Antiepidermal growth factor receptor monoclonal antibody improves survival outcomes in the treatment of patients with metastatic colorectal cancer

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The aim of this study was to determine whether or not the addition of anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAb) to standard chemotherapy or best supportive care (BSC), compared with chemotherapy or BSC alone, can improve overall survival (OS) and progression-free survival (PFS) in patients with metastatic colorectal cancer (mCRC), and evaluate the influence of KRAS mutant status on the efficacy of anti-EGFR mAb. Medline, Embase, the Cochrane controlled trials register, and the Science Citation Index were searched. Nine trials were identified, covering a total of 7941 patients. The treatment of mCRC with a combination of anti-EGFR mAb and chemotherapy or BSC, as compared with chemotherapy or BSC alone, improved the OS [hazard ratio (HR), 0.90 (0.84–0.96); $P=0.002$]. The benefit of anti-EGFR mAb in patients with KRAS wild-type tumors was apparent in relation to a marginal trend toward improved OS [HR, 0.84 (0.70–1.01); $P=0.06$], and significantly improved PFS [HR, 0.64 (0.51–0.81); $P<0.001$]. No benefit for the addition of anti-EGFR mAb was detected for any efficacy end-point in patients with KRAS mutant tumors. The summary HRs (anti-EGFR mAb vs control) were 0.98 (0.88–1.08) ($P=0.71$) for OS and 1.08 (0.94–1.25) ($P=0.27$) for PFS, respectively. In conclusion, this analysis provides confirmation that, compared with chemotherapy or BSC alone, anti-EGFR mAb with chemotherapy or BSC reduces the risk of progression and death of mCRC and that this benefit is seen only in patients with wild-type KRAS tumors.

Anti-Cancer Drugs 2012, **23:**155–160

Keywords: anti-epidermal growth factor receptor monoclonal body, colorectal cancer, overall survival

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Received 25 July 2011 **Revised form accepted** 22 August 2011

Introduction

Worldwide, one million patients are diagnosed annually with colorectal cancer (CRC), and 50% of them will develop metastatic disease [1]. Ultimately, more than 500 000 patients die every year from CRC. Approximately 25% of patients with CRC present with overt metastatic disease, and metastatic disease develops in 40–50% of newly diagnosed patients. The cytotoxic agents irinotecan, oxaliplatin, and the fluoropyrimidines, and bevacizumab, the antibody against vascular endothelial growth factor A, have increased the median survival of patients with advanced CRC [2–4], but the disease is incurable in most patients. Recent advances have led to the development of agents that specifically inhibit tumor growth. Epidermal growth factor receptor (EGFR) is often upregulated in CRC. Binding to the tumor cell also initiates antibody-dependent cell-mediated cytotoxicity [5]. Anti-EGFR monoclonal antibody (mAb), cetuximab or panitumumab, specifically targets EGFR with high affinity, competitively inhibiting endogenous ligand binding and ligand-dependent downstream signaling. The definition of relevant molecular characteristics of an individual tumor (biomarker evaluation) will increasingly enable the selection of patients most likely to benefit from particular treatments [6]. Growing evidence indicates that tumor *KRAS* mutation is associated with the inefficacy of the monoclonal anti-EGFR immunoglobulin G1 antibody cetuximab [7–10] and G2 antibody panitumumab [11,12]. In several pivotal studies, the EGFR-targeting mAbs, cetuximab or panitumumab, have been shown to improve the efficacy of standard chemotherapy regimens or best supportive care (BSC) as first-line or second-line treatments for metastatic colorectal cancer (mCRC). A previous meta-analysis showed that the tumor response was also statistically significantly enhanced by anti-EGFR mAb [13]. However, that meta-analysis did not perform continuous data analysis on progression-free survival (PFS) and overall survival (OS) and did not evaluate the influence of the *KRAS* mutant (MT) status on the efficacy of anti-EGFR mAb. Hence, we performed this pooled analysis to resolve these important issues.

Methods

Literature search strategy

Medline, Embase, the Cochrane controlled trials register, and the Science Citation Index were searched for randomized control trials (RCTs) using the medical subject headings of CRC combining with each of the

0959-4973 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32834c3256

following terms or phrases: anti-EGFR targeted therapy, anti-EGFR mAb, cetuximab, Erbitux or IMC-225, and panitumumab. Reference lists from studies selected for this review were also hand-searched.

