Targeting EGFR in head and neck cancer: a decade of progress

Chris Boshoff and Marshall Posner

It is 24 years since the discovery of EGFR1, and 12 years since the first clinical trials reported the use of monoclonal antibodies that block EGFR1. In December 2008, the European Commission approved the use of cetuximab in combination with platinum-based therapy for the management of locally recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). This approval follows the publication of a large, industry-sponsored, multicentered, randomized trial (EXTREME study), which demonstrated that addition of cetuximab to platinum and 5-fluorouracil (5-FU) for locally recurrent and/or metastatic disease significantly improved overall survival from 7.4 months to 10.1 months, and response rate from 20% to 36% compared with platinum and 5-FU.¹

In the past few years we have seen a flurry of activity in the usually bleak field of SCCHN. In 2005 and 2007 two studies were published that demonstrated cetuximab was both additive and non-cross-resistant to cisplatin in the recurrent setting.^{2,3} These studies were followed in 2008 with the publication of the EXTREME data for recurrent and metastatic disease, the results of which are discussed in a Practice Point in this issue of the journal.⁴

These advances are remarkable; EXTREME is the first study in over 25 years in which any treatment for SCCHN has shown a survival advantage in the recurrent setting. The survival advantage reported with the EXTREME study is proportionate to that seen when trastuzumab is added to chemotherapy for the treatment of patients with metastatic breast cancer that overexpresses HER2 (the median survival improved from 20.3 months to 25.4 months), and has similar implications for curative therapy in SCCHN.

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Competing interests

C Boshoff has declared associations with the following companies: Cellcentric, GlaxoSmithKline, Imclone, Merck Serono and Sanofi-Aventis. M Posner has declared associations with the following companies and organizations: Abraxis, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb, DNAR, Genentech, GlaxoSmithKline, EMD-Serono, Imclone, Merck, National Cancer Institute, National Institute of Allergy and Infectious, Novartis, OSI, Oxigene, Promedior, Sanofi-Aventis. See the article online for full details of the relationships.

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retained if patients were first treated with this chemotherapy regimen and received cetuximab upon progression. If cetuximab were as effective when given after progression on platinum and 5-FU, then combined toxicity and costs could be minimized for patients and payors. As with other targeted therapy combinations, the costs incurred are substantial; drug charges and extra weekly visits are estimated to cost at least three times more when cetuximab is added to cisplatin and 5-FU for the management of SCCHN, as observed in the EXTREME trial. Nonetheless, there is no question that patients with recurrent cancer benefit from cetuximab treatment.

Future randomized studies should address whether any benefit exists for the sequential versus the combined approach. The answer to this biologic question has a major effect on health and economics and was not investigated in the EXTREME trial.¹ It is a question that might be answered best by a government or academic supported trial, given the important implications for cost and health. In addition to the question of the optimum schedule of cetuximab is the challenge of identifying predictive markers. For example, in colorectal cancer, mutations in *KRAS* have been shown to be associated with a worse outcome in response to cetuximab.⁵ Thus, identification of markers that can predict a benefit from costly antibody-based targeted therapies in SCCHN will be important.

The approval of cetuximab is good news. It expands our ability to effectively treat patients, and our biologic understanding of SCCHN. The treatment of SCCHN is emerging from a long period of stagnation to a point where combining targeted treatment with chemotherapy has an appreciable effect.

Supplementary information in the form of a reference list is available on the *Nature Clinical Practice Oncology* website.