# Rationale and clinical validation of epidermal growth factor receptor as a target in the treatment of head and neck cancer

Francesco Caponigro[a]

**Recurrent/metastatic head and neck cancer is an area of high, unmet treatment need. There is a strong rationale for targeting the epidermal growth factor receptor (EGFR) in head and neck cancer as most of these tumors express high levels of EGFR relative to normal tissue, with high expression correlating with poor patient outcome. This rationale has been validated in extensive preclinical studies. Two small molecules with EGFR inhibitory activity, gefitinib ('Iressa', ZD1839) and erlotinib ('Tarceva', OSI-774), and a humanized monoclonal antibody against the EGFR extracellular domain, cetuximab ('Erbitux', C225), are in clinical trials for advanced head and neck cancer. The initial results of these trials are promising. Gefitinib and erlotinib show activity as monotherapy in patients with recurrent or metastatic head and neck cancer, and have an acceptable safety profile compared with conventional chemotherapy. Gefitinib, which can be given at doses below the maximum tolerated dose, is associated with slightly lower rates of adverse events than erlotinib, which is dosed at the maximum tolerated dose. Combinations of cetuximab with radiotherapy or platinum-based chemotherapy have also shown activity in phase I/II studies. Both gefitinib and cetuximab have entered phase III studies. The results of these trials, which will mature over the next few years, will help determine the optimal use of EGFR agents in head and neck cancers. *Anti-Cancer Drugs* 15:311–320 © 2004 Lippincott Williams & Wilkins.**

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[a]Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione G. Pascale', Naples, Italy.

Correspondence to F. Caponigro, Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione G. Pascale', Via M. Semmola, 80131 Napoli, Italy.
Tel: +39 081 590 3225; fax: +39 081 590 3821;
e-mail: caponigrof@libero.it

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## Introduction

Despite the continuing introduction of new cytotoxic agents, the management of many advanced solid tumors, particularly recurrent tumors, remains challenging. Current treatment options have significant toxicity, thereby impacting on quality of life (QoL), while efficacy in terms of improvement in survival outcome is often limited. Advances in our understanding of tumorigenesis and metastasis have stimulated research into more targeted therapies, with the aim of improving efficacy and/or QoL while minimizing toxicity. The epidermal growth factor receptor (EGFR), which is highly expressed by many solid tumor types [1], is one target for novel therapies. EGFR is a member of the erbB family of receptors—transmembrane glycoproteins that play an important role in cell growth and differentiation using tyrosine kinase activity as the signal transduction mechanism. EGFR signaling has been shown to be critical for many aspects of tumor biology: cell proliferation, angiogenesis, metastasis and inhibition of apoptosis [1]. Furthermore, EGFR expression has been closely related to prognosis in head and neck cancer, and other neoplasms [2].

Several rational approaches have been designed to abrogate EGFR function. One of these is the development of small molecules that compete with adenosine triphosphate (ATP) for binding to the ATP site in the EGFR tyrosine kinase domain, therefore abrogating the receptor's catalytic activity, autophosphorylation and its engagement with signal transducers [3].

The first small molecule with EGFR inhibitor activity to reach the market is gefitinib ('Iressa', ZD1839), which, based on data from two phase II trials [4], is licensed (250 mg/day dosage) in Japan, the US and some other countries as monotherapy for refractory non-small-cell lung cancer (NSCLC). Another small molecule oral EGFR inhibitor in late-stage development (phase III for NSCLC and pancreatic cancer) is erlotinib ('Tarceva', OSI-774). The development of humanized monoclonal antibodies against the EGFR extracellular domain is another sound strategy for targeting EGFR. Monoclonal antibodies, such as cetuximab ('Erbitux', C225), compete for the binding of receptor ligands and can induce EGFR down-regulation from the tumor cell surface.

This review explores the potential of EGFR as a target for therapeutic intervention in head and neck cancer. This group of cancers includes those of the oral cavity (including the lips), oropharynx, nasopharynx, hypopharynx and the larynx, but excludes brain tumors.

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## Head and neck cancer: a common tumor with a poor prognosis

Worldwide, nearly 600 000 new cases of head and neck cancer were diagnosed in 2000. These patients are at considerable risk of mortality, with more than 300 000 deaths attributable to the disease in 2000 [5]. Mortality rates tend to be higher in developing countries than elsewhere.

Head and neck cancers are the sixth most common type of cancer diagnosed in European patients. More than 100 000 cases were diagnosed in Europe in 2000 (the latest date for which data are available), of which around 60% involved the oral cavity and pharynx, with the remaining tumors arising in the larynx [5]. Across Europe, there were more than 50 000 deaths from this group of cancers in 2000.

Tobacco (including smokeless tobacco) and alcohol use are the principal risk factors for head and neck cancer [6], being implicated in more than 80% of cases. The risks associated with both are dose dependent [7]. In a large ($n = 1114$) population-based study, the odds ratios (adjusted for alcohol intake) for oropharyngeal cancer associated with smoking 20–39 and 40 + cigarettes daily versus not smoking were 2.1 and 2.8, respectively, for men, and 3.6 and 6.2, respectively, for women [7]. The corresponding odds ratios (adjusted for smoking) for consuming 30 + versus < 1 alcoholic drink/week were 8.8 and 9.1, respectively. Furthermore, tobacco and alcohol act synergistically in promoting carcinogenesis in the head and neck region; for those consuming 30 + drinks/week and smoking 40 + cigarettes/day, the risk of cancer increases by more than 35-fold compared with non-smokers who consume < 1 drink/week [7]. The patients who present in the absence of a history of tobacco smoking or alcohol consumption tend to be elderly women [6,8–11]; dietary factors, specifically low intake of fruits and vegetables rich in carotenes and iron deficiency, may play a role in promoting carcinogenesis in these cases [6]. Other important risk factors for specific tumors, both in the presence and absence of tobacco and alcohol use, include: asbestos exposure for laryngeal cancer [12]; wood and nickel dust inhalation for cancers of the nasal cavity and paranasal sinuses [13]; excessive exposure to sunlight for lip cancer [14]; human papilloma virus infection for oral cancer [15]; radiation for cancer of the salivary glands [16]; poor oral hygiene and mechanical irritation, e.g. from dentures, for oropharygeal cancers [6].

Head and neck cancers are rare in patients younger than 45 years of age [17] and occur much more frequently in men than women. In 2000, approximately 5 times as many European men as women were diagnosed with cancers of the head and neck region [5]; these trends reflect the differences between the genders with respect to exposure to the known risk factors. Likewise, the incidence varies across Europe (and worldwide), with the highest number of cases seen in regions and countries where heavy use of tobacco and alcohol is common [5,18]. Compared with the European mean, France, Portugal, and Spain have the highest incidence of cancers of the oral cavity and pharynx, while Italy, Spain, Belgium and Portugal have the highest incidence of laryngeal cancers. A slow but steady increase in rates of head and neck cancer is apparent in many European populations, particularly in Central and Eastern Europe [18], presumably as a result of increasing social use of tobacco and alcohol.