Selection of studies

Studies were eligible for inclusion in the meta-analysis if they met all the following criteria: (a) they were published up to June 2011 and written in English; (b) they dealt only with patients who had mCRC or advanced CRC; (c) they provided data on PFS and OS regardless of immunohistochemical evidence of EGFR expression; (d) intervention: anti-EGFR mAb and the same BSC or chemotherapy; and (e) control: BSC or chemotherapy alone. Multiple reports of a single study were considered as one publication, and only the most recent and complete data were examined. All potentially relevant articles were reviewed by two independent investigators (L.W. and Z.S.).

Outcome measures

The outcomes for this review were PFS and OS. PFS was measured from the date of enrollment, randomization or start of treatment until disease progression, relapse, or death. OS was measured from the date of enrollment, randomization or start of treatment until death from any cause.

Statistical analysis

All time-to-event data (PFS, OS) were pooled and reported as hazard ratio (HR) by the genetic inverse variance method. For each included RCT, for the purpose of analysis, we calculated the log-rank of HR and its SE to perform this meta-analysis. When not available from the trial reports, they were estimated by the methods proposed by Parmar *et al.* [14] and described elsewhere [11].

The between-studies and between-subgroups variations were calculated by the Cochrane χ^2-test. We defined a P value of less than 0.05 as statistically significant for all outcomes. If significant heterogeneity existed, it would be inappropriate to combine the data for further analysis using a fixed-effects model, whereas a random-effects model was used for calculations. If possible, we also a carried out subgroup analysis to descrease heterogeneity. Because of the small number of studies included, publication bias was not assessed formally. All meta-analyses were completed using RevMan version 5.1.1 (The Cochrane Collaboration, Oxford, UK).

Results

A comprehensive search of Medline, Embase, the Cochrane controlled trials register, and the Science Citation Index yielded 758 articles, of which nine studies met the predetermined inclusion criteria. The nine trials enrolled a total of 7941 patients. Their characteristics are described in Table 1. Eight included RCTs reported final analyses. None of the studies was blinded. All studies reported intention-to-treat (ITT) analyses and description of drop-outs, except for two [12,15].

Because a comparison of the baseline characteristics and efficacy data suggested that the KRAS evaluable population was comparable to the ITT population, when the survival data was not available for the overall population, we chose the KRAS evaluable population instead [20].

Figure 1 shows that the treatment of mCRC with a combination of anti-EGFR mAb and chemotherapy or BSC, as compared with chemotherapy or BSC alone,

Table 1 Characteristics of the included studies

Reference	*N*	Therapy regimen	EGFR analysis[a]	Publication status
Trials of the addition of anti-EGFR mAb to chemotherapy as first-line treatment				
Van Cutsem *et al.* [7]	1198	E: FOLFIRI + cetuximab C: FOLFIRI	Yes	Published
Borner *et al.* [15]	74	E: XELOX + cetuximab C: XELOX	No	Published
Bokemeyer *et al.* [8]	337	E: FOLFOX-4 + cetuximab C: FOLFOX-4	Yes	Published
Siena *et al.* [12]	1183	E: FOLFOX-4 + panitumumab C: FOLFOX-4	Yes	Abstract
Maughan *et al.* [9]	1630	E: OX-based therapy + cetuximab C: OX-based therapy	Yes	Published
Trials of the addition of anti-EGFR mAb to BSC as second-line treatment				
Van Cutsem *et al.* [16] Amado [17]	463	E: BSC + panitumumab C: BSC	No	Published
Jonker *et al.* [18] Karapetis *et al.* [10]	572	E: BSC + cetuximab C: BSC	Yes	Published
Trials of the addition of anti-EGFR mAb to chemotherapy as second-line treatment				
Sobrero *et al.* [19]	1298	E: Irinotecan + cetuximab C: Irinotecan	No	Published
Peeters *et al.* [20]	1186	E: FOLFIRI + panitumumab C: FOLFIRI	Yes	Published

BSC, best supportive care; EGFR, epidermal growth factor receptor; FOLFIRI, irinotecan, leucovorin, and fluorouracil; FOLFOX-4, oxaliplatin, leucovorin, and fluorouracil; mAb, monoclonal antibody; OX, oxaliplatin; XELOX, oxaliplatin and capecitabine.
[a]Whether this trial evaluated the efficacy of anti-EGFR mAb on the status of KRAS mutant.

reduced the risk of death [HR, 0.90 (0.84–0.96); $P = 0.002$], and there is no statistical heterogeneity between studies and bewteen subgroups.

