Somatic mutation of EGFR catalytic domain and treatment with gefitinib in colorectal cancer

In non-small-cell lung cancer, response to the small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib or erlotinib is associated with activating mutations including in-frame deletions and amino acids substitutions in exons 18, 19 and 21 in the catalytic domain of EGFR gene [1].

We have demonstrated recently that clinical response of metastatic colorectal cancer to the anti-EGFR monoclonal antibodies cetuximab or panitumumab is significantly associated with increased copy number of the EGFR gene as detected by fluorescence in situ hybridization, but not to mutations of the EGFR gene catalytic domain or to mutations of EGFR intracellular signal transducers in individual tumor samples [2]. In our series of 31 patients with EGFR-expressing colorectal cancer, the sequencing of EGFR exons 18, 19 and 21 revealed a somatic mutation of EGFR in a single patient with normal EGFR gene copy number and stable disease for 24 weeks with cetuximab treatment. In particular, the molecular analysis of the tumor of this patient displayed a missense heterozygous mutation in exon 21 (Gly857Arg) affecting a residue located in the activation loop of the EGFR catalytic domain, one amino acid apart from the previously reported Leu858Arg activating mutation found in gefitinib and erlotinib responders in lung cancer [1]. Similar mutations, i.e. missense mutations clustered in the EGFR kinase domain, were also recently described in Japan in four out of 33 (12%) clinical samples of colorectal carcinoma, and the authors hypothesized that these molecular alterations might be associated with clinical responsiveness to EGFR inhibitors [3].

Based on the above findings [1–3], at disease progression after failure of standard chemotherapy and cetuximab (Erbitux®; Merck, Milan, Italy), we elected to treat with gefitinib (Iressa®; AstraZeneca, London, UK) (250 mg orally daily) the patient with metastatic colorectal cancer harboring the Gly857Arg mutation. A planned computed tomography scan evaluation after 4 weeks of gefitinib therapy documented disease progression in the liver and the lungs. To the best of our knowledge, this is the first report of a metastatic colorectal cancer patient treated with a tyrosine kinase inhibitor on the basis of a documented molecular alteration of the EGFR catalytic domain. Nevertheless, this individual molecular alteration was not predictive of clinical response to gefitinib.

A recent report from the USA showed a 0.34% frequency (one mutated case out of 293) of EGFR catalytic domain mutations in colorectal cancer, leading the authors to conclude that these mutations are unlikely to be responsible for the reported success of anti-EGFR monoclonal antibody therapy, and that gefitinib or erlotinib are unlikely to be effective in patients with colorectal cancer [4]. Owing to the extremely low frequency of mutations found in the catalytic domain of the EGFR gene in colorectal cancer [2–4], we believe it will be difficult to accrue an adequate number of patients in appropriately designed clinical trials aimed at evaluating a possible association between these rare mutations and response to gefitinib or erlotinib in this disease. In this perspective, reports of limited series or single cases such as the present one are warranted.

The present report suggests that for metastatic colorectal cancer the impact of treatment with a small molecule tyrosine kinase inhibitor is expected to be limited, not only because of the rarity of mutations [2–4], but also because the role of
known *EGFR* mutations might be not as predominant as in lung cancer.

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