all cell types. Knockout studies have shown that H-ras and N-ras, either alone or in combination, are not required for normal development in the mouse, whereas K-ras is essential (Downward, J. (2002) at page 12).

[0015] Furthermore, as described in Downward, J. (2002), aberrant signaling through RAS pathways occurs as the result of several different classes of mutational damage in tumor cells. The most obvious of these mutations is in the ras genes themselves. Some 20% of human tumors have activating point mutations in ras, most frequently in K-ras (about 85% of total), then N-ras (about 15%), then H-ras (less than 1%). These mutations all compromise the GTPase activity of RAS, preventing GAPs from promoting hydrolysis of GTP on RAS and therefore causing RAS to accumulate in the GTP-bound, active form. Almost all RAS activation in tumors is accounted for by mutations in codons 12, 13 and 61 (Downward, J. (2002) at page 15).

[0016] It would be useful if cancer treatment could be tailored to the specific cancer. In particular, the present invention provides for a means of determining whether certain approved and available treatments would nevertheless not be of benefit for the particular type of cancer.

BRIEF SUMMARY ~~OF INVENTION~~

[0017] The present ~~invention~~disclosure relates to prognostic methods for identifying tumors that are not susceptible to B-Raf inhibitor treatment by detecting mutations in a K-ras gene or protein. The methods involve determining the presence or absence of a mutated K-ras gene or protein in a sample thereby identifying a tumor that is non-responsive to B-Raf inhibitor treatment. Kits are also disclosed for carrying out the methods.

[0017a] In one aspect, there is provided a method of identifying a patient nonresponsive to treatment with a B-Raf inhibitor, comprising determining the presence or absence of a K-ras mutation in a sample that has been obtained from a tumor of a patient, wherein said k-ras mutation is at least G12D, whereby the presence of a K-ras mutation indicates a patient will not respond to said B-Raf inhibitor treatment.

[0017b] In one aspect, there is provided a method of determining whether a tumor will respond to treatment with a B-Raf inhibitor, comprising determining in a sample of said tumor the presence of a mutant K-ras protein or gene, wherein said mutant k-ras is at least G12D, whereby the presence of a mutant K-ras protein or gene indicates that the tumor will not respond to treatment with a B-Raf inhibitor.

[0017c] In one aspect, there is provided a method of predicting whether a patient will be nonresponsive to treatment with a specific B-Raf inhibitor, comprising determining the presence or absence of a K-ras mutation in a sample that has been obtained from a tumor of the patient, wherein the K-ras mutation is at least G12D; and wherein if a K-ras mutation is present, the patient is predicted to be nonresponsive to treatment with a specific B-Raf inhibitor.

[0017d] In one aspect, there is provided a kit useable for the method as defined above, comprising material specific for detecting a K-ras mutant gene or protein, and material specific for detecting a B-Raf mutant gene or protein, further comprising instructions for use in identifying a patient nonresponsive to treatment with a B-Raf inhibitor.

[0018] In another ~~aspect~~embodiment, the present ~~invention~~disclosure relates to prognostic methods for identifying tumors that are not susceptible to B-Raf inhibitor treatment by detecting aberrant expression levels of RTKs. The methods involve determining the expression levels of certain RTKs in a sample, whereby overexpression of RTKs correlate non-responsiveness to B-Raf inhibitor treatment. Examples of RTKs that correlate to the responsiveness of B-Raf treatment include, but are not limited to EGFR and cMet. The methods also involve determining the induction levels of certain ligands of RTKs in a sample whereby abnormally high levels of ligand induction correlates with non-responsiveness to B-Raf inhibitor treatment. Examples of ligands

that correlate to the responsiveness of B-Raf treatment include, but are not limited to EGF and HGF. The methods also involve determining the levels of Ras-GTP in a sample whereby abnormally high levels of Ras-GTP correlates with non-responsiveness to B-Raf inhibitor treatment. Kits are also disclosed for carrying out the methods.

[0019] In another ~~aspect~~embodiment, the present ~~invention~~disclosure relates to methods of treating a tumor that is non-responsive to B-Raf inhibitor treatment. The methods include administering a B-Raf inhibitor in combination with an EGFR inhibitor.

DESCRIPTION OF THE FIGURES

[0020] Figure 1 depicts Biochemical enzyme assay data. The data show that at physiological [ATP], only GDC-0879 maintains effective potency against both B-Raf^{V600E} and WT Raf isoforms.

[0021] Figure 2 depicts Viability assays in tumor lines of different Raf/Ras mutational status.

[0022] Figure 3 depicts sustained pMEK induction by Raf inhibitors only in non-B-Raf^{V600E} lines. pMEK levels plateau relatively to inhibitors' IC_{50} against WT Raf.

[0023] Figure 4 depicts c-Raf is the Raf isoform primarily responsible for the pMEK induction by Raf inhibitors in non B-Raf^{V600E} lines.

[0024] Figure 5 depicts c-Raf specific activity induced by both inhibitors only in non-B-Raf^{V600E} lines. There was no decrease in Sprouty levels under conditions of Raf induction.

[0025] Figure 6 depicts no induction of pERK levels. Inhibitors' relative potencies correlate with their biochemical IC_{50}s.

[0026] Figure 7 depicts bell-shaped effects on pMEK levels under basal conditions. Inhibitory effects of GDC-0879 predominate after serum stimulation.

[0027] Figure 8A depicts the duration and extent of BRAF pathway inhibition determines B-Raf inhibitor, GDC-0879 efficacy in primary human tumor xenograft models. A Kaplan-Meier plot showing time to tumor doubling for patient-derived melanoma and non-small cell lung cancer tumor models treated daily with 100 mg/kg GDC-0879 or vehicle. Genotypes for BRAF, N-ras and K-ras are indicated. A statistically significant (P <0.05) delay in tumor progression was noted for MEXF