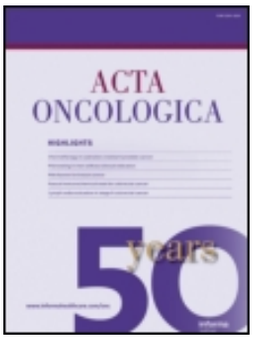

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REVIEW ARTICLE

Current situation of Panitumumab, Matuzumab, Nimotuzumab and Zalutumumab

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Abstract
EGFR overexpression usually correlates with a more advanced disease stage, a poorer prognosis and a worse chemotherapy response. EGFR expression increase has been observed in many tumours. For all the aforementioned reasons, EGFR inhibition can be considered an attractive approach in cancer treatment. One strategy has been receptor inhibition of extracellular domain using monoclonal antibodies. Cetuximab is the most developped one and there is plenty information on the literature about its current status. In this review we focus on other EGFR monoclonal antibodies under clinical development. The more developed one is Panitumumab. Its clinical development is taking place very quickly and it has mainly been studied in colorectal cancer showing pomising results. There are also other interesting drugs such as Matuzumab, Nimotuzumab and Zalutumumab.

EGFR ("Epidermal Growth Factor Receptor"), also known as erb B1 or HER1, is a receptor tyrosine kinase (RTK) belonging, along with erb B2 (or HER 2), erb B3 and erb B4, to the RTK family of EGFR [1].

EGFR is a transmembrane glycoprotein of 170 kDa, coded by the c-erbB1 proto-oncogene situated in the 7q22 chromosome and whose known ligands are: EGF, TGF alpha, amphiregulin, heparin-binding EGF, betacelulin, epiregulin, and NRG2-alpha.

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

EGFR expression increase has been observed in many tumours (Table I) [3–17]. This EGFR overexpression usually correlates with a more advanced stage of the disease, a poorer prognosis and a worst response to chemotherapy [18]. In preclinical models it was also found that the inhibition of these receptors had anti-tumour activity, and data available suggested synergy with chemotherapy as well as radiotherapy [19,20]. All this made the clinical development of drugs directed against EGFR very attractive. This development started in the 1990's and is very active nowadays.

Different possible strategies could try to inhibit EGFR signal transduction pathway (and through any RTK in general):

1. inhibition at ligand level.
2. receptor inhibition on extracellular domain using monoclonal antibodies.
3. receptor inhibition on intracytoplasmic domain using small molecule tyrosine kinase inhibitors.
4. use of antisense oligonucleotides to decrease EGFR expression.

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Table I. EGFR overexpression.

Tumour	EGFR Overexpression (%)
Squamous cell head and neck cancer [3–5]	80–100
Colorectal cancer [6]	70–90
Non-small 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

5. attempts to act at a lower level of EGFR initiated pathway within the intracellular signaling cascade.
6. toxines or radioisotopes can also be used directed towards tumour cells and binding them to monoclonal antibodies directed against EGFR.

Anti-EGFR monoclonal antibodies under clinical development are summarised in Tables II and III. Cetuximab is the most developed one and it has been mainly studied in colorectal, head and neck and lung cancer. There are also interesting studies in pancreatic, gastric, esophageal and ovarian tumours as well as in malignant gliomas. There is plenty information on the literature about its current status [21–25]. In this review we focus on other EGFR monoclonal antibodies under clinical development. The more developed one is Panitumumab and it has mainly been studied in colorectal cancer showing pomising results. There are also other interesting drugs such as Matuzumab, Nimotuzumab and Zalutumumab.