A similar treatment effect on PFS is shown in Fig. 2. Because of the high heterogeneity beween all included trials ($P = 0.008$), we undertook a subgroup analysis by the timing of anti-EGFR mAb or comparator and used a random-effects model. The benefit for anti-EGFR mAb was consistent across the three subgroups. The summary HRs (anti-EGFR mAb vs. control) were 0.87 (0.76, 1.00) ($P = 0.05$) for the trials adding anti-EGFR mAb to chemotherapy as first-line treatment, 0.61 (0.49, 0.76) ($P < 0.001$) for the trials adding anti-EGFR mAb to BSC as second-line treatment, and 0.73 (0.65, 0.82) ($P < 0.001$) for the trials adding anti-EGFR mAb to chemotheray as second-line treatment.

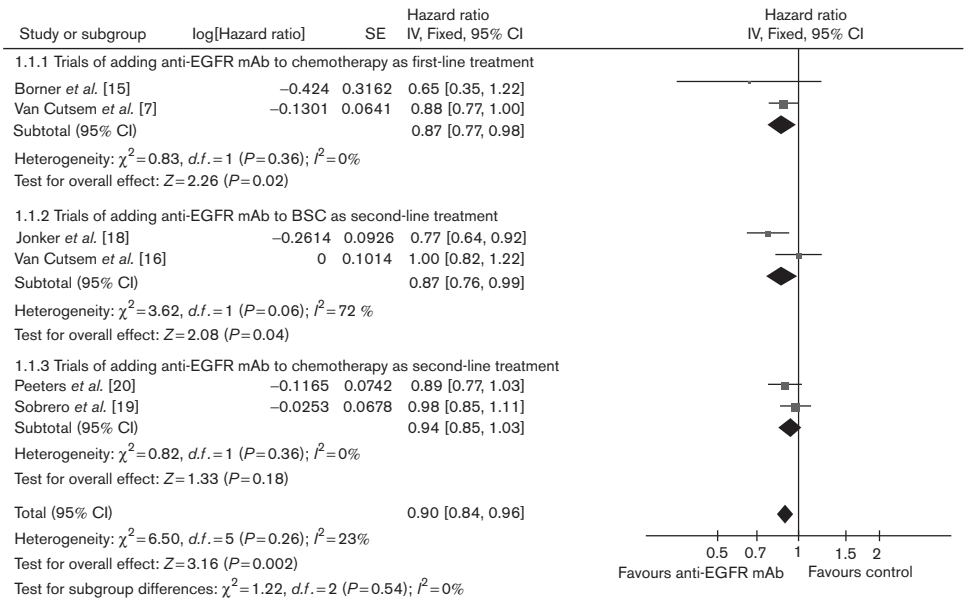
The benefits of anti-EGFR mAb in patients with KRAS wild-type (WT) tumors were apparent in relation to a marginal trend toward reduced risk of survival [HR, 0.84 (0.70–1.01); $P = 0.06$, Fig. 3] and significantly reduced risk of disease progression [HR, 0.64 (0.51–0.81); $P < 0.001$, Fig. 4]. The heterogeneity among the trials included was statistically significantly different for OS analysis ($P < 0.001$) and PFS analysis ($P < 0.001$) in patients with KRAS WT tumors.

No benefit for the addition of anti-EGFR mAb to chemotherapy and BSC was detected for any efficacy end-point in patients with KRAS MT tumors. The summary HRs (anti-EGFR mAb vs control) were 0.98 (0.88–1.08) ($P = 0.71$) for OS (Fig. 3) and 1.08 (0.94–1.25) ($P = 0.27$) for PFS (Fig. 4), respectively. Statistically significant heterogeneity was not found among the trials included for OS and PFS analyses in patients with KRAS MT tumors.

