



# Is there a role for epidermal growth factor receptor inhibition in the treatment of advanced esophagogastric tumours?

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*Comment on:* Enzinger PC, Burtness BA, Niedzwiecki D, *et al.* CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers. *J Clin Oncol* 2016;34:2736-42.

**Abstract:** Advanced esophagogastric cancers are aggressive malignancies with an extremely poor prognosis. Palliative chemotherapy remains disappointing, with median survival of <12 months in first line clinical trials. Overexpression of epidermal growth factor receptors (EGFR) in up to 80% of these cancers led to clinical trials testing the addition of EGFR-inhibitors (EGFR-I) to standard chemotherapy. Here we provide a perspective on the recent CALGB 80403 (Alliance)/E1206 trial publication which compared the safety and efficacy of three chemotherapy regimens combined with cetuximab and discuss its clinical practice implications. We identified relevant published data for discussion using a PubMed based search strategy and through the reference lists of identified studies. We focused our discussion mainly on the randomised trials that pertained to esophageal and esophagogastric junction tumours to match the population of the study in focus in this perspective.

**Keywords:** EGFR monoclonal antibodies; cetuximab; panitumumab esophagogastric cancer; esophageal/gastroesophageal junction (GEJ)/gastric tumours

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Esophageal cancers, including esophagogastric junction tumours are the sixth leading cause of cancer mortality worldwide (1). While the incidence of adenocarcinomas predominate in developed countries (2), squamous-cell carcinomas of the esophagus demonstrate an association with lower socioeconomic status (3). Gastric cancers, the vast majority are adenocarcinomas, accounting for 700,000 deaths per year, rendering this the second commonest cause of cancer mortality worldwide (4). In recent years, the site of tumor has shifted from predominantly occurring in the distal stomach to now at, or near the gastroesophageal junction (GEJ) (5). This has been attributed to a change in the prevalence of underlying risk factors for developing gastric cancer, with a decline in chronic *Helicobacter pylori* infections and an increase in gastroesophageal reflux and obesity (5). For both esophageal and gastric cancer, chemotherapy is of proven benefit in

palliating symptoms with a modest improvement in survival, however durable responses are infrequent. The therapeutic benefits of combination chemotherapy regimens must be balanced against potential toxicity in a patient population where nutritional and general debility issues frequently coexist (2).

The anti-epidermal growth factor receptor monoclonal antibodies (EGFR mAbs), cetuximab and panitumumab, competitively inhibit the epidermal growth factor receptor (EGFR) extracellular domain (6). They are widely used in the treatment of colorectal cancer, head and neck and other tumour types; improving response, progression-free and overall survival when used in combination with chemotherapy or as single agents. The rationale for evaluating the use of EGFR-inhibitors (EGFR-I) in esophagogastric cancer is based on the overexpression of EGFR in 64% of esophageal adenocarcinomas (7),

71–83% of squamous cancers (8,9) and just under 50% of gastric cancers (10), with a clinicopathological evaluation of 78 cases of gastric tumours from a single institution demonstrating a higher likelihood of EGFR expression in poorly differentiated tumours of a more advanced stage (11). EGFR gene amplification has been reported in 8% of esophageal adenocarcinomas (12,13).

Preclinical studies have demonstrated constitutive activation of the EGFR signaling pathway in esophagogastric cancer cell lines (14). Inhibition of the receptor with EGFR mAbs reduces signaling in the EGFR pathway through reduced phosphorylation of EGFR and AKT (15). *In vitro*, the addition of anti-EGFR antibodies to chemotherapy demonstrated synergistic inhibition of cell proliferation and enhanced apoptosis (13,15–17). In colorectal cancer patients, the use of EGFR-I are restricted to the 40% of patients wildtype for the *RAS* gene, with multiple studies showing lack of benefit in *RAS* mutated tumours. However, it is rare (<10%) to see *KRAS* mutations in esophagogastric cancer (18–20); this low prevalence preventing its utility as a predictive biomarker.