Monoclonal antibodies began its development in the 1970's when hybridoma technology began to be used. They have represented a major diagnostic and therapeutic advance in many diseases. The first monoclonal antibodies were exclusively *murine* and generated anti-murine antibodies when used in humans that significantly limited efficacy and security. Later on, human-mouse *chimeric* antibodies were developed (suffix: -ximab, for example: cetuximab) in them, the human constant region is combined with the mouse variable region. These antibodies have around 1/3 mouse origin, and although lesser than mouse ones, they are still potentially immunogenic. *Humanized* antibodies were also developed (suffix: -zumab; for example, trastuzumab, matuzumab) in these the mouse variable region part makes up for around 10% of the antibody which reduces immunogenicity but it does not eliminates it completely. Finally, by creating transgenic mouse strains, it was possible to develop *completely human* monoclonal antibodies (suffix: -mumab, for example: panitumumab, zalutumumab) and in them, immunogenic reaction is minimal or non-existent.

Panitumumab (ABX-EGF)

Panitumumab, previously known as ABX-EGF, is a totally human high affinity IgG2 monoclonal antibody against human EGFR. Being completely human, its immunogenicity is minimal or non-existent, therefore it avoids the problem of generating human murine antibodies, thus minimizing the risk of hypersensitivity reactions and compromising treatment efficacy in prolonged use. On the other side of the coin, is that being an IgG2 subtype, it may not act in principle on antibody dependent cell cytotoxicity (ADCC). Only IgG1 antibodies are capable of inducing ADCC and there are preclinical data suggesting that this could be an anti-tumoural mechanism of action [26]. Nevertheless, the importance of this is not clear from a clinical point of view.

Anti-tumoural activity is seen in xenografts in mouse models [27] in preclinical studies and is rapidly moving towards its clinical development in humans.

Several administration schedules have been studied. One interesting advantage seen in a pharmacokinetic study [28] is that Panitumumab can be administered either weekly (2.5 mg/kg/week), two-weekly (6 mg/kg/2 weeks), or every 3 weeks (9 mg/kg/3 weeks) which would be more convenient for the patient and would imply health resources savings. Other advantage is that loading doses are not required and inter-individual variability is low. Although its clinical development was done using 60-minute infusions, there are pharmacokinetic data suggesting that 30 minutes would be enough [29].

Table II. 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) NIMOTUZUMAB (h-R3)	ZALUTUMUMAB (HuMax^{TM}-EGFr)
IgG2 (No ADCC)			PANITUMUMAB (ABX-EGF)

ADCC: Antibody dependent cell cytotoxicity.

Table III. Anti- EGFR monoclonal antibodies: Clinical development.

Antibody	Tumour	Study phase
Cetuximab (C-225) (Erbitux)		
Chimeric IgG1	Colorectal - Advanced	III
	- Adjuvant colon	III
	- Rectal (Pre/post-op.)	III
	Head and neck - Advanced	III
	- Loc. advanced.(+RT)	III
	Non-small cell lung	III
	Esophagus	II
	Gastric	II
	Pancreas	III
Panitumumab (ABX-EGF) Completely human IgG2	Colorectal	III
	Non-small cell lung	II
	Head and neck	II
Matuzumab (EMD72000) Humanized IgG1	Ovarian	II
	Cervix	II
	Gastric	II
	Non-small cell lung	II
Nimotuzumab (h-R3) Humanized IgG1	Head and neck	III
	Malignant gliomas	III
Zalutumumab(HuMax^{TM}-EGFr)	Head-neck - Advanced	III
Completely human IgG1	- Loc. advanced (+RT)	I/II
IMC-11F8		I
RadioThera CIM		I

Regard toxicity, cutaneous toxicity is noteworthy, its incidence (but not intensity) increases with dose, appearing in 95 – 100% of patients with a dose of 2.5 mg/kg/ week [30]. The most common picture is an acneiform eruption usually of mild to moderate intensity (severe in around 10% of cases), appearing after the first or second administration, improving as the treatment progresses and disappearing when stopped. Hypersensitivity and infusion reactions are very rare (around 1%) and mild. Premedication is not required to prevent them. Moreover, although it is not yet known whether panitumumab can be safely given in patients with a previous severe reaction to cetuximab there are reported cases of a patients successfully treated with panitumumab after severe infusion reactions to cetuximab [31,32]. Other reported toxicities are usually mild (grade 3-4 in less than 3% of patients), asthenia, diarrhoea, conjunctivitis, emesis and hypomagnesemia (associated or not with hypocalcemia) [33–35].