Discussion

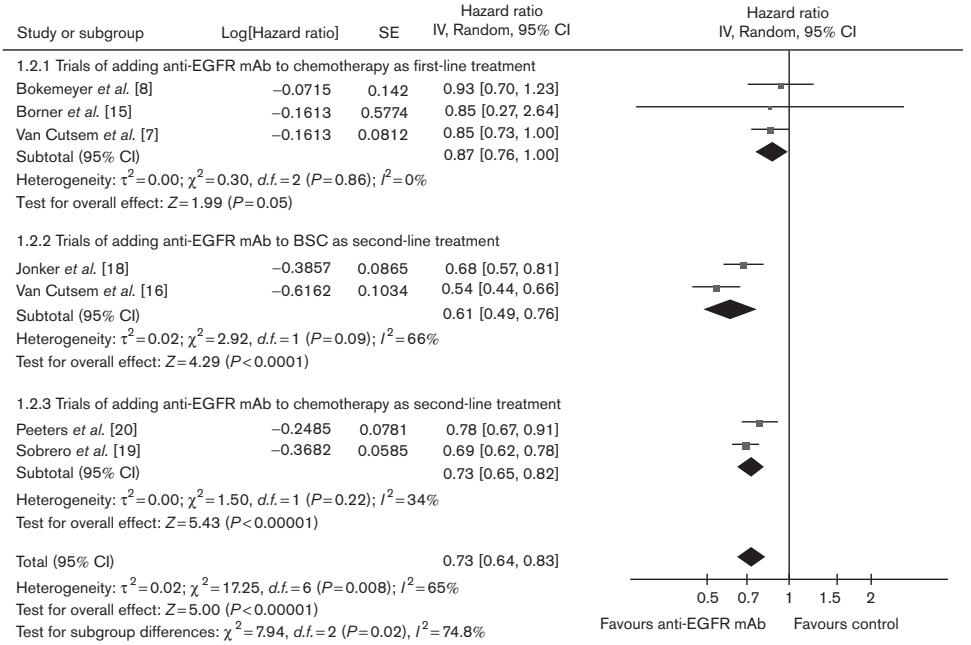
Our analysis makes an important contribution to the CRC field. First, our meta-analysis helps clarify the impact of anti-EGFR mAb on the survival of patients with mCRC. Out of the nine RCTs assessing the efficacy of anti-EGFR mAb, OS data for overall population or KRAS assessable population were available for six trials [7,15,16,18–20]. Pooling these survival data enabled us to increase the power of the survival analysis and confirmed a significant and consistent relative survival benefit with the addition of anti-EGFR mAb to chemotherapy or BSC for patients with mCRC as compared with BSC or systemic chemotherapy alone, irrespective of the timing of anti-EGFR antibody treatment or comparator. However, an imbalance in the administration of anti-EGFR mAbs in the post-study phase may have attenuated the estimated treatment effect of anti-EGFR mAbs on OS. The degree of heterogeneity with respect to OS between the included studies was small. This treatment effect on OS was consistently seen across all included studies (Fig. 1). Our data also showed that the benefit of PFS for the addition of anti-EGFR antibody to chemotherapy or BSC as second-line treatment was statistically apparent (Fig. 2); and there is a marginal trend toward improved PFS in the pooled-analysis of trials in the addition of cetuximab to chemotherapy as first-line treatment (Fig. 2).

Fig. 1



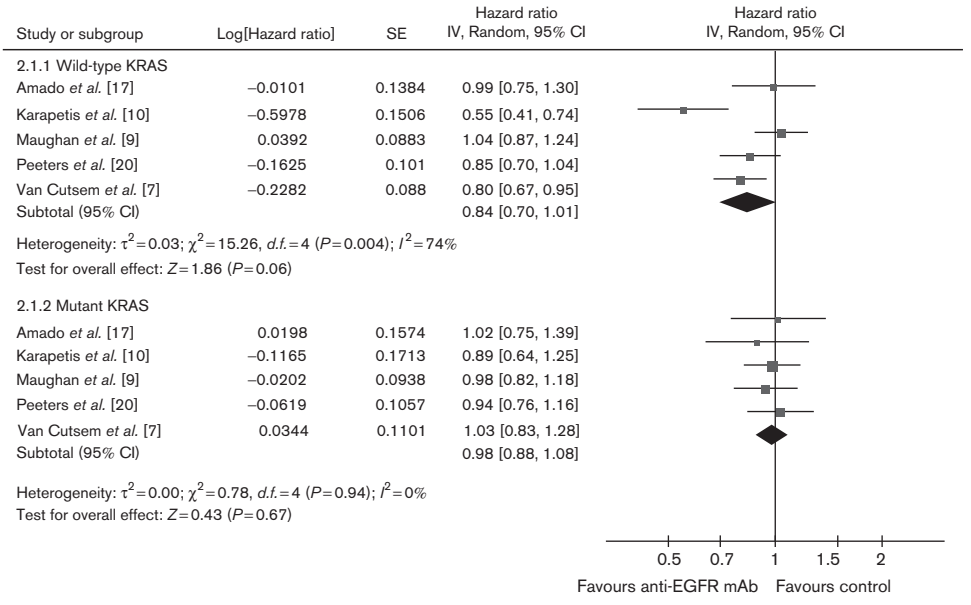
Overall and subgroup meta-analysis of the treatment effects (anti-EGFR antibody vs control) on overall survival (OS) with anti-EGFR antibody for the overall population. HR, hazard ratio; CI, 95% confidence interval; Random, random-effects model.

Fig. 2



Overall and subgroup meta-analysis of the treatment effects (anti-EGFR antibody vs control) on progression-free survival (PFS) with anti-EGFR antibody for the overall population. HR, hazard ratio; CI, 95% confidence interval; Random, random-effects model.

