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Predictive and prognostic value of *KRAS* mutations in metastatic colorectal cancer patients treated with cetuximab: A meta-analysis of 22 studies

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ABSTRACT

The published data on the predictive and prognostic value of *KRAS* mutations in metastatic colorectal cancer (mCRC) treated with cetuximab seemed inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. Systematic computerised searches of the PubMed, EMBase, BIOSIS, and SCOPUS were performed. A total of 22 studies were identified. Random-effects model or fix-effects model was used according to between-study heterogeneity. A total of 2188 mCRC patients were included in the final meta-analysis. The rate of *KRAS* mutations was 38% (829/2188). The overall response rate (ORR) of mutant *KRAS* patients was 14% (119/829), whereas the ORR of wild-type *KRAS* patients was 39% (529/1359). The overall pooled relative ratio (RR) for ORR was 0.24 (95% confidence intervals (CI): 0.16–0.38; $P < 0.01$) when mutant *KRAS* patients were compared with wild-type *KRAS* patients. Median PFS was significantly shorter in mutant *KRAS* patients compared with that in wild-type *KRAS* patients (3.0 versus 5.8 months; HR = 1.94; 95% CI: 1.62–2.33; $P < 0.01$). Similarly, median OS was significantly shorter in mutant *KRAS* patients compared with that in wild-type *KRAS* patients (6.9 versus 13.5 months; HR = 2.17; 95% CI: 1.72–2.74; $P < 0.01$). The meta-analysis strongly suggests that *KRAS* mutations represent adverse predictive and prognostic biomarkers for tumour response and survival in mCRC patients treated with cetuximab. Patients with tumours that harbour mutant-type *KRAS* are more likely to have a worse response, PFS, and OS when treated with cetuximab.

1. Introduction

Metastatic colorectal cancer (mCRC) is one of the most common human malignant diseases and one of the leading causes of cancer-related death worldwide. Despite recent advances in chemotherapeutic treatment, the overall survival (OS) is still relatively poor,[1,2] and there is a continuous need for more effective therapies. Most recently, cetuximab, an IgG1 monoclonal antibody to the epidermal growth factor receptor (EGFR), has shown relevant clinical activity in

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treatment of patients with chemotherapy-resistant mCRC.[3–5] However, resistance to cetuximab was common. Therefore, predictive and prognostic factors are needed to identify the subpopulation of patients who truly benefit from cetuximab because cetuximab is associated with increased treatment costs[6] and specific toxicity. KRAS is a small G-protein downstream of EGFR, which is an essential component of the EGFR signalling cascade. It can acquire activating mutations in codons 12 and 13, thus isolating the pathway from the effect of EGFR and rendering EGFR inhibitors ineffective.[7] Recently, data from an increasing number of studies have suggested that response to cetuximab seems confined to mCRC patients bearing tumours with wild-type *KRAS*,[8–11] but the results are still inconclusive, partially because of the relatively small sample size of each study. Therefore, it is necessary to perform a meta-analysis of the published studies to derive a more precise estimation of predictive and prognostic values of *KRAS* mutations in mCRC patients treated with cetuximab.

2. Materials and methods

2.1. Publication search

Systematic computerised searches of the PubMed, EMBase, BIOSIS, and SCOPUS (up to 30th June 2009) were performed. The following search terms were used: 'metastatic colon cancer', 'metastatic rectal cancer', 'metastatic colorectal cancer', 'mCRC', '*KRAS*', 'mutation', 'cetuximab'. The search was limited to human studies. Eligible studies that reported complete response (CR) and partial response (PR) stratified by *KRAS* mutation status were retrieved, and their bibliographies were checked for other relevant publications. When the same patient population was used in several publications, only the most recent, largest or complete study was included in the meta-analysis.

2.2. Data extraction

Information was carefully extracted from all eligible studies. The following data were collected from each study: first author's name, year of publication, study designs, number of patients screened, number of patients with *KRAS* mutations, location of *KRAS* mutations, mutation analysis methods, previous treatment protocols, study treatment protocols, response criteria, CR and PR stratified by *KRAS* mutation status, progression-free survival (PFS) and overall survival (OS) stratified by *KRAS* mutation status and hazard ratio (HR) with 95% confidence intervals (CI) for PFS or OS. Data extraction was done independently by two of the authors. Any disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes.

