

Selecting the right patient for tumor therapy

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Two clinical studies have identified mutations affecting the EGF receptor in lung cancers from patients who respond robustly to gefitinib, a small-molecule inhibitor of the receptor tyrosine kinase. This work highlights the importance of conducting clinical trials with an eye to delivering molecule-targeted therapeutics to those patients most likely to benefit.

The epidermal growth factor receptor (EGFR or erbB1) has emerged in recent years as a viable therapeutic target in human cancer¹. This transmembrane receptor tyrosine kinase is frequently detectable in a wide range of human tumors. However, tumor EGFR levels are not correlated with the level of receptor activation and use by cancer cells and, therefore, do not predict EGFR 'dependence'.

Several recent clinical trials have evaluated such inhibitors and ligand-blocking antibodies to EGFR, either alone or in combination with anticancer chemotherapy, in unselected patients with various solid tumors. Studies in lung cancer have shown modest clinical activity, with higher response rates in women, patients with lung adenocarcinoma, nonsmokers and Japanese patients²⁻⁵. In none of these trials were patients selected based on any evidence of EGFR kinase dependence, nor was there a deliberate plan for a retrospective molecular analysis of the tumors from enrolled patients. Because of these limitations, EGFR inhibitors have not lived up to their initial promise.

Two studies by Paez *et al.*⁶ and Lynch *et al.*⁷ could bring these inhibitors back into the fold. These studies, published in *Science* and the *New England Journal of Medicine*, shine a bright light on the molecular underpinnings of the overall low clinical activity

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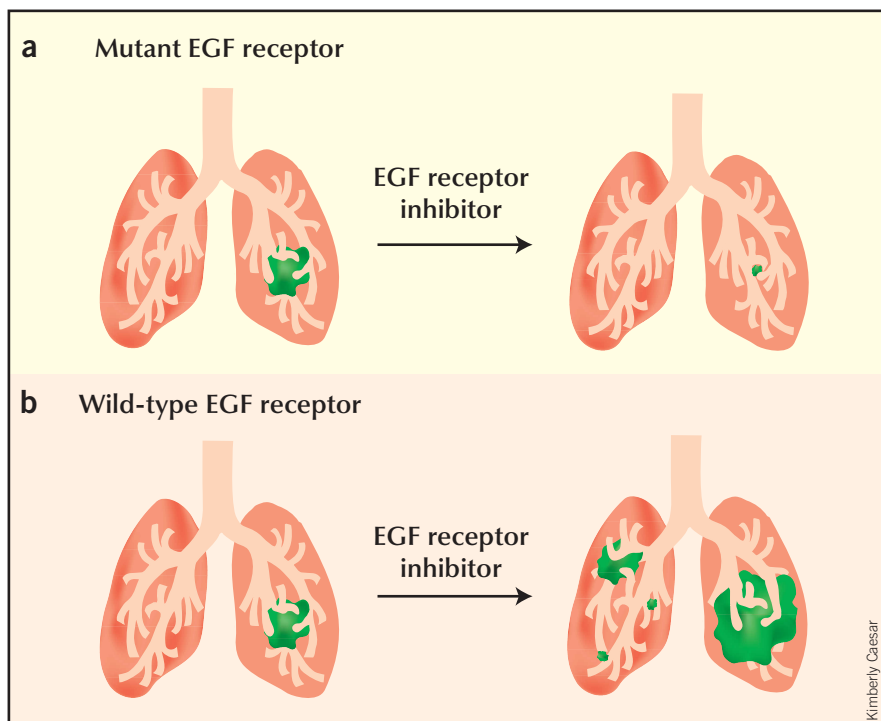


Figure 1 Selecting for tumor shrinkage. Two new studies show that, in patients with mutations in the gene encoding the EGF receptor, tumors shrink in response to gefitinib, an inhibitor of the receptor tyrosine kinase. This drug does not perform nearly as well in patients in the general population. The new work should revive enthusiasm for gefitinib and promote clinical trial designs that preselect patients based on their molecular profile.

of EGFR inhibitors and will almost certainly lead to the identification of subgroups of patients who are likely to benefit substantially from these drugs. These reports identify somatic mutations in the *EGFR* gene in patients with non-small-cell lung cancer (NSCLC) that had durable clinical responses to the EGFR tyrosine kinase inhibitor gefitinib (Fig. 1). The mutations were either short, in-frame deletions or

substitutions clustered around the region encoding the ATP-binding pocket of the receptor's tyrosine kinase domain.

