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REVIEW

Cetuximab and panitumumab in KRAS wild-type colorectal cancer: a meta-analysis

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Abstract
Background Anti-epidermal growth factor receptor monoclonal antibodies (panitumumab [P] and cetuximab [C]) are approved and effective only in KRAS wild-type patients with advanced colorectal cancer. The purpose of our meta-analysis is to evaluate the real effects of C and P in KRAS wild-type patients treated in randomized trials.
Patients and methods Eligible studies included prospective, randomized, and controlled trials in which either C or P had been added to standard antineoplastic therapy or best supportive care and data for KRAS wild-type patients only had been calculated. Six thousand three hundred ninety-five patients' tumor samples have been analyzed (total wild-type n=3,254; experimental arm n=1,608; control arm n=1,646). Relative risks (RRs) with 95% confidence intervals (CIs) for response rate were calculated, as well as hazard ratios (HRs) for progression-free survival (PFS) and overall survival.
Results The overall RR of response rate is 1.69 (p =0.003) in all trials. The overall HRs for PFS and survival are 0.65 (p = 0.0006) and 0.84 (p=0.03), respectively, and both are significant. The HRs for PFS and survival in C trials are 0.64 and 0.79, respectively, and 0.65 and 0.87, respectively, in P trials, although only the results achieved in P trials are significant (p=0.0007 and p=0.03). Both response rate (RR=10.94) and PFS (HR=0.51) have increased more in pretreated patients than in first-line trials.
Conclusion The addition of anti-EGFR monoclonal antibodies to standard anticancer therapy in KRAS wild-type colorectal cancer showed an overall significantly increased risk of objective response rate and increased progression-free and overall survival. Only the results achieved in P randomized trials are significant, and the strongest results have been achieved in pretreated patients.

Keywords Advanced colorectal cancer · KRAS · Wild-type · Cetuximab · Panitumumab

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Introduction

Unfortunately, metastatic colorectal cancer (CRC) is still far from being considered a curable disease, except in case of organ-confined (liver or lung) resectable metastatic disease. The ultimate aim of the treatment of stage IV colorectal cancer is to decrease tumor-related symptoms and to prolong the overall survival (OS) without affecting health-related quality of life parameters. In front-line and refractory settings, the introduction of new active biologically targeted agents, namely cetuximab and panitumumab (chimeric and fully human monoclonal antibodies to the epidermal growth factor receptor [EGFR]), has dramatically improved the overall response rate, progression-free survival (PFS), and the OS of subjects in this condition. The EGFR signaling pathway comprises a major target against which several new drugs are currently being developed,

considered attractive and effective for the development of cancer therapies since the molecular structure of the receptor and its tyrosine kinases are well-determined. The EGFR activation is the starting point for a variety of key processes involved in cancer cell growth and migration, including proliferation, angiogenesis, and invasion. This process encompasses an intracellular mitogenic signaling cascade via multiple pathways, mainly RAS/RAF/MAPK, P3IK/AKT, and phospholipase-C. It was previously believed that the degree of EGFR expression by immunohistochemistry was correlated with the potential efficacy of the therapy; however, EGFR expression eventually proved to have no impact on the outcome. KRAS, in particular, is a small guanosine triphosphate-binding proto-oncogene downstream of the EGFR involved in the regulation of cellular proliferation. The ability to determine which patients in particular may benefit from EGFR inhibition would allow caregivers to select potential patients for anti-EGFR therapies. KRAS is mutated in 30–50% of patients with colorectal cancer, and the presence of KRAS mutation is an early phenomenon in colorectal cancer carcinogenesis. The significance of KRAS mutation is crucial for the efficacy of EGFR inhibition. KRAS mutation is observed only in codons 12, 13, and 61 of exon 2. Earlier retrospective data collected from a series of small studies also suggested that the presence of KRAS mutation was prognostic of outcome [1, 2]. In case of KRAS mutation, the ligand binding of EGFR by cetuximab or panitumumab results in a constitutive activation of KRAS by initiating MAPK-mediated signaling without activating cell surface receptors [3]. Multiple retrospective studies indicated that the presence of KRAS mutation affected negatively the potential efficacy of therapies involving EGFR inhibition [4–6]. These findings were confirmed for the first time by a large phase III trial of panitumumab vs. best supportive care (BSC), which showed that the use of panitumumab was beneficial only for PFS in patients with KRAS wild-type (WT) tumors (12.3 weeks); when administered to patients with KRAS mutation tumor type, it achieved no better results than best supportive care (7.3 weeks vs. 7.4 weeks) [7].

This hypothesis, or the lack of efficacy of EGFR inhibition in the presence of KRAS mutation, has been therefore confirmed in a retrospective analysis of the mutation occurred in patients enrolled in prospective randomized trials. These studies compared chemotherapy (or best supportive care) alone and chemotherapy (or best supportive care) plus cetuximab or panitumumab in first or subsequent lines of therapy in advanced CRC. Subgroup analyses have been performed in at least seven trials, in order to verify the benefit of anti-EGFR monoclonal antibodies in WT patients only. We have performed a meta-analysis of the data collected from these trials in terms of relative risk ([RR] of response in treated patients vs. not treated ones), PFS, and OS (hazard ratios [HRs] for progression and survival). The data we have analyzed have been collected from published articles or abstract papers.

