Cetuximab, its clinical use and future perspectives

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Increase in the expression of epidermal growth factor receptors (EGFRs) has been observed in many tumours. EGFR overexpression usually correlates with a more advanced stage of the disease, a poorer prognosis and a worse chemotherapy response. For all the aforementioned reasons, EGFR inhibition can be considered an attractive approach in cancer treatment. One strategy has been extracellular domain receptor inhibition, using monoclonal antibodies. In this review, we summarize the current status as well as what is likely to be the future use of monoclonal antibodies directed against EGFR. We have focussed on cetuximab being the most developed one. It has been mainly studied in colorectal cancer, and the major portion of this review will focus on all the research that has been carried out on this tumour. Clinical development of cetuximab is also important in head and neck cancer and in lung cancer. Interesting studies have been carried out in pancreatic, gastric, oesophageal and ovarian tumours, as well as in malignant gliomas. *Anti-Cancer Drugs* **19:99–113 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2008, **19**:99–113

Keywords: cetuximab, epidermal growth factor receptor inhibitors, monoclonal antibodies

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Received 16 July 2007 **Revised form accepted** 14 September 2007

Introduction

Epidermal growth factor receptor (EGFR), also known as erb-B1 or HER1, is a receptor tyrosine kinase belonging, along with erb-B2 (or HER2), erb-B3 and erb-B4, to the receptor tyrosine kinase family of EGFR [1].

EGFR is a transmembrane glycoprotein of 170 kDa, coded by the c-erb-B1 proto-oncogene situated in the 7q22 chromosome. Its known ligands are EGF, transforming growth factor (TGF)-α, amphiregulin, heparin-binding EGF, betacelulin, epiregulin and NRG2-α.

When EGFR is bound to its ligand, dimerization occurs (it homodimerizes with another EGFR or heterodimerizes with a different receptor of the same family), and a signalling cascade begins at the intracellular level, activating, among others, the mitogen-activated protein kinase, the STAT and the Akt antiapoptotic kinase pathways; different genes are eventually activated and thus cellular response is produced. EGFR-transmitted signal is inactivated by receptor internalization, its degradation or recycling. EGFR is expressed in healthy tissue and in many tumours, particularly in those of epithelial origin: its activation plays a significant role in tumourogenesis, by stimulating cell proliferation and inhibiting apoptosis. It also favours angiogenesis and facilitates metastasis generation [2].

Increase in EGFR expression has been observed in many tumours (Table 1) [3–17]. This EGFR overexpression usually correlates with a more advanced stage of the disease, a poorer prognosis and a worse response to chemotherapy [18]. In preclinical models, it was also found that the inhibition of these receptors had antitumour activity and available data suggested synergy with chemotherapy as well as radiotherapy [19,20]. For all these reasons, EGFR inhibition can be considered an attractive approach for cancer treatment. Different strategies attempting to inhibit EGFR signal-transduction pathway exist. The most explored ones are receptor inhibition of the extracellular domain using monoclonal antibodies, and receptor inhibition of the intracytoplasmic domain using small-molecule tyrosine kinase inhibitors.

Anti-EGFR monoclonal antibodies under clinical development are summarized in Table 2. In this review, we will consider the current situation of cetuximab (C-225, Erbitux; Imcone Systems Incorporated, Branchburg, New Jersey, USA), the most developed anti-EGFR monoclonal antibody. It is an IgG1 subclass chimeric mouse–human antibody that binds to the extracellular portion of EGFR with a high affinity, competing with its natural ligands and preventing activation of the receptor. Apart from this competitive inhibition, another important mechanism of action could be that cetuximab binding with EGFR might trigger internalization and destruction of the receptor [21]. An antineoplastic effect mediated by immune mechanisms has also been postulated, specifically by antibody-dependent cell-mediated cytotoxicity [22].

0959-4973

Table 1 EGFR overexpression

Tumour	EGFR overexpression (%)
Squamous cell head and neck cancer [3–5]	80–100
Colorectal cancer [6]	70–90
Nonsmall cell lung cancer [7]	40–80
Gastric cancer [8,9]	20–80
Pancreatic cancer [10]	30–90
Breast cancer [11]	15–90
Ovarian cancer [12]	35–70
Renal cancer [13]	50–90
Gliomas [14,15]	40–50
Prostatic cancer [16]	40–80
Cervical cancer [17]	80–100

EGFR, epidermal growth factor receptor.

Table 2 Main anti-EGFR monoclonal antibodies under clinical development

	Chimeric (30% murine)	Humanized (10% murine)	Completely human (100% human)
IgG1 (ADCC)	Cetuximab (C-225) (Erbitux)	Matuzumab (EMD72000)	Zalutumumab (HuMax-EGFR)
IgG2 (no ADCC)		Nimotuzumab (h-R3)	Panitumumab (ABX-EGF)

ADCC, antibody-dependent cell cytotoxicity; EGFR, epidermal growth factor receptor.

This last mechanism can only occur in IgG1 subtype monoclonal antibodies (cetuximab, matuzumab, nimotuzumab and zalutumumab) and not in IgG2 (panitumumab).

Cetuximab development started with preclinical studies with cell cultures and xenografts in animals, which suggested its activity in a wide variety of different tumours. Data suggesting a significant synergy with different cytostatics and radiotherapy have been also observed [23,24].

In the initial phase I studies [25], a loading intravenous (i.v.) dose of 400 mg/m^2 was recommended (first dose), followed by 250 mg/m^2 i.v. weekly. Tolerance was good, with cutaneous toxicity and hypersensitivity reactions being noted. Other reported toxicities with cetuximab are asthenia, diarrhoea and hypomagnesaemia (with or without concomitant hypocalcaemia), which are usually easily manageable.

Skin toxicity was present in about 80% of the patients; however, it was of grade 3–4 (G3–4) only in 10–15% of the cases. It should be pointed out that a direct correlation between the level of cutaneous toxicity and the efficacy of treatment, in terms of response and survival, has been observed in several clinical studies in different tumours. This is true for cetuximab as well as for other EGFR inhibitors. An interesting study has recently been reported [26]: it explores the hypothesis that scaling of the cetuximab dose until the appearance of G3 skin toxicity might increase treatment efficacy. This study is called EVEREST, and it was carried out on patients with advanced colorectal cancer. A total of 166 irinotecan-refractory patients received treatment with irinotecan and cetuximab at the normal dose. Skin toxicity was evaluated after 3 weeks' treatment; 89 patients with toxicity less than grade 2 were randomized to carry on the normal dose of cetuximab or to start dose escalation until grade 2 toxicity was reached. The maximum weekly dose of 500-mg/m^2 i.v. was reached in 24 of the 44 patients randomized to a scaled dose. Significantly higher skin toxicity was found in the scaled-dose arm (G3–4: 9 vs. 0%), as well as a higher response rate [scaled doses: RR: 30%, 95% confidence interval (CI): 17–45%; normal doses: RR 13%, 95% CI: 5–27%].

The other noteworthy toxicity of cetuximab is hypersensitivity reactions, which appear only in 5% of patients, with only half of them being G3–4. The MABEL study has recently reported an analysis of this toxicity [27]; G3–4 hypersensitivity was only seen in 1.1% of the 700 patients who received antihistamines and corticoid prophylaxis. Of the 422 patients who only used antihistamines, these reactions increased up to 7.1%.

Another interesting issue is the possibility of administrating cetuximab every 2 weeks. This could be more convenient for both the patient and the health system by lowering the use of health resources. Exploring this issue, the preliminary results of a phase I study performed on advanced colorectal cancer were presented in ASCO-06 [28]. Patients were initially treated with 6 weeks of cetuximab monotherapy and then FOLFIRI was added. Pharmacokinetic and pharmacodynamic studies in tumour and in skin biopsies were carried out before treatment and after the first 6 weeks of treatment with cetuximab alone. They were compared between the group of patients treated with the normal weekly cetuximab schedule and the other group treated with cetuximab every 2 weeks at different dose levels. Equivalent pharmacokinetics and pharmacodynamics were observed between patients treated with the normal weekly schedule and those treated with 500 mg/m^2 i.v. every 2 weeks. In this study, the dose of cetuximab was scaled every 2 weeks. The results of higher doses, as well as the definitive results of the study, are pending. Therefore, these data must be interpreted as being still preliminary. If confirmed, however, they could justify the use of cetuximab in a much more convenient 2-week schedule. In this sense, it is also interesting to point out the results of a phase II study performed in irinotecan-refractory advanced colorectal cancer [29]: 40 patients were treated with cetuximab (500 mg/m^2) in combination with irinotecan, both administered every 2 weeks. Toxicity and efficacy (response rate 22%, median time to progression 4.8 months and survival 9.8 months)

seemed to be similar to those reported with the normal weekly schedule.

Cetuximab has been mainly studied in colorectal cancer, and most of the emphasis in this review will be given to the research in this area. Its clinical development is, nonetheless, also important in squamous-cell head and neck carcinoma, in nonsmall cell lung cancer (NSCLC) and in pancreatic cancer. Furthermore, interesting studies of cetuximab in locations such as the oesophagus have been carried out, as also its use in gastric cancer, gynaecological tumours and glioblastomas.

Cetuximab in colorectal cancer

Advanced colorectal cancer

The addition of irinotecan and oxaliplatin to the 5-fluorouracil (5-FU)-based combinations in the last 10 years has led to an important breakthrough in the treatment of advanced colorectal cancer, reaching response rates of around 50%, with a median time to progression of about 9 months and median overall survival (OS) of over 20 months. The inclusion in routine clinical practice of surgical rescues of metastatic disease (particularly at the hepatic level, but also in the lung, the peritoneum and at other sites of the disease) has also been a significant therapeutic advance and has led to long-term survivals in an interesting proportion of patients (20–40%). When, however, this type of approach is not possible, long-term survival is rare. Despite the undeniable advances achieved, research needs to continue, to improve the course of the disease for these patients. For this reason, the development of new therapeutic targets is being very actively investigated; therefore, the discovery of cetuximab is very important. We herein summarize the main studies that have been carried out, as well as the more interesting ones that are currently underway.