Aggressive surgical resection, with or without adjuvant chemoradiotherapy, is the cornerstone of treatment for early disease [19]. In many patients, the necessary surgical resection can be disfiguring and may also affect everyday functioning, including swallowing, eating, breathing, and speech, with a profound impact on QoL [20]. Swallowing difficulties occur in the majority of patients with head and neck cancer, and 20% or more of these patients require placement of a gastrostomy tube (G-tube), either on a short-term or permanent basis, in order to enable nutritional status to be maintained or improved, and drugs, normally given orally, may be able to be administered via this tube, thereby avoiding parenteral administration.

However, many patients present with advanced, unresectable disease. Evidence that concurrent chemoradiotherapy is the best approach to treating such patients has accumulated over the past few years [21]. Standard chemotherapy in this setting is a platinum-based regimen, e.g. cisplatin 100 mg/m$^2$ on day 1 with 5-fluorouracil (5-FU) 1000 mg/m$^2$/day for 4 days given by continuous infusion, repeated every 21 days. Patient survival in this setting ranges from 37–78% at 3 years for those receiving chemoradiotherapy (70 Gy or more) to 20–47% for those receiving irradiation alone [19]. Monochemotherapy with cisplatin given either weekly or every 3 weeks, in combination with radiation therapy, is another suitable approach. Recently Adelstein and colleagues [22] showed that the addition of cisplatin (3 doses of 100 mg/m$^2$ at 3-week intervals) to radiotherapy significantly improves survival over radiotherapy alone, with a projected 3-year survival of 37% (median 19.1 months) compared with 23% (median 12.6 months); the corresponding complete response rates were 40.2 and 27.4%. However, the toxicities of chemotherapy and radiotherapy are likely to be greater than with radiotherapy alone and impact severely on QoL [23]. In the Adelstein study [22], in particular, the difference in grade 3 toxicity between the two treatment arms was statistically significant ($p = 0.001$). Platinum-based chemotherapy is also generally used as palliative therapy for patients

with recurrent or metastatic disease. Other drugs that have some degree of activity include methotrexate, taxanes, gemcitabine and vinorelbine. However, tumor response rates rarely exceed 30–35% and responses are of short duration, presumably due to the development of chemoresistance [24–27]. Accordingly, the prognosis of recurrent/metastatic disease is poor, with 1-year survival below 30%. Treatment options for patients who progress on first-line chemotherapy are limited and this is an area of high unmet need; there are no standard approaches to the treatment of refractory disease and median survival is just 4 months [26].

## Rationale for EGFR as a target in head and neck cancer

The vast majority of head and neck tumors are squamous cell carcinomas and express high levels of EGFR relative to normal tissues [28–31]. In a study of 60 patients with various types of head and neck tumors, EGFR levels ranged from 3 to 2302 fmol/mg protein in tumor biopsies, compared with 0–98 fmol/mg protein in healthy tissue taken from the same anatomic region [30]; all but one patient had higher EGFR levels in their tumor than the healthy control tissue. The proportion of EGFR-positive tumors (defined as those with EGFR levels above those in all control samples, i.e. more than 100 fmol/mg protein) increased significantly with increasing tumor size (47.6% for T3–4 versus 21.4% for T1–2) and higher tumor stage (44.9% for stage III–IV versus 19.0% for stage I–II), but did not differ statistically across the different tumor sites or as a function of tumor grade.

As has been demonstrated for other tumor types [1], the level of EGFR expression has prognostic importance in head and neck cancer, with higher levels indicative of a poorer outcome in terms of progression-free survival (PFS) and overall survival (Table 1) [28,29,32–35]. Based on a threshold level of 120 fmol/mg protein, Dassonville and colleagues [32] found that in patients ($n = 109$) with newly diagnosed head and neck cancer, EGFR expression was significantly associated with PFS and overall survival. High EGFR expression was associated with reductions of more than 50% in median PFS and around 30% in median overall survival. Although patients with a complete response to first-line chemotherapy (cisplatin/5-FU) survived for longer than patients with a partial response or no response, those with a complete response and high EGFR levels had a similar survival outcome to those with a partial or no response and low EGFR levels (median around 27 months). More recently, Magne and colleagues [33] found a significant correlation between EGFR expression and resistance to chemotherapy/irradiation, as well as time to treatment failure and patient survival, in a cohort of 77 patients with unresectable pharyngeal cancer treated with conventional chemoradiotherapy (Table 1), although EGFR was not independently predictive of treatment response in multivariate analysis. When the patients in this study were divided into quartiles by tumor EGFR level, there were marked differences in the 3-year survival rates of those in the highest quartile (EGFR $> 275$ fmol/mg protein) compared with those in the lowest quartile (EGFR $< 35$ fmol/mg protein) (16 versus 95%, $p = 0.0001$; Fig. 1). However, patients who had a complete response and high EGFR levels had a lower 3-year survival rate than those with a partial or no response (13 versus 26%).

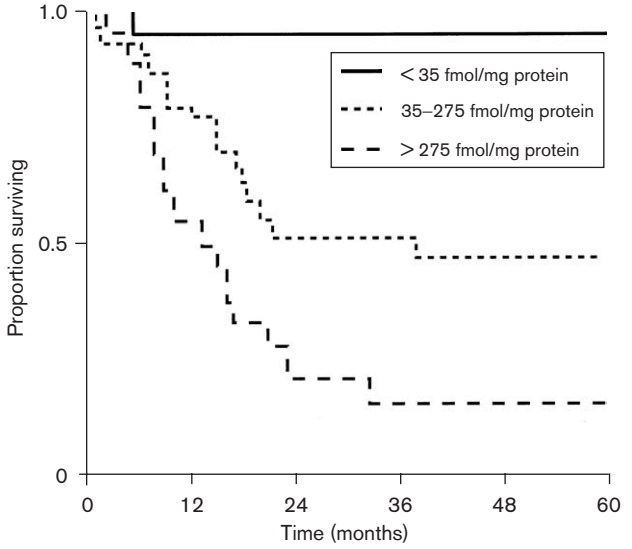
These findings provide a rationale for EGFR as a potential target in the treatment of head and neck cancer. This rationale has been validated in extensive