2.3. Statistical methods

The primary end-point was overall response rate (ORR). The ORR was defined as the sum of CR and PR. The correlation between *KRAS* mutations and ORR was expressed as a relative ratio (RR) for ORR of mutant *KRAS* patients over wild-type *KRAS* patients. Thus, a RR equal to 1 indicates a lack of association between *KRAS* mutations and cetuximab treatment; a RR more than 1 corresponds to a direct correlation between higher ORR and *KRAS* mutations and a tendency of mutant *KRAS* patients to have worse responsiveness is indicated by a RR less than 1. The secondary end-points were PFS and OS. The correlation between *KRAS* mutations and the secondary end-points was expressed as a HR of mutant *KRAS* patients over wild-type *KRAS* patients. Thus, a HR more than 1 indicates that *KRAS* mutations contribute to shorter PFS and OS; a HR less than 1 indicates that *KRAS* mutations contribute to longer PFS and OS. The association between *KRAS* mutations and efficacy of cetuximab therapy was measured by RR and HR with 95% CI. Heterogeneity was checked by a Q-test with a degree of freedom equal to the number of analyzed studies minus 1. A *P* value of more than 0.10 for the Q-test indicates a lack of heterogeneity across studies, so the pooled RR or HR was calculated by the fixed-effects model. Otherwise, the random-effects model was used.[12] To establish the effect of clinical heterogeneity among studies on meta-analyses' conclusions, subgroup analyses were conducted by study designs, line of treatment and treatment protocols. Sensitivity analyses were carried out to check if modification of the inclusion criteria of the meta-analysis affected the final results. Begg's funnel plots and Egger's linear regression test were used to assess publication bias.[13] Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the RR. The significance of the intercept was determined by the *t*-test as suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias). If publication bias existed, the Duval and Tweedie non-parametric 'trim and fill' method was used to adjust it.[14] All the statistical tests used in our meta-analysis were performed with STATA version 10.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Studies characteristics

Based on our search criteria, 22 studies were identified.[8–11,15–32] A total of 2188 patients were used in the pooled analyses. Table 1 lists the studies identified and their main characteristics. Of the 22 studies, sample sizes ranged from 20 to 277. Eighteen of these studies were of retrospective design. Four of these studies were of prospective design. Cetuximab was given as first-line treatment in three studies and as second line or more in 19 studies. The patients of four studies received cetuximab monotherapy, while the patients of 18 studies received cetuximab-based treatment.

Table 2 lists the effect of *KRAS* mutation status on the efficacy of cetuximab in mCRC patients. The rate of *KRAS* mutations ranged from 15% to 53% (median, 38%). The ORR of patients with mutant *KRAS* ranged from 0% to 46% (median, 3%); the ORR of patients with wild-type *KRAS* ranged from 13% to 65% (median, 38%). The PFS in mutant *KRAS* patients ranged from 1.3 to 8.1 months (median, 3.0 months); the PFS in wild-type patients ranged from 1.4 to 10.5 months

Table 1 – Main characteristics of studies included in the meta-analysis.

Author	Year	Study design	Mutation analysis methods	Previous treatment protocols	Study treatment protocols	Response criteria
Moroni[15a]	2005	Retrospective	DS	⩾1 Chemotherapy	C alone; or C + I based	RECIST
Lievre[8]	2006	Retrospective	DS	⩾1 Chemotherapy	C + I; or C + FOLFIRI; or C alone	RECIST
Benvenuti[9b]	2007	Retrospective	DS	I	C alone; or C + I based	RECIST
Di Fiore[10]	2007	Retrospective	DS	⩾1 Chemotherapy	C + I; or C + O	RECIST
Finocchiaro[16]	2007	Retrospective	Surveyor analysis	I and/or O	C + I; or C + O; OR C alone	RECIST
Frattini[17]	2007	Retrospective	DS	⩾1 Chemotherapy	C + I based; or C + CAPOX	RECIST
Khambata-Ford[18]	2007	Prospective	DS	⩾1 Chemotherapy	C	WHO (modified)
Bokemeyer[19]	2008	Retrospective	Quantitative PCR-based assay	NO	C + FOLFIRI	RECIST
Cappuzzo[20]	2008	Retrospective	Surveyor analysis	I and/or O	C	RECIST
De Roock[11]	2008	Retrospective	AD + DS	I	C + I; or C alone	RECIST
Gonçalves[21]	2008	Retrospective	DS	⩾1 Chemotherapy	C + I; or C alone; or I alone	WHO
Karapetis[22c]	2008	Prospective	DS	⩾1 Chemotherapy	C + supportive care	RECIST
Lievre[23]	2008	Retrospective	AD + DS	I based	C + I; or C + FOLFIRI; or C alone	RECIST
Lurje[24]	2008	Retrospective	DS	⩾1 Chemotherapy	C	WHO
Tejpar[25]	2008	Prospective	Allele-specific quantitative PCR	I based	C alone; or C + I	RECIST
Bibeau[26]	2009	Retrospective	DS	I based	C + I	RECIST
Garm Spindler[27]	2009	Prospective	DS + DxS	⩾1 Chemotherapy	C + I	RECIST
Loupakis[28]	2009	Retrospective	DS	I based	C + I	RECIST
Prenen[29]	2009	Retrospective	AD + DS	I based	C + I; or C alone;	RECIST
Sartore-Bianchi[30]	2009	Retrospective	DS	⩾1 Chemotherapy	C alone; P alone; or C + I based;	RECIST
Tol[31]	2009	Retrospective	DXS + DS	NO	Apecitabine + Bevacizumab + C	RECIST
Van Cutsem[32]	2009	Retrospective	Melting curve analysis	NO	C + FOLFIRI	WHO (modified)

