

for accurate assessment of the presence or absence of HPV DNA are formidable.

All trials to date of HPV vaccines have enrolled women, but genital HPV infections are mainly sexually transmitted and men will also need to be vaccinated if the whole population is to develop immunity. Interestingly, seroconversion rates in men with anogenital warts who are infected with HPV 6 or 11 are consistently lower than those in women,^{7,8} and trials of L1 virus-like-particle vaccines will need to also enrol men to confirm that responses are similar in men and women. Despite these caveats, we must be optimistic that the control of genital HPV infection, and morbidity and mortality associated with resultant disease is achievable—it could be the end of the affair with HPV.

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MS is an ad-hoc consultant for Merck Vaccines, West Point, PA, USA; Sanofi Pasteur, France; and GlaxoSmithKline Vaccines, Rixensart, Belgium, but is not a member of their scientific advisory boards and has no stock, share holdings, or patent interests in these companies. MS had a research collaboration with GlaxoSmithKline Immunotherapeutics, Stevenage, UK, 1998–2004, on therapeutic HPV vaccines, which resulted in several publications.

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Who will benefit from treatment against EGFR?

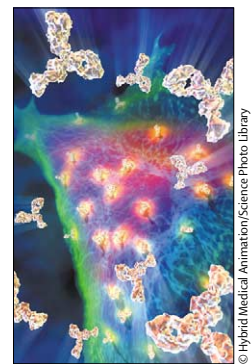
The epidermal-growth-factor receptor (EGFR) is regarded to be a relevant target of antitumour treatment because it participates in control of cell proliferation, differentiation, and migration. Monoclonal antibodies and small-molecule inhibitors designed to block EGFR have been approved for treatment of various malignant diseases, including non-small-cell lung cancer and chemotherapy-resistant metastatic colorectal cancer. However, only about 10% of patients with non-small-cell lung cancer respond positively to these drugs, although most patients who responded were found to express mutated *EGFR*.¹

Ectopic or sustained activation of EGFR leads to oncogenic transformation of cells in vitro and in genetically manipulated mice,² and cancers with a poor prognosis often overexpress EGFR or its cognate ligands. The first drugs developed from this knowledge were monoclonal antibodies directed against the extracellular domain of EGFR, which compete with ligands and thus prevent activation of the receptor.²

Non-small-cell lung cancer is the main cause of cancer-related deaths; survival 5 years after diagnosis is about 14%.¹ In this scenario, the response of a small number of patients to gefitinib and erlotinib, two potent tyrosine-kinase inhibitors selective for EGFR, was thought to be a

promising result and some subgroups (eg, female, Japanese, or non-smokers) had a higher probability of achieving clinical benefit.¹ Subsequently, several groups have sequenced *EGFR* expressed by patients given the inhibitors and found that whereas non-responders generally had wildtype *EGFR*, those who showed a striking response generally had somatic mutations in the tyrosine kinase domain of the *EGFR*.¹ Although their function is not completely understood, the mutations show how dependent some tumours are on EGFR, and open the possibility of predicting which patients will benefit from treatment with antiEGFR agents.

Unresectable, metastatic colorectal cancer is a fatal disease. Palliative treatment is based on chemotherapy, but tumours commonly become resistant.³ Thus, the finding that monoclonal antibodies against EGFR (cetuximab and panitumumab) caused a response in patients, and reversed resistance to chemotherapy, was exciting news. However, expression of EGFR did not correlate with clinical benefit. In the initial trials, in which participation was restricted to tumours positive for EGFR,⁴ patients with higher expression of EGFR derived no more benefit from cetuximab than did those with lower expression of EGFR. Furthermore, even patients with



See [Articles](#) page 279 for a study on EGFR copy number and clinical response in colorectal cancer

tumours negative for EGFR might benefit from this drug.⁵ This result is intriguing because the only expected target of these highly characterised antibodies was EGFR. Inspired by the results obtained in patients with non-small-cell-lung cancer, Moroni and co-workers⁶ analysed EGFR in patients with colorectal cancer. Their results, presented in this month's *The Lancet Oncology*, showed that although mutations in *EGFR* were rare, about 90% of those who showed objective responses to cetuximab had an increased number of gene copies of *EGFR*. Arguably, a rise in gene copy number should result in higher expression of EGFR, which would account for the susceptibility of those tumours to antibodies against EGFR. So the question arises, why did previous studies not detect a rise in EGFR by immunohistochemistry?^{4,5} Much work has been done on the technical difficulties inherent in assessing EGFR with immunocytochemistry.⁵ Thus, a plausible possibility is that immunocytochemistry is not robust enough to measure EGFR expression in tumours. Moroni and co-workers⁶ also showed that the heterogeneity of some tumours could contribute to EGFR-positive tumours being overlooked. Cells with extra copies of *EGFR* and thus overexpressing the protein, can be found in discrete foci surrounded by non-expressing cells. Confirmation of these possibilities should be mandatory, since a good correlation between gene amplification and measurement of expression of EGFR by immunohistochemistry has been reported in other tumours.⁷

As anticipated, somatic mutations of *EGFR* do not fully explain responsiveness to antiEGFR treatment. Patients with lung adenocarcinoma who carry *KRAS* mutations

will probably not respond to gefitinib.⁸ The report by Moroni and co-workers shows that, in colon cancer, increased copy numbers of *EGFR* can predict responsiveness to cetuximab. This observation, once validated, would be an additional step forward in the selection of patients who are likely to benefit from drugs against EGFR. Clearly, the search for markers of response to treatment against EGFR must go on.

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Effect of dose-intensive chemotherapy on quality of life

See **Articles** page 287 for a quality-of-life assessment for patients with locally advanced breast cancer treated with standard dose or dose-intensive chemotherapy

In an article in this month's *The Lancet Oncology*, Bottomley and colleagues¹ assessed health-related quality of life (HRQOL) in patients with locally advanced breast cancer who had been randomly assigned to standard-dose (6 months) adjuvant chemotherapy of cyclophosphamide, epirubicin, and fluorouracil, or to a dose-intensive (3 months) regimen of cyclophosphamide, epirubicin, and filgrastim in the context of a large international trial. As predicted, patients in the dose-intensive group showed greater decrements in HRQOL measured on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 compared with

those in the standard-dose group over the first 3 months. Importantly, however, no differences were seen between the groups at the 1-year assessment, and, for the most part, HRQOL scores were comparable to population norms after this assessment. These data confirm that dose-intensive regimens have a greater negative effect on HRQOL in the short term than do standard-dose regimens; however, these differences disappear over time.

Integration of HRQOL assessments into phase III trials is crucial. The authors speculate that the pattern of clinical results (no differences between groups in progression-free survival or 5-year survival) and HRQOL results suggest