Irinotecan-refractory patients

Preclinical data were found suggesting that cetuximab could counteract irinotecan resistance [30]. The efficacy results of the phase II and III trials and of the extension studies that have explored the role of cetuximab in this setting are summarized in Table 3. These studies have been carried out mainly in patients who expressed EGFR (immunohistochemistry) in the tumour [6,26,29,31–37]. Some studies included only patients who had not received oxaliplatin; other trials included only patients refractory to irinotecan and oxaliplatin, and other studies included both subgroups of patients. With irinotecan in combination with cetuximab, response rates were between 17 and 25%, time to tumour progression was between 4 and 4.8 months and OS was between 7.7 and 9.2 months [15,17,20–22]. With cetuximab alone, response rates were between 9 and 12%, time to tumour progression was 1.5 months and OS was between 6.1 and 6.9 months [18–20,23]. In all these studies except one, cetuximab was administered according to the classical weekly schedule. As mentioned before, in the phase II study of Pfeiffer *et al.* [29], 40 patients were,

Table 3 Clinical trials with cetuximab in irinotecan-refractory advanced colorectal cancer

Study	Oxaliplatin refractory	Treatment	No. of patients	PR + CR (%)	Median TTP (months)	Median Sv (months)
EGFR (IHC) +						
P. II Saltz [31]	No	Irino–Cet	121	17		7.7
P. II Saltz [32]	No	Cet	57	9		6.6
P. II Lenz [33]	Yes	Cet	346	12		6.6
Randomized. P. II BOND [6]	No/yes (63%)	Irino–Cet vs. Cet	329	22.9	4.1	8.6
				P=0.007	*P*: 0.001	*P*=0.48
				10.8	1.5	6.9
Extension study MABEL [34]	No/yes (76%)	Irino–Cet	1147			9.2
Extension study LABEL [35]	No/yes	Irino–Cet	73	25	4	
P. II Pfeiffer [29]	No/yes	Irino–Cet (every 2 weeks)	40	22	4.8	9.8
Randomized P. II EVEREST [26]	No/yes	Irino–Cet normal dose vs. Irino–Cet with dose escalation	89 Skin Tox <G2	13	3.9	
				30	4.8	
Randomized P. II EXPLORE [37]	No	FOLFOX–Cet vs. FOLFOX	105	20	4.4	
				P=NS	*P*=NS	
				15	4.1	
P. III NCIC CTG CO-17 [36]	Yes (97%)	Cet vs. BSC	572			6.1
						P: 0.0046
						4.6
EGFR (IHC) –						
Lenz *et al.* [38]	Yes	Cet	9	11		
MSKCC [39]	No/yes	Cet–Irino	16	25		

BSC, best supportive care; Cet, cetuximab; FOLFOX, folinic acid–fluorouracil–oxaliplatin; Irino, irinotecan; PR + CR, partial response + complete response; Sv, survival; TTP, time to tumour progression; P, phase.

nevertheless, treated with cetuximab (500 mg/m^2) in combination with irinotecan (180 mg/m^2), both being administered every 2 weeks. In this study, the toxicity and efficacy (response rate 22%, median time to progression 4.8 months and survival 9.8 months) seemed to be similar to those reported with the normal weekly schedule.

A randomized phase II study, the BOND study, published in 2004 [6], was designed to identify the best strategy in this group of patients. This study included 329 patients who were randomized to receive cetuximab alone or cetuximab added to irinotecan (1 : 2 randomization). A higher response rate (22.9 vs. 10.8%, $P = 0.007$), a higher disease control rate (CR + PR + stabilizations: 56 vs. 32%, $P = 0.001$) and a longer time to tumour progression (median: 4.1 months vs. 1.5 months, $P = 0.001$) were observed in the combined arm. No statistically significant differences were seen in survival (median: 8.6 months in the combined arm vs. 6.9 months in the monotherapy one; lrk: $P = 0.48$); however, this could have been influenced because, in half of the patients who had been randomized to cetuximab alone, irinotecan was added upon progression. The response rate in these patients who received cross-treatment was 3.6%; disease control rate was 39% and the median time to tumour progression was 1.5 months. Tolerance was good in both arms, with no differences being seen between the toxicity observed in the combined arm and the tolerance normally associated with irinotecan or cetuximab alone. As a consequence of these findings, cetuximab was approved by the Food and Drug Administration (FDA), as well as by the European Medicines Agency (EMEA), in irinotecan-refractory patients with EGFR-expressing advanced colorectal cancer.

We also have the data of a phase III study – the NCIC CTG CO-17 study [36] – that randomized 572 patients refractory to both irinotecan and oxaliplatin to receive monotherapy with cetuximab or best supportive care. Its main objective was survival. Only 20 patients randomized to best supportive care received cetuximab at progression. OS was significantly improved in the cetuximab arm [median survival: 6.1 vs. 4.6 months; 1-year survival: 21 vs. 16%; hazard ratio (HR): 0.77; 95% CI: 0.64–0.92 and lrk: $P = 0.0046$]. Progression-free survival (PFS) was also superior in the cetuximab arm (HR: 0.68; 95% CI: 0.57–0.8; lrk: $P < 0.0001$).

Another approach in patients refractory to irinotecan, who had not previously been treated with oxaliplatin, has been to explore the role of the addition of cetuximab to an oxaliplatin-based combination. The preliminary results of a randomized phase II trial, the EXPLORE trial, were reported in 2005 [37]. It randomized 105 irinotecan-refractory patients to receive folinic acid–FU–oxaliplatin-4 (FOLFOX-4) vs. FOLFOX-4 in combination with cetuximab. This study found statistically significant differences neither in objective response nor in PFS between the FOLFOX–cetuximab arm and the FOLFOX arm (response rate: 20 vs. 15%, *P*: NS; median PFS: 4.4 vs. 4.1 months, *P*: NS). It is, nevertheless, difficult to arrive at any conclusions from the results of this study, owing to the small number of patients included.

The clinical development of cetuximab in advanced colorectal cancer began to be carried out only for those patients whose tumours expressed EGFR by immunohistochemistry either in the primary or in metastases. No study could, however, find a relationship between the EGFR level of expression by immunohistochemistry and response, time until progression or survival. The role of cetuximab in irinotecan-refractory advanced colorectal cancer, in patients with undetectable EGFR by immunohistochemistry tumours, was examined in a study reported in 2004 [38], in which nine patients refractory to oxaliplatin and irinotecan were treated with cetuximab alone. An 11% response rate was observed, which was not different from that observed in patients with EGFR-positive tumours. A similar conclusion was drawn from a study by the MSKCC [39], which analysed responses to cetuximab in 16 irinotecan-refractory patients who had EGFR-negative tumours (14 received cetuximab–irinotecan and two received cetuximab monotherapy), and found a response rate of 25%.

This lack of predictive value of the expression (or nonexpression), as well as the level of expression of EGFR in the tumour, determined by immunohistochemistry, could be due to different causes. The first one might be that the immunohistochemical determination of EGFR is affected by the fixation method. The second might be that the tissue we used to determine it had been fixed a long time previously [40,41]. Differences arise, depending on who analyses it [42]; there might be tumour heterogenicity [43]. In addition, EGFR expression can be different between primary cancer and metastases [44]. Furthermore, a negative EGFR by immunohistochemistry does not necessarily imply a lack of EGFR in cell membranes, as low EGFR levels (less than 1000 receptors/cell) are not detected by the immunohistochemistry technique. At this point, it is of interest to mention that high-affinity and low-affinity EGF receptors cannot be distinguished by the immunohistochemical methods currently used, and that the biological activity mainly depends on the high-affinity receptors [45,46]. No studies are available on the ratio of low-affinity and high-affinity receptors in colorectal cancer. A possible hypothesis, however, is that if only the number of high-affinity receptors is important, and if these are limited in number (only 5% of the receptors

expressed by the A-431 cell line), immunohistochemistry will be of limited use if it only gives data on the extent of low-affinity EGFR, masking the presence of those with high affinity. It could thus be possible that a highly EGFR-positive tumour might actually have few receptors with high affinity. In contrast, a tumour with low positive EGFR or even negative EGFR can evidence an elevated proportion of high-affinity receptors or even a significant dependence on a small number of high-affinity receptors for cell survival. Another explanation of the activity found with cetuximab in EGFR-negative tumours could be the possible existence of an immunological mechanism of action, i.e. antibody-dependent cell-mediated cytotoxicity [22].

In view of these data, a prospective phase II study is attempting to confirm the activity of cetuximab, alone and in combination with irinotecan, in advanced colorectal cancer with immunohistochemistry EGFR-negative tumours. At the same time, most of the currently running studies are looking at the role of cetuximab in EGFR-positive and EGFR-negative colorectal cancer. The currently approved indication by the FDA and the EMEA is nonetheless, only in EGFR-positive patients. If more clinical evidence of its usefulness in EGFR-negative tumours appears, this might change soon.

Predictive factors of efficacy

Given that there is no relationship between EGFR expression by immunohistochemistry and treatment efficacy in advanced colorectal cancer, other possible predictive factors need to be investigated. These would enable us to select the patients who would be more likely to benefit from cetuximab treatment. As already mentioned, skin toxicity can be of predictive value. Regarding biological factors, Table 4 summarizes the results of the main studies reported. These studies suggest that the following factors could be positive predictors of treatment efficacy with cetuximab: an increase in the number of EGFR gene copies determined by fluorescence or chromogenic in-situ hybridization methods (FISH or CISH) [47–51], the absence of KRAS mutations [47–53], other factors such as not losing PTEN expression [49], no increased copy number of HER2 gene (FISH) [51] and higher tumoural mRNA levels of epiregulin or amphiregulin [52]. These data are, however, still preliminary,

Table 4 Biological predictive factors for cetuximab in advanced colorectal cancer

