# Re: Akt Phosphorylation and Gefitinib Efficacy in Patients With Advanced Non–Small-Cell Lung Cancer

We found the study by Cappuzzo et al. (1) to be very interesting, and we congratulate the authors on conducting this important clinical trial, which identified factors that were predictive of response to gefitinib. Cappuzzo et al. (1) designed the trial to assess the possible association between activation of epidermal growth factor receptor (EGFR) pathway downstream signaling components MAPK and Akt and response to gefitinib in patients with non-small-cell lung cancer (NSCLC).

Every year, more than 1 million patients are diagnosed with NSCLC worldwide. Most of the patients will be not curable by surgery. Consequently, even if a small percentage of patients would benefit from a targeted agent such as gefitinib, it would have a major impact on care. However, the best strategy for selecting patients who will respond to gefitinib is unclear.

The EGFR tyrosine kinase is still the only recognized target for gefitinib. However, the downstream components MAPK and Akt are activated in response to EGFR and to many other receptors. We believe that EGFR expression should always be analyzed initially as a factor that is predictive of response to an agent targeting EGFR. Indeed, some somatically acquired mutations in the EGFR gene are strongly associated with clinical responsiveness to gefitinib (2,3). For example, preliminary data from a mutation analysis of bronchioalveolar carcinoma (BAC)/adenocarcinoma tumors from patients enrolled in the SWOG 0126 trial showed that 43% of 14 patients had an EGFR mutation in exon 18, 19, or 21 (4). The BAC histotype was associated with gefitinib sensitivity.

An analysis of the relationship between EGFR mutations and activation of the downstream components should then clarify whether activation of MAPK and/or Akt is an independent factor that can increase the predictive value of EGFR mutations or whether activation of MAPK and/or Akt is just a less specific marker of a subgroup of gefitinibresponsive patients already selected by the analysis of EGFR itself. Thus, we are concerned about the missing data on lack of analysis of EGFR expression in the study by Cappuzzo et al. (1).

We are also concerned about the timing of the assessment for EGFR expression and MAPK and Akt activation in Cappuzzo et al. (1). It appears that most of the specimens were collected at the time of primary diagnosis, and that patients were treated with gefitinib after having received chemotherapy. We have found (5) that chemotherapy can induce EGFR expression in some patients with EGFR-negative tumors. In this analysis, we evaluated EGFR expression on mediastinal lymph nodes and/or primary tumors before and after chemotherapy in patients with stage IIIa/b pN2/3 NSCLC. Before chemotherapy, six patients had EGFR-negative mediastinal lymph nodes and five patients had EGFR-negative primary tumors. After chemotherapy, four of the six EGFRnegative mediastinal lymph nodes and three of the five EGFR-negative primary tumors were EGFR positive. Although this observation was very preliminary, it raised the possibility that systemic chemotherapy can change EGFR expression and activation of its downstream pathway. This possibility could explain the two responses observed among Aktnegative tumors in Cappuzzo et al. (1).

A prospective study is needed to assess the relationship between EGFR mutations and activation of downstream pathway components. The identification of a profile that is strongly predictive of the response to EGFR targeting agents will be important to increase the clinical impact of these agents in clinical care.

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#### References

- (1) Cappuzzo F, Magrini E, Ceresoli GL, Bartolini S, Rossi E, Ludovini V, et al. Akt phosphorylation and gefitinib efficacy in patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2004;96:1133–41.
- (2) LynchTJ,BellDW,SordellaR,Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of nonsmall-cell lung cancer to gefitinib. N Engl J Med 2004;350:2191–3.
- (3) Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
- (4) Franklin WA, Chansky K, West H, Gumerlock PH, Hirsch FR, Gandara DR. Association between activation of ErbB pathway genes and survival following gefitinib treatment in advanced BAC (SWOG 0126). Presentation during the "Lung Cancer II" session at ASCO, New Orleans, LA, USA, June 5–8, 2004. Available at: http://www.asco.org/ac/1,1003,\_ 12-002511-00\_18-0026-00\_19-0010095,00. asp. [Last accessed: August 23, 2004.]
- (5) De Pas T, Pelosi G, de Braud F, Veronesi G, Curigliano G, Leon ME, et al. Modulation of epidermal growth factor receptor (EGFR) status by chemotherapy in patients with locally advanced non–small-cell lung cancer is rare. J Clin Oncol 2004;22:4966–70.