DS = direct sequencing; AD = allelic discrimination; DxS = approved kit assessing the six most frequent point mutations of codon 12 and the most frequent point mutation of codon 13 (G > D) by allelic discrimination; C = cetuximab; I = irinotecan; O = oxaliplatin; FOLFIRI = fluorouracil, folinic acid, and irinotecan; CAPOX = oxaliplatin and capecitabine.

[a] Ten patients receiving single-agent Panitumumab were not extractable from the population.

[b] Twenty five patients receiving single-agent Panitumumab were not extractable from the population.

[c] Two hundred and eighty five patients receiving supportive care alone were not extractable from the population.

Table 2 – Effect of *KRAS* mutation status on the efficacy of cetuximab therapy in patients with metastatic colorectal cancer.

Author	Year	Location	Tumours evaluated	Mut KRAS (%)	ORR (%)		PFS months		
					Mut KRAS	Wt KRAS	Wt KRAS (95% CI)	Mut KRAS (95% CI)	HR (95% CI)
Moroni[15]	2005	Exon2	20	3(15)	0(0)	7(41)	–	–	–
Lievre[8]	2006	Exon1	30	13(43)	0(0)	11(65)	–	–	–
Benvenuti[9]	2007	Exon2	21	5(24)	0(0)	6(38)	–	–	–
Di Fiore[10]	2007	Exon2	59	16(27)	0(0)	12(28)	5.5	3.0	–
Finocchiaro[16]	2007	Exon2	81	32(40)	2(6)	13(27)	6.1	3.7	–
Frattini[17]	2007	Exon2	27	10(37)	1(10)	9(53)	–	–	–
Khambata-Ford[18]	2007	Exon2	80	30(38)	3(10)	24(48)	2.03	1.97	1.40(0.87–2.60)
Bokemeyer[19]	2008	Exon2	113	52(46)	17(52)	37(61)	7.7	5.5	–
Cappuzzo[20]	2008	Exon1/Exon2	80	42(53)	4(10)	10(26)	5.4	4.4	–
De Roock[11]	2008	Exon2	108	42(39)	0(0)	27(41)	6.0(4.3–7.8)	3(1.8–4.2)	–
Gonçalves[21]	2008	Exon1	34	16(47)	2(13)	7(39)	3.9(2.5–11.0)	4.7(2.7–11.3)	–
Karapetis[22]	2008	Exon2	198	81(41)	1(1)	15(13)	3.7	1.8	–
Lievre[23]	2008	Exon2	89	24(27)	0(0)	26(40)	7.9(4.9–9.0)	2.5(2.0–4.0)	3.30(2.00–5.40)
Lurje[24]	2008	Exon2	114	37(32)	0(0)	12(16)	1.4(1.3–2.4)	1.3(1.2–1.6)	
Tejpar[25]	2008	Exon2	77	30(39)	0(0)	17(36)	5.8(4.7–6.8)	2.8(2.5–3.0)	
Bibeau[26]	2009	Exon2	64	27(42)	1(4)	10(27)	5.3(4.0–8.4)	3.0(2.2–3.2)	1.80(1.10–3.10)
Garm Spindler[27]	2009	Exon2	64	22(34)	0(0)	17(40)	8.4(8.0–10.5)	2.5(2.0–5.1)	2.74(1.11–6.78)
Loupakis[28]	2009	Exon2	88	35(40)	2(6)	13(25)	4.2	3.1	2.22(1.35–3.70)
Prenen[29]	2009	Exon2	199	77(39)	1(1)	37(30)	6(5.5–6.5)	3.0(2.15–3.85)	1.79(1.30–2.44)
Sartore-Bianchi[30]	2009	Exon2	109	32(29)	2(6)	20(26)	–	–	1.50(0.89–2.52)
Tol[31]	2009	Exon2	256	98(38)	45(46)	97(61)	10.5	8.1	–
Van Cutsem[32]	2009	Exon2	277	105(38)	38(36)	102(59)	9.9	7.6	–