**Table 1 Results of studies assessing the relationship between EGFR expression and patient outcome**

| Reference | Patient details | Relationship between EGFR and outcome[a] | | |
|---|---|---|---|---|
| | | Response to treatment[b] | PFS | Survival |
| Dassonville *et al.*, 1993 [32] | 109 newly diagnosed | NS | $p=0.0125$ (EGFR $\geq 120$ versus $<120$ fmol/mg) | $p=0.0208$ (EGFR $\geq 120$ versus $<120$ fmol/mg) |
| Maurizio *et al.*, 1996 [34] | 140 laryngeal | NS | 5 year: 24% for EGFR $\geq 20$ fmol/mg versus 77% for EGFR $<20$ fmol/mg ($p< 0.01$) | 5 year: 25% for EGFR $\geq 20$ fmol/mg versus 81% for EGFR $<20$ fmol/mg ($p=0.0001$) |
| Rubin Grandis *et al.*, 1998 [28] | 91 non-metastatic | NS | 2 year: 49 versus 70 versus 90% for high, medium and low tertiles, respectively ($p=0.0001$) | 2 year: 66 versus 81 versus 100 for high, medium and low tertiles, respectively ($p=0.0001$) |
| Poon *et al.*, 2001 [29] | 78 nasopharyngeal | not stated | not stated | $p=0.05$ (strong versus moderate/low EGFR staining) |
| Magne *et al.*, 2001 [33] | 77 pharynx | $p=0.02$ (CT + RT)[c] | $p=0.0005$c | $p=0.0002$[c] |
| Numico *et al.*, 2003 [35] | 85 locally advanced | NS (CT + RT) (EGFR positive[d] versus negative) | not stated | 3 year: 46% for EGFR-positived versus 72% for EGFR-negative ($p< 0.03$) |

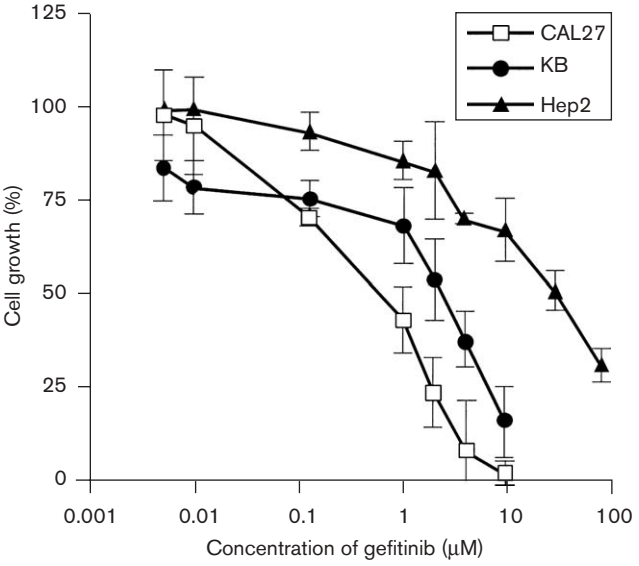
[a]Analyses are univariate unless otherwise stated.
[b]Chemotherapy unless otherwise stated.
[c]EGFR was analyzed as a continuous variable.
[d]Defined as >10% cells positive for EGFR.
CT, chemotherapy; NS, not significant; RT, radiotherapy.

**Fig. 1**




Overall survival in 77 patients with pharyngeal cancer according to EGFR tumor level. (Reproduced with the kind permission of Elsevier, 2003 [33].)

**Fig. 2**




Effects of gefitinib on cell proliferation in three head and neck cancer cell lines (CAL27, KB and Hep2). (Reproduced with the kind permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc, 2003 [36].)

preclinical studies. In human head and neck cancer cell lines, both the EGFR tyrosine kinase inhibitors and EGFR monoclonal antibodies inhibit cell proliferation in a dose-dependent manner (Fig. 2 and Table 2) [36–41]. These anti-proliferative effects occur at least partially through $G_1$ cell-cycle arrest (Table 2) [36–41]. Some studies have also demonstrated a partial $G_2$/M block [36]. Inhibition of tumor growth has also been observed in xenograft models [42,43]. In mice bearing the human HN5 xenograft, erlotinib produced 50% growth inhibition at a dose of 7 mg/kg/day and complete inhibition at 12.5 mg/kg/day [43]. Additionally, EGFR agents have anti-angiogenic and apoptotic activity in both *in vitro* and *in vivo* models [37,38,41,44], as well as anti-metastatic properties [38]. In an *in vitro* model, cetuximab dose-dependently attenuated the migration of SCC-1 head and neck tumor cells by 40–60%; this effect occurred at concentrations lower than those that inhibited cell proliferation [38]. Likewise, in mice implanted with an orthotopic floor-of-mouth xenograft, cetuximab significantly ($p < 0.05$) reduced the proportion of mice with invasion of vessel, bone and perineural tissues compared with untreated controls (37.5 versus 75%, 12.5 versus 62.5% and 0 versus 37.5%, respectively).

The efficacy of irradiation in the treatment of epithelial tumors may be limited by accelerated tumor repopulation (i.e. the proliferation of surviving tumor cells during treatment) [37]. A critical role for EGFR in mediating cytoprotective and proliferative responses in human cancer cells after ionizing irradiation, which contribute at least in part to accelerated tumor cell repopulation, provides a rationale for using EGFR agents as radiosensitizers [45,46]. Numerous investigators have reported that cetuximab and gefitinib enhance the efficacy of irradiation, with synergistic interactions seen in some studies [37,39,42,44,47,48]. For example, Harari and Huang [42] reported that, in a mouse xenograft model, the combination of cetuximab (0.2 mg/week for 4 weeks) and irradiation (8 Gy/week for 4 weeks, administered 1 day after cetuximab) delayed tumor regrowth for 3 months compared with 30–60 days for either therapy alone. This radiosensitization occurs at least partly as a result of amplification of radiation-induced apoptosis [44]. When SCC-1 and SCC-6 head and neck cancer cells were exposed to both gefitinib (1 μM for 48 h) and irradiation (6 Gy), apoptosis increased by 23%, compared with 4–8% when the cells were exposed to either alone ($p < 0.001$) [44]. The enhanced tumor response to combination therapy may also be due to inhibition of growth proliferation, inhibition of damage repair and down-regulation of the tumor angiogenic response [42].

Preclinical studies have also evaluated the anti-tumor activity of EGFR tyrosine kinase inhibitors combined with cytotoxic agents [43,49]. When gefitinib was applied either before or concurrently with 5-FU and/or cisplatin in two head and neck cell lines (Hep-2 and CAL33), the effects on cell growth were at least additive, with the best results achieved when gefitinib was applied both before and during exposure to both cytotoxic agents [49].