Methods

Study selection and data source

A literature search was carried out to identify all relevant randomized controlled trials comparing combined chemotherapy (or best supportive care) with or without cetuximab or panitumumab in advanced CRC. A systematic search has been performed among all the Pubmed and ASCO articles published up to August 2010 in which the terms cetuximab (or Erbitux®), panitumumab (or Vectibix®), KRAS, and colorectal cancer were included. The reference lists of all traced articles for this topic have been manually examined. The quotes selected from this initial search have then been screened for eligibility by the following criteria: (1) patients with advanced CRC; (2) combined chemotherapy (or best supportive care) with vs. without cetuximab or panitumumab and not confounded by additional biologic agents or interventions (i.e., in combination chemotherapy, control, and experimental arms had to differ only by monoclonal antibody component); (3) RCT; and (4) analysis of the outcome and the efficacy of the treatment restricted to the WT population only. We have calculated pooled hazard ratios and the RR (HRs and RRs) with 95% confidence intervals of the seven anti-EGFR monoclonal antibodies trials in terms of response rate, PFS, and OS, by collecting data from different publications (published full articles or abstracts). Two trials conducted on refractory and pretreated patients (by Amado and Karapetis) have been published in full paper [7, 8]. The number of responses as well as the HRs for PFS and OS are taken from this publication. The results obtained in available KRAS WT patients have been analyzed in other five trials (after the first publication of global population outcomes). Three of them were cetuximab first-line trials and the other two were panitumumab trials (one as first-line and one as second-line). The number of responses (events) and the HRs for PFS and OS are taken from the presentation (abstract form) of these latter trials held at a congress [9–12].

Hypothesis and clinical endpoints

Cetuximab and panitumumab are superior in terms of response rate, PFS, and OS in patients with KRAS WT advanced CRC, if added to standard of care (chemotherapy or best supportive care) vs. standard of care alone. No

studies had been originally designed to treat WT patients only; however, a KRAS mutational analysis has been prospectively or retrospectively performed during the trial.

The primary endpoint of the panitumumab trial in refractory patients was PFS. The secondary endpoints included objective response, OS, and safety. In a similar cetuximab trial, the primary endpoint was OS, defined as the time from randomization until death from any cause. The secondary endpoints were PFS, defined as the time from randomization until first objective observation of disease progression or death from any cause, response rates, defined according to the Modified Response Evaluation Criteria in Solid Tumors, and quality of life assessed by mean changes in scores of physical function and global health status at 8 and 16 weeks. In the CRYSTAL trial, the primary endpoint was PFS time, defined as the time from randomization to disease progression or death from any cause within 60 days after the last tumor assessment or after randomization. The secondary endpoints included OS time, rates of best overall response (the proportion of patients with a confirmed complete or partial response, persisting for at least 28 days), and safety endpoints (including incidence and type of adverse events, laboratory variables, and vital signs). In the OPUS trial, the only randomized phase II trial, the primary objective was to assess whether the best confirmed overall response rate of cetuximab plus folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin (FOLFOX)-4 was superior to that of FOLFOX-4 alone. In the COIN trial, two major questions are asked. The first one investigates whether the addition of cetuximab to combination chemotherapy may increase OS, whereas the second one investigates whether intermittent chemotherapy treatment may be comparable to continuous treatment to progression or cumulative toxicity. In the KRAS mutational analysis, the primary endpoint is OS in patients with no mutations detected in codons 12, 13, or 61 of the KRAS gene (the secondary endpoints were OS in KRAS mutant, 'all' wild-type [KRAS, NRAS, and BRAF], 'any' mutant, PFS, response, quality of life, and health economic evaluation).

Two trials investigated whether KRAS WT patients have gained any benefit from panitumumab plus chemotherapy vs. chemotherapy alone. The primary objective of first-line PRIME study is to assess the effects of FOLFOX + panitumumab on PFS by *KRAS* status determined by blinded, independent central testing (the primary endpoint is PFS by blinded central radiology review, while the secondary endpoints are OS, objective response rate, time to progression, duration of response and safety). The primary objective of the 20050181 second-line trial is to assess the effects of folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan (FOLFIRI) + panitumumab on PFS and OS by *KRAS* mutational status determined by blinded, independent central testing (the primary endpoint is PFS by blinded central radiology review and OS; other key endpoints are response rate, time to progression, duration of response, safety and patient-reported outcomes).

Patients and methods

The characteristics of randomized patients are reported in Table 1. In the trial by Karapetis and colleagues, 394 out of 572 tumor samples (68.9% of all randomized patients assigned to receive cetuximab plus best supportive care or best supportive care alone) have been analyzed to investigate activating mutations in exon 2 of the *KRAS* gene. Of the tumors evaluated for *K-ras* mutations, 42.3% showed at least one mutation in exon 2 (codon 12) of the gene. In the panitumumab vs. best supportive care trial, the *KRAS* status was ascertained in 427 (92%) out of 463 patients (208 panitumumab, 219 BSC). *KRAS* mutations were found in 43% of patients. In the pooled analysis of CRYSTAL and OPUS trials (first-line FOLFIRI + cetuximab and FOLFOX + cetuximab) presented at the ASCO Meeting in 2010, the number of samples evaluable for *KRAS* mutations was 1,063 (89%) in the CRYSTAL study (increased by 45% from the original publication) and 315 (93%) in the OPUS study (increased by 69% from the original publication). In the COIN trial, an analysis (intent-to-treat included) was available for 1,316 patients out of 1,630, and 729 of them resulted to be KRAS WT. In PRIME and 20050181 studies, the *KRAS* tumor status was determined by using the DxS kit (Manchester, UK), which tests the seven most common *KRAS* mutations in codons 12 and 13. Of the 1,183 randomized patients, 93% were included in mutational analyses, and 60% of them were KRAS WT. Of the 1,186 patients randomized in the 20050181 study, 91% were included in mutational analyses, and 55% of them resulted to have KRAS WT.