In the study by Paez *et al.*, these mutations were more frequent in patients with adenocarcinoma than other histological types of NSCLC, in women and in Japanese patients. In both studies combined, *EGFR* mutations were detected in 18/144 (13%) specimens with 15/18

mutations detected in Japanese patients. Adding together data from both studies, a total of 13/14 patients (93%) who underwent a durable reduction in the size of their tumors had *EGFR* mutations affecting the kinase domain of the protein, but none of 11 patients whose disease progressed on therapy did.

Lynch *et al.*⁷ provided suggestive evidence that two of the mutant receptors were hyper-responsive to exogenous *EGFR* ligand. Although the authors did not provide rigorous molecular evidence that these are gain-of-function mutations, the striking association with a durable clinical response after gefitinib treatment indicate that they represent a functional marker of *EGFR* dependence. Such strong responses are almost unheard of in chemotherapy-refractory advanced NSCLC.

These results do not come as a total surprise, as it is known that the wild-type *EGFR* is limited in its ability to activate a large repertoire of signaling pathways and is, therefore, weakly oncogenic⁸. The variant III *EGFR* deletion mutant, which is present in 40% of high-grade gliomas, is a constitutively active, endocytosis-resistant receptor with broad signaling specificity and high oncogenicity^{9,10}. Notably, more than 20% of patients with recurrent high-grade gliomas respond to the *EGFR* inhibitor erlotinib¹¹, but interpretation of these results await determination of the *EGFR* gene status in these tumors. Thus, the mutants identified by Paez *et al.* and Lynch *et al.* might encode receptors that, compared with wild-type *EGFR*, engage additional signal transducers, dimerize with *erbB* coreceptors with higher efficiency, have higher stability because of altered intracellular trafficking, or more efficiently bind ATP (and hence the ATP mimetic gefitinib).

Whether these mutant receptors depend on ligand for activation *in situ* is a crucial question. Ligand-independent activation could anticipate therapeutic resistance to ligand-blocking *EGFR* antibodies currently in clinical development.

It is not clear from these studies whether only tumors with *EGFR* mutations respond to gefitinib. Of note, one of nine responding patients in the study by Lynch *et al.* had a wild-type receptor. This raises the question of whether exons other than those encoding the kinase domain were examined in all patients. Nonetheless, excluding Japanese patients, only 3/86 (3.5%) of patients in the combined studies were identified with *EGFR* mutations, far lower than the 11% response rate reported by Kris *et al.* in the phase 2 study of gefitinib in the United States³.

A recently completed phase 3 trial comparing the *EGFR* inhibitor erlotinib against best supportive care in advanced NSCLC showed an improvement in overall survival in patients treated with the inhibitor (see <http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=7387>). It remains to be determined whether the benefit from erlotinib in this trial, which was powered to achieve a 33% improvement in overall survival, is limited to patients with receptor mutations. With the overall low incidence of mutations, it is unlikely that the anticipated improvement in overall survival can be explained exclusively by durable clinical responses in patients bearing NSCLC with mutant *EGFR*.

In previous gefitinib studies in NSCLC^{2,3}, there was a group of patients that showed marked symptom improvement and prolonged disease stabilization with no measurable reduction in tumor size. The *EGFR* gene status of such tumors was not reported in the studies by Paez *et al.* and Lynch *et al.* and would also be of considerable interest. The status of the *EGFR* gene should also be informative in other tumors, such as colon cancers, where a similar small number of robust clinical responses have been seen in patients treated with *EGFR* antibodies^{12,13}.