**Table 2 Summary of the growth-inhibitory and cell-cycle effects of EGFR agents in head and neck cancer cell lines**

| Reference | Head and neck cancer cell line | Results |
|---|---|---|
| Moyer *et al.*, 1997 [41] | HN 5 | Growth inhibition occurred with erlotinib 50 nM, with complete blockade at 250 nM. Treatment with erlotinib 1 μM for 48 h reduced the proportion of cells in S phase from 55 to 24% and increased the proportion in G1 phase from 24 to 56%. |
| Huang *et al.*, 1999 [37] | SCC-13Y, SCC-1, SCC-11B, SCC-38 | Cetuximab inhibited cell proliferation by 20–75% compared with controls. After 2 days, the proportion of cells in $G_0/G_1$ phase was 64.6 versus 54.4% in controls, while the proportion in S phase was 8.0 and 23.1%, respectively. The $G_0/G_1$ accumulation and S phase depletion were even more pronounced after 4 days of cetuximab treatment (70.5 and 4.5%, respectively). |
| Huang *et al.*, 2002 [38] | SCC-1, SCC-6, SCC-13Y | All three cell lines showed significant growth inhibition with gefitinib at a concentration $\leq$ 10 μM. Treatment with 1 μM for 48 h induced accumulation of cells in $G_1$ phase with a significant decrease in cells in S phase. |
| Magne *et al.*, 2002 [39] | CAL27, CAL33, CAL60, CAL165, CAL166, Hep2, Detroit562 | CAL33 cells were the most sensitive to gefitinib ($IC_{50}$ 6.1 μM) and Hep2 the least sensitive ($IC_{50}$ 31.2 μM). The $IC_{50}$ for gefitinib was inversely correlated with the EGFR level ($p = 0.022$). |
| Di Gennaro *et al.*, 2003 [36] | | Gefitinib inhibited cell proliferation in all cell lines, with $IC_{50}$ values ranging from 1 to 30 μM. After 72 h, the proportion of Hep2 cells in $G_0/G_1$ phase increased from 52.5 to 70.6%, while the proportion in S phase decreased from 34.3 to 17.6%. Similar results were seen in the KB and CAL27 cell lines. The proportion of cells in $G_2$/M phase decreased in the KB and CAL27 cell lines. |
| Matheny *et al.*, 2003 [40] | SCC-012 | Gefitinib induced a 2-fold increase in $G_1$ phase cells and a 3.5-fold decrease in S phase cells, consistent with growth arrest. |

Activity was, however, sequence dependent, with an antagonistic effect observed if gefitinib was applied after the cytotoxic agents. In contrast, the inhibitory effects of erlotinib and cisplatin did not appear to be sequence dependent in an HN5 xenograft model [43].

## Early clinical data on EGFR agents in head and neck cancer

### Gefitinib

Pharmacokinetic studies in human volunteers demonstrated that gefitinib is orally available, with a predictable pharmacokinetic profile consistent with once-daily dosing [50]. Gefitinib monotherapy was subsequently evaluated in a large phase I program involving more than 250 patients, mainly heavily pretreated, with a variety of tumor types associated with EGFR pathway activation, of whom 28 had head and neck cancer [51–54]. Findings were broadly consistent across the four studies in the program. The profile of adverse events contrasted with that of chemotherapy; the most common events were mild (grade 1/2) reversible skin rash and diarrhea, both of which have been observed with other EGFR inhibitors and appear to be inherently related to EGFR inhibition. Dose-limiting toxicity occurred at doses of 700 mg or above, with the most common being diarrhea. Anti-tumor activity was observed in these phase I studies, both in terms of partial response and prolonged stable disease (in some cases 1 year or more), particularly in NSCLC. Activity was observed across a wide range of doses and tumor types, irrespective of prior treatment. Clinically meaningful stable disease was achieved in 50% of patients with head and neck cancer. QoL ratings for patients with head and neck cancer remained stable during treatment and, in the US trial, improved significantly over time [55]. Across the program as a whole, maximum anti-tumor efficacy was obtained at gefitinib doses lower than the maximum tolerated dose (MTD), allowing dose selection for phase II evaluation (250 and 500 mg once daily) to be based on the optimum biologic dose rather than the MTD.

A phase II study evaluating gefitinib 500 mg/day as first- or second-line monotherapy in patients with advanced (recurrent or metastatic) head and neck cancer has been completed (Table 3) [56]. The study protocol allowed gefitinib to be administered via a G-tube where necessary ($n = 14$). Approximately 50% of the 47 evaluable patients had failed prior chemotherapy (typically platinum based) for recurrent/metastatic disease. Five patients (10.6%) had a partial response, with a further 20 patients (42.6%) having stable disease or minor responses, giving an overall disease control rate of 53.2%. The response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different to those of patients who had received prior chemotherapy. The profile of anti-tumor response was also similar in patients who received gefitinib via a G-tube as in the study population as a whole. Overall, the median times to progression and death were 3.4 and 8.1 months, respectively (Fig. 3 and Table 3). The estimated 1-year survival rate was 29%. These results are more favorable than those achieved with chemotherapy in this setting, with the additional benefit of greatly reduced treatment-related toxicity. The incidence of grade 3 toxicities was low (anorexia 6%, diarrhea 6%, nausea 4% and hypercalcemia 4%) and there was only a single case of grade 4 toxicity (hypercalcemia). Grade 1/2 skin rash occurred in 48% of patients and grade 1/2 diarrhea in 50% (Table 3). One patient discontinued therapy due to toxicity (grade 2

**Table 3 Summary of clinical studies of EGFR agents conducted solely in patients with recurrent or metastatic head and neck cancer**