Author	Year	Location	OS months		
			Wt KRAS (95% CI)	Mut KRAS (95% CI)	HR (95% CI)
Moroni[15]	2005	Exon2	–		–
Lievre[8]	2006	Exon1	16.3	6.9	–
Benvenuti[9]	2007	Exon2	–	–	–
Di Fiore[10]	2007	Exon2	–	–	–
Finocchiaro[16]	2007	Exon2	10.8	8.3	–
Frattini[17]	2007	Exon2	–	–	–
Khambata-Ford[18]	2007	Exon2	–	–	–
Bokemeyer[19]	2008	Exon2	–	–	–
Cappuzzo[20]	2008	Exon1/Exon2	10.8	9.5	–
De Roock[11]	2008	Exon2	10.8(8.9–12.6)	6.8(3.0–10.7)	–
Gonçalves[21]	2008	Exon1	20.8	13.8	–
Karapetis[22]	2008	Exon2	9.5	4.5	–
Lievre[23]	2008	Exon2	14.3(9.4–20.0)	10.1(5.1–13.0)	2.40(1.40–4.10)
Lurje[24]	2008	Exon2	6.6(4.3–8.9)	4.9(2.8–6.6)	–
Tejpar[25]	2008	Exon2	–	–	–
Bibeau[26]	2009	Exon2	–	–	–
Garm Spindler[27]	2009	Exon2	17.0(11.1–18.2)	5.9(3.8–9.8)	3.22(1.19–8.67)
Loupakis[28]	2009	Exon2	13.5	6.1	2.22(1.54–4.55)
Prenen[29]	2009	Exon2	11.25(9.0–13.5)	6.5(4.7–8.3)	2.00(1.45–2.70)
Sartore-Bianchi[30]	2009	Exon2	–	–	–
Tol[31]	2009	Exon2	21.8	17.2	–
Van Cutsem[32]	2009	Exon2	24.9	17.5	–

Mut *KRAS* = mutant *KRAS*; Wt *KRAS* = wild-type *KRAS*; HR = hazard ratio.

(median, 5.8 months). The OS in mutant *KRAS* patients ranged from 4.5 to 17.5 months (median, 6.9 months); the OS in wild-type patients ranged from 6.6 to 24.9 months (median, 13.5 months).

3.2. *Main results of overall response rate*

The association between *KRAS* mutations and ORR is summarised in Table 3. The ORR of mCRC patients with mutant *KRAS* was 14% (119/829), whereas the ORR of mCRC patients with wild-type *KRAS* was 39% (529/1359). When the mutant *KRAS* patients were compared with the wild-type *KRAS* patients, the overall RR was 0.24 (95% CI: 0.16–0.38; $P < 0.01$). In the subgroup analysis by retrospective design or prospective design, the pooled RR was 0.30 (95% CI: 0.19–0.46; $P < 0.01$) and 0.11 (95% CI: 0.05–0.26; $P < 0.01$), respectively. In the subgroup analysis by first line treatment or more, the pooled RR was 0.65 (95% CI: 0.55–0.78; $P < 0.01$) and 0.13 (95% CI: 0.09–0.20;

Table 3 – Meta-analysis of the correlation between *KRAS* mutations and overall response rate.