Here we provide a perspective on the recently published randomised phase II CALGB 80403 (Alliance)/E1206 study comparing cetuximab efficacy and toxicity when combined with three different standard chemotherapy backbones in patients with metastatic esophagogastric cancer and discuss its clinical practice implications. This study commenced at a time when there was great hope that the addition of biological agents to standard chemotherapy would improve outcomes in a disease where little progress had been made for some time. The trial sought to identify the optimum chemotherapy—EGFR-I combination using standard chemotherapies active in metastatic esophagogastric cancer (1), including oxaliplatin (1), docetaxel (21), capecitabine (22) and irinotecan (18,21,23–25), to give rise to the optimal regimen to be taken forward into randomised phase III trials. The rationale for this direct comparison was further stimulated by emerging studies in colorectal cancer (CRC) suggesting that the chemotherapy partner for anti-EGFR treatments may influence efficacy, although this still remains controversial (26–30). Unfortunately, large studies published during the trial period showed no benefit for the addition of EGFR-I in this disease (13,31), so that the conclusion of 80,403 demonstrating no statistical difference between the regimens of little clinical importance (32).

Unlike CRC, no biomarker selection for EGFR-I use in esophagogastric cancer has been identified. Earlier phase I/II studies contained an unselected population, with the

exception of the phase II study by Lorenzen *et al.* which only included patients with evidence of EGFR overexpression by standardised immunohistochemical (IHC) testing (19). However, IHC overexpression has not been shown to be a predictive marker in any tumour subtype (33–35). We reflect on these earlier studies to provide context for our discussion on the recent CALGB 80403 (Alliance)/ E1206 study publication.

### Phase I/II studies in first line treatment of metastatic esophagogastric cancer

Two early phase I/II studies were conducted in patients with gastric cancer and GEJ tumours comprising approximately half of each study population (6,20). The 2010 Lordick study was a single arm study of 52 participants evaluating response rate (RR), safety and efficacy of cetuximab addition to oxaliplatin and 5-fluorouracil (FU) (6). An encouraging RR of 65% was seen, with a suggestion of higher response in GEJ tumours compared to a gastric primary (77% *vs.* 54%). The median time to progression (TTP) was 7.6 months with a 9.5-month median overall survival (OS). There was no clear association with degree of EGFR expression by IHC.

The Pinto *et al.* study was a single arm trial in 72 patients of cetuximab addition to cisplatin and docetaxel, also in a predominant gastric cancer population (82%) (20). RR was encouraging at 41% with a median duration of response of 5 months and median OS of 9 months. This RR was higher than reported in historical docetaxel plus cisplatin trials (36,37). This study demonstrated a non-significant trend between increased severity of skin toxicity and treatment activity, an observation seen in other tumour types (38,39). A small number (n=16) of patients who had at least stable disease (SD) after 6 cycles on trial went on to maintenance treatment with cetuximab alone, demonstrating a trend for both longer TTP, 9.2 *vs.* 6.6 months (P=0.10) and improved OS, 19.8 *vs.* 7.7 months (P=0.22). Overall, treatment was reasonably tolerated and chemotherapy toxicities were not significantly increased by addition of cetuximab. The lower rates of grade 3–4 toxicities and febrile neutropenia compared to that reported in the SAKK42/99 trial (36) can be explained by the lower doses of both chemotherapy agents (20).

A multicentre phase II Austrian study evaluated the safety and feasibility of a unique chemotherapy backbone of oxaliplatin and irinotecan with cetuximab in 51 patients with advanced gastric cancer (40). The triplet was deemed safe (primary endpoint); secondary endpoints of efficacy were

evaluable in 35 patients. One patient (3%) demonstrated a CR, 21 patients (60%) a PR and 7 patients (20%) SD. The median TTP was 25 weeks, with median OS of 38 weeks.

