



Original Research

# A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with *RAS* wild-type metastatic colorectal cancer



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## KEYWORDS

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**Abstract Background:** Head-to-head trials comparing first-line epidermal growth factor receptor inhibitor (EGFRI) versus vascular endothelial growth factor inhibitor (bevacizumab) therapy yielded differing results, and debate remains over optimal first-line therapy for patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC).

**Methods:** A PubMed search identified first-line mCRC trials comparing EGFRI plus chemotherapy versus bevacizumab plus chemotherapy; data were subsequently updated using recent congress presentations. This study-level meta-analysis estimated the overall survival (OS) treatment effect of first-line chemotherapy plus EGFRI or bevacizumab in patients with *RAS* WT mCRC. Secondary end-points were progression-free survival (PFS), objective response rate (ORR), resection rate and safety. Early tumour shrinkage (ETS) of  $\geq 20\%$  at week 8 was an exploratory end-point.

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**Results:** Three trials comprising data from 1096 patients with *RAS* WT mCRC were included. OS (hazard ratio [HR]: 0.80 [95% confidence interval: 0.68–0.93]), ORR (odds ratio [OR]: 0.57) and ETS (OR: 0.48) favoured EGFRIs plus chemotherapy versus bevacizumab plus chemotherapy. PFS (HR: 0.98) and resections (OR: 0.93) were similar between treatments. For patients with *KRAS* exon 2 WT/‘other’ *RAS* mutant mCRC the OS HR was 0.70. A safety meta-analysis was not possible due to a lack of data; in the individual studies, skin toxicities and hypomagnesaemia were more common with EGFRIs, nausea and hypertension were more common with bevacizumab.

**Conclusions:** This meta-analysis supports a potential benefit for first-line EGFRi plus chemotherapy versus bevacizumab plus chemotherapy with respect to OS, ORR and ETS in patients with *RAS* WT mCRC. A patient-level meta-analysis is awaited.

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## 1. Introduction

Irinotecan- or oxaliplatin-based chemotherapy combined with epidermal growth factor receptor inhibitors (EGFRIs: cetuximab and panitumumab) or the vascular endothelial growth factor inhibitor (VEGFI) bevacizumab are standard first-line treatments for patients with metastatic colorectal cancer (mCRC) [1–3]. The efficacy of FOLFIRI and FOLFOX appears similar in these patients, although toxicity profiles differ [4]. Choice of chemotherapy backbone appears to have no significant impact when given alongside biological therapy in the first-line setting [5–7]; therefore, the key treatment choice is which targeted agent to give upfront. Evaluation of mutations in exons 2, 3 and 4 of *KRAS* and *NRAS* (extended *RAS* analysis) improves identification of patients unlikely to respond to EGFRIs compared with evaluating *KRAS* exon 2 alone and is essential before beginning EGFRi therapy [8,9]. The importance of evaluating tumour *RAS* status ahead of bevacizumab treatment is less clear [10–12].

Data from three head-to-head first-line trials have been reported evaluating EGFRIs versus bevacizumab in patients with mCRC [13–17]. In general, progression-free survival (PFS) was similar between treatments, but two of the three trials indicated an overall survival (OS) benefit for EGFRIs in patients with *RAS* wild-type (WT) mCRC [14,17]. In contrast, the largest trial reported no PFS or OS differences [15]. Debate, therefore, remains over optimal first-line therapy for patients with *RAS* WT mCRC and the potential impact of treatment sequencing on long-term survival. The aim of this study-level meta-analysis was to determine the relative efficacy of first-line treatment with EGFRIs + chemotherapy versus bevacizumab + chemotherapy, specifically in patients with *RAS* WT mCRC.

## 2. Methods

### 2.1. Search strategy and selection criteria

A PubMed search was conducted in July 2015 including the search terms ‘EGFR’ or ‘VEGF’ and ‘panitumumab/

cetuximab/bevacizumab’ and ‘metastatic CRC’ and ‘trial or study’. From the results obtained, first-line trials comparing EGFRIs + chemotherapy versus VEGFI (bevacizumab) + chemotherapy were manually selected. Once relevant trials were identified, key congresses (ASCO 2014, ESMO 2014, ECC 2015) in the prior 2 years were manually searched for updated data. More up-to-date, unpublished data on file were included, where available.