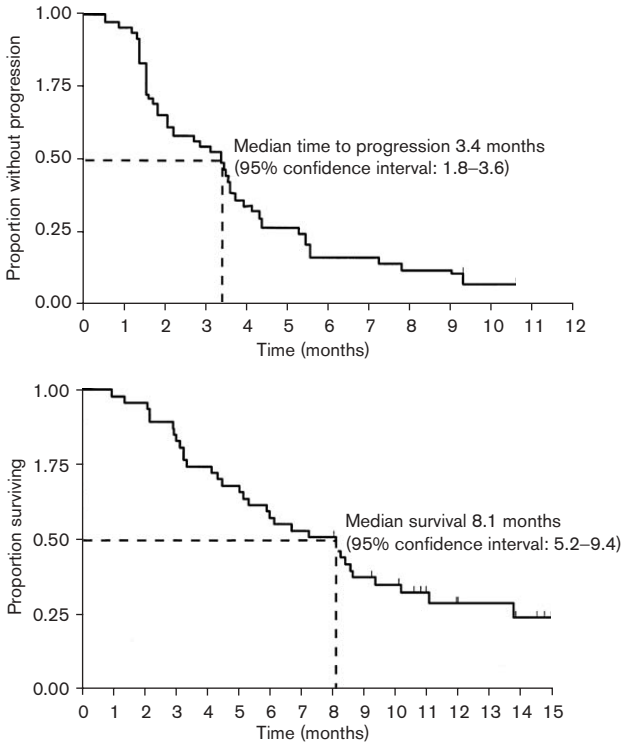
| Reference | Phase/design | Doses of study drugs | Evaluable patients (safety/ efficacy) | Prior chemotherapy | Common ( $\geq$ 10%) AEs, irrespective of causality | Response rates | Time to progression | Survival |
|---|---|---|---|---|---|---|---|---|
| Gefitinib monotherapy | | | | | | | | |
| Cohen *et al.*, 2003 [56] | phase II | 500 mg/day | 50/47 | 49% | diarrhea 50%; skin rash 48%; anorexia 26%; hypercalcemia 20%; nausea 18%; vomiting 12%; increased AST 12% | PR 11%; SD 42% | median 3.4 months | median 8.1 months (1 year 29%) |
| Cohen *et al.*, 2003 [57][a] | phase II | 250 mg/day | 32/30 | not stated (no restriction) | skin rash 66%; diarrhea 34%; increased ALT 28%; hypercalcemia 22%; anorexia 19%; dyspnea 13% | PR 3%; SD 27% | not stated | not stated |
| Erlotinib monotherapy | | | | | | | | |
| Soulieres *et al.*, 2004 [60][d] | phase II | 150 mg/day | 115 | 1 prior: 100% | skin rash 79%; diarrhea 31%; nausea 13%; fatigue 11%; vomiting 7% | PR 4.3%; SD 38.3% | median 9.6 weeks | median 6 months |
| Cetuximab in combination with chemotherapy | | | | | | | | |
| Shin *et al.*, 2001 [62] | phase Ib | LD 100–500 mg/ $m^2$, MD 100 or 250 mg/$m^2$/wk; P 100 mg/ $m^2$/3 wk | 12/9 | 33% | neutropenia 50%; fatigue 42%; anemia 33%; peripheral neuropathy 17%; orthostatic hypotension 17%; allergic reaction 17%; rash 17% | CR 22%; PR 44%; MR/SD 22% | not stated | not stated |
| Vega Villegas *et al.*, 2003 [63][a,b] | phase I/P + 5-FU versus Cp +5-FU | Ce LD 400 mg/$m^2$, MD 250 mg/$m^2$/wk; P 100 mg/$m^2$/3 wk; Cp not stated/3 wk; 5-FU 600–1000 mg/ $m^2$/day for 5 days every 3 wk | 28/24 | none | grade 3/4 events only: vomiting 13% | PR 42%; SD 33% | not stated | not stated |
| Kies *et al.*, 2002 [65] | phase II | LD 400 mg/$m^2$, MD 250 mg/ $m^2$/wk; P 75–100 mg/ $m^2$/3 wk | 79/78 | 100% | nausea 51%; asthenia 49%; acne 39%; rash 38%; vomiting 38%; pain 35%; hyponatremia 18%; leukopenia 14%; anemia 15% | PR 12%; SD 17% | 155 days (PR only) | not stated |
| Baselga *et al.*, 2002 [67] | phase II | LD 400 mg/$m^2$, MD 250 mg/ $m^2$/wk; P/Cp not stated | 75/96 | 100% | rash 45%; acne 25%; dry skin 16%; asthenia 16%; fever 13%; vomiting 10% | CR 2%; PR 9%; SD/MR 40% | 66 days | 178 days (269 days in responders) |
| Chan *et al.*, 2003 [66][b] | phase II | LD 400 mg/$m^2$, MD 250 mg/ $m^2$/wk; Cp not stated/3 wk | 45/53[c] | 100% | rash 91%; nausea 51%; vomiting 49%; asthenia 36%; anemia 33%; thrombocytopenia 24% | PR 17%; SD 49% | not stated | not stated |
| Burtness *et al.*, 2002 [69][a] | phase III/P + placebo versus P + Ce | LD 400 mg/$m^2$, MD 250 mg/ $m^2$/wk; P 100 mg/$m^2$/4 wk | 57 | none | grade 3/4 events only: neutropenia 25%; nausea 23%; hyponatremia 19%; rash 12%; hypokalemia 11%; thrombocytopenia 9%; anorexia 7%; hypersensitivity 7% | CR 6% (versus 4%); PR 17% (versus 6%); SD 66% (versus 70%) | not stated, but NS different from P (3.4 months) | 1 year 37% (versus 27%); 2 years 29% (versus 17%) |

[a]Ongoing studies.
[b]Updated at meeting but data not available.
[c]Patients had nasopharyngeal cancer only.
[d]Data are the final data presented at the meeting rather than the preliminary data in the abstract. AE, adverse event; AST, aspartate aminotransferase; Ce, cetuximab; Cp, carboplatin; CR, complete response; 5-FU, 5-flourouracil; LD, loading dose; MD, maintenance dose; MR, minor response; NS, not significant; P, cisplatin; PR, partial response: SD, stable disease.

skin rash), while four patients required dose reduction for diarrhea.

Preliminary results from an ongoing trial evaluating gefitinib 250 mg/day for recurrent head and neck cancer have been presented (Table 3) [57]. Of the 30 patients evaluable for efficacy to date, nine (30%) have had a partial response or stable disease (Table 3). Grade 3/4 toxicities have been minimal (three of 32 evaluable patients). Overall, the adverse-event profile was similar to

**Fig. 3**




Time to progression and survival in a phase II study of gefitinib 500 mg/day in patients ($n=47$) with head and neck cancer. (Adapted with kind permission from the American Society of Clinical Oncology, 2003 [56].)

that with the 500 mg/day dose (Table 3). In addition to evaluating anti-tumor activity and toxicity, this trial is also assessing QoL in this setting. Although there were no overall improvements in mean ratings, patients with a partial response or stable disease did report an improvement in QoL in the first 8 weeks of treatment. A total of 63 patients are to be recruited to this trial. The final results may provide information on the optimum dose of gefitinib in this setting.

A number of phase II trials assessing the potential of gefitinib in combination with radiotherapy and other agents in head and neck cancer are ongoing and a phase III trial is planned. The latter trial will compare two doses of gefitinib (250 and 500 mg/day) with methotrexate (40–60 mg/m$^2$/week i.v.) in patients with advanced disease who have progressed on or are unsuitable for platinum-based chemotherapy.

### Erlotinib

Erlotinib is also an orally available small molecule EGFR tyrosine kinase inhibitor [58]. The mean elimination half-life is approximately 24 h, and both weekly and daily schedules were evaluated in phase I studies [58,59]. Clinical development is proceeding with a once-daily dosing schedule. The phase I study of once-daily erlotinib monotherapy involved 40 patients with various types of solid tumors, including three with head and neck cancer [58]. Diarrhea and skin rash were the most common toxicities, occurring with an unacceptable frequency at doses exceeding 150 mg/day. Eight patients (20%), including one with head and neck cancer, had a tumor response or stable disease (duration 5–20 + months). The dose of erlotinib selected for phase II studies was the MTD in this study (150 mg/day).

Senzer and colleagues [60] have recently published the final data from a phase II trial of erlotinib monotherapy in patients with advanced head and neck cancer who had progressed on first-line chemotherapy (Table 3). In this large study, a total of 115 patients were accrued. Five patients (4.3%) had a partial response and 44 (38.3%) had stable disease, for a disease control rate of 42%. Erlotinib was generally well tolerated in this study, with the most common adverse events being cutaneous effects, diarrhea, nausea, vomiting, headache and fatigue. Skin toxicity was the predominant toxicity, observed in 79% of patients. Diarrhea was manageable with either dose reduction or loperamide. Nine patients withdrew from the study due to adverse events.