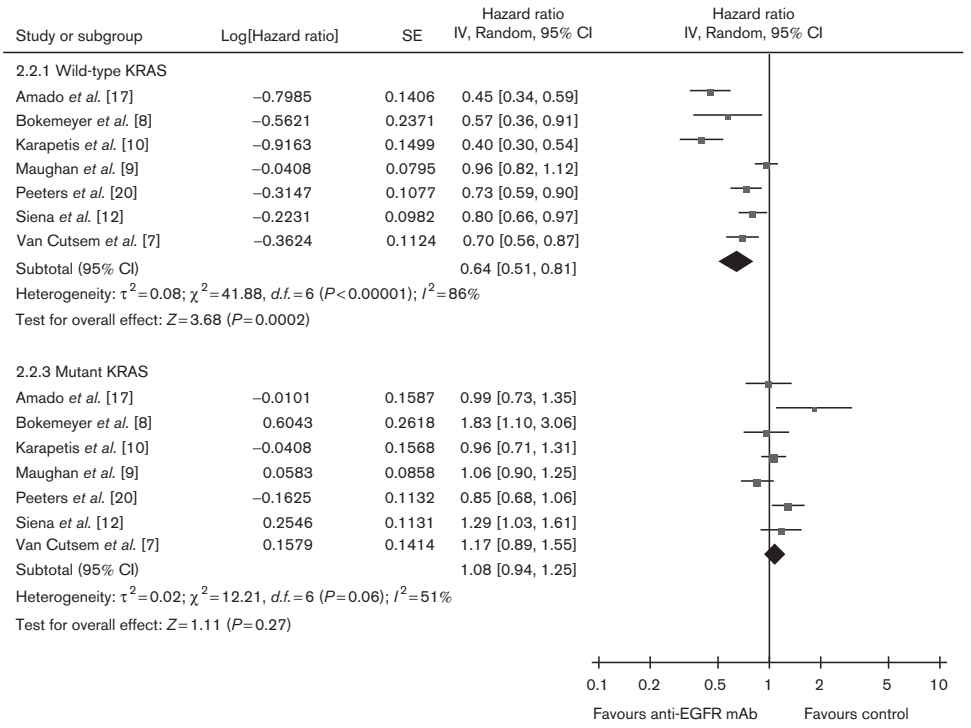
Fig. 3



Meta-analysis of the treatment effects (anti-EGFR antibody vs control) on overall survival (OS) with anti-EGFR monoclonal antibody for the subpopulation based on KRAS mutant status. HR, hazard ratio; CI, 95% confidence interval; Random, random-effects model.

Subgroup analysis based on the KRAS MT status indicated that the benefit in patients with KRAS WT tumors was apparent in relation to a significantly reduced risk of disease progression and reduced risk of survival. These benefits are confined to those mCRC patients whose tumors are WT for KRAS. (Fig. 2). Our analysis also indicates that, in patients with MT KRAS tumors, there was no evidence of a benefit when anti-EGFR mAb was added to chemotherapy or BSC , and in contrast to what was observed in the two studies [8,12], there was no

Fig. 4



Meta-analysis of the treatment effects (anti-EGFR antibody vs control) on progression-free survival (PFS) with anti-EGFR monoclonal antibody for the subpopulation based on KRAS mutant status. HR, hazard ratio; CI, 95% confidence interval; Random, random-effects model.

evidence of a detrimental effect in the MT KRAS subpopulation that received anti-EGFR mAb with chemotherapy or BSC. These results are consistant with an earlier analysis that a significant interaction between the tumor KRAS mutation status and treatment effect was demonstrated for all key efficacy end-points (response, PFS, and OS) [7]. Further investigations are needed to yield additional molecular markers enabling the accurate prediction of which patients with KRAS WT mCRC are most likely to derive a clinical benefit from cetuximab treatment.

There are some caveats in our analysis: first, our review is vulnerable to publication bias and it is possible that negative trials of anti-EGFR antibody may not have been published or presented at these venues. Second, our meta-analysis was based on aggregate study data, and not on individual patient data. Third, the quality of a meta-analysis is always subject to the quality of included studies. Eight of the nine trials included in this meta-analysis were moderate to large RCTs that used ITT analyses. Finally, as is often the case with meta-analyses, the effect of heterogeneity needs to be taken into account.

Despite these limitations, we believe that it is still helpful in the CRC field. Our analysis has demonstrated unequivocally that the addition of anti-EGFR mAb to standard chemotherapy or BSC for mCRC improves PFS and OS compared with standard chemotherapy or BSC alone, and the benefits conferred by EGFR-targeting antibody was limited to patients with KRAS WT tumor.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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