Another encouraging study reported by Moehler *et al.* reporting a 48% RR in 48 patients with the addition of cetuximab to irinotecan plus 5-FU with promising longer term outcomes [median progression free survival (PFS) 9 months and median OS 16.5 months] (18). Predictive biomarkers were evaluated in 34 patients; *KRAS*, *BRAF* and *PIK3CA* mutations were detected in 3 (9%), 4 (12%) and 2 (6%) of tumours respectively, each mutually exclusive. Amongst the tumours with *KRAS* mutations, two exhibited a response to treatment: one complete response (CR) and one partial response (PR). Whilst no patients whose tumours harboured *BRAF* or *PIK3CA* mutations responded, the low numbers limit conclusions. EGFR expression by IHC was detected in 26/39 (67%) of tumours, with no correlation to outcome. There was no statistical difference in best tumour response or survival based on development of a treatment-related rash.

Not all early phase studies reported high RRs however, with a German study by Lorenzen *et al.* reporting modest RRs (<40%) with no differences in PFS or OS in a 2-arm randomised design of cisplatin/5-fluorouracil (CF) ± cetuximab (19). Some data of interest arose from the unplanned subgroup analysis of the small number of patients in the chemotherapy arm who crossed over to receive cetuximab as monotherapy (n=2) or had cetuximab added to continued CF chemotherapy (n=3) on progression. One of the patients who received cetuximab monotherapy achieved a PR and the other achieved SD; one of the three patients where cetuximab was added to refractory chemotherapy achieved a PR. The median PFS from time of crossover was 6.8 months and median OS 7.1 months in this small cohort. This raised speculation also about whether RECIST measured RR was the most appropriate method of characterising cetuximab benefit, or whether cetuximab could reverse chemotherapy refractoriness, as was being discussed in other tumour types.

Similarly, a 150-patient phase II study evaluated a docetaxel and oxaliplatin backbone ± cetuximab (41). There was a near even split of patients with gastric and GEJ tumours. The primary endpoint of PFS was not improved and there was a greater rate of treatment discontinuation due to adverse events (AEs) with the addition of cetuximab. The RR improved from 27% to 38% with its addition.

Rather than cetuximab, the ATTAX3 trial evaluated the safety and efficacy of adding panitumumab to chemotherapy

in patients with advanced esophagogastric cancer (42). Of the 71 participants, 61% had esophageal or GEJ tumours and 90% were adenocarcinoma. No benefit was seen in RR, PFS or OS, but increased toxicity.

### Phase I/II studies in refractory metastatic and locally advanced disease

A 35-patient phase II U.S. study evaluated the safety and efficacy of single agent cetuximab beyond the first line setting (43). This included one third with advanced esophageal tumours, 23% with GEJ tumours and the remainder gastric. Despite rash (all grades) being reported in 77% of patients, the primary endpoint of RR was documented at only 3%. The median PFS and OS were 1.6 months and 3.1 months respectively.

Two single arm, phase II studies evaluating the addition of cetuximab to 5-fluorouracil and oxaliplatin (FOLFOX) (44), or irinotecan and cisplatin (IC) chemotherapy (45) with radiation, demonstrated mixed results in the locally advanced esophageal cancer setting. The 79-patient trial using FOLFOX plus cetuximab met its primary endpoint with an objective response rate (ORR) of 77% (expected rate >50%), with 40% of patients achieving a CR (44); the study evaluating the IC backbone suffered from poor accrual, demonstrating significant toxicity in the 19 evaluable patients and an insufficient pCR rate to warrant further evaluation (45).

