[0016] In one ~~aspect~~embodiment, methods are provided for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is likely to develop B-raf resistant cancer. In some embodiments, the patient's cancer has been shown to express B-raf biomarker. In some embodiments, c-met biomarker expression is protein expression and is determined in a sample from the patient using IHC. In some embodiments, the patient is treated with B-raf antagonist and c-met antagonist. In some embodiments, high amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or

IHC) indicates that the patient is likely to have B-raf antagonist resistant cancer. In some embodiments, high c-met is low, moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, high c-met is moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met is low or no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met expression is no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein.

[0016a] In one aspect, there is provided a method for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is a candidate for treatment with c-met antagonist and B-raf antagonist: to increase sensitivity of the patient's cancer to B-raf antagonist, restore sensitivity of the patient's cancer to B-raf antagonist, to extend the period of sensitivity of the patient's cancer to B-raf antagonist, and/or to prevent development of HGF-mediated B-raf antagonist resistance in the patient's cancer.

[0017] In one ~~aspect~~embodiment, methods are provided for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is a candidate for treatment with c-met antagonist and B-raf antagonist: to increase sensitivity of the patient's cancer to B-raf antagonist, restore sensitivity of the patient's cancer to B-raf antagonist, to extend the period of sensitivity of the patient's cancer to B-raf antagonist, and/or to prevent development of HGF-mediated B-raf antagonist resistance in the patient's cancer. In some embodiments, the patient's cancer has been shown to express B-raf biomarker. In some embodiments, c-met biomarker expression is protein expression and is determined in a sample from the patient using IHC. In some embodiments, the patient is treated with B-raf antagonist and c-met antagonist. In some embodiments, high amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or IHC) indicates that the patient is likely to have B-raf antagonist resistant cancer. In some embodiments, high c-met is low, moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, high c-met is moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met is low or no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met expression is no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein.

[0018] In one ~~aspect~~embodiment, methods are provided for selecting a therapy for a patient with cancer which has been shown to express B-raf biomarker comprising determining expression of c-met biomarker in a sample from the patient, and selecting a cancer medicament based on the level

of expression of the biomarker. In some embodiments, the patient is selected for treatment with a c-met antagonist in combination with B-raf antagonist if the cancer sample expresses c-met biomarker. In some embodiments, the patient is treated for cancer using therapeutically effective amount of the c-met antagonist and B-raf antagonist. In some embodiments, the patient is selected for treatment with a cancer medicament other than c-met antagonist if the cancer sample expresses substantially undetectable levels of the c-met biomarker. In some embodiments, high amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or IHC) indicates that the patient is likely to have B-raf antagonist resistant cancer. In some embodiments, high c-met is low, moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, high c-met is moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met is low or no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met expression is no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein.

[0018a] In one aspect, there is provided a method for identifying a patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist.

[0019] In one ~~aspect~~embodiment, methods are provided for identifying a patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist, comprising determining that the patient's cancer expresses c-met biomarker. In some embodiments, high amount of c-met biomarker (e.g., as determined using c-met IHC or detection of HGF using, e.g., ELISA or IHC) indicates that the patient is likely to have B-raf antagonist resistant cancer. In some embodiments, high c-met is low, moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, high c-met is moderate or high c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met is low or no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein. In some embodiments, "low" c-met expression is no c-met expression determined, e.g., relative to c-met staining intensity of control cell pellets A549, H441, H1155, and HEK-293 as described herein.

[0019a] In one aspect, there is provided a method for identifying a patient as at risk of developing resistance to a B-raf antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as at risk of developing resistance to a B-raf antagonist

[0020] In one ~~aspect~~embodiment, methods are provided for identifying a patient as at risk of developing resistance to a B-raf antagonist, comprising determining that the patient's cancer expresses c-met biomarker.