Study treatment no. of patients	EGFR gene copies FISH/CISH	KRAS mutations	Other	No predictive value
Moroni *et al.* [47]	FISH+: −30% of patients	KRAS-mutated: −32% of patients		Mutations in
Cetuxi/panitu	RR: 89% (vs. 5%)	RR: 20% (vs. 38%)		EGFR
31 patients	$P=0.0001$	$P=0.42$		B-RAF
				PI3K
Lièvre *et al.* [48]	CISH+: −10% of patients	KRAS-mutated: −43% of patients		Mutations in
Cetuxi ± irino	RR: 100% (vs. 30%)	RR: 0% (vs. 65%)		B-RAF
30 patients	$P=0.04$	$P<0.0001$		PI3K
		Sv: 6.9 m (vs. 16.3 m)		
		$P=0.016$		
Romagnani *et al.* [49]	FISH+: −11% of patients	KRAS-mutated: −37% of patients	pTEN (IHC)−: −38% of patients	
Cetuxi + chemoth	RR: 42% (vs. 0%)	RR: 10% (vs. 53%)	RR: 0% (vs. 62%)	
27 patients	$P<0.05$	$P<0.05$	$P<0.05$	
Personeni *et al.* [50]	FISH+: −10% of patients	KRAS-mutated: −24% of patients		Mutations in
Cetuxi ± irino	RR+SD: 63% (vs. 33%)	RR: 0% (vs. 34%)		B-RAF
54 patients	$P<0.05$	$P=0.04$		HER 2 (FISH)
Finocchiaro *et al.* [51]	FISH+: −48% of patients	KRAS-mutated: −39% of patients	HER 2 (FISH)+: −23% of patients	EGFR (IHC)
Cetuxi ± irino	RR: 29% (vs. 6%)	RR: 6% (vs. 26%)	RR: 15% (vs. 19%)	
85 patients	$P=0.007$	$P=0.02$	$P=1$	
	TTP: 6.6 m (vs. 3.7 m)	TTP: 3.7 m (vs. 6.3 m)	TTP: 3.7 m (vs. 5.8 m)	
	$P=0.05$	$P=0.07$	$P=0.01$	
	TTP: 11.3 m (vs. 8.5 m)	Sv: 8.3 m (vs. 10.8 m)	Sv: 6.6 m (vs. 11.3 m)	
	$P=0.7$	$P=0.2$	$P=0.03$	
Khambata-Ford *et al.* [52]		KRAS-mutated: −37% of patients	EREG[a] (high expression): −50% of patients	
Cetuxi		RR+SD: 10% (vs. 48%)	TTP: 3.4 m (vs. 1.9 m)	
110 patients		$P=0.0003$	$P=0.0001$	
		TTP: 3.7 m (vs. 6.3 m)	AREG[a] (high expression): −50% of patients	
		$P=0.07$	TTP: 3.8 m (vs. 1.9 m)	
		Sv: 8.3 m (vs. 10.8 m)	$P=0.0001$	
		$P=0.2$		
De Roock *et al.* [53]		KRAS-mutated: −46% of patients		
Cetuxi ± irino		RR: 0% (vs. 40%)		
37 patients		$P<0.05$		

AREG: amphiregulin; cetuxi, cetuximab; chemoth, chemotherapy; EREG: epiregulin; IHC, inmunohistochemistry; irino, irinotecan; panitu, panitumumab; RR, response rate; SD, stable disease; Sv, survival; TTP, time to tumour progression; m, months; FISH, fluorescence in-situ hybridisation; CISH, chromogenic in-situ hybridization.
[a]Tumor mRNA levels.

Table 5 Phase II trials with cetuximab plus oxaliplatin or irinotecan in first-line treatment of metastatic colorectal cancer

Study	No. of patients	PR + CR (CR) (%)	PR + CR + SD (%)	Median Sv (m)	Surgical rescue (%)
Cetuxi–IFL [58]	29	48	90	–	–
Cetuxi–FOLFIRI [59]	42	57	83	23	24
Cetuxi–Iri–FU (AIO) [60]	21	67 (10)	96	33	24
Cetuxi–FOLFOX [61]	42	81 (10)	98	30	23
Cetuxi–FUFOX [62]	49	69 (2)	79	31	–
Cetuxi–XELIRI [63]	70	40 (4)	80	–	–

Cetuxi, cetuximab; CR, complete response; FOLFIRI, leucovorin–FU–irinotecan; FOLFOX, leucovorin–FU–oxaliplatin; IFL, irinotecan–FU–leucovorin; PR, partial response; SD, stable disease; Sv, survival; XELIRI, capecitabine–irinotecan; Iri, irinotecan; FU, fluorouracil.

and need to be confirmed with more properly designed studies before taking them into routine clinical practice.

Cetuximab in second-line therapy after progression to oxaliplatin

The role of cetuximab in second-line therapy has also been explored. The EPIC phase III study randomized 1298 patients to receive irinotecan vs. irinotecan in combination with cetuximab, in oxaliplatin-refractory EGFR-expressing tumours. The main objective was survival and the secondary objectives were PFS and response rate. The inclusion of patients was completed in January 2006, and definitive results have just been reported [54]. PFS was significantly improved in the cetuximab arm (median PFS: 4 months vs. 2.6 months; HR: 0.69; 95% CI: 0.61–0.77 and lrk: $P < 0.0001$) as well as response rate (16 vs. 4%, $P < 0.05$) and disease control rate (61 vs. 46%). OS was, nevertheless, similar in both arms (median survival: 10.7 vs. 9.99 months; HR: 0.97; 95% CI: 0.85–1.11 and lrk: $P = 0.71$) perhaps owing to the fact that 47% of the patients randomized to irinotecan alone received cetuximab upon progression. In a recently presented analysis [55], health-related quality of life was better preserved on the combination arm, with less deterioration in symptom scores (pain, nausea and insomnia), as well as in global health status scores.

Another feasible option in oxaliplatin-refractory patients is to explore the combination of oxaliplatin in combination with cetuximab. Preclinical data are found suggesting that cetuximab can reverse resistance to oxaliplatin [56]. In 2006, the results of a phase II study that included 40 oxaliplatin-refractory patients with EGFR-expressing tumours were reported [57]. The chemotherapy schedule was XELOX in combination with cetuximab, obtaining a response rate of 19% with a median time to progression of 3 months and a survival rate of 9 months.

Cetuximab in first-line therapy

Regarding the role of cetuximab in first-line therapy, several phase II studies have been carried out exploring combinations of cetuximab with irinotecan-based or oxaliplatin-based schedules (Table 5) [58–63]. All these studies included patients with EGFR-expressing tumours, and reported promising results in terms of response rates (48–81%), median OSs (23–31 months) and surgical rescue rates of metastasis (23–24%).

In an attempt to clarify whether cetuximab added anything in first-line therapy and whether it was better to combine it with FOLFOX or FOLFIRI in this setting, the CALGB designed a phase III study with four arms: FOLFOX vs. FOLFOX–cetuximab vs. FOLFIRI vs. FOLFIRI–cetuximab. It was planned to include 2200 patients; however, owing to slow recruitment, it was redesigned as a randomized phase II, and the number of patients was reduced to 238. The preliminary results of this study were reported in ASCO-06 [64]. Response rates were FOLFIRI: 36%, FOLFIRI-cetuximab: 44%, FOLFOX: 40% and FOLFOX–cetuximab: 60%. Better responses were seen in the cetuximab arms than in those without it (52 vs. 38%, $P = 0.029$), and differences between FOLFOX and FOLFIRI were not statistically significant. Significant differences were seen neither in PFS nor in survival between the four arms. Data were, nevertheless, still preliminary, and the study was dimensioned to spot differences neither in survival nor in PFS.

Preliminary results of three other randomized phase II studies exploring combinations with cetuximab in first-line therapy have recently been reported. The first is the SAKK study [65], which randomized 74 patients to XELOX vs. XELOX + cetuximab, showing more responses in the cetuximab arm (43 vs. 21%). The second study is from the AIO [66], and it randomized 92 patients to receive XELOX–cetuximab vs. XELIRI–cetuximab, showing response rates of 66 and 42% ($P = 0.08$). The third one is the OPUS study [67]. It randomized 300 patients to receive FOLFOX vs. FOLFOX–cetuximab and showed a trend towards higher response rates in the cetuximab arm [45 vs. 35%; odds ratio (OR): 1.51; *P*: 0.06]. This difference was statistically significant when only patients with performance status 0–1 were considered (49 vs. 36%; OR: 1.65, *P*: 0.03).

Finally, two large phase III studies have been carried out, to find out whether cetuximab adds something to FOLFIRI or to FOLFOX in the first-line setting. The main objective of both studies is PFS. The first of these trials is the CRYSTAL study [68], which has randomized

1212 patients with EGFR-expressing tumours to receive FOLFIRI vs. FOLFIRI–cetuximab. A statistically significant advantage in terms of PFS (median PFS: 8.9 vs. 8 months; 1 year PFS: 34 vs. 23%; HR: 0.85; 95% CI: 0.72–0.99 and $P = 0.036$) and response rate (46.9 vs. 38.7%, $P = 0.0032$) was observed in the cetuximab arm. An improvement in the liver metastasis resection rate (no residual tumour after resection) was also found, in the cetuximab arm, both in the overall population (4.3 vs. 1.5%; OR: 3; 95% CI: 1.4–6.5 and $P = 0.003$) and in the subgroup of patients with only liver metastasis (9.8 vs. 4.5%). OS, quality of life and biomarker analysis are still pending. The other large phase III study is the British COIN trial, for which we still do not have the results. It plans to randomize 2421 patients (they are not required to be EGFR +) to receive FOLFOX vs. FOLFOX + cetuximab vs. FOLFOX, stopping at 12 weeks and restarting if there is progression.

First-line therapy in patients with only liver metastasis

A special scenario exists when patients have only liver metastases that are not initially resectable. In these patients, as has been previously pointed out, obtaining a response sometimes enables a secondary surgical rescue to be performed; when this is achieved, long-term survival is about 20%. A direct relationship has been observed between response rate and the number of patients in whom a secondary surgical rescue is possible. The high response rates seen in the majority of first-line studies combining oxaliplatin or irinotecan with cetuximab, along with the low cetuximab toxicity and its noninterference with surgery, make these schedules very attractive in this setting. Various randomized studies exploring the role of cetuximab in this situation are being carried out. In the TTD-04-02 study, 136 patients with only nonresectable liver metastasis (including EGFR + and EGFR– patients) are being randomized to receive FOLFOX vs. FOLFOX–cetuximab. Its objectives are response rate, percentage of surgical rescues, PFS and survival. The EMR-CELIM study has similar inclusion criteria and objectives and will randomize 108 patients to receive oxaliplatin–FU–leucovorin + cetuximab vs. irinotecan–FU–leucovorin + cetuximab.

The EORTC is carrying out a randomized phase II study (BOS) in first-line therapy, which plans to recruit 100 patients with colorectal cancer resectable metastasis. It will randomize them to receive FOLFOX + cetuximab vs. FOLFOX + cetuximab + bevacizumab for 3 months, followed by surgery in both arms. Adjuvant treatment will be given with the same schedule that had previously been given for another 3 months. Its endpoints are safety and response rates.