SCOPE 1 was another negative phase II study evaluating cetuximab addition to chemoradiation with cisplatin and capecitabine (46), this time as definitive therapy. The primary endpoint was freedom from treatment failure at 24 weeks. Recruitment ceased due to meeting criteria for futility before the planned continuation to a phase III study, with boundaries set based on treatment-failure-free rate of <60% at week 24 not deemed sufficient to warrant further investigation, but a rate of >75% worthy of further study. All study participants (n=258) had esophageal cancer with the majority having squamous histology (~75%). Fewer patients were free from treatment failure at 24 weeks in the cetuximab plus chemoradiation arm (66.4%) compared to chemoradiation alone. Median OS was also shorter in the former, with an adjusted hazard ratio (HR) of 1.53 (95% CI, 1.03–2.27). The study concluded that the addition of cetuximab to a standard definitive chemoradiation regimen resulted in increased toxicity and postulated that the reduced efficacy resulted from the reduction in delivery of both components of

standard chemoradiation.

### Phase III trials

The disappointment of existing treatments together with promising clinical activity in many (but not all) phase II cetuximab-chemotherapy combination trials led to an evaluation of cetuximab in larger phase III trials. This coincided with excitement regarding the efficacy of the EGFR-I in metastatic CRC.

The EXPAND phase III study evaluated cetuximab benefit when added to capecitabine and cisplatin in patients with previously untreated, advanced gastric cancer (31). There was no molecular selection or stratification. The first patient was enrolled in June 2008 and last in December 2010, with the study published in 2013. Only 17% of patients had GEJ tumours. The primary endpoint, median PFS, for the 455 participants who received cetuximab + chemotherapy was 4.4 *vs.* 5.6 months for the 449 patients receiving chemotherapy alone (HR 1.09; 95% CI, 0.92–1.29; *P*=0.32). The regimen was toxic with 83% and 77% of participants in the cetuximab + chemotherapy and chemotherapy alone arms experiencing grade 3–4 AEs, respectively. This study made the disappointing conclusion that there was no benefit from the addition of cetuximab to a capecitabine-cisplatin chemotherapy backbone.

REAL3 was a phase II/III study that evaluated the safety and efficacy of adding panitumumab to epirubicin, oxaliplatin and capecitabine (EOC) in an unselected patient population with advanced esophagogastric adenocarcinoma. The phase II component, which recruited patients in 2008–2009, identified a high level of toxicity that mandated dose modifications (47) before proceeding to the phase III component (13). Enrolment was completed in October 2011. Despite great anticipation, this study which was published in 2013 did not demonstrate any benefit for the addition of panitumumab; on the contrary there was evidence of harm with the OS HR 1.37 (95% CI, 1.07–1.76; *P*=0.013). Subgroup analyses revealed no clear biomarkers predictive for panitumumab benefit, although the presence of a *KRAS* mutation in 10 participants showed a nonsignificant improvement in OS (HR 0.23; 95% CI, 0.05–1.15). In contrast to data in CRC, OS was reduced amongst participants with *KRAS* wild type tumours who received panitumumab (*n*=164), HR 1.50 (95% CI, 1.03–2.18). The dose intensity did not vary significantly between study arms, thus was not an explanation for the inferior outcome. As expected, there was increased toxicity

with the addition of the EGFR-I (13). These studies are summarised in *Table 1*.

In a combined modality setting, a phase III trial evaluated the addition of cetuximab to a paclitaxel and cisplatin backbone with radiation in 344 patients with locally advanced esophageal cancer (T1N1M0 or T2–4 any N, M0 or any T/N, M1a) treated without surgery. This study demonstrated no improvement in its primary endpoint of OS, nor in RR, irrespective of histological subtype (48).