[0020a] In one aspect, there is provided a method of determining therapeutic efficacy of a B-raf antagonist for treating cancer in a patient comprising determining the presence of c-met biomarker and/or B-raf biomarker in a sample obtained from said patient by immunoassay, elisa, hybridization assay, PCR, 5' nuclease assay, IHC, and/or RT-PCR, and selecting the patient for treatment with a B-raf antagonist.

[0021] In one ~~aspect~~embodiment, methods are provided of determining therapeutic efficacy of a B-raf antagonist for treating cancer in a patient comprising determining the presence of c-met biomarker and/or B-raf biomarker in a sample obtained from said patient by immunoassay, elisa, hybridization assay, PCR, 5' nuclease assay, IHC, and/or RT-PCR, wherein the presence of c-met biomarker is indicative of B-raf antagonist being therapeutically effective to treat cancer in said subject. In some embodiments, the patient's cancer has been shown to express B-raf biomarker. In some embodiments, B-raf biomarker is mutant B-raf. In some embodiments, mutant B-raf is constitutively activated B-raf. In some embodiments, mutant B-raf is B-raf V600. In some embodiments, B-raf V600 is B-raf V600E. In some embodiments, mutant B-raf is one or more of B-raf V600K (GTG>AAG), V600R (GTG>AGG), V600E (GTG>GAA) and/or V600D (GTG>GAT). In some embodiments, mutant B-raf biomarker expression is determined using a method comprising (a) performing one or more of gene expression profiling, PCR (such as rtPCR or allele-specific PCR), RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH on a sample (such as a patient cancer sample); and (b) determining expression of mutant B-raf biomarker in the sample. In some embodiments, mutant B-raf biomarker expression is determined using a method comprising (a) performing PCR on nucleic acid extracted from a patient cancer sample (such as a FFPE fixed patient cancer sample); and (b) determining expression of mutant B-raf biomarker in the sample. In some embodiments, the patient's cancer has been shown to express c-met biomarker. In some embodiments, c-met biomarker expression is determined using immunohistochemistry (IHC). In some embodiments, c-met expression is determined relative to c-met staining intensity of control cell pellets and high c-met expression is low, medium and strong c-met expression determined relative to cell line HEK-293, A549 and cell line H441. In some embodiments, c-met expression is determined relative to c-met staining intensity of control cell pellets and high c-met expression is medium and strong c-met expression determined relative to cell line A549 and cell line H441. In some embodiments, c-met expression is low c-met expression. In some embodiments, c-met expression is determined relative to c-met staining intensity of control cell pellets and low c-met expression is no or low c-met expression determined relative to cell line H1155 and cell line HEK-293. In some embodiments, c-met expression is determined relative to c-met staining intensity of control cell pellets and low c-met expression is no c-met expression determined relative to cell line H1155. In some embodiments, c-met biomarker expression is nucleic acid expression and is determined in a sample from the patient using PCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH. In some embodiments, c-met biomarker expression is determined using phospho-ELISA. In some embodiments, c-met biomarker expression is

phospho-met expression. In some embodiments, c-met biomarker expression is determined by determining expression of hepatocyte growth factor (HGF) (e.g., using ELISA). In some embodiments, HGF expression is autocrine. In some embodiments, HGF is expressed in tumor or tumor stroma (e.g., determined using IHC. In some embodiments, expression is determined in the patient's serum (e.g., determined using ELISA). In some embodiments, cancer is melanoma, colorectal, breast, ovarian or thyroid. In some embodiments, cancer is melanoma. In some embodiments, the cancer is papillary thyroid.

[0021a] In one aspect, there is provided a method of determing prognosis for a melanoma patient, comprising determining expression of c-met biomarker in a sample from the patient, wherein c-met biomarker is HGF and expression of HGF is prognostic for cancer in the subject.