Statistical analysis

RevMan 5.0.24 (Cochrane IMS) has been used for statistical analysis. For the meta-analysis, we have used either a fixed effect model (weighted with inverse variance) or a random effect model. In each meta-analysis, Cochran's Q statistic and I^2 statistics have been calculated first in order to assess the heterogeneity among the proportions of the included trials. In case the p value was found to be less than 0.1, the assumption of homogeneity was deemed invalid and the random effect model was reported. Otherwise, the fixed effect model was reported. A two-tailed p value of less than 0.05 was considered statistically significant. RR>1 for response and HRs<1 for PFS and OS provide greater benefit in anti-EGFR-associated treatments

Table 1 Characteristics of patient in randomized trials

Author/ref	Phase	*N* pts examined for K-ras mutation status/%	Standard arm	Experimental arm	Sex/ median age	KRAS WT % (stand/exp) / centralization (Y/N)/ main mutation (%)	RR WT % (stand/exp)	PFS WT (stand/exp)	OS WT (stand/exp)
Karapetis C.S. N Engl J Med 2008	III	572 / 68.9%	BSC	Cetuximab + BSC	Male 64.8% / 63 .2 years	57.7% vs. 59.1% / Y / [Codons 12 (G12D 35.7%)]	0% vs 12.8 %	1.9 vs. 3.7 months; HR 0.40 ($p<0.001$)	4.8 vs. 9.5 months HR 0.55 ($p<0.001$)
Amado R.G. J Clin Oncol 2008	III	463 / 92%	BSC	Panitumumab + BSC	Male 62.7% / 62.3 years	60.0% vs. 57.0% / Y / 12 Asp(37%)	0% vs. 17%	7.3 vs. 12.3 weekly; HR 0.45 ($p<0.001$)	7.6 vs. 8.1 months; HR 0.99 ($p=0.067$)
Siena S. ASCO 2010	III	1183 / 93%	FOLFOX	FOLFOX + panitumumab	Male 63.2% / 61.7 years	60% vs. 60% / Y / NR	48 % vs. 55%	9.6 vs. 8 months; HR 0.8 ($p=0.02$)	17.7 vs. 23.9 months; HR 0.83 ($p=0.07$)
Peeters M. ASCO 2010	III	1186 / 91%	FOLFIRI	FOLFIRI + panitumumab	Male 60.9% / 61.5 years	54% vs. 56% / Y / codon 12/13	10% vs. 35%	3.9 vs. 5.9 months; HR 0.73 ($p=0.004$)	12.5 vs. 14.5 months; HR 0.85 ($p=0.12$)
Van Cutsem E. N Engl J Med 2009	III	1063 / 89%	FOLFIRI	FOLFIRI + cetuximab	Male 60.5% / 61 years	66.9 vs. 62.1%[a] / Y/ codons 12/13	OR 2.07	HR 0.70	HR 0.80
Bokemeyer C. J Clin Oncol 2009	III	315 / 93% (pooled analysis Bokemeyer ASCO 2010)	FOLFOX	FOLFOX + cetuximab	Male 54% / 61 years	60.8% vs. 54% [a]/ Y / codons 12/13	OR 2.55 pooled analysis Bokemeyer ASCO 2010: 38.5 vs. 57.3; OR 2.16 ($p<0.0001$)	HR 0.57 pooled analysis Bokemeyer ASCO 2010: 7.6 vs. 9.6 months; HR 0.66 ($p<0.0001$)	HR 0.85 pooled analysis Bokemeyer ASCO 2010: 19.5 vs. 23.5 months; HR 0.81 ($p=0.0062$)
Maughan TS ASCO 2010	III	1613 / 81%	5FU or capecitabine + oxaliplatin	5FU or capecitabine + oxaliplatin + cetuximab	Male 66.5% / 63.5 years	45% vs. 44.4% / Y / NR	57% vs. 64%; OR 1.35 ($p=0.049$)	8.8.vs 9.2 months; HR 0.922 ($p=0.36$)	17.9 vs. 17 months; HR 1.038 ($p=0.68$)

BSC best supportive care; *Ref* reference; *N* number; *OS* overall survival; *Y* yes; *N* no; *RR* response rate; *PFS* progression free survival; *OR* odds ratio; *HR* hazard ratio; *WT* wild-type; *FOLFOX* folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin; *FOLFIRI* folinic acid (leucovorin), fluorouracil (5-FU), irinotecan

[a] according to the first published analysis

rather than in no anti-EGFR treatments (chemotherapy or best supportive care alone).

Results

We have performed three different analyses (RR of obtaining a response, HR for PFS, and OS) based on all the studies together, cetuximab vs. panitumumab trials only and first-line vs. second or beyond line trials. The meta-analysis of the risk of obtaining an objective response (events experimental/events control) shows a RR of 1.69 [95% CI 1.20, 2.38; p =0.003 random effect model] with anti-EGFR monoclonal antibody vs. no monoclonal antibody. The HRs for PFS and survival are 0.65 [95% CI 0.51, 0.83; p=0.0006 random effect model] and 0.84 [95% CI 0.73, 0.98; p=0.03 random effect model], respectively, and both of them are significant (Figs. 1, 2, and 3).

We have then performed a meta-analysis of cetuximab and panitumumab trials separately. The RRs for response are 1.35 and 3, respectively, but none of them are significant (p=0.08 for both, comparison performed according to a random effect model). Even after the exclusion of pretreated and refractory patients (trials by Amado and Karapetis), the results were still not significant (data not showed) (Figs. 4, 5, 6, 7, 8, and 9).