Although there are some studies in other tumours, such as non-small cell lung cancer, [34,36] renal cancer [30], and head and neck squamous cell cancer, most Panitumumab's studies have been done in advanced colorectal cancer.

Panitumumab in chemotherapy refractory advanced colorectal cancer

The main clinical development of antiEGFR monoclonal antibodies in colorectal cancer has been done with cetuximab. This drug was approved within the EU for irinotecan-refractory patients with advanced colorectal cancer expressing EGFR in 2005 [25]. Panitumumab has been also studied in this setting with interesting results. A first Phase II [33] study including 148 patients refractory to 5-FU plus Irinotecan, Oxaliplatin or both, immunohistochemistry EGFR positive tumours with Panitumumab 2.5 mg/kg/week monotherapy reported a response rate of 9% (all were partial responses). Median duration of response was 4.2 months, disease control was 38%, progression-free survival was 3.5 months and median survival was 8.7 months. The study searched for Human anti-human antibodies (HAHAs) synthesis and it was not detected in any patient. No significant differences were shown in the level of EGFR expression by immunohistochemistry. Preliminary results have been recently reported on a Phase II [37] study that examined Panitumumab monotherapy activity in 118 patients immunohistochemistry weakly positive (1 – 10% of the cells) or negative (< 1% of the cells) EGFR with advanced colorectal cancer refractory to 5-FU, Oxaliplatin and Irinotecan. It was seen a response rate of 7%, with 29% stabilizations and a progression-free survival of 2 months (no differences were seen between weak positives and negatives). Moreover, these results seemed to be similar to those of EGFR positive patients.

There was carried out a Phase III study, whose results had been recently published [38] in which

463 refractory to 5-FU, Irinotecan, and Oxaliplatin, immunohistochemistry positive EGFR patients,were randomized to receive Panitumumab 6 mg/kg every 2 weeks vs. Best supportive care. The patients included in this latter arm could be treated with Panitumumab at the same doses after progression. Main endpoint was progression-free survival. A statistically significant increase was seen in the arm with Panitumumab (median PFS 7.3 weeks vs 8 weeks, HR: 0.54; 95 CI%: 0.44–0.66, $p < 0.0001$). In the subgroup analysis, this advantage is maintained independently of the level of EGFR overexpression by immunohistochemistry. The number of previous chemotherapy schedules, age, sex, PS, primary tumour localization and number of metastatic locations did not either influence. The Panitumumab arm obtained 10% partial responses and 28% stabilizations, which lasted for 3.9 months. At progression, from 232 patients (76%) randomised to receive only symptomatic treatment, 176 were treated with Panitumumab in a extension study [39] obtaining a response rate of 11% and 33% stabilizations. Survival was similar in both arms (HR: 1; 95% CI: 0.82–1.22; $p = 0.60$) but it could be due to the high percentage of crossover. There was seen a significantly better survival in patients treated with Panitumumab if they had a G-2-4 skin toxicity than if they had a lower toxicity grade (HR: 0.61; 95% CI: 0.40–0.91; $p = 0.02$). HAHAs potential generation was studied but they were not detected in any case. A subset analyses that inluded elderly and patients with poor performance status reported by Van Cutsem et al. [40] suggests that the efficacy and tolerability of Panitumumab was similar regardless of age and ECOG status.

Due to these results, in 2006, the FDA approved the indication of Panitumumab for the treatment of advanced colorectal cancer after failure of conventional chemotherapy [41]. The decision to approve this indication is still pending in Europe.

Panitumumab as first and second line in advanced colorectal cancer

There is a Phase II [42] study of 43 patients with advanced colorectal cancer that received first line treatment with Panitumumab + Irinotecan-FU (IFL or FOLFIRI). It had a good toxicity profile with a 39% response rate of 39% and 78% disease control.