[0022] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods for determining prognosis for a melanoma patient, comprising determining expression of c-met biomarker in a sample from the patient, wherein c-met biomarker is HGF and expression of HGF is prognostic for cancer in the subject. In some embodiments, increased HGF expression is prognostic of, e.g., decreased progression-free survival and/or decreased overall survival when the patient is treated with B-raf inhibitor (e.g., vemurafenib). In some embodiments, HGF expression is determined in patient serum, e.g., using ELISA. In some embodiments, HGF expression in patient serum is above a median HGF expression level (such as a median HGF expression level in a population). In some embodiments, HGF expression in patient serum is above, for example, about 330 ng/ml. In some embodiments, HGF expression in patient serum is above about 300 ng/ml, 310 ng/ml, 320 ng/ml, 330 ng/ml, 340 ng/ml, 350 ng/ml, 360 ng/ml, 370 ng/ml, 380 ng/ml, 390 ng/ml, 400 ng/ml, 420 ng/ml, 440 ng/ml, 460 ng/ml, 480 ng/ml, 500 ng/ml, or greater. In some embodiments, the patient is selected for treatment with an effective amount of c-met antagonist and B-raf antagonist. In some embodiments, the patient is treated with an effective amount of a c-met antagonist and B-raf antagonist. In some embodiments, the melanoma expresses (has been shown to express) B-raf V600.

[0023] In some embodiments, the patient's cancer has been shown to express B-raf biomarker. B-raf biomarker may be mutant B-raf. Mutant B-raf is constitutively activated B-raf. In some embodiments, mutant B-raf is B-raf V600. B-raf V600 may be B-raf V600E. A non-limiting exemplary list of mutant B-raf is: B-raf V600K (GTG>AAG), V600R (GTG>AGG), V600E (GTG>GAA) and/or V600D (GTG>GAT). In some embodiments, mutant B-raf polypeptide is detected. In some embodiment, mutant B-raf nucleic acid is detected. "V600E" refers to a mutation in BRAF (T>A) at nucleotide position 1799 that results in substitution of a glutamine for a valine at amino acid position 600 of B-raf. "V600E" is also known as "V599E" (1796T>A) under a previous numbering system (Kumar et al., Clin. Cancer Res. 9:3362-3368, 2003).

[0024] In some embodiments, mutant B-raf biomarker expression is determined using a method comprising (a) performing one or more of gene expression profiling, PCR (such as rtPCR or

present as a complex and form a single antigen binding arm, wherein the first and second Fc polypeptides are present in a complex and form a Fc region that increases stability of said antibody fragment compared to a Fab molecule comprising said antigen binding arm.

[0029] In some embodiments, the c-met antagonist is one or more of crizotinib, tivantinib, carbozantinib, MGCD-265, ficlatuzumab, humanized TAK-701, rilotumumab, foretinib, h224G11, DN-30, MK-2461, E7050, MK-8033, PF-4217903, AMG208, JNJ-38877605, EMD1204831, INC-280, LY-2801653, SGX-126, RP1040, LY2801653, BAY-853474, GDC-0712, and/or LA480. In some embodiments, the c-met antagonist is crizotinib. In some embodiments, the c-met antagonist is tivantinib. In some embodiments, the c-met antagonist is GDC-0712.

[0030] In some embodiments, the B-raf antagonist is one or more of sorafenib, PLX4720, PLX-3603, GSK2118436, GDC-0879, N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide, vemurafenib, GSK 2118436, RAF265 (Novartis), XL281, ARQ736, BAY73-4506. In further embodiments, the B-raf antagonist is vemurafenib. In further embodiments, the B-raf antagonist is GSK 2118436. The B-raf antagonist may be selective for B-raf V600E.

[0031] The B-raf antagonist and the c-met antagonist may be administered simultaneously. The B-raf antagonist and the c-met antagonist may be administered sequentially. In some embodiments, the B-raf antagonist is administered prior to the c-met antagonist. In some embodiments, the c-met antagonist is administered prior to the B-raf antagonist.

[0032] In one ~~aspect~~embodiment, provided are methods comprising administering at least one additional treatment (such as a cancer medicament) to said subject.

[0033] The cancer may be melanoma, colorectal, ovarian, breast or papillary thyroid. Other cancers are described herein. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is resistant to B-raf antagonist. In some embodiments, the patient has been previously treated with B-raf antagonist. In some embodiments, the patient has not been previously treated with B-raf antagonist. In some embodiments, the patient is refractory to B-raf antagonist.