As regards PFS and OS, the HRs in cetuximab and panitumumab trials are 0.64 and 0.79, respectively, in the first trial and 0.65 and 0.87, respectively, in the other trials, although the results are significant only in the panitumumab one (p=0.0007 and p=0.03, respectively, according to a random and fixed effect model).

We have finally performed a different analysis on first- and second-line (and beyond) trials separately, and we have found out that the relative RRs are 1.24 [95% CI 1.04, 1.48; p=0.02 according to a random effect model] and 10.94 [95% CI 1.55, 77.11; p=0.02 according to a random effect model], respectively (Figs. 10 and 11). The chances of obtaining a response are therefore tenfold higher in second or further lines of therapy (pretreated patients) with cetuximab or panitumumab. This chance is 30-fold higher compared to best supportive care alone (RR 33.84; p= 0.0005) also in patients who have been pretreated with all available agents (fluoropyrimidine, oxaliplatin, and irinotecan) (Fig. 10 and 11).

The HR for PFS in first-line trial is 0.80 [95% CI 0.64, 1.00; p=0.05] and 0.51 in further line trials [95% CI 0.35, 0.76; p=0.0007] (Figs. 12 and 13).

As regards to survival, the HRs are 0.89 [95% CI 0.75, 1.06; p=0.19] and 0.78 [95% CI 0.57, 1.06; p=0.11], but none of them are significant (Figs. 14 and 15).

Discussion

The results of this meta-analysis confirm that the addition of an anti-EGFR monoclonal antibody to standard therapy (chemotherapy in first- and second-line or best supportive care) increases by 69% chances of achieving an objective response and significantly reduces the risk of progression and death by 35% and 16%. The results are different if cetuximab and panitumumab are considered separately, as a confirmation of the fact that the two agents have different mechanisms of action and related antitumor effects. Therefore, in this case, neither cetuximab nor panitumumab significantly increase the chance of achieving an objective response, although both of them show a progression delaying effect (they both reduce the hazard of progression by a third). Only panitumumab significantly reduces the risk of death (HR 0.87). A positive effect of panitumumab has been recently observed even in KRAS-mutant patients (especially in patients with severe cutaneous rash), a setting where anti-EGFR agents are overall ineffective. The response-predictive role of rash may be linked to an immunomediated effect of the drug (antibody-dependent cell-mediated cytotoxicity), not necessarily dependent to

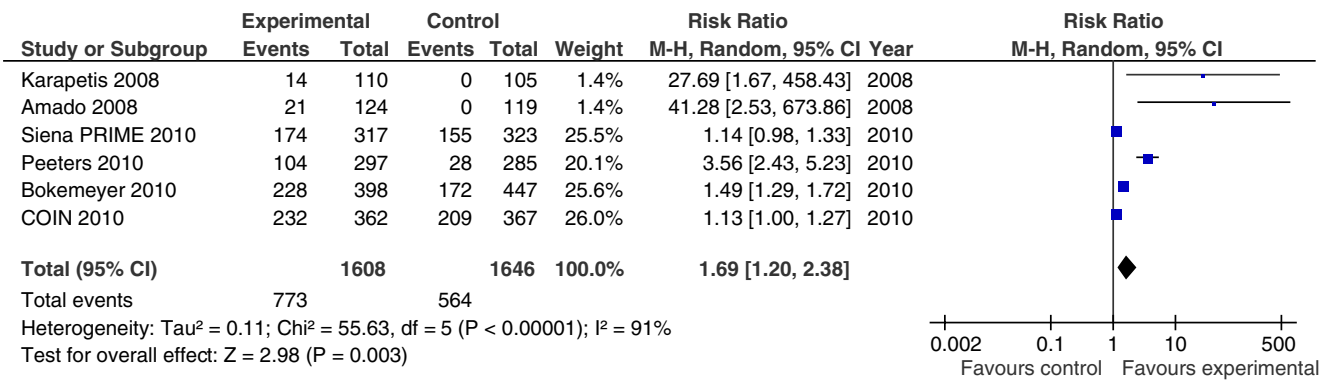

Fig. 1 RR of obtaining a response with anti-EGFR monoclonal antibodies added to standard therapy (chemotherapy or best supportive care)

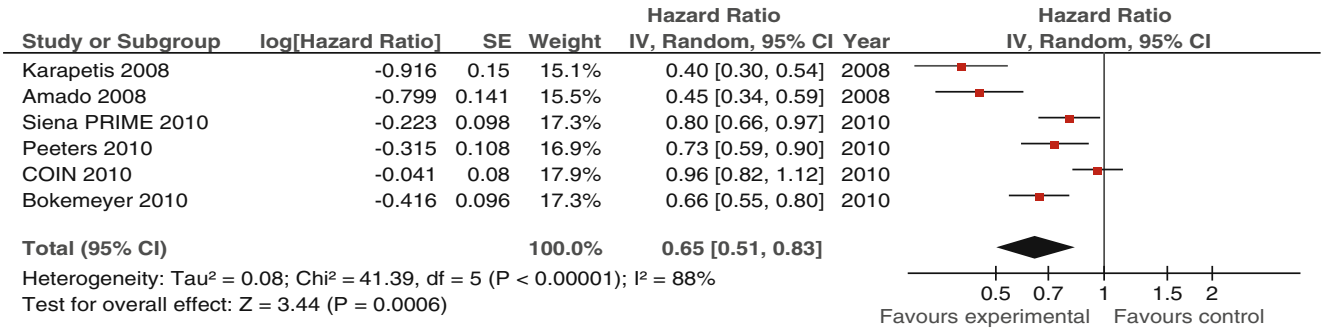

Fig. 2 HR for PFS with anti-EGFR monoclonal antibodies added to standard therapy (chemotherapy or best supportive care)

EGFR pathway, and may be useful to obtain a cytostatic effect [13, 14].

