Reply: Her2 (ErbB2) receptors, a potential therapeutic target in squamous cell carcinoma of oesophagus?

Sir,

At first, we would like to thank you for giving us the opportunity to reply to this letter. It may be worth reminding that our study showed a potential impact of EGFR status, and HER2 was found to be overexpressed by only 2.8% of the tumours (Gibault et al, 2005a). It is important to note that the differences observed between these different studies have led us to consider the high heterogeneity in the methodologies used in the two very interesting and recent papers by Mimura and others.

Before replying to the letter by Khan, it sounds us worth (i) recalling that there is a consensus among the scientific community about the difficulty of comparing data relative to the assessment of angiogenesis by immunohistochemistry (Vermeulen et al, 2002) and (ii) indicating that our bibliography section did not refer to the two very interesting and recent papers by Mimura et al (2005a, b) only because our manuscript had been submitted and accepted before the publication of both articles.

The remarks by Khan and co-workers are focused on the low rate reported by our team and on the potential role of HER2 in squamous cell carcinoma of the oesophagus. We totally agree with them about the fact that several analyses of HER2 carried out by immunohistochemistry or other methods (Shiga et al, 1993; Hardwick et al, 1997; Tanaka et al, 1997; Friess et al, 1999; Wang et al, 1999; AkatRESULTS: The aim of this study was to analyze and compare the performance of the FDA-approved 10- and 22-gene recurrence assays with the PAM50 genomic classification system. Both the 10- and 22-gene tests identified a greater proportion of patients with a high risk of recurrence compared with patients classified as high-risk by the PAM50 system, with the 22-gene test showing a trend toward better discrimination. The 10- and 22-gene tests were significantly better than the PAM50 system at predicting death from breast cancer, while the 22-gene test was the most accurate in predicting distant recurrence. However, the 22-gene test did not outperform the PAM50 system in predicting recurrence in the absence of distant metastasis.

CONCLUSIONS: Both the 10- and 22-gene tests show promise for improving the classification of breast cancer recurrence risk, but their clinical utility should be further evaluated in prospective studies.

**References**

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found to show no staining in Herceptest despite Her2 expression in flow cytometric analysis. In the second study (Mimura et al., 2005b) published in the British Journal of Cancer, they evaluated only HER2 in a homogenous series (66 cases) of squamous cell carcinoma of the oesophagus treated by surgery; one should note that, despite the lower number of cases under study, these investigations and ours can be compared. Among their cohort of patients, only three of them denoted (3 +) were identified by immunohistochemistry as being positive; six others, denoted (2 +), were considered as positive cases. When they compared the HER2 status between primary and metastatic lymph nodes, they clearly found a strong correlation, but only in the three HER2 (3 +) (45.5% of the cases). FISH analysis revealed that a gene amplification in the three strongly positive cases, that is (3 +), in three out of the six samples denoted (2 +) and in one out of the 11 weak positive patients termed (1 +). To our knowledge, this study is the only report describing HER2 status in oesophageal neoplasms from results of the two FDA-approved tests. The finding that one patient with herceptest 1 + was positive for gene amplification suggests an underestimation of the rate of HER2-positive cases by this test.

Ongoing experiments within our laboratory are focused on a FISH analysis of our cohort of 126 patients. It should allow us to get data comparable with those reported by Mimura about 66 cases.

As we also wonder about the impact of cultural habits, ethnic differences between populations of the different continents, it would be also worth carrying out an intercomparison of HER2 and EGFR data in cohorts of patients from geographical areas where the incidence of squamous cell carcinoma is high (Japan, China, France or other countries) obtained by strictly using the same methodology to eventually highlight a difference of status in relation with the origin of patients and their food habits. Her-2 status is generally determined by FISH and immunohistochemistry. To our opinion, the serum HER2 is worth being analysed. Indeed, we reported at the ASCO GI 2006 symposium preliminary results about HER2, EGF, P53, VEGF and IL6 analysed by ELISA in the serum of patients treated by radiochemotherapy for oesophageal squamous cell carcinoma; pretherapeutic serum HER2 and serum EGF levels seemed to be strongly correlated (P = 0.017). Moreover, serum HER2 levels suggested an association with progression (P = 0.059) and metastatic status (P = 0.006); but only pretherapeutic serum EGF levels were associated with overall survival (P = 0.046) (Metges et al., 2006).

In conclusion, we think that HER2 is a potentially interesting target in oesophageal neoplasms. According to Mimura, Herceptest 3 + patients are the best candidates for anti-Her2 immune targeting; this subgroup of patients represents a relatively low proportion of the total population of oesophageal squamous cell carcinoma (Mimura et al., 2005b). However, further investigations needed to confirm these data. Prospective and homogenous series of patients required to analyse the potential interest of HER2 status by immunohistochemistry, serum analysis and gene amplification in the clinical course of patients with oesophageal squamous cell carcinoma.

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