[0034] Moreover, the ~~invention~~ disclosure concerns methods for advertising a cancer medicament (e.g., a c-met antagonist) comprising promoting, to a target audience, the use of the cancer medicament for treating a patient with cancer based on expression of c-met biomarker, and in some embodiments, further based on expression of B-raf biomarker (e.g. mutant B-raf biomarker). Promotion may be conducted by any means available. In some embodiments, the promotion is by a package insert accompanying a commercial formulation of the c-met antagonist (such as an anti-c-met antibody). The promotion may also be by a package insert accompanying a

commercial formulation of a second medicament (when treatment is combination therapy with a c-met antagonist and a second medicament, e.g., a B-raf antagonist such as vemurafenib). Promotion may be by written or oral communication to a physician or health care provider. In some embodiments, the promotion is by a package insert where the package insert provides instructions to receive therapy with c-met antagonist, and in some embodiments, in combination with a second medicament, such as a B-raf antagonist (such as vemurafenib). In some embodiments, the promotion is followed by the treatment of the patient with the c-met antagonist with or without the second medicament (e.g., vemurafenib). In some embodiments, the promotion is followed by the treatment of the patient with the second medicament with or without treatment with c-met antagonist. In some embodiments, the package insert indicates that the c-met antagonist is to be used to treat the patient if the patient's cancer sample expressed high c-met biomarker. In some embodiments, the package insert indicates that the c-met antagonist is not to be used to treat the patient if the patient's cancer sample expresses low c-met biomarker.

[0035] In some ~~aspects~~embodiments, the ~~invention~~ disclosure features methods of instructing a patient with cancer (such as melanoma) expressing c-met biomarker by providing instructions to receive treatment with a c-met antagonist (for example, an anti-c-met antibody), and in some embodiments, treatment with a second medicament (such as B-raf antagonist, e.g. vemurafenib), for example, to increase survival of the patient, to decrease the patient's risk of cancer recurrence and/or to increase the patient's likelihood of survival. In some embodiments, the treatment comprises administering to the melanoma patient an anti-c-met antibody (e.g., MetMAb) administered in combination with a B-raf antagonist, such as vemurafenib. In some embodiments the method further comprises providing instructions to receive treatment with at least one chemotherapeutic agent. In certain embodiments the patient is treated as instructed by the method of instructing.

[0036] The ~~invention~~ disclosure also provides business methods, comprising marketing an c-met antagonist (e.g., anti-c-met antibody) for treatment of cancer (e.g., melanoma) in a human patient, wherein the patient's cancer expressed high (elevated) c-met biomarker expression, for example, to increase survival, decrease the patient's likelihood of cancer recurrence, and/or increase the patient's likelihood of survival. In some embodiments, the treatment comprises administering to a cancer patient an anti-c-met antibody (e.g., onartuzumab (MetMAb)), and in some embodiment, a second medicament (e.g., a B-raf antagonist, such as vemurafenib).

[0036a] In one aspect, there is provided a kit comprising a c-met antagonist and a B-raf antagonist.

[0037] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides diagnostic kits comprising one or more reagent for determining expression of a c-met biomarker in a sample from a cancer (e.g., melanoma) patient. The diagnostic kit is suitable for use with any of the methods described herein. In

some embodiments, the kit further comprises instructions to use the kit to select a c-met medicament to treat the melanoma patient. In some embodiments, the treatment comprises administering to a cancer patient an anti-c-met antibody (e.g., onartuumab (MetMAb)), and in some embodiment, a second medicament (e.g., a B-raf antagonist, such as vemurafenib).

[0037a] In one aspect, there is provided an article of manufacture comprising, packaged together, a c-met antagonist in a pharmaceutically acceptable carrier and a package insert indicating that the c-met antagonist is for treating a patient with melanoma based on expression of B-raf biomarker, wherein the treatment is in combination with a B-raf antagonist.