Cetuximab first-line monotherapy

Owing to the limited toxicity of cetuximab, it makes it an attractive approach for elderly people. Taking this into account, the TTD 04-01 [69] was designed to explore cetuximab activity as first-line treatment for patients aged above 70 years. Its response rate was 15%, the stabilization rate 36% and the median PFS was 3 months. In another recently reported phase II trial [70], 39 patients with EGFR-expressing tumours were treated at first with cetuximab alone. The response rate was 10% and median time to progression was 2 months.

Cetuximab in combination with other drugs against new targets in advanced colorectal cancer

Primary or acquired cetuximab resistance can be due to the fact that EGFR does not really play an important enough role in this particular tumour. It might be that receptor is not adequately inhibited, or that tumour survival depends not just on one, but on several signalling pathways. How to prevent these resistances is being examined, using different strategies combining cetuximab with different drugs against new targets.

Epidermal growth factor receptor tyrosine kinase inhibitors

By combining **cetuximab with other EGFR tyrosine kinase inhibitors**, a more complete inhibition of the receptor is being sought. There are some data that suggest a synergy between cetuximab and gefitinib [71]. In a recently reported phase I study [72], promising activity was shown in 11 patients with advanced colorectal cancer, who had been treated with cetuximab–gefitinib: the response rate was 45% and PFS was 3.2 months. It was carried out as a pharmacodynamic study, and found a more complete EGFR signal transmission inhibition with the combination than with both drugs separately.

Some tyrosine kinase inhibitors act on several receptors. Vandetanib, for example, inhibits EGFR, VEGFR and RET, and there are preclinical studies suggesting synergy between cetuximab and vandetanib [73].

Cetuximab in combination with bevacizumab

Preclinical data exist suggesting synergy between EGFR and VEGF inhibition [74,75]. A randomized phase II study, the BOND II [76], included 81 patients with irinotecan-refractory advanced colorectal cancer (EGFR-positive or EGFR-negative) and randomized them to receive cetuximab–bevacizumab–irinotecan vs. cetuximab–bevacizumab. In the irinotecan arm, a higher response rate was found (37 vs. 20%), as well as a longer median time to progression (7.9 vs. 5.6 months). When comparing these data with those of the BOND trial, which included a similar sample of patients, the addition of bevacizumab seemed to generate more responses (cetuximab–irinotecan: 23% vs. cetuximab–irinotecan–

bevacizumab: 37%; cetuximab: 11% vs. cetuximab–bevacizumab: 20%) and a longer median time to tumour progression (cetuximab–irinotecan: 4.1 months vs. cetuximab–irinotecan–bevacizumab: 7.9 months; cetuximab: 1.5 months vs. cetuximab–bevacizumab: 5.6 months).

A study of great interest is the phase III CALGB/SWOG 80405 study, which is trying to establish what the real value of the cetuximab and bevacizumab combination might be. It is currently going on, and it plans to include 2289 patients. It has either FOLFOX-6 or FOLFIRI as basal treatment (depending on the investigator's or patient's criteria) and randomizes patients to a combination with cetuximab vs. bevacizumab vs. both.

As we had previously mentioned, the EORTC is also carrying out a randomized phase II study (BOS), planning to include 100 patients with resectable metastases of colorectal cancer. It randomizes them to receive FOLFOX + cetuximab vs. FOLFOX + cetuximab + bevacizumab for 3 months as first-line treatment, followed by surgery and subsequent administration of the same treatment for another 3 months. Its endpoints are safety and response.

In an attempt to study what the best second-line treatment for a patient who has progressed to first-line treatment with oxaliplatin–fluoropyrimidine–bevacizumab might be, the SWOG group is carrying out a phase III study (SWOG 0600, IBET study). It plans to recruit 1600 patients and to randomize them to receive (FOLF) irinotecan + cetuximab vs. (FOLF) irinotecan + cetuximab + bevacizumab (5 mg/kg) every 2 weeks vs. (FOLF) irinotecan + cetuximab + bevacizumab (10 mg/kg) every 2 weeks. Its main endpoint is survival.

Adjuvant treatment in colon cancer

Two ongoing phase III studies are examining the role of cetuximab in this setting. The PETACC-8 trial envisages randomizing 2000 patients with stage III colon cancer to receive 6 months' adjuvant treatment with only FOLFOX-4 vs. FOLFOX-4 in combination with cetuximab, its main endpoint being disease-free survival. Having a similar design, the INT NO 147 study plans to randomize 2200 patients to FOLFOX-6 vs. FOLFOX-6 in combination with cetuximab.

Preoperative treatment in rectal cancer

Several phase I/II studies have been carried out with cetuximab in combination with preoperative chemoradiotherapy in rectal cancer.

- The Chung *et al.* study [77] included 20 patients, treating them with cetuximab in combination with continuous 5-FU infusion, concomitant with preoperative radiotherapy. The usual dose of 5-FU (225 mg/m^2/day continuous infusion), with a good toxicity profile, could be administered, achieving a 15% pathological complete response (pCR) rate.
- The study by Machiels *et al.* [78] included 20 patients treated with cetuximab with capecitabine, concomitant with preoperative radiotherapy. Tolerance was good, with the normal dose of capecitabine (1650 mg/m^2/day) achieving a pCR rate of 11%.
- The study by Arnold *et al.* [79] included 60 patients treated with cetuximab with capecitabine–oxaliplatin, concomitant with preoperative radiotherapy. The toxicity profile was favourable at the usual dose of capecitabine (1650 mg/m^2/day, days 1–14 and 22–35) and oxaliplatin (50 mg/m^2 days 1, 8, 22 and 29). The pCR rate was 9%.

A European randomized phase II study is currently being carried out with resectable rectal cancer patients who are either EGFR + or EFGR – and MRI has shown poor prognosis. It plans to randomize 162 patients to receive XELOX concomitant with preoperative radiotherapy vs. XELOX concomitant with preoperative radiotherapy combined with cetuximab. Afterwards, surgery with total mesorectal excision will be performed in both arms. All patients will receive 3 months' adjuvant treatment with XELOX vs. XELOX combined with cetuximab.

Cetuximab in head and neck squamous-cell carcinoma

Head and neck squamous-cell carcinomas (HNSCCs) very often overexpress EGFR (80–100% of cases), and this overexpression is associated with more advanced stages and worse survival [4,5].

In preclinical studies, antiproliferative and proapoptotic activity in HNSCC cell lines [80] has been observed, as also synergy with radiotherapy [81] and cisplatin [23].

It is noteworthy that clinical development of cetuximab in HNSCCs was carried out including patients who had both EGFR-positive and EGFR-negative tumours by immunohistochemistry.

Recurrent or metastatic head and neck squamous-cell carcinoma

Its role began to be studied in second-line therapy after platin failure. In two phase II studies, cetuximab was added to cisplatin. In the first one [82], 96 patients with progressive disease after cisplatin were included: responses were seen in 10% of the patients, achieving a control rate of 53%, a median time to tumour progression of 2.8 months and a median survival of 6.1 months. In the second phase II trial [83], 51 patients with stable disease after two cycles of a cisplatin-based regimen (SD), 25 patients with progressive disease (PD/1) and 54 patients who had developed PD within 90 days of platinum-based

treatment (PD/2) were treated with cisplatin in combination with cetuximab. Response rates for the SD, PD/1 and PD/2 groups were 18, 20 and 6%, respectively, with median OS times being 11.7, 6.1 and 4.3 months.

Another phase II study that explored cetuximab alone [84] obtained similar efficacy, with a response rate of 13%, median time to progression of 2 months and median survival of 5.2 months. In view of these results, the FDA approved, in 2006, the indication of cetuximab monotherapy in patients with recurrent/metastatic HNSCCs refractory to cisplatin. To date, the EMEA has not approved the use of cetuximab in this context.

The results of a phase III study in first-line recurrent/metastatic HNSCC disease, carried out by the ECOG, have been published [85]. This study included 116 patients and compared cisplatin–cetuximab with cisplatin–placebo.It obtained a significant increase in response rates (26 vs. 10%, $P = 0.029$) and a tendency towards longer survival (median 9.3 vs. 8 months, $P = 0.21$), although the latter was not statistically significant. The study also analysed the predictive value of skin toxicity with cetuximab, observing a significantly longer survival when patients had skin toxicity.

To examine the combination of cetuximab with cisplatin/carboplatin and 5-FU in recurrent/metastatic HNSCC first-line treatment, a phase I/II study [86] was carried out, obtaining an interesting result (response rate 43 and 37% stabilizations). No statistically significant differences were seen between patients treated with cisplatin or carboplatin. A phase III study in the same setting, the EXTREME study, has compared cisplatin or carboplatin + 5-FU against the same chemotherapy, in combination with cetuximab. It included 422 patients and its results were recently reported [87]. A statistically significant improvement in OS was seen in the cetuximab arm (median: 10.1 vs. 7.4 months; HR: 0.79; 95% CI: 0.64–0.98 and $P = 0.03$). These results suggest that cetuximab has an important role in the treatment of recurrent/metastatic HNSCC, but its optimal timing has not been defined properly yet [88].

Locally advanced head and neck squamous-cell carcinoma

The results of a phase III study that included 424 patients and compared radiotherapy alone with combination radiotherapy and cetuximab have been published [89]. Toxicity was not higher in the combined arm and, a significant increase was found both in locoregional control (2-year LRC: 50 vs. 41%; HR: 0.68; 95% CI: 0.52–0.89 and $P = 0.005$) and in OS (3-year OS: 55 vs. 44%; HR: 0.74; 95% CI: 0.57–0.97 and $P = 0.02$). Recently a report of the quality-of-life assessments that were performed as part of this trial was published: the conclusion is that quality of life was not worse for patients receiving combination radiotherapy and cetuximab than for those treated with cetuximab alone [90]. It is noteworthy that this study included patients with resectable locally advanced tumours, in whom radiotherapy might have formed part of an organ-preservation strategy, as well as patients with nonresectable tumours for whom radiotherapy could be the definitive treatment; however, it did not analyse the two subgroups separately. The percentage of patients who underwent surgery was similar in both arms. Laryngeal preservation was also analysed in 171 patients who had primary cancers of the larynx or hypopharynx [91], and a higher laryngeal preservation was seen in the cetuximab arm (at 3 years 88 vs. 80%). It has, nevertheless, to be pointed out that this subgroup analysis was not planned; stages III, IVA and IVB were mixed; the proportion of stage III was higher in the group with cetuximab (38 vs. 28%), and the proportion of T4a and T4b in each of the arms was not specified. Moreover, another important criticism of this study has been the use of radiotherapy alone, instead of the up-to-date reference treatment in locally advanced HNSCCs (concomitant chemoradiotherapy with cisplatin). Despite this, in 2006, the FDA and the EMEA approved the indication of radiotherapy with cetuximab in this setting.

