

BIOMARKERS FOR PREDICTING SENSITIVITY TO CANCER TREATMENTS

Cross-reference to Related Application(s)

5 This patent application claims the benefit of priority of U.S. application serial No. 61/471,036, filed April 01, 2011, which application is herein incorporated by reference.

Background

10 Cancer can arise when cells have mutations that ultimately confer a growth advantage to the cells. Somatic mutations include, *e.g.*, nucleotide base substitutions, deletions, insertions, amplifications, and rearrangements. Identification of somatic mutations that occur in cancer provides valuable information regarding the development of cancer. Such information is also
15 useful for the identification of diagnostic markers and therapeutic targets in cancer. (*see, e.g.*, Bamford *et al.* (2004) *British Journal of Cancer* 91:355-358.) The identification of somatic mutations associated with cancer has proven valuable in clinical settings, *e.g.*, in distinguishing patient populations that would be responsive to a particular therapy. (*see, e.g.*, Lynch *et al.* (2004) *N. Engl. J.*
20 *Med.* 350:2129-2139; O'Hare (2004) *Blood* 104:2532-2539.) Thus, a continuing need exists to identify somatic mutations that occur in cancer.

 Germline variations, or polymorphisms, are heritable variations that are present in an organism's genome. Polymorphisms include restriction fragment length polymorphisms (RFLPs), short tandem repeats (STRs), and single
25 nucleotide polymorphisms (SNPs). Germline variations can also be associated with susceptibility to certain diseases, including cancer. (*see, e.g.*, Vierimaa *et al.* (2006) *Science* 312:1228-1230; Landi *et al.* (2006) *Science* 313:521-522; Zhu *et al.* (2004) *Cancer Research* 64:2251-2257.) Thus, a continuing need exists to identify polymorphisms associated with cancer.

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Summary of Certain Embodiments of the Invention

 The inventions described herein meet the above-described needs and provide other benefits.

Applicants have discovered that biomarkers can predict the efficacy of AKT inhibitors in treating hyperproliferative disorders, such as cancer.

Applicants have discovered that certain mutations in *AKT* can lead to disrupted interactions between the AKT PH domain and kinase domain. A
5 disruption between these domains, caused by the mutation(s), appears to lead to constitutive phosphorylation of AKT and to constitutive AKT signaling. These effects also allow for the transformation of cells. These mutations confer resistance to PI3K and allosteric Akt inhibitors. Accordingly, the presence of such mutations indicate that the effective dosage for PI3K and allosteric Akt
10 inhibitors will be higher, and also indicates that inhibitors other than PI3K and/or allosteric Akt inhibitors should be used, such as ATP-competitive Akt inhibitors. The use of this biomarker, either alone or in combination with other biomarkers described herein, is useful for predicting the sensitivity of the growth of a tumor cell to an AKT inhibitor, administered either alone, or in combination with
15 another therapeutic compound, such as 5-FU, a platinum agent (carboplatin, cisplatin, oxaliplatin, etc.) irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 and other MEK inhibitors.

20 In one aspect, the present invention refers to an *in vitro* method of predicting the sensitivity of the growth of a tumor cell to an AKT inhibitor, comprising determining the presence of a mutation to AKT, wherein the presence of a mutation to AKT correlates with sensitivity of the cell to the AKT inhibitor, wherein the mutation corresponds to, or aligns with, L52, K189 or
25 D323.

Brief Description of the Figures

Figure 1 depicts AKT and the interactions of the PH and kinase domain (1A and 1B) and also depicts the locations of interactions between those domains
30 (1C).

Figure 2 depicts results indicating that synthetic mutations at sites thought to disrupt the interactions of PH domain with the kinase domain lead to constitutive phosphorylation of Akt.

Figure 3 depicts somatic mutations.

Figure 4 depicts results indicating that somatic mutations, which lead to constitutive Akt phosphorylation, lead to constitutive Akt signaling.

Figure 5 depicts results indicating that Akt1 mutants can transform cells.