[0038] The ~~invention~~disclosure also concerns articles of manufacture comprising, packaged together, a c-met antagonist in a pharmaceutically acceptable carrier and a package insert indicating that the c-met antagonist is for treating a patient with cancer based on expression of c-met biomarker. Treatment methods include any of the treatment methods disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0039] FIGURE 1: RTK ligands attenuated kinase inhibition in oncogene addicted cancer cell lines. **a,** Illustration depicting results from the RTK ligand matrix screen. Kinase addicted cancer cell lines were treated with an increasing concentration range of the appropriate kinase inhibitor in the presence or absence of RTK ligands (50ng/mL). **b,** Summary of matrix screen results from forty-one kinase-addicted cancer cell lines co-treated with the effective kinase inhibitor and each of six individual RTK ligands. NR denotes no rescue, P denotes partial rescue and R denotes complete rescue. **c,** Cell viability assay demonstrating the diversity of RTK ligand effects on drug-treated cancer cell lines (72h). Cells were co-treated with 50ng/mL RTK ligand as indicated, with three different consequences observed – no rescue, partial rescue or complete rescue. Error bars represent mean +/- s.e.m.

[0040] FIGURE 2: pro-survival pathway re-activation correlated with RTK ligand rescue. **a,** Immunoblots showing the effect of acute RTK ligand treatment (50ng/mL) on AKT and ERK phosphorylation following kinase inhibition (1μM, 2h). RTK ligand rescue is indicated, grey squares indicates complete rescue and black squares indicates partial rescue as determined by the initial screen (Fig. 1b). **b,** Cell viability assay demonstrated suppression of cell proliferation in three kinase addicted cancer cell lines following drug treatment (72h). Cells were co-treated with 50ng/mL RTK ligand in the presence of the appropriate secondary kinase inhibitor (0.5μM) as indicated. PD: PD173074, Lap: lapatinib, Criz: crizotinib. Error bars represent mean +/- s.e.m. **c,** Immunoblots showing the effect of acute kinase inhibition (1μM) in the presence and absence of RTK ligands (50ng/mL, 2h) on AKT and ERK phosphorylation. Cells were co-treated with secondary kinase inhibitor (0.5μM) as appropriate. Sun: sunitinib, PD: PD173074, PLX: PLX4032, Lap: lapatinib, Erl: erlotinib, Criz: crizotinib.

[0041] FIGURE 3: HGF promoted lapatinib resistance in *HER2* amplified cell lines. **a,** Immunoblots showing the suppression of apoptosis (cleaved PAPR) in AU565 *HER2* amplified breast cancer cells following treatment with lapatinib (Lap, 1μM), HGF (50ng/mL) and

WHAT IS CLAIMED IS:

1. A method for treating a patient with cancer comprising administering an effective amount of B-raf antagonist and c-met antagonist.

2. A method for treating a cancer patient who has increased likelihood of developing resistance to B-raf antagonist comprising administering an effective amount of B-raf antagonist and c-met antagonist.

3. A method for increasing and/or restoring sensitivity to B-raf antagonist comprising administering to a cancer patient an effective amount of B-raf antagonist and c-met antagonist.

4. A method for extending period of B-raf antagonist sensitivity comprising administering to a cancer patient an effective amount of B-raf antagonist and c-met antagonist.

5. A method for treating a patient with B-raf antagonist resistant cancer comprising administering an effective amount of B-raf antagonist and c-met antagonist.

6. A method for extending duration of response to B-raf antagonist comprising administering an effect amount of B-raf antagonist and c-met antagonist.

7. A method for delaying or preventing development of HGF-mediated B-raf antagonist resistant cancer in a patient comprising administering an effective amount of B-raf antagonist and c-met antagonist.