### 2.2. Objectives

The primary objective of this meta-analysis was to estimate the treatment effect on OS of first-line EGFRIs + chemotherapy versus first-line bevacizumab + chemotherapy in patients with *RAS* WT mCRC. Secondary objectives included estimation of the treatment effect on PFS, objective response rate (ORR), resection rates and safety (grade 3/4 adverse events [AEs]). Early tumour shrinkage (ETS) of  $\geq 20\%$  at week 6 or 8 was an exploratory end-point.

### 2.3. Analyses

Data for patients with *RAS* WT mCRC were extracted into SAS datasets. Where investigator assessed and independent, centrally reviewed response data were available, the latter were included in the analysis. The *RAS* WT population included all patients without detectable mutations in *KRAS* or *NRAS* exons 2, 3 or 4. The primary analysis set was based on the *RAS* WT population, assumed that FOLFOX and FOLFIRI were equivalent and used both stratified and unstratified hazard ratios (HRs), where data were available. Random- and fixed-effects models were used for the primary analysis. Sensitivity analyses were conducted to evaluate the primary and secondary end-points using FOLFOX only and FOLFIRI only as the backbone chemotherapy.

For dichotomous data, the number of patients with the outcome of interest was collected by treatment group. Rates and odds ratios (ORs), and relative

differences with corresponding 95% confidence intervals (CIs) and p-values, were extracted where available, or calculated (where possible). For continuous outcomes, medians, range, with corresponding 95% CIs and p-values were collected by treatment group, where available, or calculated (where possible). Time-to-event outcomes (OS and PFS) were reported using HRs with corresponding 95% CIs and p-values. Meta-analysis techniques, including fixed-effects modelling (unconditional maximum likelihood method) and random-effects modelling (DerSimonian and Laird modelling methods) [18], were used to pool study-level trial data using the inverse-variance of each study as the weight. Meta-analysis of trial HRs or ORs (dependent on end-point) were performed using SAS version 9.2 or higher. Heterogeneity was statistically assessed using the I<sup>2</sup> statistic. Baseline demographics/disease characteristics were indirectly compared across trials and key safety/tolerability data summarised for each study. The most recently reported data for each trial were included in the analyses; data for the *KRAS* exon 2 WT population were included for completeness where corresponding data for the *RAS* WT population were not available.

### 3. Results

Three first-line, head-to-head mCRC trials were included in the meta-analysis (one trial had only been published in abstract form, but was included in a meta-analysis identified on PubMed). These were CALGB/SWOG 80405 (phase III trial comparing bevacizumab or cetuximab + FOLFOX or FOLFIRI [NCT00265850]) [13,15], FIRE-3 (phase III trial comparing cetuximab + FOLFIRI versus bevacizumab + FOLFIRI [NCT00433927]) [16,19] and PEAK (phase II trial comparing panitumumab + FOLFOX versus bevacizumab + FOLFOX [NCT00819780]) [17,20].

These studies included a total of 1096 patients with *RAS* WT mCRC. This comprised 526 [15], 400 [16] and 170 [20] patients from CALGB/SWOG 80405, FIRE-3 and PEAK, which represented 46%, 68% and 60% of the study intent-to-treat populations, respectively.

Baseline data were reported for the *RAS* assessable/evaluable populations in CALGB [15] and FIRE-3 [14] and for the *RAS* WT population in PEAK [17]. In general (where reported), study populations appeared similar with respect to sex, age, Eastern Cooperative Oncology Group performance status, prior adjuvant therapy and number of metastatic sites (Table 1). Primary colon cancer was more common in PEAK than FIRE-3 (71% and 59% [not reported in CALGB]), whereas liver-only metastases were present in 34%, 25% and 27% of patients in CALGB, FIRE-3 and PEAK, respectively. For the reader's reference, a summary of key efficacy data for the *RAS* WT population from each trial is included in Table 2.

Table 1  
Summary of key baseline characteristics and demographics for the clinical studies comparing first-line epidermal growth factor receptor inhibitors + chemotherapy versus first-line bevacizumab + chemotherapy and reporting results for patients with *RAS* wild-type metastatic colorectal cancer.

