

Response of Intracranial Metastases to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: It May All Depend on *EGFR* Mutations

TO THE EDITOR: We read with great interest the case description by Fekrazad and colleagues¹ in the *Journal*. They describe a nonsmoking Native American woman with brain metastases from a lung adenocarcinoma who had a marked response to monotherapy with erlotinib at 150 mg/d. Although they do not provide these data, it is very likely that the patient had an activating epidermal growth factor receptor (*EGFR*) mutation, based on her clinical characteristics and response to the oral tyrosine kinase inhibitor (TKI) erlotinib.²

In the recently reported phase II trials of gefitinib 250 mg/d³ and erlotinib 150 mg/d^{4,5} for patients with the L858R and exon 19 deletion *EGFR* mutations, patients with CNS metastases were included. The overall response rate in these and other prospective trials of gefitinib and erlotinib exceed or equal 75% for all sites.³⁻⁶ In both instances, it seems that patients with intracranial metastases also have a similar high level of tumor responses in their CNS.^{3,4} The Spanish Lung Cancer Group^{4,5} followed the CNS response of seven chemotherapy-naïve patients with an *EGFR* mutation given erlotinib 150 mg/d (available as part of the 2006 ASCO Annual Meeting's slide presentation of their abstract⁴). They reported four patients with a complete response and three with a partial response to this *EGFR* inhibitor: a 100% response rate of brain metastases. These results are astounding, and indicate that in a molecularly selected population with brain metastases, both gefitinib and erlotinib can achieve high response rates in a metastatic site that historically has not been sensitive to systemic chemotherapeutic agents used in non-small-cell lung cancer. Despite the striking efficacy of these *EGFR* inhibitors, secondary resistance is common and the brain may actually be the first site of loss of response

to *EGFR* TKIs.⁷ Others have speculated that over time the effective dose of gefitinib in the CNS may wane to levels that are subtherapeutic to inhibit *EGFR* mutations.⁷

We look forward to mature results of prospective trials that evaluate the clinical benefit of *EGFR* TKIs in patients who have *EGFR* mutations with brain metastases. It is not inconceivable to think that in this patient population, oral TKIs may replace or supplement radiation therapy for management of brain metastases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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CYP2D6 and Ockham's Razor

TO THE EDITOR: Heredity has been both an explicative and a predictive tool for a long time. Not surprisingly, genes—its biologic component—are used for understanding the past and reading the future. We live in societies with more and more focus on the individuals,¹ who claim for individualized care and prevention. Gene analysis, both somatic and germline, could help to achieve that goal; however, having a hammer in the hand does not mean everything is a nail.²

With regard to the contribution of Lim et al,³ I will challenge neither the validity nor the scientific value of this article but rather the meaning of the title "Clinical implication." It is crystal clear that the real end point, the gold standard, is the individual effectiveness of the treatment, tamoxifen in that case. A close surrogate, used in this

contribution, is the concentration of active metabolites. Does having a surrogate (CYP2D6) for that surrogate, improve care and challenge current clinical practice?

The rule of Ockham, "*Pluralitas non est ponenda sine necessitate*," means that new entities are required only if necessary. Figure 3 tells us that CYP2D6 does predict outcome, but does it do it better than plasma concentration at steady-state stage? These data are available in that survey, and therefore comparative analysis should be disclosed. It is unlikely to expect an improved discrimination, because plasma concentration of active metabolite is the end-product of many steps, each of them partially under genetic determinism: absorption, bio-transformation from inactive to active product, and elimination of the active product (partially discussed in the article). The dosage of the critical product (the active metabolite) should in that case be more accurate, concerning both calibration and discrimination.