Paradoxically, these agents provide the best results in pretreated patients (exposed to at least one line or to all available agents) when no other chances of cure are available. This is important because patients can now live longer and are exposed to multiple lines of chemotherapy. Unfortunately, this valid option is not available for KRAS-mutated patients who can undergo a limited number of active treatments, where all active agents have to be necessarily administered in first- and second-line therapy. Thus, cetuximab and panitumumab can be administered to all KRAS WT patients not only in first-line therapy, where even other agents work (e.g., bevacizumab). In fact, it is well known that anti-angiogenetic agents, such as anti-vascular endothelial growth factor (VEGF) ones are equivalent in WT populations, but ineffective in heavy pretreated patients [15]. It is also important to consider other types of mutations that might circumvent anti-EGFR activity and the prognosis of patients. Particular groups of KRAS WT patients who show no response to treatment include BRAF-, NRAS-, and PI3K-mutant patients [16].

However, it must be said that no survival gain is now likely to be obtained with first-line therapy in a sequence of multiple lines of systemic therapy, but, if any, it would be confounded by post-progression therapies. It is also well known that a PFS advantage is a good surrogate endpoint of survival in colorectal cancer with upfront treatments [17].

Anti-EGFR agents in KRAS WT populations seem best suited as first-line therapy in patients with (resectable or borderline resectable) liver-confined disease (in the presence of positive data with FOLFOX plus or minus cetuximab) [18, 19]. However, in patients with unresectable liver metastases, aggressive multi-agent chemotherapy (e.g., FOLFOXIRI plus or minus bevacizumab or FOLFIRI plus or minus bevacizumab) provides similar or even better results in unselected patients (response rates are 47.2 and 57.9%, respectively, with FOLFIRI alone and with bevacizumab in the BICC-C study). In particular, in the Falcone GONO phase-III trial, the response rate achieved with FOLFOXIRI schedules was 60% and the HRs for progression and death were 0.63 and 0.70, respectively. In this setting, bevacizumab is effective if added to chemotherapy even in unselected populations (including KRAS-mutant ones) [20–25]. A similar meta-analysis of bevacizumab randomized trials in metastatic CRC showed a significant PFS benefit (HR=0.66) and an OS benefit (HR=0.77) in favor of the combined treatment. The overall response rate was significantly higher in the bevacizumab arm (RR=1.5). This result is very similar to ours [26]. The advantage of anti-EGFR agents is that they produce virtually no cardiovascular toxicity, which

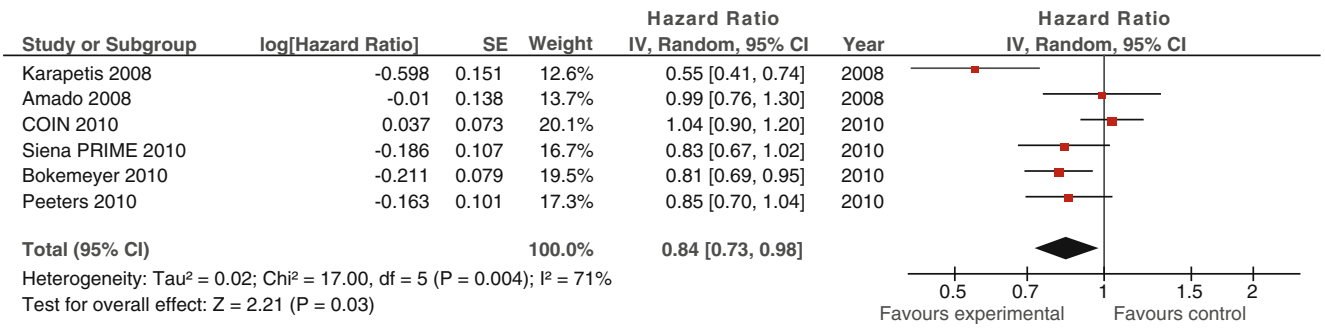

Fig. 3 HR for OS with anti-EGFR monoclonal antibodies added to standard therapy (chemotherapy or best supportive care)

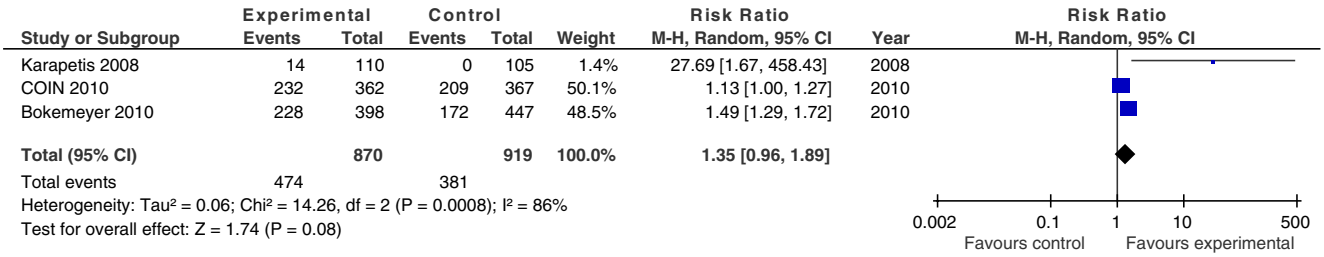

Fig. 4 RR for response with cetuximab added to standard therapy (chemotherapy or best supportive care)

makes them particularly suitable also for patients with contraindications to bevacizumab.