Study phase	<i>RAS</i> assessable/evaluable <sup>a</sup> population [14,16,20]	n	Median age, years (range)	Male sex, %	ECOG PS 0/1, %	Primary colon cancer, %	Prior radiotherapy, %	Prior adjuvant chemotherapy, %	≥2 metastatic sites, %	Liver metastases only, %
III	CALGB/SWOG 80405 (ITT N = 1137)	346	59 (21–90)	62	NR	NR	9	14	NR	36
	Cetuximab + chemotherapy <sup>b</sup> Bevacizumab + chemotherapy <sup>b</sup>	324	60 (23–84)	64	NR	NR	9	15	NR	33
III	FIRE-3 (ITT N = 592)	205	64 (41–76)	71	98	59	9	17	55	37
	Cetuximab + FOLFIRI Bevacizumab + FOLFIRI	202	65 (33–76)	66	99	59	14	20	55	34
II	PEAK (ITT N = 285)	88 <sup>a</sup>	62 (23–82)	66	100	73	NR	NR	64	26
	Panitumumab + FOLFOX Bevacizumab + FOLFOX	82 <sup>a</sup>	60 (39–82)	68	99	70	NR	NR	59	27

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported.  
<sup>a</sup> Data for the *RAS* wild-type population reported for PEAK; ITT, intent-to treat (*KRAS* exon 2 wild-type) population.  
<sup>b</sup> Chemotherapy included FOLFOX for ~75% of patients and FOLFIRI for ~25% of patients.

**Table 2**  
Summary of key efficacy data from clinical studies comparing first-line epidermal growth factor receptor inhibitors + chemotherapy versus first-line bevacizumab + chemotherapy and reporting results for patients with *RAS* wild-type metastatic colorectal cancer.

	Primary end-point	<i>RAS</i> wild-type population [15,16,20]					
		n	Median OS, months	Median PFS, months	ORR (%)	ETS <sup>a</sup> (%)	Median DpR <sup>b</sup> (%)
CALGB/SWOG 80405	OS						
Cetuximab + chemotherapy <sup>c</sup>		270	32.0	11.4	69	NR	NR
Bevacizumab + chemotherapy <sup>c</sup>		256	31.2	11.3	54	NR	NR
HR or OR (95% CI)			HR: 0.9 (0.7, 1.1); p = 0.40	HR: 1.1 (0.9, 1.3); p = 0.31	NR; p < 0.01	NR	NR
FIRE-3	ORR						
Cetuximab + FOLFIRI		199	33.1	10.3	72	68	49
Bevacizumab + FOLFIRI		201	25.0	10.2	56	49	32
HR or OR (95% CI)			HR: 0.70 (0.54, 0.90); p = 0.0059	HR: 0.97 (0.78, 1.20); p = 0.77	OR: 2.01 (1.27, 3.19); p = 0.003	OR: 2.22 (1.41, 3.47); p = 0.0005	NR; p < 0.0001
PEAK	PFS						
Panitumumab + FOLFOX		88	36.9	12.8	65	75	65
Bevacizumab + FOLFOX		82	28.9	10.1	60	62	46
HR or OR (95% CI)			HR: 0.76 (0.53, 1.11); p = 0.15	HR: 0.68 (0.48, 0.96); p = 0.029	OR: 1.12 (0.56, 2.22); p = 0.86	OR: 1.67 (NR); p = 0.21	p = 0.0018

Abbreviations: CI, confidence intervals; DpR, depth of response; ETS, early tumour shrinkage; HR, hazard ratio; NR, not reported; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

<sup>a</sup> Proportion of patients with ETS of  $\geq 20\%$  at week 6 or 8.

<sup>b</sup> Percentage of maximal tumour shrinkage at nadir versus baseline.

<sup>c</sup> Chemotherapy included FOLFOX for  $\sim 75\%$  of patients and FOLFIRI for  $\sim 25\%$  of patients.