The comparison between chemoradiotherapy (with cisplatin) and cetuximab–radiotherapy is currently being carried out in a phase III study by the EORTC. Given the positive results of the new induction chemotherapy schedules that incorporate taxanes, it would also be interesting to investigate the usefulness of incorporating cetuximab into induction chemotherapy followed by radiotherapy. A French randomized phase II study (TREMPLIN) is investigating this approach. It includes patients with resectable locally advanced laryngeal or hypopharyngeal tumours, who had achieved a clinical response of more than 50% after 3 induction chemotherapy cycles with docetaxel–cisplatin–5-FU. This study randomizes the patients to receive concomitant radiotherapy with cisplatin vs. concomitant radiotherapy with cetuximab.

It would also be interesting to study the role of cetuximab concomitant with chemoradiotherapy. It is theoretically very attractive, given the synergy of cetuximab with both treatments at the preclinical level. The results of a phase II study in this setting have been published. It examines the combination of radiotherapy, cisplatin and cetuximab in 21 patients with locally advanced HNSCCs. It obtained promising results with a 76% survival rate at 3 years [92].

As in the case of colorectal cancer, it would also be theoretically interesting to investigate the combination of cetuximab with other new targets (tyrosine kinase

inhibitors, inhibitors of VEGF, STAT3, AKT inhibitors, etc.) and to identify the predictive factors.

Cetuximab in nonsmall cell lung cancer

Overexpression of EGFR in NSCLC is found very often and this is associated with a poorer prognosis [7].

Second-line treatment in advanced nonsmall cell lung cancer

In a phase II study [93] with docetaxel and cetuximab, a 28% response rate and a 66% stabilization rate were seen in patients with NSCLC (EGFR-positive), who had progressed to first-line treatment with cisplatin. In another phase II study, patients (any EGFR) refractory to cisplatin were given cetuximab monotherapy [94]. The response rate was 4.5%; control of disease, 30%; median time to progression, 2.3 months; median survival, 8.9 months and 1-year survival was 43%.

First-line treatment in advanced nonsmall cell lung cancer

We have several studies in this setting. A phase I/ II study [95] that included 31 patients (EGFR +), who were treated with paclitaxel–carboplatin–cetuximab, obtained 26% response and a median survival of 11 months. Another phase II [96] study that included 35 patients (EGFR +) explored the combination carboplatin–gemcitabine–cetuximab therapy, achieving a 29% response rate, a 60% stabilization rate and a median survival of 10 months.

A randomized phase II [97] study included 86 EGFR + patients who received cisplatin–vinorelbine–cetuximab vs. cisplatin–vinorelbine. The cetuximab arm obtained a higher response rate (35 vs. 28%), a better control rate (84 vs. 67%) and a tendency towards longer survival (median: 8.3 vs. 7 months).

Other randomized phase II trials [98] included 131 patients who were treated with cisplatin–gemcitabine–cetuximab vs. cisplatin–gemcitabine alone. Statistically no significant trends towards higher response rates (27 vs. 18%), better PFS (median PFS: 5 vs. 4.2 months; *P*: NS) and improved OS (median OS: 11.99 vs. 9.26 months, *P*: NS) were observed in the cetuximab arm.

Another randomized phase II study, the SWOG 0432 study, included 242 patients (any EGFR) and randomized them to receive four cycles of paclitaxel–carboplatin concomitant with cetuximab and then cetuximab maintenance vs. four cycles of paclitaxel–carboplatin with cetuximab being given sequentially. The results were reported at ASCO-07 [99]. No statistically significant differences were found between the concomitant and the sequential arms in terms of response rate (34 vs. 31%), stable disease rate (34 vs. 39%), median PFS (4 months in both arms) and OS (11 vs. 10 months).

A clear need for phase III studies exists, comparing chemotherapy with chemotherapy in combination with cetuximab in this setting. The results of a phase III trial that compared taxane/carboplatin vs. taxane/carboplatin in combination with cetuximab have been recently reported [100]. This trial included 676 patients and did not find statistically significant differences between the two arms in terms of its primary endpoint, PFS, by Independent Radiologic Review Committee evaluation (median PFS by IRRC: cetuximab + taxane/carboplatin, 4.4 months vs. taxane/carboplatin, 4.24 months; HR = 0.902; 95% CI 0.761–1.069 and $P = 0.2358$). When considering PFS by investigator assessment (secondary endpoint), a statistically significant improvement in favour of the cetuximab arm was, nevertheless, observed (median PFS by investigator assessment: 4.3 vs. 3.78 months; HR 0.76; 95% CI 0.649–0.903 and $P = 0.0015$). Another important phase III trial is the FLEX study. It recruited patients until 2006: 1125 NSCLC EGFR + patients, who received cisplatin–vinorelbine–cetuximab vs. cisplatin–vinorelbine, its main endpoint being OS.The intermediate analysis of toxicity was reported at ASCO-06 [101] and definitive results are still pending.

Cetuximab in combination with chemoradiotherapy in nonsmall cell lung cancer

A phase II study has explored cetuximab combined with chemoradiotherapy (carboplatin–paclitaxel) in 93 patients with stage IIIA/B NSCLCs. Its preliminary results were communicated in 2007 [102]: the toxicity was moderate, the response rate was 62% and 1-year OS was 68%.

Cetuximab in other tumours

Preclinical data suggest the possible use of cetuximab in other tumours. Table 6 summarizes the results of phase II cetuximab studies in gastric [9,103,104], oesophageal [105,106], pancreatic [107] and ovarian cancers [110].

A phase III trial is now being designed to compare chemotherapy vs. chemotherapy combined with cetuximab in advanced gastric adenocarcinoma.

Concerning advanced pancreatic adenocarcinoma, a phase III trial (SWOG-S0205) randomized 735 patients to receive gemcitabine vs. gemcitabine combined with cetuximab. Its results have been recently reported [111]. No statistically significant differences in terms of survival (median: 5.9 vs. 6.4 months; HR 1.09 and $P = 0.14$), PFS (median: 3 vs. 3.5 months, HR 1.11, $P = 0.058$) or response (14 vs. 12%) were seen between the two arms of the study. Moreover, another randomized phase II study (also reported in ASCO-07 [112]) failed to

Table 6 Phase II and III studies with cetuximab in gastric, oesophageal, pancreatic and ovarian cancers

Gastric adenocarcinoma					
Scheme	Population	N	PR/CR	TPT	Sv
P. II FOLFIRI-Cetuxi [103]	Advanced first-line, EGFR-positive	38	44%	8 m	16 m
P. II FUFOX–Cetuxi [9]	Advanced first-line, any EGFR	53	64%		
P. II Iri–Cetuxi [104]	Advanced second-to-fourth-line any EGFR	13	38%	2.5 m	3.5 m
Esophageal carcinoma					
Scheme	Population	*N*	pCR	TPT	Sv
P. II Cis–Iri–Cetuxi/RT [105]	Locally advanced any EGFR	17	13%		
P. II Pac-Carb-Cetu/RT [106]	Locally advanced any EGFR	47	15%		
Pancreatic adenocarcinoma					
Scheme	Population	*N*	PR/CR	TPT	Sv
P. II Cetuxi–Gem [107]	Locally advanced/metastatic EGFR-positive	42	12%	3.8 m	7.1 m
P. II Cetuxi–Gem–Ox [108]	Metastatic any EGFR	64	35%	5 m	
P. II Cetuxi–Gem/RT [109]	Locally advanced any EGFR	24	40%		
P. III Cetuxi–Gem vs. Gem [111]	Locally advanced/metastatic any EGFR	735	12 vs. 14%	3.5 vs. 3 m P=NS	5.9 vs. 6.4 m P=0.14
Rand. P. II Cetuxi–Gem–Cis vs. Gem–Cis [112]	Locally advanced/metastatic any EGFR	74	16 vs. 8%	5 vs. 5 m P=NS	
Ovarian carcinoma					
Scheme	Population	*N*	cCR		
P. II Cetuxi-Pac-Carb [110]	Stage III-IV EGFR-positive	27	63%		

Carb, carboplatin; Cetuxi, cetuximab; Cis, cisplatin; CR, complete response; FOLFIRI, leucovorin–FU–irinotecan; FUFOX, FU–leucovorin–oxaliplatin; Gem, gemcitabine; Iri, irinotecan; m, months; Ox, oxaliplatin; Pac, paclitaxel; PR, partial response; pCR, pathological complete response; Rand, randomized; RT, radiotherapy; Sv, survival; TPT, time to tumour progression.

show any significant improvement by adding cetuximab to a gemcitabine/cisplatin combination in advanced pancreatic cancer. This study included 74 patients; although a nonstatistically significant trend towards a higher response rate (16 vs. 8%) and disease control (75 vs. 54%) was seen in the cetuximab arm, the time to tumour progression (5 months) was similar in both arms. These disappointing results suggest the low value of cetuximab in advanced pancreatic cancer. Nevertheless, a subgroup analysis looking for predictive factors that can identify the patients who could benefit more by the addition of cetuximab is pending in both trials.

It would also be interesting to clinically develop the use of cetuximab in malignant gliomas. Between 40 and 50% of glioblastoma multiforme (GBM) tumours show HER1/EGFR dysregulation, and almost half of them coexpress the constitutively active mutant receptor subtype EGFRvIII, which might contribute to the aggressive and refractory course of GBM [14,15]. Promising preclinical data [113] and cases of promising results in patients treated with cetuximab [114] are available. Preclinical data suggest that the combination of radiotherapy, temozolomide and cetuximab can lead to additive cytotoxic effects in glioma cell lines [115]: this combination is currently being explored in an ongoing phase I/II trial [116].