8. The method of any of claims 1-7, wherein the patient's cancer has been shown to express B-raf biomarker.

9. The method of claim 8, wherein the B-raf biomarker is B-raf V600.

10. The method of claim 8, wherein B-raf biomarker is B-raf V600E.

11. The method of any of claims 8-10, wherein mutant B-raf biomarker expression in the patient's cancer is determined using a method comprising (a) performing one or more of gene expression profiling, PCR hybridization assay, in situ hybridization, 5' nuclease assay mutation detection assay, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH on a sample and (b) determining expression of mutant B-raf biomarker in the sample.

12. The method of claim 11, wherein mutant B-raf biomarker expression in the patient's cancer is determined using a method comprising (a) performing PCR on genomic DNA extracted from a patient cancer sample and (b) determining expression of mutant B-raf biomarker in the sample.

13. The method of any of claims 1-12, wherein the patient's cancer has been shown to express c-met biomarker.

14. The method of claim 13, wherein c-met biomarker is polypeptide.

15. The method of claim 14, wherein c-met biomarker expression is determined using immunohistochemistry (IHC).

16. The method of claim 15, wherein c-met biomarker expression is determined by determining expression of hepatocyte growth factor (HGF).

17. The method of claim 16, wherein HGF is expressed in tumor or tumor stroma

18. The method of claim 16, wherein HGF expression is determined in the patient's serum.

19. The method of any of claims 1-18, wherein the c-met antagonist is an antagonist anti-c-met antibody.

20. The method of any of claims 1-19, wherein the c-met antagonist is one or more of onartuzumab, crizotinib, tivantinib, carbozantinib, MGCD-265, ficlatuzumab, humanized TAK-701, rilotumumab, foretinib, h224G11, DN-30, MK-2461, E7050, MK-8033, PF-4217903, AMG208, JNJ-38877605, EMD1204831, INC-280, LY-2801653, SGX-126, RP1040, LY2801653, BAY-853474, and/or LA480.

21. The method of any of claims 1-20 wherein the B-raf antagonist is one or more of sorafenib, PLX4720, PLX-3603, GSK2118436, GDC-0879, N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide, vemurafenib, GSK 2118436, RAF265 (Novartis), XL281, ARQ736, BAY73-4506.

22. The method of claim 21, wherein the B-raf antagonist is vemurafenib.

23. The method of claim 21, wherein the B-raf antagonist is GSK 2118436.

24. The method of any of claims 1-23 wherein the B-raf antagonist and the c-met antagonist are administered simultaneously.

25. The method of any of claims 1-23 wherein the B-raf antagonist and the c-met antagonist are administered sequentially.

26. The method of claim 25, wherein the B-raf antagonist is administered prior to the c-met antagonist.

27. The method of claim 26, wherein the c-met antagonist is administered prior to the B-raf antagonist.

28. The method of any of claims 1-27 further comprising administering at least one additional treatment to said subject.

29. The method of any of claims 1-28, wherein the cancer is melanoma, colorectal, ovarian, breast or papillary thyroid.

30. The method of claim 29, wherein the cancer is melanoma that has been shown to express B-raf V600.

31. The method of any of claims 1-30, wherein the cancer is resistant to B-raf antagonist.

32. The method of any of claims 1-30 wherein the patient has not been previously treated with B-raf antagonist.

33. A method for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is a candidate for treatment with c-met antagonist and B-raf antagonist: to increase sensitivity of the patient's cancer to B-raf antagonist, restore sensitivity of the patient's cancer to B-raf antagonist, to extend the period of sensitivity of the patient's cancer to B-raf antagonist, and/or to prevent development of HGF-mediated B-raf antagonist resistance in the patient's cancer.

34. A method for identifying a patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist.

35. A method for identifying a patient as at risk of developing resistance to a B-raf antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as at risk of developing resistance to a B-raf antagonist

36. The method of claim 34 or 35, wherein subsequent to steps (a) and (b), the patient is treated with an effective amount of a c-met antagonist and a B-raf antagonist.

37. A method of determining therapeutic efficacy of a B-raf antagonist for treating cancer in a patient comprising determining the presence of c-met biomarker and/or B-raf biomarker in a sample obtained from said patient by immunoassay, elisa, hybridization assay, PCR, 5' nuclease assay, IHC, and/or RT-PCR, and selecting the patient for treatment with a B-raf antagonist.