### 3.1. Meta-analysis of efficacy

Meta-analysis results for OS in the *RAS* WT population favoured EGFRIs + chemotherapy versus bevacizumab + chemotherapy (HR: 0.80 [95% CI: 0.68, 0.93]; Fig. 1A). For patients with *KRAS* exon 2 WT/other *RAS* mutant mCRC, the OS HR (95% CI) was 0.70 (0.50, 0.99) (Supplemental Fig. A1; includes previously unpublished FIRE-3 data). In the PFS analysis of *RAS* WT patients, the HR (95% CI) for the EGFRIs + chemotherapy versus bevacizumab + chemotherapy was 0.98 (0.86, 1.12), suggesting no difference between treatments (Fig. 1B). For ORR, the OR favoured the EGFRIs (0.57 [95% CI: 0.42, 0.76]; Fig. 2A) and the relative difference (EGFRIs + chemotherapy [%] minus

bevacizumab + chemotherapy [%]) was  $-13.1$  (95% CI:  $-19.7, -6.6$ ) (Fig. 2B).

Sensitivity analyses of OS and PFS by chemotherapy backbone are shown in Supplemental Figs. A2 and A3.

ETS data for the *RAS* WT population were available from FIRE-3 (ETS at week 6 reported) and PEAK (ETS at week 8 reported). ETS occurred at a significantly higher rate in EGFRi-treated patients (OR: 0.48 [95% CI: 0.33, 0.71]; Supplemental Fig. A4A). The relative difference in ETS rates was  $-17.0$  (95% CI:  $-25.4, -8.5$ ; Supplemental Fig. A4B).

At the time of analysis, resection data for the *RAS* WT population were only available from FIRE-3 and PEAK (Supplemental Fig. A5; includes previously unpublished FIRE-3 data). The OR