### Cetuximab

In contrast to small molecules with EGFR inhibitory activity, cetuximab is administered by i.v. infusion (over 1 h) on a weekly basis. Pharmacokinetic data from the initial phase I studies involving patients with various tumor types, including head and neck cancer, indicated that cetuximab displays non-linear pharmacokinetics and that complete saturation of systemic clearance occurs at doses of 200–400 mg/m$^2$ [61].

Clinical studies of cetuximab in head and neck cancer for which data are available have involved combination with standard treatment regimens (chemotherapy, irradiation) rather than single-agent treatment, making it more difficult to establish the contribution of cetuximab to the observed activity over that of standard regimens alone.

Three phase I dose-escalation studies of cetuximab have solely enrolled patients with head and neck cancer. In two of these, cetuximab has been administered in combination with platinum-based chemotherapy (cisplatin or carboplatin ± 5-FU) to patients with recurrent/metastatic disease [62,63]. The toxicities of cetuximab did not overlap with those of chemotherapy, with the most clinically important adverse events associated with cetuximab being skin rashes and allergic reactions (due to stimulation of an immunogenic response by the chimeric antibody) (Table 3). A high proportion of

objective tumor responses were observed with these multi-modality approaches (Table 3).

A third phase I study has evaluated cetuximab in combination with radiotherapy (conventional or hyperfractionated) in patients with locally advanced disease [64]. Most adverse events reported in this study were grade 1 or 2 and did not appear to be dose related. There was one case of grade 3 skin rash outside the radiation field and one reversible grade 4 anaphylactic reaction. There was a suggestion that cetuximab may enhance the toxicity of radiotherapy, but the small number of patients in the study precludes any definite conclusion on this issue. All 15 evaluable patients had an objective response (13 complete responses) that lasted for 3–39 + months.

The dosing schedule of cetuximab selected for the phase II program was a loading dose of 400 mg/m$^2$/week followed by a maintenance dose of 250 mg/mg$^2$/week. Three phase II studies have evaluated the combination of cetuximab with platinum-based chemotherapy in patients with recurrent/metastatic head and neck cancer (Table 3) [65–67]. In total, these studies have enrolled more than 200 patients, all of whom received prior chemotherapy with palliative intent (Table 3). While the toxicities of cetuximab and chemotherapy do not overlap, the toxicity burden is inevitably higher than that of EGFR monotherapy (Table 3). Disease control rates with combination therapy have been good, ranging from 29–66%, although the precise contribution of cetuximab to the observed response rates cannot be established from these studies. In the largest of these studies [67], which involved 75 assessable patients with refractory head and neck cancer who had documented disease after receiving at least 2 cycles of platinum-based therapy, an 11% response rate was observed when cetuximab was added to the platinum regimen. The observed anti-tumor activity of cetuximab in platinum-refractory patients, which parallels that observed in irinotecan-refractory advanced colorectal cancer [68], could be ascribed to cetuximab single-agent activity, reversal of chemotherapy resistance, or both. Additional studies with cetuximab have been conducted. Accordingly, a phase III placebo-controlled trial was initiated to address this issue, with patients ($n = 121$) randomized to either cisplatin alone or cisplatin combined with cetuximab [69]. The incidences of some toxicities (hyponatremia, anemia and thrombocytopenia) were slightly higher in the cetuximab group, but the only statistically significant difference between the groups was rash of any grade (36 versus 7%; $p = 0.0001$). There have been four cases of grade 3 hypersensitivity. Preliminary results suggest that the addition of cetuximab to cisplatin does not significantly improve median PFS or response rates (Table 3). Survival rates at 1 and 2 years were 37 and 29%, respectively, in the combination group versus 27 and 17%, respectively, in the chemotherapy-alone group (Table 3).

A large phase III trial of cetuximab combined with irradiation in locally advanced head and neck cancer has completed recruitment (more than 400 patients). Data from this trial are awaited.

## EGFR agents in early development

### Small molecules

Other small molecules in development target EGFR by different mechanisms to that of gefitinib and erlotinib [70]. EKB-569 is an EGFR tyrosine kinase inhibitor that binds irreversibly to EGFR ($IC_{50}$ of 38.5 nmol/l). GW2016 is a reversible PAN-HER tyrosine inhibitor, which could be particularly effective in those situations where co-expression of the EGFR (erbB1) and HER2 (erbB2) occurs. CI-1033 irreversibly inhibits *in vitro* the three catalytic active members of the EGFR family.

### Monoclonal antibodies

Other anti-EGFR monoclonal antibodies that have a similar mechanism of action to cetuximab are currently under clinical investigation [70]. ABX-EGF is a fully human IgG2 anti-EGFR monoclonal antibody that binds with high affinity, inhibits ligand-dependent receptor activation and effectively inhibits the growth of human tumor xenografts. ABX-EGF has shown clinical activity in advanced renal cell carcinoma. EMD 72 000, another humanized anti-EGFR monoclonal antibody, has a prolonged half-life that may allow for a less frequent administration schedule; it is currently in phase I studies. Bispecific monoclonal antibodies (carrying two antigen-binding arms) are also being investigated. These antibodies bind to EGFR with one arm and to an immunologic effector cell with the other. The result is an antibody that binds to EGFR and concomitantly enhances the host's anti-tumor cellular immune response.

## Conclusions

The treatment of advanced head and neck cancer is an area of high, unmet need. There is a strong rationale for targeting the EGFR in this setting and this rationale has been validated in extensive preclinical studies, which have shown that EGFR inhibitors such as gefitinib and erlotinib are active as monotherapy, and that monoclonal antibodies such as cetuximab are additive/synergistic in combination with radiotherapy or chemotherapy. The initial clinical results with EGFR inhibitors in head and neck cancer are promising. Gefitinib and erlotinib monotherapies are active in patients with recurrent or metastatic head and neck cancer and have acceptable safety profiles, which may be beneficial in terms of QoL compared with conventional chemotherapy. Combinations of cetuximab with radiotherapy or platinum-based chemotherapy have shown activity in phase I/II studies

and have entered phase III studies. These studies should help to establish the additional benefit of combination therapy over single-agent therapy.

The different properties of the available EGFR inhibitors may impact on clinical profile and use, e.g. in terms of administration and toxicity. Cetuximab requires i.v. administration, whereas the EGFR tyrosine kinase inhibitors can be given orally (gefitinib has also been successfully given via a G-tube). The data presented in this review also suggest that gefitinib, which can be given at doses below the MTD, is associated with slightly lower rates of adverse events (particularly skin rash and diarrhea) compared with erlotinib, which is dosed at the MTD. Additionally, as a monoclonal antibody, cetuximab is associated with a low incidence of allergic reactions.

The promising results of the early clinical studies with EGFR inhibitors in head and neck cancer need to be established in phase III studies, the results of which are eagerly awaited. It is hoped that the results of these trials, which will mature over the next few years, will help determine the optimum use of EGFR agents in head and neck cancers.

