IN THE SPOTLIGHT

CRKL as a Lung Cancer Oncogene and Mediator of Acquired Resistance to EGFR Inhibitors: Is It All That It Is Cracked Up to Be?

Marc Ladanyi

Summary: Cheung and colleagues demonstrate that amplified CRKL can function as a driver oncogene in lung adenocarcinoma, activating both RAS and RAP1 to induce mitogen-activated protein kinase signaling. In addition, they show that CRKL amplification may be another mechanism for primary or acquired resistance to epidermal growth factor receptor kinase inhibitors. Cancer Discovery; 1(7):560–1. ©2011 AACR.

Commentary on Cheung et al., p. 608 (1).
plasmid into the gefitinib-sensitive, EGFR-mutant HCC827 cell line (1). It will be of interest to see whether secondary amplification of CRKL ever emerges spontaneously after long-term selection of EGFR mutant cell lines in the presence of EGFR inhibitor, like the 2 major mechanisms of resistance, the EGFR T790M mutation and MET amplification (13–15). The spectrum of acquired resistance mechanisms for EGFR inhibitors has recently been found to be more accurately defined by 2 large series in which the authors analyzed rebiopsy specimens from patients who progressed (16, 17). When high-sensitivity assays are used, the EGFR T790M or other rare second-site mutations are detected in 60% to 70% of patients (13–15). The spectrum of acquired resistance mechanisms for lung cancer presenting acquired resistance to crizotinib, especially those lacking ALK mutations (18–20), because the biology of CRKL-induced resistance should in principle also apply to this subset. It is increasingly clear that the delinea-
tion of molecular subsets of lung cancer has dramatically clarified its biologic and clinical heterogeneity, leading to new therapeutic opportunities (21); the elucidation of the subset of lung cancers with focal CRKL amplification repre-
sents a further advance in this direction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received November 10, 2011; revised November 10, 2011; accepted November 10; published online December 14, 2011.

REFERENCES


CRKL as a Lung Cancer Oncogene and Mediator of Acquired Resistance to EGFR Inhibitors: Is It All That It Is Cracked Up to Be?

Marc Ladanyi


Updated version
Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/1/7/560

Cited articles
This article cites 20 articles, 10 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/1/7/560.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.