38. The method of claim 37, further comprising selecting the patient for treatment with a c-met antagonist.

39. The method of claim 38, further comprising treating the patient with an effective amount of B-raf antagonist and c-met antagonist.

40. A method of determing prognosis for a melanoma patient, comprising determining expression of c-met biomarker in a sample from the patient, wherein c-met biomarker is HGF and expression of HGF is prognostic for cancer in the subject.

41. A kit comprising a c-met antagonist and a B-raf antagonist.

42. The kit of claim 41, further comprising instructions for a method for treating a melanoma patient comprising administering an effective amount of a c-met antagonist and B-raf antagonist to the patient.

43. An article of manufacture comprising, packaged together, a c-met antagonist in a pharmaceutically acceptable carrier and a package insert indicating that the c-met antagonist is for treating a patient with melanoma based on expression of B-raf biomarker, wherein the treatment is in combination with a B-raf antagonist.

WHAT IS CLAIMED IS:

1. Use of a B-raf antagonist for the manufacture of a medicament for treating a patient with cancer wherein the medicament is to be administered with a c-met antagonist.

2. Use of a B-raf antagonist for the manufacture of a medicament for treating a cancer patient who has increased likelihood of developing resistance to B-raf antagonist wherein the medicament is to be administered with a c-met antagonist.

3. Use of a B-raf antagonist for the manufacture of a medicament for increasing and/or restoring sensitivity to B-raf antagonist in a cancer patient wherein the medicament is to be administered with a c-met antagonist.

4. Use of a B-raf antagonist for the manufacture of a medicament for extending period of B-raf antagonist sensitivity in a cancer patient wherein the medicament is to be administered with a c-met antagonist.

5. Use of a B-raf antagonist for the manufacture of a medicament for treating a patient with B-raf antagonist resistant cancer wherein the medicament is to be administered with a c-met antagonist.

6. Use of a B-raf antagonist for the manufacture of a medicament for extending duration of response to B-raf antagonist wherein the medicament is to be administered with a c-met antagonist.

7. Use of a B-raf antagonist for the manufacture of a medicament for delaying or preventing development of HGF-mediated B-raf antagonist resistant cancer in a patient wherein the medicament is to be administered with a c-met antagonist.

8. The use of any of claims 1-7, wherein the patient's cancer has been shown to express B-raf biomarker.

9. The use of claim 8, wherein the B-raf biomarker is B-raf V600.

10. The use of claim 8, wherein B-raf biomarker is B-raf V600E.

11. The use of any of claims 8-10, wherein mutant B-raf biomarker expression in the patient's cancer is determined using a method comprising (a) performing one or more of gene expression profiling, PCR hybridization assay, in situ hybridization, 5' nuclease assay mutation detection assay, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH on a sample and (b) determining expression of mutant B-raf biomarker in the sample.

12. The use of claim 11, wherein mutant B-raf biomarker expression in the patient's cancer is determined using a method comprising (a) performing PCR on genomic DNA extracted from a patient cancer sample and (b) determining expression of mutant B-raf biomarker in the sample.

13. The use of any of claims 1-12, wherein the patient's cancer has been shown to express c-met biomarker.

14. The use of claim 13, wherein c-met biomarker is polypeptide.

15. The use of claim 14, wherein c-met biomarker expression is determined using immunohistochemistry (IHC).

16. The use of claim 15, wherein c-met biomarker expression is determined by determining expression of hepatocyte growth factor (HGF).

17. The use of claim 16, wherein HGF is expressed in tumor or tumor stroma

18. The use of claim 16, wherein HGF expression is determined in the patient's serum.

19. The use of any of claims 1-18, wherein the c-met antagonist is an antagonist anti-c-met antibody.

20. The use of any of claims 1-19, wherein the c-met antagonist is one or more of onartuzumab, crizotinib, tivantinib, carbozantinib, MGCD-265, ficlatuzumab, humanized TAK-701, rilotumumab, foretinib, h224G11, DN-30, MK-2461, E7050, MK-8033, PF-4217903, AMG208, JNJ-38877605, EMD1204831, INC-280, LY-2801653, SGX-126, RP1040, LY2801653, BAY-853474, and/or LA480.