Overall, one of the most important roles of anti-EGFR monoclonal antibodies is played in pretreated settings (second or further lines), where the risk of obtaining an objective response is tenfold higher than in standard therapy and the risk of progression or death is overall reduced by half, especially with cetuximab (HRs are 0.4 and 0.55, respectively, for PFS and OS as in the trial by Karapetis). In this phase of the natural history of colorectal cancer, anti-angiogenetic agents are minimally effective or not at all; therefore, they are best reserved for upfront therapy. In first-line settings, chemotherapy + bevacizumab are probably as suitable as anti-EGFR agents in patients with no contraindications for this drug (e.g., elderly or severe cardiovascular disease), and may represent one of the best choices. In second or further line settings, cetuximab (also associated with irinotecan) or panitumumab monotherapies are probably the standard of care in WT patients pretreated with chemotherapy (FOLFOX or FOLFIRI) and bevacizumab.

The ideal characteristics of patients suitable for anti-EGFR monoclonal antibodies are not defined yet, although WT patients (WT for KRAS, BRAF, NRAS, PTEN, and PI3K) seem to be the most responsive candidates. Overall, the best sequence of targeted agents (anti-EGFR followed by anti-VEGF or vice versa) has yet to be identified and needs further clinical investigation with specifically addressed trials.

Finally, the above mentioned BRAF mutational status seems to be related to lower outcome and response in patients with KRAS WT CRC. Thus, screening for BRAF and other mutations [9, 10, 16, 27–29] may improve the selection of patients for anti-EGFR monoclonal antibodies.

Conclusion

To our knowledge, this meta-analysis is the first of its kind confirms that cetuximab and panitumumab increase the response rate and significantly reduce the risk of progression and death only in KRAS WT populations with advanced CRC. These data have been collected from seven randomized phase-II and III trials in which the outcome was reported after analysis of the enrolled non-mutated population. The two drugs do not exert the same effects, and panitumumab provides more robust results. In fact, if analyzed separately, both cetuximab and panitumumab increase the RR of obtaining a response and reduce the risk of progression, but only panitumumab significantly reduces the risk of death (by 13%). Overall, their activity in terms of tumor regression is tenfold higher in pretreated patients and the progression-delaying effect is stronger in the same population (50% reduction in risk of progression). No effects were observed in the OS, either in first or subsequent lines of therapy.

In conclusion, all patients with advanced CRC should be tested for KRAS mutation and possibly for other mutations (e.g., BRAF), and, if already exposed to all available agents (fluoropyrimidine, oxaliplatin, and irinotecan), they should receive cetuximab or panitumumab (if they have not been

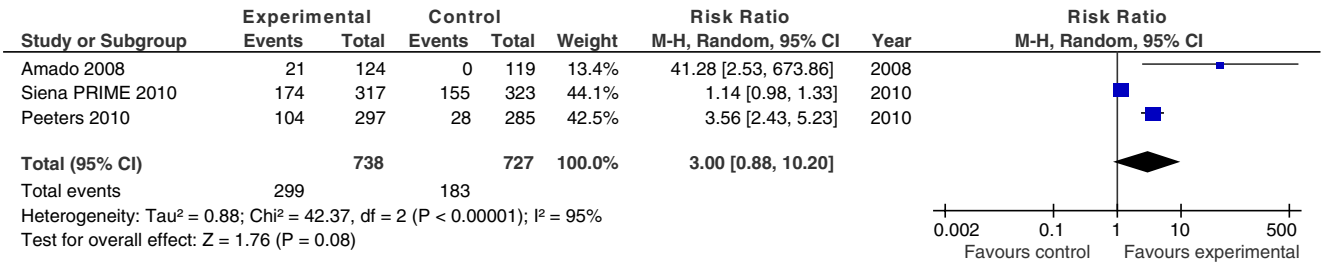

Fig. 5 RR for response with panitumumab added to standard therapy (chemotherapy or best supportive care)

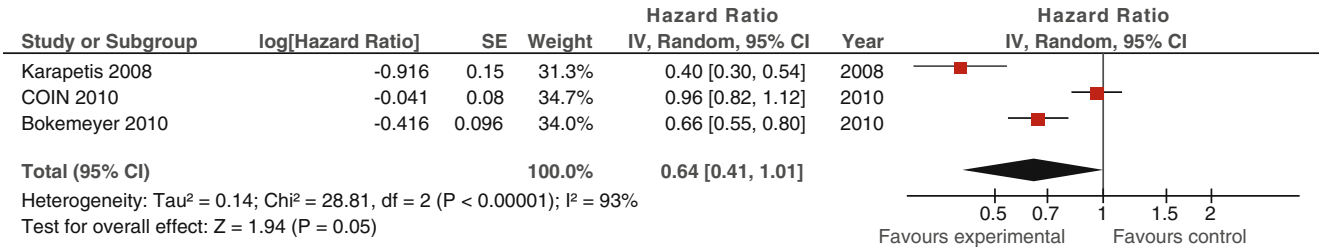

Fig. 6 HR for PFS with cetuximab added to standard therapy (chemotherapy or best supportive care)