Summary

Nowadays, the clinical development of cetuximab is being very actively investigated, mainly in advanced colorectal cancer. We have the results from a phase III trial suggesting a significant improvement in OS when cetuximab is used as third-line treatment in patients refractory to irinotecan and oxaliplatin (NCIC CTG CO-17 [36]). In this setting, a randomized phase II trial suggests that there are better results with cetuximab in combination with irinotecan than with cetuximab alone (BOND [6]). We also have phase III trials that have shown an improvement in the response rate and in PFS when cetuximab is added to irinotecan as second-line treatment, in patients refractory to oxaliplatin (EPIC [54]) and when cetuximab is added to FOLFIRI as first-line treatment (CRYSTAL [68]). In these two trials, nevertheless, a significant improvement in OS has not been found, possibly owing to the short follow-up or to crossover treatment with cetuximab on progression. Concerning the combination of cetuximab with oxaliplatin, we have only the results from randomized phase II trials that suggest higher response rates with the addition of cetuximab as first-line treatment (SAKK [65], OPUS [67]) and an underpowered but negative randomized phase II trial in second line (EXPLORE [37]; we have no results from the phase III trials yet.

Considering all these results, we can conclude that, nowadays, cetuximab has an important role in the treatment of advanced colorectal cancer. Some points, nevertheless, remain unclear and should be further investigated.

- It is not clear if cetuximab should be used in the first, second or third line.
- It would be interesting to have more data coming up from phase III trials of cetuximab combined with oxaliplatin-based regimens.
- The improvement in response and surgical rescue rates, observed in randomized trials, make the combination of cetuximab and irinotecan or oxaliplatin a very attractive option as first-line treatment in patients with only liver metastasis. We, nevertheless, do not have data from phase III trials that is selectively focussed on this group of patients.
- It is not clear how cetuximab can be combined with other drugs against new targets, particularly, bevacizumab. The ongoing CALGB/SWOG 80405 phase III trial can be very important in this setting.
- We need to identify predictive factors. Although the number of EGFR gene copies (FISH), KRAS mutations and perhaps PTEN expression (IHC), HER2 gene copy number (FISH) or epiregulin and amphiregulin levels in the tumour might be predictive factors for treatment efficacy with cetuximab, data are still preliminary and need to be confirmed with more properly designed studies. This is needed for being able to select, in routine clinical practice, the patients who should or should not be treated with cetuximab.

The role of cetuximab as adjuvant treatment in colon cancer and as preoperative treatment in rectal cancer is being explored in ongoing randomized trials.

Clinical development of cetuximab has been also important in squamous-cell head and neck cancer. A phase III trial has shown a significant improvement in OS when cetuximab is added to platin–5-FU in recurrent or metastatic disease (EXTREME [87]). These results suggest that cetuximab has an important role in this setting although its optimal timing has not been defined clearly yet. Concerning locally advanced disease, a phase III trial showed an improvement in OS and in laryngeal preservation without increased toxicity when cetuximab was added to radiotherapy [89–91], making this combination an interesting treatment in these settings. We, nevertheless, do not have data from any phase III trial comparing cetuximab–radiotherapy vs. cisplatin–radiotherapy, which is the standard treatment in these patients. It would also be interesting to explore the combination of cetuximab with cisplatin–radiotherapy or with induction chemotherapy in this setting.

Concerning advanced NSCLCs, we have negative results from a phase III trial [100]. The results of another phase III trial that has already finished patient recruitment (FLEX) are awaited, to establish the role of cetuximab in these patients.

Furthermore, interesting studies in other tumours (Table 6) are found. We have negative results from a phase III trial [111] and from a randomized phase II trial [112] in advanced pancreatic cancer. Although subgroup analysis is pending, these results suggest a low value for cetuximab in these patients. Concerning oesophageal, gastric, gynaecological tumours and malignant gliomas, some phase II trials have shown promising results, and we need phase III trials to establish the role of cetuximab.

References

1 Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. *Oncogene* 2000; **19**:5548–5557.

2 Harari PM, Huang SM. Searching for reliable epidermal growth factor receptor response predictors. *Clin Cancer Res* 2004; **10**:691–700.

3 Chung CH, Ely K, McGavran L, Varella-Garcia M, Parker J, Parker N, *et al*. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol* 2006; **24**:4170–4176.

4 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. El 63.

5 Hitt R, Ciruelos E, Amador ML, Benito A, Sanchez JJ, Ballestin C, *et al*. Prognostic value of the epidermal growth factor receptor (EGRF) and p53 in advanced head and neck squamous cell carcinoma patients treated with induction chemotherapy. *Eur J Cancer* 2005; **41**:453–460.

6 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al*. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337–345.

7 Brabender J, Danenberg KD, Metzger R, Schneider PM, Park J, Salonga D, *et al*. Epidermal growth factor receptor and HER2-NEU mRNA expression in non-small cell lung cancer is correlated with survival. *Clin Cancer Res* 2001; **7**:1850–1855.

8 Dragovich T, McCoy S, Fenoglio-Preiser CM, Wang J, Benedetti JK, Baker AF, *et al*. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. *J Clin Oncol* 2006; **24**:4922–4927.

9 Lordick F, Lorenzen S, Hegewisch-Becker S, Folprecht G, Wöll E, Decker T, *et al.* Cetuximab plus weekly oxaliplatin/5FU/FA (FUFOX) in 1st line metastatic gastric cancer. Final results from a multicenter phase II study of the AIO upper GI study group. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4526.

10 Burtness B. HER signaling in pancreatic cancer. *Expert Opin Biol Ther* 2007; **7**:823–829.

11 Giltnane JM, Rydén L, Cregger M, Bendahl PO, Jirström K, Rimm DL. Quantitative measurement of epidermal growth factor receptor is a negative predictive factor for tamoxifen response in hormone receptor positive premenopausal breast cancer. *J Clin Oncol* 2007; **25**: 3007–3014.

12 Rocha-Lima CM, Soares HP, Raez LE, Singal R. EGFR targeting of solid tumors. *Cancer Control* 2007; **14**:295–304.

13 Cohen D, Lane B, Jin T, Magi-Galluzzi C, Finke J, Rini BI, *et al*. The prognostic significance of epidermal growth factor receptor expression in clear-cell renal cell carcinoma: a call for standardized methods for immunohistochemical evaluation. *Clin Genitourin Cancer* 2007; **5**: 264–270.

14 Raizer JJ. HER1/EGFR tyrosine kinase inhibitors for the treatment of glioblastoma multiforme. *J Neurooncol* 2005; **74**:77–86.

15 Pelloski CE, Ballman KV, Furth AF, Zhang L, Lin E, Sulman EP, *et al*. Epidermal growth factor receptor variant III status defines clinically distinct subtypes of glioblastoma. *J Clin Oncol* 2007; **25**:2288–2294.

16 Edwards J, Traynor P, Munro AF, Pirret CF, Dunne B, Bartlett JM. The role of HER1–HER4 and EGFRvIII in hormone-refractory prostate cancer. *Clin Cancer Res* 2006; **12**:123–130.

17 Bellone S, Frera G, Landolfi G, Romani C, Bandiera E, Tognon G, *et al.* Overexpression of epidermal growth factor type-1 receptor (EGF-R1) in cervical cancer: implications for cetuximab-mediated therapy in recurrent/metastatic disease. *Gynecol Oncol* 2007; **106**:513–520.

18 Arteaga CL. The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. *J Clin Oncol* 2001; **19**:32s–40s.

19 Baselga J. Targeting the epidermal growth factor receptor: a clinical reality. *J Clin Oncol* 2001; **19**:41s–44s.

20 Nyati MK, Morgan MA, Feng FV, Lawrence TS. Integration of EGFR inhibitors with radiochemotherapy. *Nat Rev Cancer* 2006; **6**: 876–885.

21 Waksal HW. Role of an anti-epidermal growth factor receptor in treating cancer. *Cancer Metastasis Rev* 1999; **18**:427–436.

22 Bier H, Hoffmann T, Haas I, van Lierop A. Anti (epidermal growth factor) receptor monoclonal antibodies for the induction of antibody-dependent cell-mediated cytotoxicity against squamous cell carcinoma lines of the head and neck. *Cancer Immunol Immunother* 1998; **46**:167–173.

23 Wild R, Kan D, Inigo I. Antitumor activity of cetuximab in human carcinoma xenografts: potentiation in combination with cisplatin and comparisons with gefitinib monotherapy [abstract]. *Clin Cancer Res* 2003; **9** (**Suppl**):127.

24 Milas L, Mason K, Hunter N, Petersen S, Yamakawa M, Ang K, *et al. In vivo* enhancement of tumor radio response by C225 antiepidermal growth factor receptor antibody. *Clin Cancer Res* 2000; **6**:701–708.

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

26 Tejpar S, Peeters M, Humblet Y, Gelderblom H, Vermorken J, Viret F, *et al.* Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. *J Clin Oncol, 2007 ASCO Ann Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4037.

27 Siena S, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aranda Aguilar E, *et al.* MABEL: a large multinational study of cetuximab plus irinotecan in irinotecan-resistant metastatic colorectal cancer: Update on infusion related reactions (IRR). *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 353.

28 Tabernero J, Cervantes A, Martinelli E, Vega-Villegas E, Rojo F, Pérez-Fidalgo A, *et al.* Optimal dose of cetuximab (C) given every 2 weeks (q2w): A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC). *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3085.

29 Pfeiffer P, Bjerregaard JK, Qvortrup C. Biweekly cetuximab (Cet) and irinotecan (Iri) as third-line therapy in patients with advanced colorectal cancer (ACRC). *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 305.

30 Prewett MC, Hooper AT, Bassi R, Ellis LM, Waksal HW, Hicklin DJ. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res* 2002; **8**:994–1003.

31 Saltz L, Rubin M, Hochster H, Tchekmeydian NS, Waksal H, Needle M, *et al*. Cetuximab plus irinotecan is active in CPT-11 refractory colorectal cancer that expresses epidermal growth factor receptor [abstract]. *Proc Am Soc Clin Oncol* 2001; **20**:7.

32 Saltz LB, Meropol NJ, Loehrer PJ, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with colorectal cancer that express the epidermal growth factor receptor. *J Clin Oncol* 2004; **22**:1201–1218.

33 Lenz HJ, Mayer RJ, Mirtsching B, Cohn AL, Pippas A, Windt P, *et al.* Consistent response to treatment with cetuximab monotherapy in patients with metastatic colorectal cancer. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 3536.

34 Wilke H, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aranda Aguilar E, *et al.* MABEL: a large multinational study of cetuximab plus irinotecan in irinotecan resistant metastatic colorectal cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3549.