## References


1 Baselga J. New technologies in epidermal growth factor receptor-targeted cancer therapy. *Signal* 2000; **1**:12–21.
2 Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. *Eur J Cancer* 2001; **37**(**suppl 4**):S9–S15.
3 Arteaga CL, Baselga J. Clinical trial design and end points for epidermal growth factor receptor-targeted therapies: implications for drug development and practice. *Clin Cancer Res* 2003; **9**:1579–1589.
4 Kris MG, Natale RB, Herbst RS, Lynch Jr TJ, Prager D, Belani CP, *et al.* Efficacy of gefitinib (ZD1839, Iressa™), an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer previously treated with cisplatin or carboplatin and docetaxel. *J Am Med Ass* 2003; **290**:2149–2158.
5 Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, version 1.0. *IARC CancerBase* **5**. Limited version available from: http://www-dep.iarc.fr/globocan/globocan.html. Last updated 03/02/2001.
6 Johnson N. Tobacco use and oral cancer: a global perspective. *J Dent Educ* 2001; **65**:328–339.
7 Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988; **48**:3282–3287.
8 Hodge KM, Flynn MB, Drury T. Squamous cell carcinoma of the upper aerodigestive tract in nonusers of tobacco. *Cancer* 1985; **55**:1232–1235.
9 Koch WM, Lango M, Sewell D, Zahurak M, Sidransky D. Head and neck cancer in nonsmokers: a district clinical and molecular entity. *Laryngoscope* 1999; **109**:1544–1551.
10 Rich AM, Radden BG. Squamous cell carcinoma of the oral mucosa: a review of 244 cases in Australia. *J Oral Pathol* 1984; **13**:459–471.
11 Wiseman SM, Swede H, Stoler DL. Squamous cell carcinoma of the head and neck in nonsmokers and nondrinkers: an analysis of clinicopathologic characteristics and treatment outcomes. *Ann Surg Oncol* 2003; **10**:551–557.
12 Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. *Occup Environ Med* 1998; **55**:393–400.
13 Nylander LA, Dement JM. Carcinogenic effects of wood dust: review and discussion. *Am J Ind Med* 1993; **24**:619–647.
14 Perea-Milla Lopez E, Miñarro-del Moral RM, Martinez-Garcia C, Zanetti R, Rosso S, Serrano S, *et al.* Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. *Br J Cancer* 2003; **88**:1702–1707.
15 Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982–1997. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**:622–635.
16 Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997; **8**:414–419.
17 Hart AK, Karakla DW, Pitman KT, Adams JF. Oral and oropharyngeal squamous cell carcinoma in young adults: a report on 13 cases and review of the literature. *Otolaryngol Head Neck Surg* 1999; **120**:828–833.
18 Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S. Head and neck cancer: a global perspective on epidemiology and prognosis. *Anticancer Res* 1998; **18**:4779–4786.
19 Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med* 2001; **345**:1890–1900.
20 Hanna E, Sherman AC. Quality-of-life issues in head and neck cancer. *Curr Oncol Rep* 1999; **1**:124–128.
21 Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000; **355**:949–955.
22 Adelstein DJ, Li Y, Adams GL, Wagner Jr. H, Kish JA, Ensley JF, *et al.* An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003; **21**:92–98.
23 Magne N, Marcy PY, Chamorey E, Guardiola E, Pivot X, Schneider M, *et al.* Concomitant twice-a-day radiotherapy and chemotherapy in unresectable head and neck cancer patients: A long-term quality of life analysis. *Head Neck* 2001; **23**:678–682.
24 Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, *et al.* Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992; **10**:1245–1251.
25 Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, *et al.* A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992; **10**:257–263.
26 Clark JI, Hofmeister C, Choudhury A, Matz G, Collins S, Bastian R, *et al.* Phase II evaluation of paclitaxel in combination with carboplatin in advanced head and neck carcinoma. *Cancer* 2001; **92**:2334–2340.
27 Basaran M, Bavbek SE, Gullu I, Demirelli F, Sakar B, Tenekeci N, *et al.* A phase II study of paclitaxel and cisplatin combination chemotherapy in recurrent or metastatic head and neck cancer. *J Chemother* 2002; **14**:207–213.
28 Rubin Grandis J, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MM, *et al.* Levels of TGF-α and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst* 1998; **90**:824–832.
29 Poon TCW, Chan ATC, To KF. Expression and prognostic significance of epidermal growth factor receptor and HER2 protein in nasopharyngeal carcinoma. *Proc Am Soc Clin Oncol* 2001; **20**:229a, (abstr 913).
30 Santini J, Formento JL, Francoual M, Milano G, Schneider M, Dassonville O, *et al.* Characterization, quantification, and potential clinical value of the epidermal growth factor receptor in head and neck squamous cell carcinomas. *Head Neck* 1991; **13**:132–139.
31 Stanton P, Richards S, Reeves J, Nikolic M, Edington K, Clark L, *et al.* Epidermal growth factor receptor expression by human squamous cell carcinomas of the head and neck, cell lines and xenografts. *Br J Cancer* 1994; **70**:427–433.
32 Dassonville O, Formento JL, Francoual M, Ramaioli A, Santini J, Schneider M, *et al.* Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol* 1993; **11**:1873–1878.
33 Magne N, Pivot X, Bensadoun R-J, Guardiola E, Poissonnet G, Dassonville O, *et al.* The relationship of epidermal growth factor receptor levels to the prognosis of unresectable pharyngeal cancer patients treated by chemo-radiotherapy. *Eur J Cancer* 2001; **37**:2169–2177.
34 Maurizi M, Almadori G, Ferrandina G, Distefano M, Romanini ME, Cadoni G, *et al.* Prognostic significance of epidermal growth factor receptor in laryngeal squamous cell carcinoma. *Br J Cancer* 1996; **74**:1253–1257.
35 Numico G, Colantonio I, Comino A, Lantermo RA, Vitiello R, Sorentino R, *et al.* EGFR and survival of patients with locally advanced head and neck cancer (HNC) and treated with alternating chemotherapy radiation (CT-RT). Results of a retrospective analysis. *Proc Am Soc Clin Oncol* 2003; **22**:501 (abstr 2018).

36 Di Gennaro E, Barbarino M, Bruzzese F, De Lorenzo S, Caraglia M, Abbruzzese A, *et al.* Critical role of both p27KIP1 and p21CIP1/WAF1 in the antiproliferative effect of ZD1839 ('Iressa'), an epidermal growth factor receptor tyrosine kinase inhibitor, in head and neck squamous carcinoma cells. *J Cell Physiol* 2003; **195**:139–150.

37 Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res* 1999; **59**:1935–1940.

38 Huang SM, Li J, Harari PM. Molecular inhibition of angiogenesis and metastatic potential in human squamous cell carcinomas after epidermal growth factor receptor blockade. *Mol Cancer Ther* 2002; **1**: 507–514.

39 Magne N, Fischel JL, Dubreuil A, Formento P, Poupon MF, Laurent-Puig P, *et al.* Influence of epidermal growth factor receptor (EGFR), p53 and intrinsic MAP kinase pathway status of tumour cells on the antiproliferative effect of ZD1839 ('Iressa'). *Br J Cancer* 2002; **86**:1518–1523.