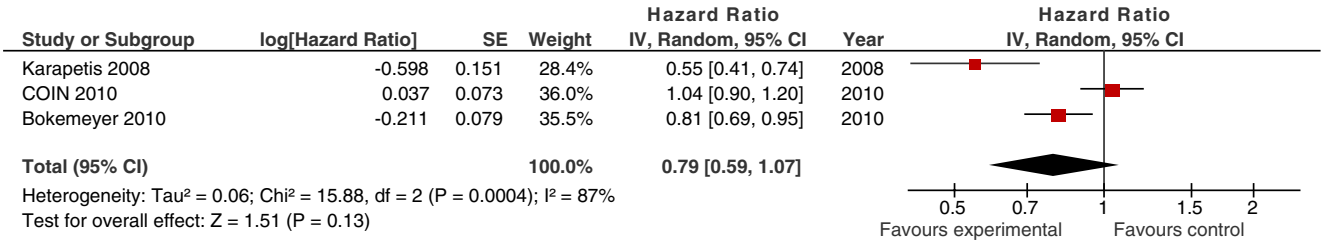

Fig. 7 HR for OS with cetuximab added to standard therapy (chemotherapy or best supportive care)

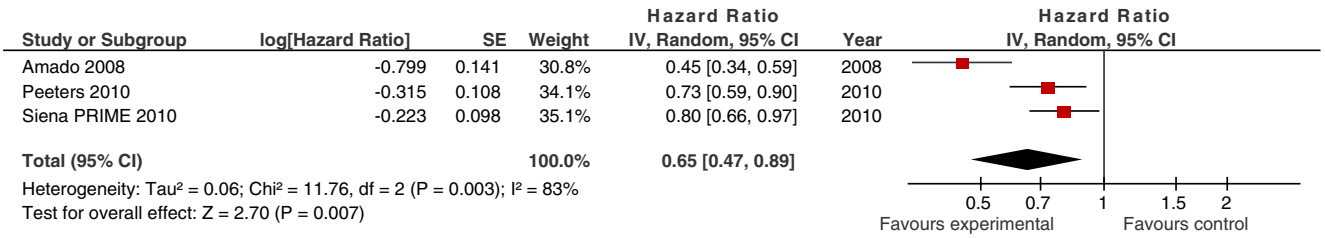

Fig. 8 HR for PFS with panitumumab added to standard therapy (chemotherapy or best supportive care)

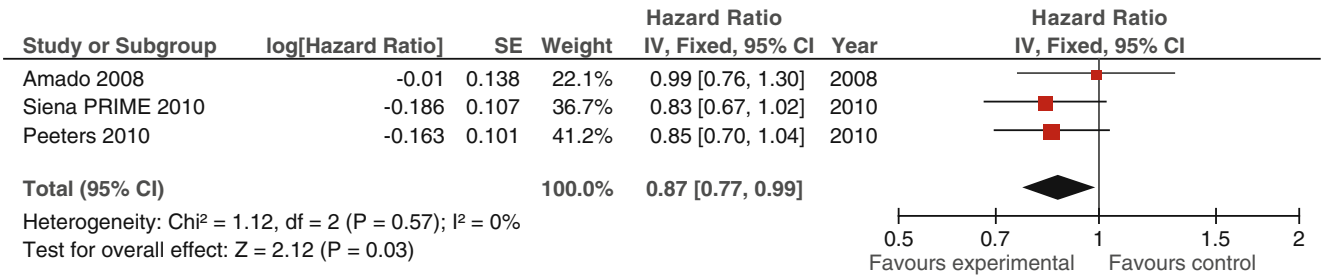

Fig. 9 HR for OS with panitumumab added to standard therapy (chemotherapy or best supportive care)