The activity of Panitumumab in second line treatment is being investigated in different studies. Thus, the TTD-06-04 explores the efficacy of Irinotecan + Panitumumab in patients who are refractory to first line oxaliplatin-based chemotherapy. Schwartberg et al. [43] reported the preliminary results of a phase I trial that explored the combination of Panitumumab, FOLFOX or FOLFIRI and AMG 706 (an oral multikinasa inhibitor targeting VEGF, PDGF and Kit receptors) in 45 patients with advanced colorectal cancer refractory to first line oxaliplatin or irinotecan based chemotherapy. This combination was well tolerated with little effect on AMG 706 pharmacokinetics and an interesting 50% response rate was observed.

Finally, three Phase III studies attempt to establish the role of Panitumumab in first and second line treatment of advanced colorectal cancer [44].

1. The PACCE Phase III trial was carried out in the US and randomized 1054 patients to receive FOLFOX or FOLIRI-Bevacizumab with or without Panitumumab (6 mg/kg every 2 weeks). Its main endpoint was progression-free survival. A planned interim analysis of safety and efficacy focusing on the cohort of patients treated with FOLFOX-Bevacizumab +/− Panitumumab (812 patients) has been recently reported [45]. This analysis demonstrated a reduced progression free survival in the panitumumab arm (median PFS: 8.8 vs 10.5, HR: 1.44, 95% CI: 1.13–1.85, $p = 0.004$). Additional toxicity and lower dose intensity was observed in the panitumumab arm and response rate was similar (39% vs 41%). Further data collection and analyses are ongoing, including subset analyses based on biomarkers. Due to these disappointing results, the continuation of the other two currently ongoing panitumumab phase III trials was evaluated by their independent data monitoring committees and they recommended continuation of both trials without protocol modification.

2. The first trial is an ongoing multinational Phase III study sponsored by AMGEN (Study: 20050203). It has randomised nearly 900 previously untreated advanced colorectal cancer patients to receive FOLFOX with or without Panitumumab (6 mg/kg every 2 weeks). The main endpoint is progression-free survival.

3. The second trial is the Amgen Study 20050181. It is comparing FOLFIRI alone vs FOLFIRI + Panitumumab in patients with advanced colorectal cancer in second line.

The disappointing results of the PACCE trial suggest that an antagonism between Panitumumab and the FOLFOX-Bevacizumab combination could exist in advanced colorectal cancer. These antagonism could be against FOLFOX, against Bevacizumab or against both and the results of the aforementioned two ongoing Panitumumab phase III trials perhaps could help us to clarify this question. We should improve our understanding of EGFR biology in human cancer [46] in order to know how better combine EGFR inhibitors with other cancer therapies and how select those patients

(or tumors) most likely to get benefit from an EGFR inhibition strategy.

Predictive factors of efficacy

Immunohistochemical determination of EGFR in the tumour. The results of the previously cited Phase II studies [33,37], suggest that Panitumumab monotherapy activity in advanced colorectal 5-FU, Oxaliplatin and Irinotecan refractory cancer patients seems to be similar in immunohistochemistry positive EGFR (>10% of cells), weakly positive (1–10% of the cells) and negative (<1% of the cells) tumours. A similar conclusion was drawn from two clinical studies conducted with Cetuximab in this type of patients [47,48]. The reason for this lack of predictive value of the expression (or non-expression) as well as the level of expression of EGFR in the tumour, determined by immunohistochemistry, could be due to different causes. The first is that immunohistochemical determination of EGFR can be affected by fixation method another one might be because the tissue we use to determine it has been fixed long time ago [49,50]. There can be differences depending on who analyses it [51] and there might be tumour heterogenicity [52]. Also, EGFR expression may be different between primary cancer and metastases [53]. Furthermore, a negative EGFR by immunohistochemistry does not necessarily implies lack of EGFR in cell membrane, since low EGFR levels (less than 1 000 receptors per cell) are not detected by the immunohistochemistry technique. At this point, it is of interest to mention that it has been described high and low affinity of EGFR, which cannot be distinguished by the immunohistochemical methods currently used, and that the biological activity mainly depends on the high affinity receptors [54,55]. There are no studies on the ratio of low and high affinity receptors in colorectal cancer. A possible hypothesis however is that if only the number of high affinity receptors is important, and 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 us data on the amount of low affinity EGFR, masking it up the presence of those with high affinity. Thus, it could be possible that a highly EGFR positive tumour might actually have few receptors with high affinity, and, on the contrary, a tumour with low positive EGFR or even negative EGFR can have an elevated proportion of high affinity receptors or even a significant dependence on a small number of high affinity receptors for cell survival.

