PREDICTING RESPONSE TO EGFR INHIBITORS

FIELD

The present invention generally relates to genetic variations associated with responsiveness to EGFR inhibitors.

BACKGROUND

The Serine/Threonine kinase LKB1 was first identified as the gene mutated in the familial cancer syndrome Peutz-Jeghers syndrome (Hemminki et al., 1998, *Nature*, 391: 184-187). Subsequently, somatic mutations in LKB1 were found in a variety of sporadic cancers, including up to 30% of non-small cell lung cancers (NSCLC) (Sanchez-Cespedes, 2007, *Oncogene*, 26: 7825-7832). The molecular function of LKB1 as a tumor suppressor remains unknown.

Similarly, mutations in the Epidermal Growth Factor Receptor (EGFR) have long been associated with many types of cancer, including lung (Pastorino et al., 1993, *J. Cell. Biochem. Suppl.*, 17F: 237-248). A number of pharmaceuticals targeting EGFR have been developed and used successfully in the clinic to treat several types of cancer, including erlotinib (Tarceva®, approved in 2004), gefitinib (Iressa®, 2003), panitumumab (Vectibix®, 2006) and cetuximab (Erbitux®, 2004). However, secondary resistance to these treatments frequently results (Wei et al., 2011, *Anticancer Drugs*, 22: 963-970; Brugger and Thomas, 2012, *Lung Cancer*, 77: 2-8). While activating mutations of EGFR (EGFR-Mut+) are thought to be predictive for responsiveness to EGFR targeted therapies, they are not sufficient. Furthermore, responsiveness to EGFR-targeted therapies in the absence of EGFR mutations has been observed (Piperdi and Perez-Soler, 2012, *Drugs*, 72 Suppl. 1: 11-19). These results suggest the need for diagnostics to better predict patient response to EGFR-targeted therapies.

Activating EGFR mutations and loss of function LKB1 mutations, while both frequently observed in lung and other types of cancer, have been reported by several groups to be mutually exclusive; that is, if one mutation is present the other is statistically less likely to occur than if the mutations were assorting randomly within the patient population (Reungwetwattana et al., 2012, *Clin. Lung Cancer*, 13: 252-266; Chitale et al., 2008, *Oncogene*,28: 2773-2783; Koivunen et al., 2008, *Br. J. Cancer*, 455: 245-252; Ding et al., 2008, *Nature*, 455: 1069-1075). This suggests that they may be involved in the same molecular pathway, and that mutation of one or the other is sufficient to deregulate this pathway and drive tumor progression.

SUMMARY

Disclosed are~~In some embodiments,~~ methods for predicting whether a cancer will respond to an EGFR inhibitor~~are provided~~. In some embodiments, a method comprises determining whether the cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer will respond to the EGFR inhibitor.

In one aspect, there is provided a method for predicting whether a cancer will respond to an EGFR inhibitor, comprising determining whether the cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer will respond to the EGFR inhibitor.

Disclosed are~~In some embodiments,~~ methods of identifying cancer patients who are likely to benefit from an EGFR inhibitor~~are provided~~. In some embodiments, a method comprises determining whether the patient's cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer patient will likely benefit from the EGFR inhibitor.

In another aspect, there is provided a method of identifying a cancer patient who is likely to benefit from an EGFR inhibitor, comprising determining whether the patient's cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer patient will likely benefit from the EGFR inhibitor.

Disclosed are~~In some embodiments,~~ methods of selecting a therapy for cancer patients~~are provided~~. In some embodiments, a method comprises (a) determining whether the patient's cancer comprises a LKB1 mutation; and (b) if the patient's cancer comprises a LKB1 mutation, selecting an EGFR inhibitor for the therapy.

In another aspect, there is provided a method of selecting a therapy for a cancer patient, comprising (a) determining whether the patient's cancer comprises a LKB1 mutation; and (b) if the patient's cancer comprises a LKB1 mutation, selecting an EGFR inhibitor for the therapy.

Disclosed are~~In some embodiments,~~ methods of treating a cancer in a mammal~~are provided~~. In some embodiments, a method comprises (a) determining whether the cancer comprises a LKB1 mutation; and (b) if the cancer comprises a LKB1 mutation, administering to the mammal a therapeutically effective amount of an EGFR inhibitor.

In another aspect, there is provided use of an EGFR inhibitor in the manufacture of a medicament for treating a cancer in a mammal, wherein the mammal is one whose cancer has been determined to comprise a LKB1 mutation.

Disclosed are~~In some embodiments,~~ methods of treating cancer comprising a LKB1 mutation in a mammal~~are provided~~. In some embodiments, a method comprises administering to the mammal having the cancer a therapeutically effective amount of an EGFR inhibitor. In some embodiments, prior to administration~~ering~~ of the EGFR inhibitor, the cancer was determined to comprise a LKB1 mutation.

In another aspect, there is provided use of an EGFR inhibitor in the manufacture of a medicament for treating a cancer comprising a LKB1 mutation in a mammal having the cancer.

In any of the embodiments described herein, the cancer may be a solid tumor. In any of the embodiments described herein, the cancer may be selected from a large cell carcinoma, carcinoid cancer, cancer of neuroendrocrine origin, head and neck squamous cell carcinoma (HNSCC), colorectal cancer, cervical cancer, melanoma, skin cancer, leiomyoma, gastric cancer, glioblastoma,

ovarian cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), pancreatic cancer, esophageal cancer, gastric cancer and thyroid cancer. In any of the embodiments described herein, the cancer may be selected from lung cancer, pancreatic cancer, colorectal cancer, and head and neck cancer. In any of the embodiments described herein, the cancer may be a tissue selected from the tissues in Table 2.