35 Mathias C, Buzaid A, Perazzo F, Simon SD, Fein L, Hidalgo J, *et al.* Phase II study of cetuximab with irinotecan in patients with epidermal growth factor (EGFR)-expressing metastatic colorectal cancer (mCRC): LABEL preliminary data. *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 293.

36 Jonker DJ, Karapetis CS, Moore M, Zalcberg JR, Tu D, Berry S, *et al.* Randomized Phase III trial of cetuximab monotherapy plus best supportive care (BSC) vs. BSC alone in patients with pretreated metastatic epidermal growth factor receptor (EGFR)-positive colorectal carcinoma: a trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG). AACR 2007.

37 Jennis A, Polikoff J, Mitchell E, Badarinath S, Graham C, Chen TT, *et al.* Erbitux (cetuximab) plus FOLFOX for colorectal cancer (EXPLORE): preliminary efficacy analysis of a randomized phase III trial. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 3574.

38 Lenz HJ, Mayer RJ, Gold PJ, Mirtsching B, Stella PJ, Cohn AL, *et al.* Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin. *J Clin Oncol, 2004 ASCO Annu Meet Proc* (Post-Meeting Edition). Vol 22, No 14S (July 15 Suppl), 2004: 3510.

39 Chung KY, Shia J, Kemeny NE, Shah M, Schwartz GK, Tse A, *et al.* Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 2005; **23**:1803–1810.

40 Atkins D, Reiffen KA, Tegtmeier CL, Winther H, Bonato MS, Störkel S. Immunohistochemical detection of EGFR in paraffin-embedded tumor tissues: variation in staining intensity due to choice of fixative and storage time of tissue sections. *J Histochem Cytochem* 2004; **52**:893–901.

41 Dei Tos AP, Ellis I. Assessing epidermal growth factor receptor expression in tumors: what is the value of current test methods? *Eur J Cancer* 2005; **41**:1383–1392.

42 Younes M. Is immunohistochemistry for epidermal growth factor receptor expression a poor predictor of response to epidermal growth factor receptor-targeted therapy? *J Clin Oncol* 2005; **23**:923. Reply: Saltz L, 923–924.

43 Goldstein NS, Armin M. Epidermal growth factor receptor immunohistochemical reactivity in patients with American Joint Committee on Cancer Stage IV colon adenocarcinoma: implications for a standardized scoring system. *Cancer* 2001; **92**:1331–1346.

44 Scartozzi M, Bearzi I, Berardi R, Mandolesi A, Fabris G, Cascinu S. Epidermal growth factor receptor (EGFR) status in primary colorectal tumors does not correlate with EGFR expression in related metastatic sites: implications for treatment with EGFR-targeted monoclonal antibodies. *J Clin Oncol* 2004; **22**:4772–4778.

45 Defize LH, Boonstra J, Meisenhelder J, Kruijer W, Tertoolen LG, Tilly BC, *et al*. Signal transduction by epidermal growth factor occurs through the subclass of high affinity receptors. *J Cell Biol* 1989; **109**:2495–2507.

46 Bellot F, Moolenaar W, Kris R, Mirakhur B, Verlaan I, Ullrich A, *et al*. High affinity epidermal growth factor binding is specifically reduced by a monoclonal antibody, and appears necessary for early responses. *J Cell Biol* 1990; **110**:491–502.

47 Moroni M, Veronese S, Benvenuti S, Marrapese G, Sartore-Bianchi A, Di Nicolantonio F, *et al*. Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to anti-EGFR treatment in colorectal cancer: a cohort study. *Lancet Oncol* 2005; **6**:279–286.

48 Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, *et al*. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006; **66**:3992–3995.

49 E. Romagnani, V. Martin, M. Ghisletta, A. Camponovo, L. L. Etienne, F. Caval, *et al.* EGFR gene status, K-RAS mutation and PTEN expression predict cetuximab response in metastatic colorectal cancer (mCRC). *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 427.

50 Personeni N, De Schutter J, De Hertogh G, Debiec-Rychter M, Geboes K, van Cutsem E, *et al.* Response prediction to cetuximab-based therapy: The role of EGFR copy number by fluorescence *in situ* hybridization and downstream effectors gene mutations. *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 400.

51 Finocchiaro G, Cappuzzo F, Jänne PA, Bencardino K, Carnaghi C, Franklin WA, *et al.* EGFR, HER2 and KRAS as predictive factors for cetuximab sensitivity in colorectal cancer. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4021.

52 Khambata-Ford S, Garrett CR, Meropol NJ, Basik M, Harbison CT, Wu S, *et al*. Expression of epiregulin and amphiregulin and K-RAS mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 2007; **25**:3230–3237.

53 De Roock W, de Schutter J, de Hertogh G, Janssens M, Biesmans B, Personeni N, *et al.* KRAS mutations preclude tumor shrinkage of colorectal cancers treated with cetuximab. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4132.

54 Sobrero AF, Fehrenbacher L, Rivera F, Steinhauer EU, Prausova J, Borg C, *et al.* Randomized phase III trial of cetuximab plus irinotecan vs. irinotecan alone for metastatic colorectal cancer in 1298 patients who have failed prior oxaliplatin-based therapy: The EPIC trial. AACR 2007.

55 Eng C, Maurel J, Scheithauer W, Wong L, Lutz M, Middleton G, *et al.* Impact on quality of life of adding cetuximab to irinotecan in patients who have failed prior oxaliplatin-based therapy: the EPIC trial. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4003.

56 Prewett M, Tonra JR, Bassi R. Enhanced anti-tumor activity with cetuximab (ERBITUX®) in combination with oxaliplatin in human colon carcinoma xenografts. *Proceedings of AACR-05*. Abstract 5048.

57 Souglakos J, Androulakis N, Tzardi M, Kalykaki A, Vardakis N, Sfakiotaki G, *et al.* Cetuximab plus capecitabine (CAP) and oxaliplatin (LOHP) (CAPOX) as salvage treatment for patients with metastatic colorectal cancer (CRC) relapsing after oxaliplatin-based chemotherapy. *Proceedings of 2006 Gastrointestinal Cancers Symposium*. Abstract: 235.

58 Rosenberg AH, Loehrer PJ, Needle MN, Waksal H, Hollywood E, Ramos L, *et al*. Erbitux (IMC-C225) plus weekly irinotecan (CPT-11), fluorouracil (5FU) and leucovorin (LV) in colorectal cancer (CRC) that expresses the epidermal growth factor receptor (EGFR) [abstract]. *Proc Am Soc Clin Oncol* 2002; **21**.

59 Peeters M, Raoul JL, van Laethem JL. Cetuximab in combination with irinotecan/5-fluorouracil/(5-FU)/folinic acid (FA) (FOLFIRI) in the first-line treatment of metastatic colorectal cancer. *Eur J Cancer* 2005; **3/2** (**Suppl**):188. Proc ECCO-05 Abst: 664.

60 Folprecht G, Lutz MP, Schöffski P, Seufferlein T, Nolting A, Pollert P, *et al*. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006; **17**: 450–456.

61 Díaz Rubio E, Tabernero J, van Cutsem E, Cervantes A, André T, Humblet Y, *et al.* Cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with epidermal growth factor receptor (EGFR) expressing metastatic colorectal cancer: An international phase II study. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 3535.

62 Dittrich C, Hoeler T, Lordick F. A phase I/II study of cetuximab in combination with 5-fluorouracil (5FU)/folinic acid (FA) plus weekly oxaliplatin in the first line treatment of patients with metastatic colorectal cancer expressing epidermal growth factor receptor. Preliminary results. *World Congress on GI Cancer* 2006; Abstract. O-019.

63 Cartwright TH, Kuefler P, Cohn A, Hyman W, Yoffe M, Boehm KA, *et al.* Results of a phase II trial of cetuximab + XELIRI as first-line therapy of patients with advanced and/or metastatic colorectal cancer. *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 292.

64 Venook A, Niedzwiecki D, Hollis D, Sutherland S, Goldberg R, Alberts S, *et al.* Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3509.

65 Borner M, Mingrone W, Koeberle D, von Moos R, Rauch D, Saletti P, *et al.* The impact of cetuximab on the capecitabine plus oxaliplatin (XELOX) combination in first-line treatment of metastatic colorectal cancer (MCC): A randomized phase II trial of the Swiss Group for Clinical Cancer Research (SAKK). *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3551.

66 Heinemann V, Fischer von Weikersthal L, Moosmann N, Vehling-Kaiser U, Stauch M, Oruzio D, *et al.* Cetuximab + capecitabine + irinotecan (CCI) vs. cetuximab + capecitabine + oxaliplatin (CCO) as first line therapy for patients with metastatic colorectal cancer (CRC): Preliminary results of a randomized phase II trial of the AIO CRC Study Group. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3550.

67 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, Zampino M, *et al.* Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) vs. FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4035.

68 Van Cutsem E, Nowacki M, Lang I, Cascinu S, Shchepotin I, Maurel J, *et al.* Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4000.

69 Sastre J, Aranda E, Grávalos C, Massutí B, Veja-Villegas ME, Soler G, *et al.* Single-agent cetuximab as first-line treatment for elderly patients with advanced colorectal cancer. Preliminary results of a TTD phase II study. *Proc ESMO-06*. Abstract: 324 O.

70 Pessino A, Artale S, Guglielmi A, Sciallero S, Fornarini G, Andreotti IC, *et al.* First-line single-agent cetuximab in patients with advanced colorectal cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3553.

71 Matar P, Rojo F, Cassia R, Moreno-Bueno G, Di Cosimo S, Tabernero J, *et al.* Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting. *Clin Cancer Res* 2004; **10**:6487–6501.

72 Baselga J, Schöffski P, Rojo F, Dumez H, Ramos FJ, Macarulla T, *et al.* A phase I pharmacokinetic (PK) and molecular pharmacodynamic (PD) study of the combination of two anti-EGFR therapies, the monoclonal antibody (MAb) cetuximab (C) and the tyrosine kinase inhibitor (TKI) gefitinib (G), in patients (pts) with advanced colorectal (CRC), head and neck (HNC) and non-small cell lung cancer (NSCLC). *Proc ASCO-06*. Abstract: 3006.

73 Morelli MP, Cascone T, Troiani T, Tuccillo C, Bianco R, Normanno N, *et al.* Anti-tumor activity of the combination of cetuximab, an anti-EGFR blocking monoclonal antibody, and ZD6474, an inhibitor of VEGFR and EGFR tyrosine kinases. *J Cell Physiol* 2006; **208**:344–353.