Other predictive factors of efficacy. Given that there is no relationship between EGFR expression by immunohistochemistry and treatment efficacy, other possible predictive factors need to be investigated. These would enable population selection that would more likely benefit from Panitumumab treatment. It would also demonstrate its benefit easier avoiding that negative results in those patients who have no benefit would lead to overall negative clinical trials that are not able to identify the benefit in the favourable subgroup of patients. We would have more likelihood of individualizing treatment; that is, administering Panitumumab to those patients with favourable predictive factors and treating the unfavourable group with other therapeutic options), and with a better rationalization of cost (a factor that is very significant nowadays. As we have already mentioned skin toxicity can be of predictive value [38,56]. Regarding biomarkers, Table IV summarizes the studies performed with antiEGFR monoclonal antibodies in advanced colorectal cancer. Moroni et al. [57] published a study carried out on 31 patients with advanced colorectal cancer treated with Cetuximab or Panitumumab in whom copies of the EGFR gene were determined by *in situ* hybridisation (FISH), and it was observed that 8 of the 9 responding patients had an increased number of copies (3 or more copies of the gene in the nucleus) vs. only 1 of the 22 non-responding patients ($p < 0.05$). Response rate was 89% in the subgroup with the increased number of copies vs. 5% ($p = 0.0001$) in the one that did not have an increased number of copies. The mutation profile of the EGFR catalytic domain and the K-RAS, B-RAF and PIK3CA exons was also studied and it did not showed an statistically significant correlation between any of them and response, founding a response rate of 20% when it had the mutation vs. 38% ($p = 0.42$) when it did not had it. In another study, recently published [58], an analysis of EGFR gene copies (GCN) determined by FISH was performed in a subset of the patients included in the aforementioned Phase III trial [38] that compared Panitumumab vs. best supportive care (BSC) in chemotherapy refractory advanced colorectal cancer. Fifty eight patients treated with panitumumab, as well as 34 patients included in the BSC arm, were included in this analysis. A mean EGFR GCN of less than 2.5/nucleus was found in 38 (65%) of these patients and less than 40% of tumor cells displaying chromosome 7 polysomy within the tumor was found in 39 (67%) of them. These two biomarkers were associated in most cases (both: 37 patients, only low GCN: 1 patient, only low chromosoma 7 polysomy: 2 patients). In patients treated

Table IV. Biomarkers for anti EGFR monoclonal antibodies in advanced colorectal cancer.