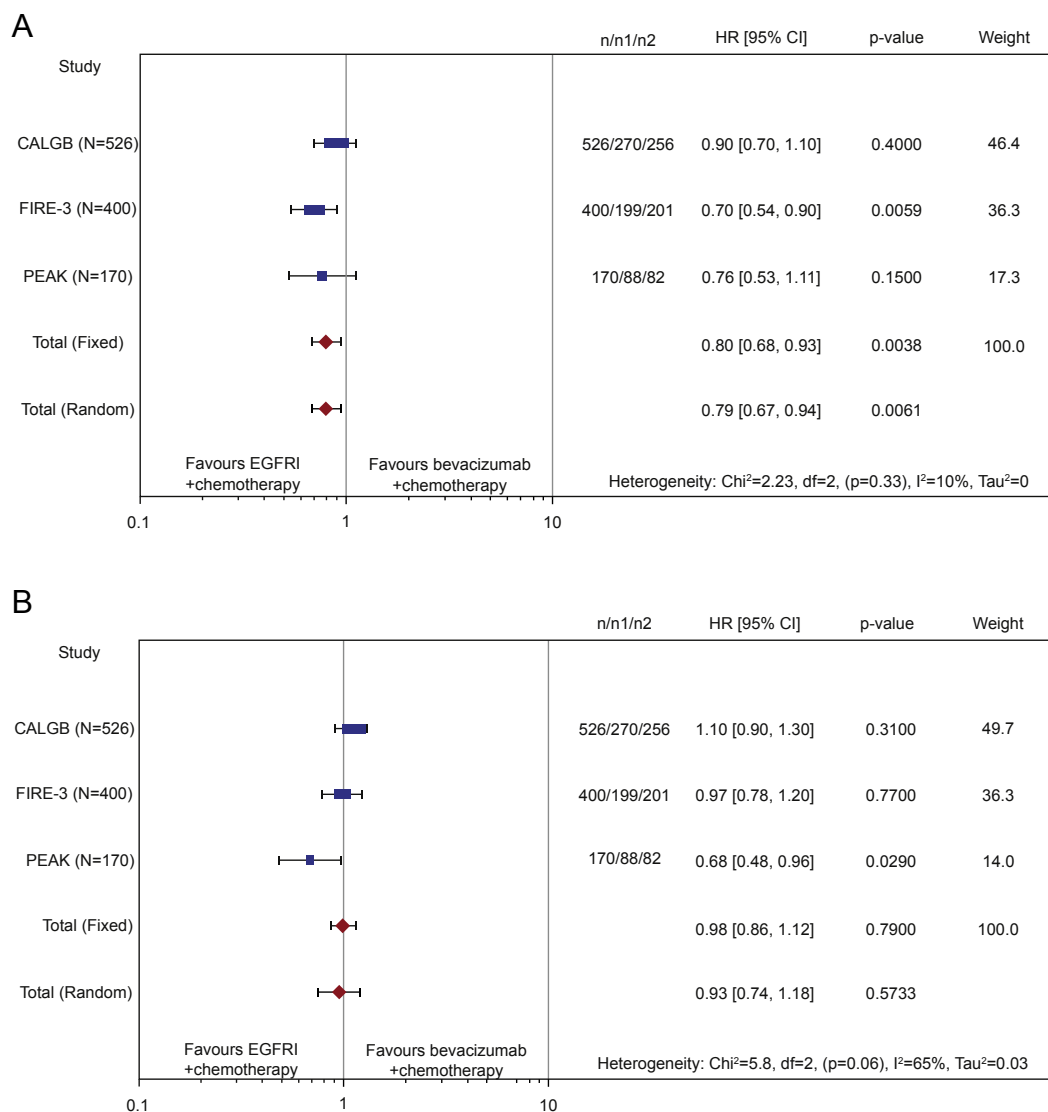


Fig. 1. Forest plots showing meta-analysis results for (A) overall survival, (B) progression-free survival (*RAS* wild-type population). Weight is relative weight (%) from the fixed-effect model. p-value is two sided. CI, confidence interval; EGFRi, epidermal growth factor receptor inhibitor; HR, hazard ratio; N, total study size, n, total number evaluable; n1, number evaluable in the EGFRi arm; n2, number evaluable in the bevacizumab arm.