74 Ciardiello F, Troiani T, Bianco R, Orditura M, Morgillo F, Martinelli E, *et al.* Interaction between the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) pathways: a rational approach for multi-target anticancer therapy. *Ann Oncol* 2006; **17** (**Suppl_7**): vii109-vii114.

75 Tonra JR, Deevi DS, Corcoran E, Li H, Wang S, Carrick FE, *et al.* Synergistic antitumor effects of combined epidermal growth factor receptor and vascular endothelial growth factor receptor-2 targeted therapy. *Clin Cancer Res* 2006; **12** (**7 Pt 1**):2197–2207.

76 Saltz LB, Lenz H, Hochster H, Wadler S, Hoff P, Kemeny N, *et al.* Randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) vs. cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 3508.

77 Chung KY, Minsky B, Schrag D, O'Reilly E, D'Adamo D, Hollywood E, *et al.* Phase I trial of preoperative cetuximab with concurrent continuous infusion 5-fluorouracil and pelvic radiation in patients with local-regionally advanced rectal cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3560.

78 Machiels JP, Sempoux C, Scalliet P, Coche JC, Coster B, Cannon JL, *et al.* Phase I study of preoperative cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 3552.

79 Arnold D, Hipp M, Liersch T, Dellas K, Koelbl O, Hohenberger W, *et al.* Cetuximab, capecitabine, and oxaliplatin (Cet-CapOx) with concurrent radiotherapy (RT) in advanced rectal cancer (RC): Results of a phase I/II trial. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4042.

80 Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockage with C-225 modulates proliferation, apoptosis and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res* 1999; **59**:1935–1940.

81 Bonner JA, Raisch KP, Trummell HQ, Robert F, Meredith RF, Spencer SA, *et al.* Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol* 2000; **18**:47S–53S.

82 Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortés-Funes H, Hitt R, *et al.* Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005; **23**:5568–5577.

83 Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, *et al.* Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005; **23**:5578–5587.

84 Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, *et al.* Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007; **25**:2171–2177.

85 Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. Phase III randomized trial of cisplatin plus placebo vs. cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005; **23**:8646–8654.

86 Bourhis J, Rivera F, Mesia R, Awada A, Geoffrois L, Borel C, *et al*. Phase I/II Study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006; **24(18)**:2866–2872.

87 Vermorken J, Mesia R, Vega V, Remenar E, Hitt R, Kawecki A, *et al.* Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy – results of a randomized phase III (EXTREME) study. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 6091.

88 Forastiere AA, Burtness BA. Epidermal growth factor receptor inhibition in head and neck cancer: more insights, but more questions. *J Clin Oncol* 2007; **25**:2152–2155.

89 Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Eng J Med* 2006; **354**:567–578.

90 Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS, *et al*. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. *J Clin Oncol* 2007; **25**:2191–2197.

91 Bonner JA, Harari PM, Giralt J, Baselga J, Shin D, Cohen R, *et al.* Improved preservation of larynx with the addition of cetuximab to radiation for cancers of the larynx and hypopharynx. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 5533.

92 Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, Aliff TB, *et al*. Concurrent cetuximab, cisplatin and concomitant boost radiation therapy for locoregionally advanced squamous cell head and neck cancer: a pilot phase II study of a new combined modality paradigm. *J Clin Oncol* 2006; **24**:1072–1078.

93 Kim ES, Mauer AM, Tran HY, Liu D, Gladish G, Dicke K, *et al*. A phase II study of cetuximab, an epidermal growth factor receptor (EGFR) blocking antibody, in combination with docetaxel in chemotherapy refractory/ resistant patients with advanced non-small cell lung cancer [abstract]. *Proc Am Soc Clin Oncol* 2003; **22**:2581.

94 Hanna N, Lilenbaum R, Ansari R, Lynch T, Govindan R, Jänne PA, *et al*. Phase II trial of cetuximab in patients with previously treated non-small-cell lung cancer. *J Clin Oncol* 2006; **24**:5253–5258.

95 Thienelt CD, Bunn PA, Hanna N, Rosenberg A, Needle MN, Long ME, *et al*. Multicenter phase I/II study of cetuximab with paclitaxel and carboplatin in untreated patients with stage IV non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:8786–8793.

96 Robert F, Blumenschein G, Herbst RS, Fossella FV, Tseng J, Saleh MN, *et al*. Phase I/IIa study of cetuximab with gemcitabine plus carboplatin in patients with chemotherapy-naive advanced non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:9089–9096.

97 Rosell R, Daniel C, Ramlau R, Szczesna A, Constenla M, Mennecier B, *et al.* Randomized phase II study of cetuximab (Erbitux®) in combination with cisplatin/vinorelbine vs. cisplatin/vinorelbine alone in the first-line treatment of patients with EGFR-expressing advanced NSCLC (Study EMR 62202–011 'LUCAS'). *J Clin Oncol, 2004 ASCO Annu Meet Proc* (Post-Meeting Edition). Vol 22, No 14S (July 15 Suppl), 2004: 7012.

98 Butts A, Bodkin D, Middleman EL, Englund CW, Ellison D, Alam YZ, *et al.* Gemcitabine/platinum alone or in combination with cetuximab as first-line treatment for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 7539.

99 Herbst RS, Chansky K, Kelly K, Atkins JN, Davies AM, Dakhil SR, *et al.* A phase II randomized selection trial evaluating concurrent chemotherapy plus cetuximab or chemotherapy followed by cetuximab in patients with advanced non-small cell lung cancer (NSCLC): Final report of SWOG 0342. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 7545.

100 Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann R, *et al.* A randomized multicenter phase III study of cetuximab (Erbitux) in combination with taxane/carboplatin vs. taxane/carboplatin alone as first-line treatment for patients with advanced/metastatic non-small cell lung cancer (NSCLC). *12th World Conference on Lung Cancer*. Seoul; 2007. B3–03.

101 Von Pawel J, Park K, Pereira JR, Szczesna A, Yu C, Ganul VL, *et al.* Phase III study comparing cisplatin/vinorelbine plus Erbitux vs. cisplatin/ vinorelbine as first-line treatment for patients with epidermal growth factor (EGFR)-expressing advanced non-small cell lung cancer (NSCLC) (FLEX). *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 7109.

102 Blumenschein G, Moughan J, Curran W, Robert F, Fossella F, Werner-Wasik M, *et al.* A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (pts) with stage III A/B non-small cell lung cancer (NSCLC): an interim report of the RTOG 0324 trial. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 7531.

103 Pinto C, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, *et al*. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Ann Oncol* 2007; **18**: 510–517.

104 Stein A, Al-Batran SE, Arnold D, Peinert S, Siewczynski R, Schmoll HJ, *et al.* Cetuximab with irinotecan as salvage therapy in heavily pretreated patients with metastatic gastric cancer. *Proc ASCO-GI-2007.* Abstract: 47.

105 Enzinger PC, Yock T, Suh W, Fidias P, Mamon H, Choi N, *et al.* Phase II cisplatin, irinotecan, cetuximab and concurrent radiation therapy followed by surgery for locally advanced esophageal cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 4064.

106 Suntharalingam M, Dipetrillo T, Akerman P, Wanebo H, Daly B, Doyle LA, *et al.* Cetuximab, paclitaxel, carboplatin and radiation for esophageal and gastric cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 4029.

107 Xiong HQ, Rosenberg A, LoBuglio A, Schmidt W, Wolff RA, Deutsch J, *et al*. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. *J Clin Oncol* 2004; **2**:2610–2616.

108 Kullmann F, Hollerbach S, Dollinger M, Harder J, Fuchs M, Messmann H, *et al.* Cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in 1st line metastatic pancreatic cancer. first results from a multicenter phase II study. *Proceedings of 2007 Gastrointestinal Cancers Symposium*. Abstract: 128.

109 Krempien RC, Münter MW, Timke C, Huber PE, Friess H, Heeger S, *et al.* Phase II study evaluating trimodal therapy with cetuximab intensity modulated radiotherapy (IMRT) and gemcitabine for patients with locally advanced pancreatic cancer. *J Clin Oncol, 2006 ASCO Annu Meet Proc Part I*. Vol 24, No. 18S (June 20 Suppl), 2006: 4100.

110 Aghajanian C, Sabbatini P, Derosa F, Gerst S, Spriggs DR, Dupont J, *et al.* A phase II study of cetuximab/paclitaxel/carboplatin for the initial treatment of advanced stage ovarian, primary peritoneal, and fallopian tube cancer. *J Clin Oncol, 2005 ASCO Annu Meet Proc*. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005: 5047.

111 Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, *et al.* Phase III study of gemcitabine [G] plus cetuximab [C] vs. gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: LBA4509.

112 Cascinu S, Berardi R, Siena S, Labianca R, Falcone A, Aitini E, *et al.* The impact of cetuximab on the gemcitabine/cisplatin combination in first-line treatment of EGFR-positive advanced pancreatic cancer (APC): A randomized phase II trial of GISCAD. *J Clin Oncol, 2007 ASCO Annu Meet Proc Part I*. Vol 25, No. 18S (June 20 Suppl), 2007: 4544.

113 Eller JL, Longo SL, Kyle MM, Bassano D, Hicklin DJ, Canute GW. Anti-epidermal growth factor receptor monoclonal antibody cetuximab augments radiation effects in glioblastoma multiforme *in vitro* and *in vivo*. *Neurosurgery* 2005; **56**:155–162; discussion 162.

114 Belda-Iniesta C, Carpeno Jde C, Saenz EC, Gutierrez M, Perona R, Baron MG. Long term responses with cetuximab therapy in glioblastoma multiforme. *Cancer Biol Ther* 2006; **5**:912–914.

115 Combs SE, Schulz-Ertner D, Roth W, Herold-Mende C, Debus J, Weber KJ. In vitro responsiveness of glioma cell lines to multimodality treatment with radiotherapy, temozolomide, and epidermal growth factor receptor inhibition with cetuximab. *Int J Radiat Oncol Biol Phys* 2007; **68**:873–882.

116 Combs SE, Heeger S, Haselmann R, Edler L, Debus J, Schulz-Ertner D. Treatment of primary glioblastoma multiforme with cetuximab, radiotherapy and temozolomide (GERT) phase I/II trial: study protocol. *BMC Cancer* 2006; **6**:133.