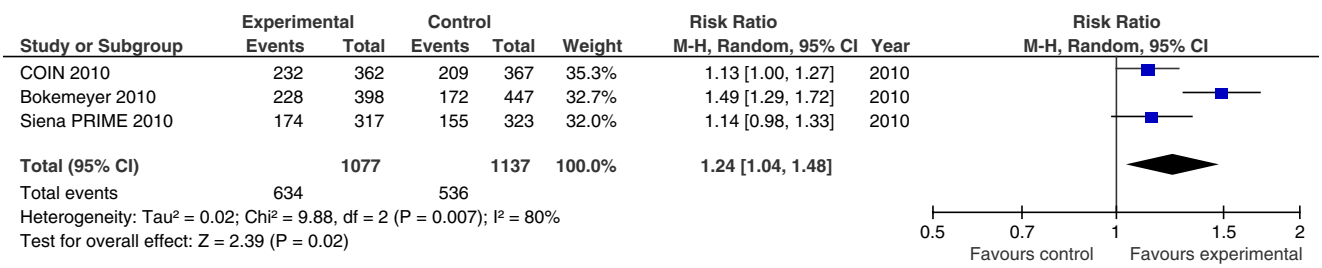

Fig. 10 RR for response rate in first-line trials

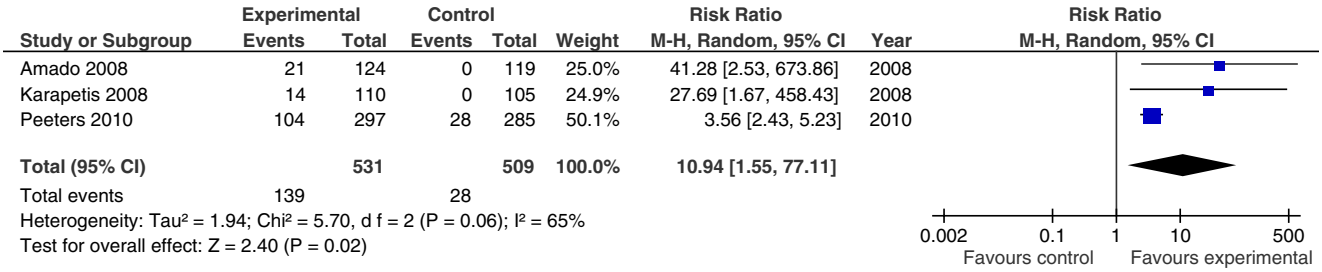

Fig. 11 RR for response rate in further line (second and beyond) trials

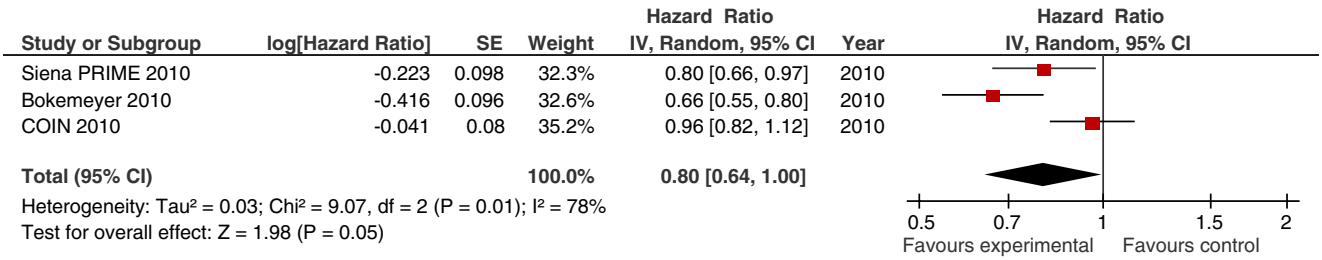

Fig. 12 HR for PFS in first-line trials

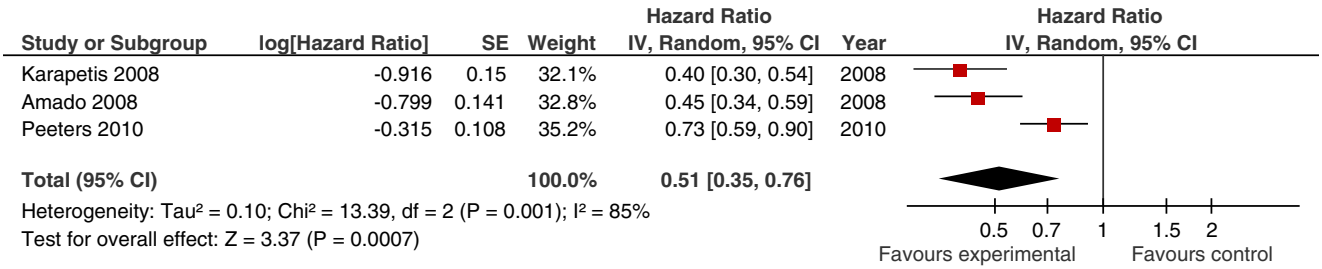

Fig. 13 HR for PFS in further line (second and beyond) trials

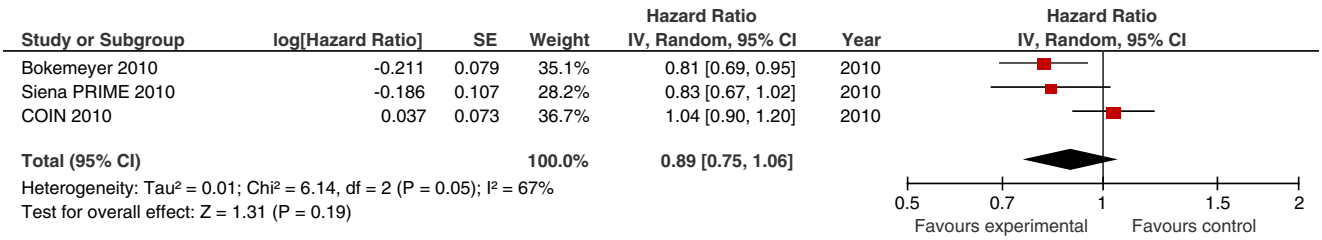

Fig. 14 HR for OS in first-line trials

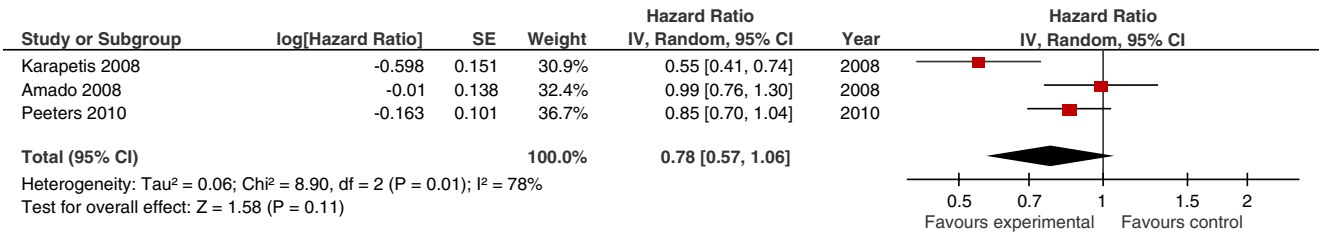

Fig. 15 HR for OS in further line (second and beyond) trials

treated with such agents during the natural history of the disease). In first-line settings, anti-EGFR agents combined with chemotherapy are a suitable alternative to anti-angiogenetic agents with neoadjuvant (conversion therapy) or palliative aims (unresectable disease). Second-line settings may be optimal for such combinations, since bevacizumab was found to be substantially ineffective in heavily pretreated disease. The study of their role as adjuvant therapy in high risk (resected) CRC is still in progress.

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Conflict of interest The authors disclose any potential conflict of interest with any of the commercially available drugs quoted in the paper.

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