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## RESPONSE

Gefitinib is a tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR). Although approximately 10% of non-small-cell lung cancer (NSCLC) patients who received gefitinib had a dramatic response and increased long-term survival, patients not selected for any biologic characteristic who received the drug as a first-line therapy in combination with standard chemotherapy had no survival advantage (1,2). The mechanisms underlying gefitinib sensitivity have recently been discovered. It is now known that specific EGFR gene mutations can confer a gefitinib-sensitive phenotype (3), that a consequence of these mutations is the activation of the antiapoptotic protein Akt (4), and that patients whose tumors have activated Akt are more sensitive to the drug than patients whose tumors do not (5). In December 2004, AstraZeneca announced the results of the ISEL trial, a phase III randomized study comparing gefitinib with placebo in pretreated NSCLC patients. In this trial, the survival benefit observed in patients who received gefitinib was not statistically significant (hazard ratio of death = 0.89, P = .11). The negative results of the ISEL trial and those of all trials using a TKI in combination with chemotherapy clearly indicate that it is not possible to propose a TKI to all patients with NSCLC and that TKIs should be offered to patients selected for the presence of the drug target, i.e., the presence of EGFR gene mutations or amplification. Unfortunately, the problem of patient selection is further complicated because different mechanisms are involved in TKI sensitivity. For example, erlotinib was shown to improve survival compared with placebo in pretreated patients (6), but benefit was not confined to responders or to patients with EGFR gene mutations.

For several years, we have focused on identifying a biological predictor of gefitinib sensitivity. We observed that patients whose tumors had activated Akt had a statistically significantly higher response rate and disease control rate and longer time to progression than patients whose tumors did not have activated Akt,

but the difference in overall survival was not statistically significant (5). Because several receptors can activate Akt, we hypothesized that patients with Akt activation would be sensitive to the inhibitory effect of gefitinib only if Akt activation was sustained by an EGFR-dependent mechanism. Therefore, as correctly suggested by de Braud et al., we recently performed EGFR and Akt analyses in a large cohort of NSCLC patients treated with gefitinib. The results of this study confirm that Akt activation is required for gefitinib sensitivity in patients with EGFR-positive tumors, irrespective of the method used for EGFR assessment, and support the idea of analyzing Akt status to aid in identifying patients for TKI therapy.

De Braud et al. also raised the issue of timing of Akt assessment. Although no trial to date has specifically addressed this question, preclinical data suggest that NSCLC tumors become more dependent on the EGFR signalling pathway and more sensitive to EGFR blocking strategies as they are exposed to different chemotherapies (7). Therefore, I agree that, because of the possible effects of previous therapies on EGFR pathways, it is possible that our results underestimated the true association between the molecular variables and response to gefitinib.

FEDERICO CAPPUZZO

### References

- (1) Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. J Clin Oncol 2004;22: 777–84.
- (2) Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. J Clin Oncol 2004;22: 785–94.
- (3) Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
- (4) Sordella R, Bell DW, Haber DA, Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science 2004;305:1163–7.
- (5) Cappuzzo F, Magrini E, Ceresoli GL, Bartolini S, Rossi E, Ludovini V, et al. Akt phosphorylation and gefitinib efficacy in patients with advanced non-small cell lung cancer. J Natl Cancer Inst 2004;96:1133–41.
- (6) Shepherd FA, Pereira J, Ciuleanu TE, Tan EH, Hirsh V, Thongprasert S, et al. A randomized

placebo-controlled trial of erlotinib in patients with advanced non–small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Trial Group (NCIC CTG) trial. Proc Am Soc Clin Oncol 2004;23:622.

(7) Perez-Soler R, Dai Q, Ling YH, Lee M, Kroog G, Zou Y, et al. Molecular mechanisms of sensitivity and resistance to the HER1/EGFR tyrosine kinase inhibitor erlotinib [abstract O-247]. Lung Cancer 2003;41:s72.

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