Study Treatment N of pts	EGFR gene copies FISH/ CISH	K-Ras mutations	Other	No predictive value
Moroni [57] Cetuxi/panitu 31 pts	FISH +: −30% of pts RR: 89% (vs 5%) p: 0.0001	K-Ras mutated: −32% of pts RR: 20% (vs 38%) p: 0.42		Mutations in EGFR B − RAF PI3K
Sartore-Bianchi [58] Panitu 58 pts	FISH +: −38% of pts RR: 30% (vs 0%) p: 0.0009 TTP: 3.4m (vs 1.6m) p: 0.03			
Lièvre [59] Cetuxi +/− irino 30 pts	CISH +: −10% of pts RR: 100% (vs 30%) p: 0.04	K-Ras mutated: −43% of pts RR: 0% (vs 65%) p <0.0001 Sv: 6.9m (vs 16.3m) p: 0.016		Mutations in B-RAF PI3K
Romagnani [60] Cetuxi + chemoth. 27 pts	FISH +: −11% of pts RR: 42% (vs 0%) p <0.05	K-Ras mutated: −37% of pts RR: 10% (vs 53%) p <0.05	pTEN (IHC) -: −38% of pts RR: 0% (vs 62%) p <0.05	
Personeni [61] Cetuxi +/− irino 54 pts	FISH +: −10% of pts RR+SD: 63% (vs 33%) p < 0.05	K-Ras mutated: −24% of pts RR: 0% (vs 34%) p: 0.04		Mutations in B-RAF HER 2 (FISH)
Finocchiaro [62] Cetuxi +/− irino 85 pts	FISH +: −48% of pts RR: 29% (vs 6%) p: 0.007 TTP: 6.6m (vs 3.7m) p: 0.05 Sv:11.3m (vs8.5m) p: 0.7	K-Ras mutated: −39% of pts RR: 6% (vs 26%) p: 0.02 TTP: 3.7m (vs 6.3m) p: 0.07 Sv: 8.3m (vs 10.8m) p: 0.2	HER 2 (FISH) +: −23% of pts RR: 15% (vs 19%) p: 1 TTP: 3.7m (vs 5.8m) p: 0.01 Sv: 6.6m (vs 11.3m) p: 0.03	EGFR (IHC)
Khambata-F [63] Cetuxi 110 pts		K-Ras mutated: −37% of pts RR+ SD: 10% (vs 48%) p: 0.0003 TTP: 3.7m (vs 6.3m) p: 0.07 Sv: 8.3m (vs 10.8m) p: 0.2	Epiregulin* (high expression): −50% of pts TTP: 3.4m (vs1.9m) p: 0.0001 Amphiregulin* (high expression) −50% of pts TTP: 3.8m (vs1.9m) p: 0.0001	
De Roock [64] Cetuxi+/− irino 37 pts		K-Ras mutated: −46% of pts RR: 0% (vs 40%) p: <0.05		

Cetuxi: cetuximab; Panitu: panitumumab; irino: irinotecan; chemoth.: chemotherapy; RR: response rate; SD: stable disease; TTP: time to tumour progression; Sv: survival; IHC: inmunohistochemistry.
*Tumor mRNA levels.

with panitumumab, a mean EGFR GCN of less than 2.5/nucleus or less than 40% of tumor cells displaying chromosome 7 polysomy within the tumor predicted for shorter progression-free survival (PFS; $p = 0.039$ and $p = 0.029$, respectively), shorter overall survival ($p = 0.015$ and $p = 0.014$, respectively) and lower response rate (0% vs. 30%, $p < 0.001$). Evaluation of BSC-treated patients showed no correlation between EGFR GCN or chromosome 7 polysomy status and progression free survival. Other studies carried out in advanced colorectal cancer patients treated with Cetuximab [59–64] are summarized in Table IV. These studies suggest that an increase in the number of EGFR gene copies determined by *in situ* hybridisation methods (FISH or CISH) [57–62], as well as the absence of KRAS mutations [57,59–64], and perhaps other factors as well, such as not losing PTEN expression [60], no increased HER2 gene copy number (FISH) [62], or higher tumoral mRNA levels of epiregulin or amphiregulin [63] could be positive predictive factors of treatment efficacy with anti EGFR monoclonal antibodies. However, these data are still preliminary and need to be confirmed with more properly designed studies before taking them into routine clinical practice. There would be also important to study if the results with these biomarkers are similar for different antiEGFR monoclonal antibodies.