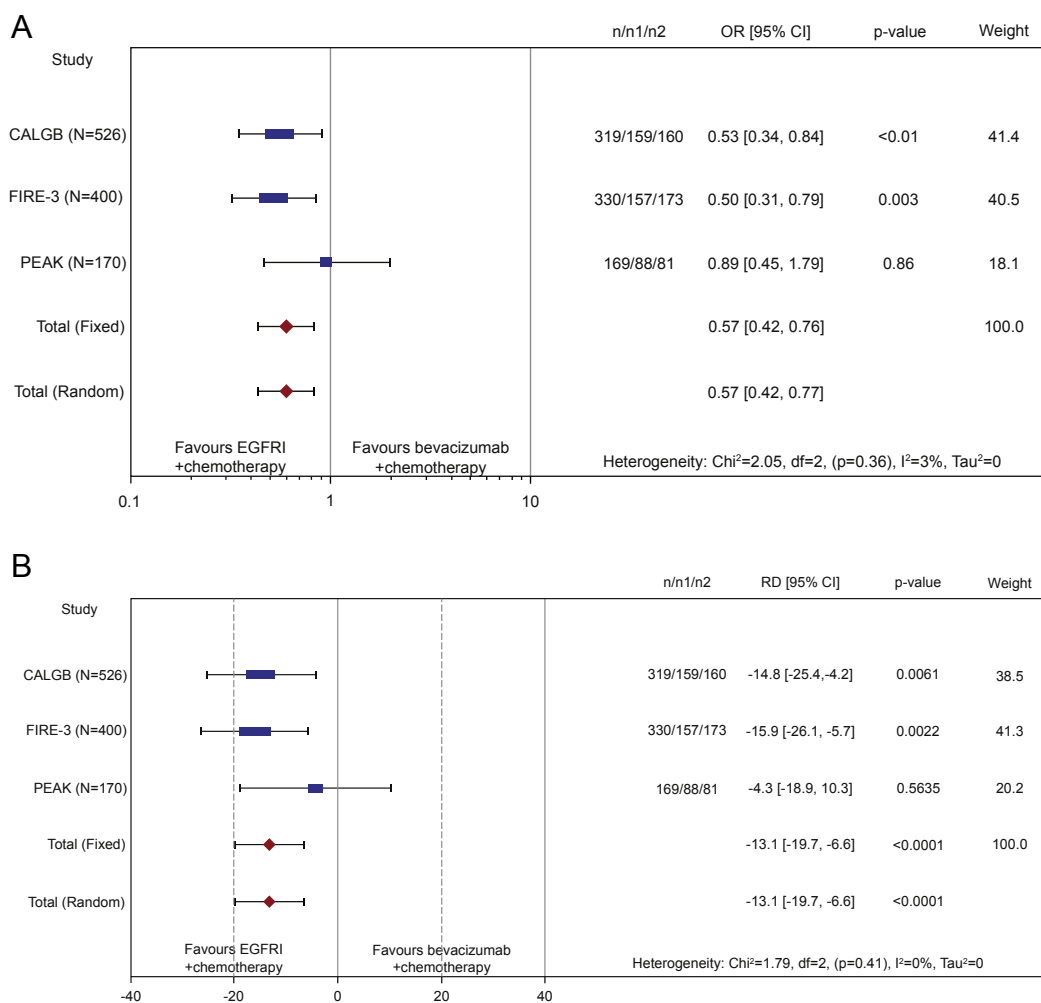


Fig. 2. Forest plot showing meta-analysis results for (A) objective response rate, (B) relative difference in objective response rates (*RAS* wild-type population). Weight is relative weight (%) from the fixed-effect model. p-value is two sided. CI, confidence interval; EGFRi, epidermal growth factor receptor inhibitor; N, total study size, n, total number evaluable; n1, number evaluable in the EGFRi arm; n2, number evaluable in the bevacizumab arm; OR, odds ratio, EGFRi + chemotherapy/bevacizumab + chemotherapy; RD, risk difference, bevacizumab + chemotherapy (%) – EGFRi + chemotherapy (%).

(95% CI) for EGFRi + chemotherapy versus bevacizumab + chemotherapy was 0.93 (0.57, 1.51), suggesting no difference between treatments.

### 3.2. Safety

A meta-analysis of safety was not possible because comparable *RAS* WT data were not available for all three studies. Grade 3/4 AE data were reported for the *KRAS* exon 2 WT population in CALGB/SWOG 80405 (Supplemental Table A1A) [13]. Grade 3 rash (7% versus 0%) and grade  $\geq 3$  diarrhoea (11% versus 8%) were more common for cetuximab versus bevacizumab, respectively. Grade  $\geq 3$  neuropathy (14% versus 12%), hypertension (7% versus 1%) and gastrointestinal events (2% versus 0.5%) were more common for bevacizumab versus cetuximab, respectively. There were 10 grade 5 AEs (bevacizumab n = 7 [1%], cetuximab n = 3 [0.5%]).

AEs were also reported for the *KRAS* exon 2 WT population in FIRE-3 (Supplemental Table A1B) [14]. Of the grade 3/4 AEs with a  $\geq 2\%$  difference in incidence between treatments, skin reactions (26% versus 2%), haematotoxicity (25% versus 21%), acneiform rash (17% versus 0%), hypokalaemia (7% versus 3%), desquamation (7% versus 0.7%), paronychia (6% versus 0%), hypomagnesaemia (4% versus 0.7%), infusion-related allergic reaction (4% versus 0%), and hand-foot syndrome (3% versus 0.7%) were more common for cetuximab versus bevacizumab, respectively. Diarrhoea (14% versus 11%), pain (7% versus 5%) and nausea (5% versus 3%) were more common for bevacizumab versus cetuximab, respectively. There were eight grade 5 AEs (affecting five patients [2%]) all in the bevacizumab group.

PEAK [17] was the only trial to report AEs in the *RAS* WT population. Of the grade 3/4 AEs with a  $\geq 2\%$

difference in incidence between treatments, skin disorders (34% versus 1%), fatigue (12% versus 10%), hypomagnesaemia (8% versus 0%), mucosal inflammation (7% versus 3%), stomatitis (7% versus 0%), dehydration (6% versus 1%), decreased appetite (6% versus 0%), and paronychia (2% versus 0%) were more common for panitumumab versus bevacizumab, respectively. Hypertension (8% versus 0%) and dysaesthesia (3% versus 0%) were more common for bevacizumab versus panitumumab, respectively. Eleven patients experienced grade 5 AEs (panitumumab  $n = 4$  [5%], bevacizumab  $n = 7$  [9%]).

In general, skin toxicities and hypomagnesaemia were more common with EGFRIs, whereas nausea and hypertension were more common with bevacizumab.