The recent publication of the randomised phase II Cancer and Leukemia Group B (CALGB) 80403 (Alliance)/E1206 study reported in July 2016 by Enzinger *et al.* in the *Journal of Clinical Oncology*, is now discussed having set the scene of its historical context. This study aimed to compare differences in the ORR (the primary endpoint) with cetuximab when used in combination with three different chemotherapy backbones—epirubicin, cisplatin and 5-fluorouracil (ECF), 5-FOLFOX or IC (32). Planned secondary objectives included OS, PFS and time to treatment failure (TTF). This multicentre trial was a collaborative effort by CALGB and ECOG, recruiting a total of 245 patients with metastatic esophageal (56%) and GEJ tumours (43%) across the US, in a time period prior to reporting of the large phase III trials discussed above. Ninety-one percent of patients had adenocarcinoma and there was no molecular selection. Whilst the data from this trial was maturing following full enrolment, results of the large REAL-3 and EXPAND studies were published. This prompted unplanned pair-wise comparisons of TTF, PFS, OS and toxicity end points across the three regimens. For the ECF, FOLFOX and IC regimens respectively, RR was 60.9%, 54.3% and 45.0%; median OS was 11.6, 11.8 and 8.6 months; and median PFS 7.1, 6.8 and 4.9 months. Participants who received FOLFOX plus cetuximab required less treatment modifications (*P*=0.013) and withdrawal from study, due to AEs compared to the other regimens. The study authors concluded that there was a similar efficacy when adding cetuximab to ECF as to FOLFOX, with the latter reported as the better tolerated regimen by toxicity grading. Cetuximab addition to IC seemed to be the least effective and most toxic regimen, although differences were not statistically significant. There was no formal evaluation of quality of life (QoL). Tissue collection was not reported nor any translational work proposed within this study (32).

The CALGB 80403 (Alliance)/E1206 study, in the context of large negative phase III studies of adding



**Table 1** Summary of studies evaluating the safety and toxicity of EGFR-inhibition in the first line, metastatic setting of esophagogastric cancers

Study	Phase [N]	Population	Study arm(s)	Primary endpoint	Secondary endpoint
Lordick <i>et al.</i> [2010] (6)	II [52]	Metastatic gastric cancer	5FU + oxaliplatin + cetuximab	Proportion of patients who responded; ORR 65%; 95% CI, 50–79% (4 CR and 26 PR). In GEJ tumours 77% achieved an ORR, in gastric 54%. EGFR status showed no correlation with treatment outcome	Toxicity – diarrhoea 33%, skin toxicity 24%; TTP 7.6 months; 95% CI 5.0–10.1; OS 9.5 months; 95% CI, 7.9–11.1
DOCETUX; Pinto <i>et al.</i> [2009] (20)	II [72]	Advanced gastric and GEJ adenocarcinoma	Docetaxel, cisplatin + cetuximab ± maintenance cetuximab in patients with non-PD	ORR 41.2%; 95% CI, 29.5–52.9% (1 CR + 27 PR); 33% SD; 23.5% PD. Study concluded that the ORR improved with the addition of cetuximab	Toxicity – not affected by the addition of cetuximab; both OS and TTP – did not improve with cetuximab addition; median OS 9 months; 95% CI, 7–11 and TTP 5 months; 95% CI, 3.7–5.4
Wöll <i>et al.</i> [2011] (40)	II [51]	Advanced gastric cancer	Irinotecan + oxaliplatin + cetuximab	Safety	Treatment response; TTP 25 weeks; median OS 38 weeks
Moehler <i>et al.</i> [2011] (18)	II [49]	Advanced gastroesophageal cancer	Irinotecan + 5FU + cetuximab	ORR 46%; 95% CI, 31–61; SD in 33%; disease control rate 79%. Strong EGFR expression was positively associated with tumour response (P=0.006). Tumour response was not associated with presence of a rash	Disease control – 79%; median PFS – 9.0 months; 95% CI, 7.1–15.6 and OS 16.5 months; 95% CI, 11.7–30.1
Lorenzen <i>et al.</i> [2009] (19)	II [62]	Metastatic esophageal squamous cell carcinoma	CF ± cetuximab; tumours expressing EGFR (by IHC)	Tumour response – ORR for CF + cetuximab 29%; 95% CI, 7–36%; CF alone 13%; 95% CI, 4–31% (P=0.73)	PFS – CF + cetuximab vs. CF: 5.9 vs. 3.6 months; median OS: 9.5 vs. 5.5 months
DOCOX; Richards <i>et al.</i> [2012] (41)	II [150]	Advanced gastric and GEJ tumours	Docetaxel + oxaliplatin ± cetuximab	PFS: no difference	Toxicity – greater rate of treatment discontinuation due to AEs; RR 38% vs. 27% with the addition of cetuximab
ATTAX3; Tebbutt <i>et al.</i> [2016] (42)	II [77]	Advanced esophagogastric cancer	Docetaxel + cisplatin + F or C ± panitumumab vs. 58% with the same + P	RR: 49% with TCF docetaxel, cisplatin + F alone vs. 58% with the same + P	Toxicity; PFS – EOC: 6.9 vs. EOC + P 6.0 months, median OS 11.7 vs. 10.0 months; QOL – dry mouth and dysphagia worse with P; trend to worsening diarrhoea. Overall, global health status was stable across trial period. REAL3 study demonstrating questionable efficacy led to cessation of new patient enrolment to ATTAX3
REAL3; Okines <i>et al.</i> [2010] (47); Waddell <i>et al.</i> [2013] (13)	III [29]; III [553]	Advanced esophagogastric cancer, otherwise unselected	EOC ± panitumumab (capecitabine dose modified for phase III)	RR (not reported until subsequent publication) OS: EOC + P: HR 1.37; 95% CI, 1.07–1.76; P=0.013; OS based on KRAS status: KRAS mutation 0.23; 95% CI, 0.05–1.15; KRAS wildtype 1.50; 95% CI, 1.03–2.18	Safety; preplanned IDMC review in Oct 2011 – halted trial; EOC + P had an increased risk of G3–4 diarrhoea, rash mucositis and low Mg, but reduced hematological toxicity
EXPAND; Lordick <i>et al.</i> [2013] (31)	III [904]	Advanced gastric cancer	Cisplatin + capecitabine ± cetuximab	PFS: chemo + cetuximab, median PFS 4.4 (with cetuximab) vs. chemo alone, 5.6 months; HR 1.09; 95% CI, 0.92–1.29; P=0.32	Toxicity – G3/4 AEs 77% and safety