Panitumumab in other tumours

A randomized phase II trial of carboplatin/paclitaxel with or without panitumumab in 166 patients with previously untreated advanced stage IIIB/IV NSCLC did not find any benefit for the panitumumab arm compared with the chemotherapy alone arm with regard to response rates, time to disease progression, or median survival time [65]. It seems

important to develop biomarkers to identify a subset of NSCLC patients who may derive benefit from this agent before initiating further trials of panitumumab in NSCLC.

A phase I trial is exploring the combination of Panitumumab, Carboplatin, Paclitaxel and Radiotherapy for locally advanced head and neck cancer [66]. Preliminary results of this study suggest that this combination is feasible and has interesting activity. There are various ongoing phase II trials exploring the activity of panitumumab in recurrent/metastatic as well as locally advanced head and neck cancer

Matuzumab (EMD 72000)

Matuzumab, previously known as EMD 72000, is a humanized IgG1 monoclonal antibody against human EGFR. As it only has approximately 10% murine origin it has limited immunogenicity, and being IgG1 it is capable of inducing antibody dependent cell cytotoxicity (ADCC). As it was previously mentioned, there are preclinical data suggesting that this could be an anti-tumoural mechanism of action [26].

Anti-tumoural activity has been observed in preclinical studies of xenograft models of different human tumours in mice [67]. In Phase I studies maximum tolerable dose was found to be 1600 mg/m^2 every week. Toxicity was maneagable, being skin toxicity noteworthy (Grade 1-2 in two thirds of the patients). No signs nor symptoms of hypersensitivity were found, despite premedication not being used [68]. Although most studies have looked at weekly schedules (doses of 400 – 800 mg/m^2), there are pharmacokinetic and pharmacodynamic data that suggest dose equivalence with every two or three weeks schedules [69].

Preliminary results of a Phase II study [70] with Matuzumab monotherapy (800 mg/m^2 weekly) had been reported in advanced cervix EGFR+cancer Cisplatin-refractory. It included 41 patients and obtained 5% partial responses as well as 17% stabilizations, with a median time to progression of 7 weeks.

It has also been carried out a phase II study [71] with Matuzumab monotherapy (800 mg/m^2 weekly) in patients with ovarian or peritoneal primary cancer refractory to platin based schedules. It included 37 patients and although no responses were seen, it obtained 21% stabilizations which lasted for more than 6 months.

The results of different Phase I trials exploring the combination of Matuzumab with chemotherapy have been recently reported. In the phase I study reported by Kollmannsberger et al. [72], 19 patients with NSCLC were treated with weekly Matuzumab plus Paclitaxel with no apparent drug interactions and interesting activity (response rate 22%). Graven et al. have reported the results of a phase I trial [73] that explored the combination of weekly or biweekly Matuzumab with Gemcitabine in 17 chemotherapy-naive advanced pancreatic adenocarcinoma patients. Pharmacokinetic data were consistent with results of Matuzumab monotherapy and its combination with standard dose of Gemcitabine appeared to be well tolerated. Disease control was achieved in 66% of the patients.

Matuzumab treatment is also being examined in Phase II studies on other tumours such as gastric cancer.

Nimotuzumab (h-R3)

Nimotuzumab, previously known as h-R3, is a humanized IgG1 monoclonal antibody against human EGFR [74]. Good tolerance and interesting activity were seen in initial Phase I studies, [75,76]. It is noteworthy the absence or mild skin toxicity and hypersensitivity reactions reported in these trials [77].

A phase I/II study [78] with nimotuzumab in combination with radiotherapy in locally advanced head and neck squamous cell cancer has been published. Due to the promising results of this trial, Nimotuzumab has been approved in Columbia, Argentina, China, Cuba and India for the treatment of these patients. There is an ongoing phase III trial that explore the role of Nimotuzumab in this setting

Nimotuzumab has been also explored in malignant gliomas. In a phase II trial 47 children and adolescents with refractory or relapsed high-grade gliomas were treated with Nimotuzumab [79]. The tolerability was good and the activity promising (PR: 9%, SD: 22%). In another phase II study [80] the combination of Nimotuzumab plus radioteherapy was explored in 21 patients with malignant gliomas. There were 17% complete responses, 21% partial responses, and median survival was 22 months. In view of these promising results, Nimotuzumab is currently in a phase 3 trial in Europe in combination with radiation for the treatment of pediatric pontine glioma. The combination of Nimotuzumab with various chemotherapeutic agents (docetaxel, carboplatin and capecitabine) were explored in 19 patients with malignant gliomas or squamous cell head and neck tumors [81] finding acceptable toxicity.