#### 4. Discussion

Although there was heterogeneity between trials, the overall results of this study-level meta-analysis are supportive of a potential benefit for first-line EGFRi + chemotherapy versus bevacizumab + chemotherapy with respect to OS, ORR and ETS. However, most patients with mCRC receive several lines of treatment, all of which may impact OS, and currently second- and third-line therapy use is not always reported. It has been argued that the apparent disconnect between PFS and OS may be due to potential imbalances in the use of subsequent therapy. However, a recent analysis indicated that second- or third-line therapies did not explain the superior survival observed in the cetuximab arm of FIRE-3 [21]. In PEAK and FIRE-3, the proportions of patients crossing over to EGFRi (38% [17] and 41% [14]) or bevacizumab (40% [17] and 47% [14])-containing regimens, respectively, appears similar between arms, as was subsequent chemotherapy use. However, the largest of the three trials (CALGB/SWOG 80405) has reported no data on the incidence/type of subsequent therapy use. Therefore, a potential imbalance in this study cannot be discounted. Independent, centrally reviewed response data were only available for inclusion from the FIRE-3 trial [16].

There have been two other recent meta-analyses evaluating EGFRi treatment in mCRC [22,23]. The first demonstrated the benefits of EGFRi versus no EGFRi treatment in patients with *RAS* WT mCRC receiving first- to third-line therapy and showed that patients with *RAS* mutations beyond *KRAS* exon 2 had outcomes indistinguishable from patients with *KRAS* exon 2 mutant tumours [22]. The second meta-analysis, which included the same three trials as the present study, demonstrated improved ORR and OS with first-line EGFRi versus bevacizumab in patients with *RAS* WT mCRC [23]. The present meta-analysis adds to this by including updated ORR and OS data from these studies and by looking at resection rates as well as the new end-point: ETS. Exploratory analyses have shown ETS and also depth of response (DpR) to influence long-term

outcomes in patients with mCRC [24–28] and a meta-analysis was considered relevant to evaluate any treatment differences with respect to these new end-points. Although ETS data were only available from PEAK [20] and FIRE-3 [16], a meta-analysis was undertaken with results favouring EGFRis versus bevacizumab. Unfortunately, a meta-analysis of DpR was not possible due to the nature of how these data are reported. Nonetheless, data from the individual trials reported significantly higher median percentage DpR for EGFRis versus VEGFi (Table 2) [20,29]. Given the apparent differences in ORR and ETS, it was of interest to perform a meta-analysis of resection rates in these trials. Resection data for the *RAS* WT population were only available for PEAK [30] and FIRE-3 (previously unpublished) and rates were similar between arms.

The current meta-analysis also assessed the impact of EGFRis versus VEGFi in patients with *KRAS* exon 2 WT/‘other’ *RAS* mutant mCRC. Patients with these less common *KRAS* and *NRAS* mutations do not benefit from EGFRis, and the effects of these mutations appear similar to those seen in *KRAS* exon 2 mutant mCRC [31,32]. The apparent lack of benefit for bevacizumab relative to the comparator EGFRi in patients with *KRAS* exon 2 WT/‘other’ *RAS* mutant mCRC is unexpected, but the small number of patients in this subgroup ( $n = 221$ ) may limit interpretation of these data. Furthermore, these analyses may be complicated by the fact that some patients received FOLFIRI-based chemotherapy and a detrimental effect of *RAS* mutations in patients receiving EGFRis + FOLFIRI has not been reported. Nonetheless, the effect of any less common *RAS* mutations cannot be determined in this analysis, and additional biomarker research from large bevacizumab studies would be of interest.

More research is presently being performed to define the optimum first-line treatment in patients with *RAS* WT mCRC. The ongoing Japanese phase III PARADIGM study (NCT02394795) will prospectively compare the efficacy/safety of first-line mFOLFOX6 plus either panitumumab or bevacizumab in patients with *RAS* WT mCRC [33] and should confirm if EGFRis are associated with an OS benefit in these patients. An associated study (NCT02394834) will investigate the relationship between OS and potential predictive biomarkers of efficacy/safety using tumour tissue samples from patients in PARADIGM. The impact of possible biomarkers in circulating tumour DNA will also be assessed. Results from both trials are awaited with interest.