PFS, progression free survival; HR, hazard ratio; FU, fluorouracil; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; RR, response rate; TTP, time to progression; GEJ, gastroesophageal junction; CF, cisplatin and 5-fluorouracil; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; EOC, epirubicin, oxaliplatin and capecitabine; w, weekly; F or C, fluorouracil or capecitabine; AEs, adverse events; G, grade; Mg, magnesium.

EGFR-I to chemotherapy for advanced esophagogastric cancer, does not yield conclusions that would reinvigorate this direction of therapeutic manipulation. This data can be used to support the FOLFOX regimen as a standard of care for patients with advanced esophageal or GOJ cancer, although it was not superior to the other two regimens.

Sadly, once again, we see a new therapeutic class failing when combined with chemotherapy in large phase III trials despite (some) encouraging phase II trials. This underscores the importance of robust large trials but additionally reinforces the need for translational research and QoL data collection. It also highlights the enormous effort and lengthy process of bringing a trial from inception to fruition. The “retrospectroscope” is indeed a powerful tool. The CALGB’s methodical evaluation of testing the optimal chemotherapy doublet in the phase II setting should be applauded and research efforts to identify molecular predictive factors must continue, as it is possible that there is a subgroup of patients with esophageal and gastric cancer that may indeed benefit from targeting the EGFR pathway.

The historical publication bias against negative trials has been well recognised, hence the prominent publication and editorial and review articles regarding this trial allow for appropriate reflection despite the outcome cementing, rather than changing current clinical practice. We can conclusively state that there is no role for the addition of EGFR-inhibitors to chemotherapy in unselected patients with advanced esophagogastric cancer, but that we can only come to such conclusions with the conduct of high quality clinical trials made possible because of the dedication of patients and their families.

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