Different phase II studies are currently being carried out to examine the role of Nimotuzumab in other epithelial tumours: non-small cell lung cancer, pancreatic, esophageal, prostate, cervical, breast and colorectal cancer.

Zalutumumab (HuMax-EGFr)

Zalutumumab, previously known as HuMax-EGFr, is a completely human IgG1 monoclonal antibody against human EGFR. There are preclinical data that suggest interesting activity against different tumours in animal model xenografts. Since Zalutumumab is a IgG1, it has been observed in preclinical studies a high capacity to induce antibody-dependent cell cytotoxicity (ADCC) [82].

Clinical development is mainly being carried out on head and neck squamous cell cancers. The first phase I/II study reported [83] included 27 patients with recurrent or metastatic disease after failure to conventional treatments and showed promising activity: 11% responses and 47% stabilizations, obtaining a higher response rate with higher doses. It had optimal tolerance, suffering a 56% skin toxicity, usually mild. Its incidence increased with the dose, but severity remained stable. There is a phase III in this advanced refractory setting which plans to randomise 273 patients to receive Zalutumumab monotherapy vs. symptomatic treatment. Its primary endpoint is survival. There has also been recently started a phase I/II study examining the combination of Zalutumumab with radiotherapy and chemoradiotherapy in locally advanced squamous cell head and neck carcinoma.

Conclusions

EGFR inhibition with monoclonal antibodies is nowadays considered an attractive approach in cancer treatment. Although Cetuximab is the most developed one, another anti EGFR monoclonal antibodies have been studied in different tumors with promising results.

In contrast with Cetuximab, which is a chimeric antibody that produces severe hypersensitivity reactions in some patients, other antibodies are completely human (Panitumumab, Zalutumumab) or humanized (Matuzumab and Nimotuzumab) and in both cases hypersensitivity reactions are unfrequent. There are also differences in their pharmacokinetics and only IgG1 antibodies (Cetuximab, Matuzumab, Nimotuzumab and Zalutumumab) have the capacity of induce antibody dependent cell cytotoxicity (ADCC), a potential anti-tumoural mechanism of action, although the importance of this is not clear from a clinical point of view.

Panitumumab has been mainly studied in advanced colorectal cancer. It demonstrate in a phase III trial an improvement in progression free survival in chemotherapy refractory advanced colorectal cancer. Regarding first line treatment, an interim analyses of the PACCE phase III trial has found reduced progression free survival when Panitumumab was added to FOLFOX-Bevacizumab. This could be due to an antagonism between Panitumumab and Bevacizumab or between Panitumumab and FOLFOX. The results of two ongoing phase III trials that explore the addition of Panitumumab to chemotherapy (without Bevacizumab) in first and second line advanced colorectal cancer should clarify the role of Panitumumab in this setting.

Matuzumab has been studied in phase II trials in gynaecological tumors, in NSCLC and in gastric cancer with interesting results but we need phase III trials to stablish its role in these settings.

Nimotuzumab has shown interesting efficacy in head and neck cancer and malignant gliomas and there are ongoing phase III trials exploring these issues. It is noteworthy the absence or mild skin toxicity found with this compound.

Zalutumumab is being mainly developed in head and neck cancer showing promising results in phase II trials.

Finally we should improve our understanding of EGFR biology in human cancer in order to know how select those patients (or tumors) most likely to benefit from a EGFR inhibition strategy, which could be the best EGFR inhibitor and how better combine EGFR inhibitors with other cancer therapies.

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