40 Matheny KE, Barbieri CE, Sniezek JC, Arteaga CL, Pietenpol JA. Inhibition of epidermal growth factor receptor signaling decreases p53 expression in head and neck squamous carcinoma cells. *Laryngoscope* 2003; **113**: 936–939.

41 Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boman B, Cunningham A, *et al.* Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* 1997; **57**:4838–4848.

42 Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. *Int J Radiat Oncol Biol Phys* 2001; **49**:427–433.

43 Pollack VA, Savage DM, Baker DA, Tsaparikos KE, Sloan E, Moyer JD, *et al.* Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: dynamics of receptor inhibition in situ and antitumor effects in athymic mice. *J Pharmacol Exp Ther* 1999; **291**:739–748.

44 Huang SM, Li J, Armstrong EA, Harari PM. Modulation of radiation response and tumor-induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 (Iressa). *Cancer Res* 2002; **62**:4300–4306.

45 Schmidt-Ullrich RK, Mikkelsen RB, Dent P, Todd DG, Valerie K, Kavanagh BD, *et al.* Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on EGFR tyrosine phosphorylation. *Oncogene* 1997; **15**:1191–1197.

46 Gupta AK, McKenna WG, Weber CN, Feldman MD, Goldsmith JD, Mick R, *et al.* Local recurrence in head and neck cancer: relationship to radiation resistance and signal transduction. *Clin Cancer Res* 2002; **8**:885–892.

47 Trummel JHQ, Raisch KP, Ahmed A. The biological effects of anti-epidermal growth factor receptor and ionizing radiation in human head and neck tumor cell lines. *Proc Am Ass Cancer Res* 1999; **40**:144 (abstr 958).

48 Nasu S, Ang KK, Fan Z, Milas L. C225 antiepidermal growth factor receptor antibody enhances tumor radiocurability. *Int J Radiat Oncol Biol Phys* 2001; **51**:474–477.

49 Magne N, Fischel JL, Dubreuil A, Formento P, Marcie S, Lagrange J-L, *et al.* Sequence-dependent effects of ZD1839 ('Iressa') in combination with cytotoxic treatment in human head and neck cancer. *Br J Cancer* 2002; **86**:819–827.

50 Swaisland HC, Smith R, Jones H, Farebrother J, Laight A. Pharmacokinetics of single and multiple oral doses of ZD1839 ('Iressa'), a selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), in healthy male volunteers. Poster presented at *ECCO 11*, Lisbon, Portugal; 2001, poster 236.

51 Ranson M, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, *et al.* ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J Clin Oncol* 2002; **20**:2240–2250.

52 Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, *et al.* Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor in patients with five selected solid tumor types. *J Clin Oncol* 2002; **20**: 4292–4302.

53 Herbst RS, Maddox AM, Rothenberg ML, Small EJ, Rubin EH, Baselga J, *et al.* Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol* 2002; **20**:3815–3825.

54 Nakagawa K, Tamura T, Negoro S, Kudoh S, Yamamoto N, Yamamoto N, *et al.* Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumours. *Ann Oncol* 2003; **14**: 922–930.

55 LoRusso PM, Herbst RS, Rischin D, Ranson M, Calvert H, Raymond E, *et al.* Improvements in quality of life and disease-related symptoms in phase I trials of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in non-small cell lung cancer and other solid tumors. *Clin Cancer Res* 2003; **9**:2040–2048.

56 Cohen EEW, Rosen F, Stadler WM, Recant W, Stanson K, Huo D, *et al.* Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2003; **21**:1980–1987.

57 Cohen EEW, Stenson K, Gustin DM, Lamont E, Mauer AM, Blair E, *et al.* A phase II study of 250-mg gefitinib (ZD1839) monotherapy in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). *Proc Am Soc Clin Oncol* 2003; **22**:502, (abstr 2021).

58 Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, *et al.* Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001; **19**:3267–3279.

59 Karp DD, Ferrante KJ, Tensfeldt TG. A phase I dose escalation study of epidermal growth factor receptor tyrosine kinase inhibitor CP 358,774 in patients with advanced solid tumours. *Lung Cancer* 2000; **29**:72.

60 Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2004; **22**: 77–85.

61 Baselga J, Pfister D, Cooper MR, Cohen R, Burtness B, Bos M, *et al.* Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol* 2000; **18**:904–914.

62 Shin DM, Donato NJ, Perez-Soler R, Shin HJC, Wu JY, Zhang P, *et al.* Epidermal growth factor receptor-targeted therapy with C225 and cisplatin in patients with head and neck cancer. *Clin Cancer Res* 2001; **7**: 1204–1213.

63 Vega-Villegas E, Awada A, Mesi R, Geoffrois L, Borel C, Humblet Y, *et al.* A phase I study of cetuximab in combination with cisplatin or carboplatin and 5-fluorouracil (5-FU) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R&M SCCHN). *Proc Am Soc Clin Oncol* 2003; **22**:502, (abstr 2020).

64 Robert F, Ezekiel MP, Spencer SA, Meredith RF, Bonner JA, Khazaeli MB, *et al.* Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. *J Clin Oncol* 2001; **19**: 3234-3243.

65 Kies MS, Arquette MA, Nabell L, Quinn D, Shin D, Needle MN, *et al.* Final report of the efficacy and safety of the anti-epidermal growth factor antibody Erbitux (IMC-C225), in combination with cisplatin in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) refractory to cisplatin containing chemotherapy. *Proc Am Soc Clin Oncol* 2002; **21**:232a (abstr 925).

66 Chan ATC, Hsu MM, Goh BC, Hui EP, Liu TW, Millward M, *et al.* A phase II study of cetuximab (C225) in combination with carboplatin in patients (pts) with recurrent or metastatic nasopharyngeal carcinoma (NPC) who failed to a platinum-based chemotherapy. *Proc Am Soc Clin Oncol* 2003; **22**:497 (abstr 2000).

67 Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortes-Funes H, Hitt R, *et al.* Cetuximab (C225) plus cisplatin/carboplatin is active in patients (pts) with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) progressing on a same dose and schedule platinum-based regimen. *Proc Am Soc Clin Oncol* 2002; **21**:226a (abstr 900).

68 Saltz L, Meropol NJ, Loehrer PJ, Waksal H, Needle MN, Mayer RJ. Single agent IMC-C225 (Erbitux) has activity in CPT-11-refractory colorectal cancer (CRC) that express the epidermal growth factor receptor (EGFR). *Proc Am Soc Clin Oncol* 2002; **21**:127a (abstr 504).

69 Burtness BA, Li Y, Flood W, Mattar BI, Forastiere AA. Phase III trial comparing cisplatin (C) + placebo (P) to C + anti-epidermal growth factor antibody (EGF-R) C225 in patients (pts) with metastatic/recurrent head & neck cancer (HNC). *Proc Am Soc Clin Oncol* 2002; **21**:226a (abstr 901).

70 Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol* 2003; **21**:2787–2799.