21. The use of any of claims 1-20 wherein the B-raf antagonist is one or more of sorafenib, PLX4720, PLX-3603, GSK2118436, GDC-0879, N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide, vemurafenib, GSK 2118436, RAF265 (Novartis), XL281, ARQ736, BAY73-4506.

22. The use of claim 21, wherein the B-raf antagonist is vemurafenib.

23. The use of claim 21, wherein the B-raf antagonist is GSK 2118436.

24. The use of any of claims 1-23 wherein the B-raf antagonist and the c-met antagonist are to be administered simultaneously.

25. The use of any of claims 1-23 wherein the B-raf antagonist and the c-met antagonist are to be administered sequentially.

26. The use of claim 25, wherein the B-raf antagonist is to be administered prior to the c-met antagonist.

27. The use of claim 26, wherein the c-met antagonist is to be administered prior to the B-raf antagonist.

28. The use of any of claims 1-27 further comprising administration of at least one additional treatment to said subject.

29. The use of any of claims 1-28, wherein the cancer is melanoma, colorectal, ovarian, breast or papillary thyroid.

30. The use of claim 29, wherein the cancer is melanoma that has been shown to express B-raf V600.

31. The use of any of claims 1-30, wherein the cancer is resistant to B-raf antagonist.

32. The use of any of claims 1-30 wherein the patient has not been previously treated with B-raf antagonist.

33. A method for determining c-met biomarker expression, comprising the step of determining whether a patient's cancer expresses c-met biomarker, wherein c-met biomarker expression indicates that the patient is a candidate for treatment with c-met antagonist and B-raf antagonist: to increase sensitivity of the patient's cancer to B-raf antagonist, restore sensitivity of the patient's cancer to B-raf antagonist, to extend the period of sensitivity of the patient's cancer to B-raf antagonist, and/or to prevent development of HGF-mediated B-raf antagonist resistance in the patient's cancer.

34. A method for identifying a patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as a candidate for treatment with a B-raf antagonist and a c-met antagonist.

35. A method for identifying a patient as at risk of developing resistance to a B-raf antagonist, comprising (a) determining that the patient's cancer expresses c-met biomarker; and (b) identifying the patient as at risk of developing resistance to a B-raf antagonist

36. The method of claim 34 or 35, wherein subsequent to steps (a) and (b), the patient is to be treated with an effective amount of a c-met antagonist and a B-raf antagonist.

37. A method of determining therapeutic efficacy of a B-raf antagonist for treating cancer in a patient comprising determining the presence of c-met biomarker and/or B-raf biomarker in a

sample obtained from said patient by immunoassay, elisa, hybridization assay, PCR, 5' nuclease assay, IHC, and/or RT-PCR, and selecting the patient for treatment with a B-raf antagonist.

38. The method of claim 37, further comprising selecting the patient for treatment with a c-met antagonist.

39. The method of claim 38, wherein the patient is to be treated with an effective amount of B-raf antagonist and c-met antagonist.

40. A method of determing prognosis for a melanoma patient, comprising determining expression of c-met biomarker in a sample from the patient, wherein c-met biomarker is HGF and expression of HGF is prognostic for cancer in the subject.

41. A kit comprising a c-met antagonist and a B-raf antagonist.

42. The kit of claim 41, further comprising instructions for a method for treating a melanoma patient comprising administering an effective amount of a c-met antagonist and B-raf antagonist to the patient.

43. An article of manufacture comprising, packaged together, a c-met antagonist in a pharmaceutically acceptable carrier and a package insert indicating that the c-met antagonist is for treating a patient with melanoma based on expression of B-raf biomarker, wherein the treatment is in combination with a B-raf antagonist.