In some embodiments, the LKB1 mutation comprises a variation in a LKB1 polynucleotide. In some embodiments, the variation in the LKB1 polynucleotide is in the coding sequence of a LKB1 polynucleotide. In some embodiments, the variation in the LKB1 polynucleotide comprises at least one variation selected from an insertion, a deletion, an inversion, and a substitution. In some embodiments, the variation in the LKB1 polynucleotide results in a frame shift in the LKB1 coding sequence. In some embodiments, the variation in the LKB1 polynucleotide is a nucleotide variation at a nucleotide position selected from Table 1 that results in (a) significantly reduced or absent levels of LKB1 protein and/or (b) expression of a LKB1 protein with significantly reduced activity. In some embodiments, the variation in the LKB1 polynucleotide is a nucleotide change selected from Table 1.

In some embodiments, the variation in the LKB1 polynucleotide results in a variation in the LKB1 polypeptide. In some embodiments, the variation in the LKB1 polypeptide is selected from an

WHAT IS CLAIMED IS:

1. A method for predicting whether a cancer will respond to an EGFR inhibitor, comprising determining whether the cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer will respond to the EGFR inhibitor.

2. A method of identifying a cancer patient who is likely to benefit from an EGFR inhibitor, comprising determining whether the patient's cancer comprises a LKB1 mutation, wherein the presence of the LKB1 mutation indicates that the cancer patient will likely benefit from the EGFR inhibitor.

3. A method of selecting a therapy for a cancer patient, comprising (a) determining whether the patient's cancer comprises a LKB1 mutation; and (b) if the patient's cancer comprises a LKB1 mutation, selecting an EGFR inhibitor for the therapy.

4. Use of an EGFR inhibitor in the manufacture of a medicament for~~A method of~~ treating a cancer in a mammal, wherein the mammal is one whose cancer has been determined to comprise a LKB1 mutation~~comprising (a) determining whether the cancer comprises a LKB1 mutation; and (b) if the cancer comprises a LKB1 mutation, administering to the mammal a therapeutically effective amount of an EGFR inhibitor~~.

5. Use of an EGFR inhibitor in the manufacture of a medicament for~~A method of~~ treating a cancer comprising a LKB1 mutation in a mammal~~, comprising administering to the mammal~~ having the cancer~~ a therapeutically effective amount of an EGFR inhibitor~~.

6. The ~~method~~use of claim 4, wherein prior to administration of~~ering~~ the EGFR inhibitor, the cancer was determined to comprise a LKB1 mutation.

7. The method or use of any one of the preceding claims, wherein the cancer is a solid tumor.

8. The method or use of claim 7, wherein the cancer is selected from a large cell carcinoma, carcinoid cancer, cancer of neuroendrocrine origin, head and neck squamous cell carcinoma (HNSCC), colorectal cancer, cervical cancer, melanoma, skin cancer, leiomyoma, gastric cancer, glioblastoma, ovarian cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), pancreatic cancer, esophageal cancer, gastric cancer and thyroid cancer.

9. The method or use of claim 7, wherein the cancer is selected from lung cancer, pancreatic cancer, colorectal cancer, and head and neck cancer.

10. The method or use of any one of claims 1 to 6, wherein the cancer is in a tissue selected from the tissues in Table 2.

11. The method or use of any one of the preceding claims, wherein the LKB1 mutation comprises a variation in a LKB1 polynucleotide.

12. The method or use of claim 11, wherein the variation in the LKB1 polynucleotide is in the coding sequence of a LKB1 polynucleotide.

13. The method or use of claim 11 or claim 12, wherein the variation in the LKB1 polynucleotide comprises at least one variation selected from an insertion, a deletion, an inversion, and a substitution.

14. The method or use of any one of claims 11 to 13, wherein the variation in the LKB1 polynucleotide results in a frame shift in the LKB1 coding sequence.

15. The method or use of any one of claims 11 to 14, wherein the variation in the LKB1 polynucleotide results in a variation in the LKB1 polypeptide.

16. The method or use of claim 15, wherein the variation in the LKB1 polypeptide is selected from an insertion, a substitution, a deletion, and a truncation.

17. The method or use of claim 15 or claim 16, wherein at least one variation in the LKB1 polypeptide is an amino acid variation at an amino acid position selected from Table 1 that results in (a) significantly reduced or absent levels of LKB1 protein and/or (b) expression of a LKB1 protein with significantly reduced activity.

18. The method or use of claim 17, wherein at least one variation in the LKB1 polypeptide is an amino acid change selected from Table 1.

19. The method or use of any one of claims 11 to 16, wherein the variation in the LKB1 polynucleotide is a nucleotide variation at a nucleotide position selected from Table 1 that results in (a) significantly reduced or absent levels of LKB1 protein and/or (b) expression of a LKB1 protein with significantly reduced activity.

20. The method or use of claim 19, wherein the variation in the LKB1 polynucleotide is a nucleotide change selected from Table 1.

21. The method or use of any one of the preceding claims, wherein the mammal is a human.

22. The method or use of any one of the preceding claims, wherein the EGFR inhibitor is an antibody that binds EGFR.

23. The method or use of any one of the preceding claims, wherein the EGFR inhibitor is cetuximab or panitumumab.

24. The method or use of any one of claims 1 to 21, wherein the EGFR inhibitor is a small molecule.

25. The method or use of any one of claims 1 to 21, wherein the EGFR inhibitor is erlotinib or gefitinib.