Biological rationales for the improved OS observed for first-line EGFRi versus bevacizumab have been proposed, which may support use of first-line EGFRi followed by VEGFi in patients with *RAS* WT mCRC. Based on the available data, it appears that resistance to EGFRis may result in biological changes permitting tumours to retain sensitivity to subsequent therapy,

whereas resistance to VEGFIs may also result in resistance to EGFRIs [34]. These hypotheses require testing in prospectively designed trials. Although the available clinical trial data presently support the EGFR1 → VEGFI sequence, none of these trials were actually designed to assess sequencing. Therefore, there is a need for randomised, prospective trials to define the optimum sequence of biological therapy in mCRC. The phase III, randomised STRATEGIC-1 trial (NCT01910610) will compare two different strategies: first-line treatment with FOLFIRI-cetuximab, followed by oxaliplatin-based chemotherapy with bevacizumab versus first-line OPTIMOX-bevacizumab, followed by irinotecan-based chemotherapy with bevacizumab, followed by EGFR1 ± irinotecan.

Also, potential differences in safety and treatment scheduling may influence patient preferences when choosing first-line treatment. The EGFRIs and bevacizumab have different side-effect profiles; in general, skin toxicities and hypomagnesaemia are more common with EGFRIs, whereas nausea and hypertension occur more frequently with bevacizumab. Data from the phase III ASPCCCT trial suggest similar efficacy for the EGFRIs panitumumab and cetuximab, although there were small differences in the incidence of certain grade 3/4 AEs and in treatment scheduling (2-weekly versus weekly) [35].

We acknowledge several limitations to the present meta-analysis: only three head-to-head trials were available for inclusion and study-level rather than patient-level data were utilised. With regard to the CALGB study, it was necessary to utilise congress abstracts rather than full publications. Notably, the preliminary report from CALGB only had *RAS* data available for 55% of patients. There were also differences in methodology, outcome assessment and patient populations between trials that may have impacted on the meta-analysis findings. It was assumed that the efficacy of FOLFOX and FOLFIRI was the same [6,7], although some differences were apparent in the OS/PFS sensitivity analyses (Supplemental Figs. A2 and A3). It was also assumed that subsequent therapy use was similar and balanced between arms/trials. Unfortunately, there were insufficient patient numbers to evaluate the impact of individual *RAS* mutations on efficacy, although it was assumed that each mutation had the same effect.

In summary, chemotherapy plus EGFRIs or bevacizumab are effective first-line treatments for patients with mCRC. The present meta-analysis as well results from two of the three individual studies favour EGFRIs + chemotherapy versus bevacizumab + chemotherapy for some efficacy outcomes in patients with *RAS* WT tumours. A meta-analysis of the relative safety of these combinations is awaited, and an independent patient-level meta-analysis of efficacy would also be useful. The

comparative efficacy and safety of the available first-line options need to be carefully considered as part of the overall treatment strategy of patients with *RAS* WT mCRC.

### Conflict of interest statement

V. Heinemann has received honoraria for participating in symposia and advisory boards for Amgen, Roche, Merck Serono, Sanofi, Lilly, SIRTEX, BAXALTA, Boehringer, and Servier. He has also received research funding from Amgen, Roche, Merck Serono, SIRTEX and Boehringer and travel support from Merck Serono, Roche, Amgen, BAXALTA, Lilly, and SIRTEX. F. Rivera has acted on advisory boards and received research funding from Amgen. He has also acted on advisory boards and received research funding from Sanofi, Merck-Serono and Roche. B. O'Neil has consulted for Genentec. S. Stintzing has received honoraria for talks/presentations and advisory board participation from Amgen, Roche, Merck KgaA, Bayer, and Sanofi. R. Koukakis is an employee of Amgen Ltd. J.-H. Terwey is an employee of Amgen Switzerland AG. J.-Y. Douillard has participated in steering committees on behalf of Amgen and Bayer, participated in advisory boards, symposia and acted as a consultant for Amgen, Merck Serono, Roche, Takeda, and Sirtex, participated in advisory board for Boehringer Ingelheim and Sanofi and received research funding from Merck Serono.

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### Appendix A. Supplemental data

Supplemental data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2016.07.019>.

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