It becomes important now to determine whether, in *EGFR*-mutant lung cancers that eventually escape gefitinib, the resistance is *EGFR*-dependent or *EGFR*-independent. This can be done by obtaining new biopsies and resequencing the *EGFR* gene at the time of relapse. Although such biopsies would be 'only for research purposes', the information that they can generate could be of enormous benefit to patients. If resistance is *EGFR* dependent, secondary mutations occurring or enriched for as a response to therapy may help in the identification of second-line inhibitors. These may include other, already available small-molecule kinase inhibitors or *EGFR* antibodies. Perhaps the best example of the strength of this approach is the demonstration that dual *Abl*-*Src* inhibitors can bind the activation loop of the *Abl* tyrosine kinase in a conformation not accessible to imatinib¹⁴, thus explaining their ability to inhibit chronic myelogenous leukemia (CML) cells with imatinib-resistant *Abl* mutations¹⁵.

Finally, these results highlight the potential benefit of comprehensive sequencing approaches for human kinases across tumor types, as has been recently accomplished in several primary tumors^{16,17}.

Such studies should be able to identify additional activating tyrosine kinase mutations that can lead drug discovery and development and, eventually, inform the approval process.

The seminal studies of Paez *et al.* and Lynch *et al.* show yet again that even late cancers remain dependent on specific molecular alterations and that reversion of the effects of these alterations with specific, well-tolerated molecular therapies can induce dramatic clinical responses. Does anybody doubt that a trial with gefitinib in patients with *EGFR*-mutant NSCLC should be able to achieve a greater than 80% clinical response rate and meaningfully prolong survival? And that the refinement of anti-*EGFR* therapies and the deliberate discovery of mechanisms of acquired resistance to these therapies will lead to the cure or prevention of this particular syndrome within the next five to ten years? If we consider that every year, in the United States alone, NSCLC kills 160,000 patients, the potential impact of these results is quite remarkable.

It is clear from these studies that molecular target dependence and patient selection should be central to the development of molecular therapeutics in human cancer. This approach should avoid spuriously negative or overall weak signals of clinical activity of otherwise very active drugs when used in the right group of patients, prevent unnecessary large costly trials, and limit the exposure of patients to drugs unlikely to produce any clinical benefit.

1. Arteaga, C.L. *J. Clin. Oncol.* **19**, 32S–40S (2001).
2. Fukuoka, M. *et al. J. Clin. Oncol.* **21**, 2237–2246 (2003).
3. Kris, M.G. *et al. JAMA* **290**, 2149–2158 (2003).
4. Giaccone, G. *et al. J. Clin. Oncol.* **22**, 777–784 (2004).
5. Herbst, R.S. *et al. J. Clin. Oncol.* **22**, 785–794 (2004).
6. Paez, J.G. *et al. Science* published online 29 April 2004 (doi: 10.1126/science.1099314).
7. Lynch, T.J. *et al. N. Engl. J. Med.* published online 29 April 2004 (doi: 10.1056/NEJMoa040938).
8. Yarden, Y. & Sliwkowski, M.X. *Nat. Rev. Mol. Cell Biol.* **2**, 127–137 (2001).
9. Antonyak, M.A., Moscatello, D.K. & Wong, A.J. *J. Biol. Chem.* **273**, 2817–2822 (1998).
10. Huang, H.S. *et al. J. Biol. Chem.* **272**, 2927–2935 (1997).
11. Prados, M. *et al. Proc. Am. Soc. Clin. Oncol.* **22**, 99 (2003).
12. Schwartz, G. *et al. Proc. Am. Soc. Clin. Oncol.* **21**, 24a (2002).
13. Saltz, L. *et al. Proc. Am. Soc. Clin. Oncol.* **21**, 127a (2002).
14. Nagar, B. *et al. Cancer Res.* **62**, 4236–4243 (2002).
15. Huron, D.R. *et al. Clin. Cancer Res.* **9**, 1267–1273 (2003).
16. Bardelli, A. *et al. Science* **300**, 949 (2003).
17. Samuels, Y. *et al. Science* **304**, 554 (2004).