	No. of studies	Overall response rate (%)		Test of association		Test of heterogeneity		
		Mutant *KRAS*	Wild-type *KRAS*	RR (95% CI)	*P*	Q	*P*	I^2 (%)
All studies								
Total	22	119/829(14)	529/1359(39)	0.24(0.16–0.38)	<0.01	68.87	<0.01	70
Study design								
Prospective	4	4/163(2)	73/256(29)	0.11(0.05–0.26)	<0.01	1.96	0.58	0
Retrospective	18	115/666(17)	456/1103(41)	0.30(0.19–0.46)	<0.01	49.98	<0.01	66
Line of treatment								
First-line	3	100/255(39)	236/391(60)	0.65(0.55–0.78)	<0.01	2.11	0.35	5
>Fist-line	19	19/574(3)	293/968(30)	0.13(0.09–0.20)	<0.01	12.86	0.80	0
Study treatment								
C alone	4	8/190(4)	61/282(22)	0.19(0.10–0.39)	<0.01	2.17	0.54	0
C based	18	111/639(17)	468/1077(43)	0.26(0.16–0.42)	<0.01	57.54	<0.01	71
Studies (second-line treatment or more)								
Total	19	19/574(3)	293/968(30)	0.13(0.09–0.20)	<0.01	12.86	0.80	0
Study design								
Prospective	4	4/163(2)	73/256(29)	0.11(0.05–0.26)	<0.01	1.96	0.58	0
Retrospective	15	15/411(4)	220/712(31)	0.14(0.09–0.22)	<0.01	10.46	0.73	0
Study treatment								
C alone	4	8/190(4)	61/282(22)	0.19(0.10–0.39)	<0.01	2.17	0.54	0
C based	15	11/384(3)	232/686(34)	0.11(0.07–0.19)	<0.01	9.55	0.79	0

C alone = cetuximab monotherapy; C based = cetuximab-based treatment and RR = relative ratio.

$P < 0.01$), respectively. For studies evaluating cetuximab monotherapy and *KRAS* mutations, the pooled RR was 0.19 (95% CI: 0.10–0.39; $P < 0.01$); for studies evaluating cetuximab-based treatment and *KRAS* mutations, the pooled RR of 0.26 (95% CI: 0.16–0.42; $P < 0.01$) was estimated.

3.3. *Main results of progression-free survival*

Data for *KRAS* mutations and PFS were reported in 17 studies, with 1981 patients. However, only seven studies provided data on HR with 95% CI for PFS. The median of PFS in *KRAS* mutant or wild-type patients was 3.0 and 5.8 months, respectively. *KRAS* mutations had adverse effect on PFS (HR = 1.94; 95% CI: 1.62–2.33; $P < 0.01$), with no heterogeneity between studies ($P = 0.25$; $I^2 = 24\%$).

3.4. *Main results of overall survival*

Information concerning OS was available in thirteen studies, with 1618 patients. Only four studies presented data on HR with 95% CI for OS. The median of OS in *KRAS* mutant or wild-type patients was 6.9 and 13.5 months, respectively. *KRAS* mutations had adverse effect on OS (HR = 2.17; 95% CI: 1.72–2.74; $P < 0.01$), with no heterogeneity between studies ($P = 0.80$; $I^2 = 0\%$).

3.5. *Sensitivity analyses*

Sensitivity analyses were conducted in an attempt to check if modification of the inclusion criteria of this meta-analysis affected the final results. These were carried out by limiting the meta-analysis to studies evaluating the effect of *KRAS* mutation status in response to cetuximab in second-line treatment or more. All the results were not materially altered, which suggests that the results are statistically robust (Table 3). Also, no heterogeneity was found in overall or subgroup analysis.

3.6. *Publication bias*

Begg's funnel plot for RRs of ORR seemed asymmetry (figure not shown). Egger's test ($P < 0.01$) provided statistically significant evidence for the funnel plot asymmetry in the comparison of the RR of ORR in mutant *KRAS* patients versus the wild-type *KRAS* patients in overall studies. Publication bias was also found for *KRAS* mutations and OS by Egger's test ($P = 0.02$). The Duval and Tweedie non-parametric 'trim and fill' method was used to adjust for publication bias. Meta-analyses with and without 'trim and fill' method did not draw different conclusions (data not shown), indicating that our results were statistically robust. No publication bias was found for *KRAS* mutations and PFS by Egger's test ($P = 0.62$).

4. Discussion

A previous meta-analysis including eight studies and a total of 817 cases of mCRC has provided evidence that *KRAS* mutations are highly specific negative predictors of response to anti-EGFR monoclonal antibodies alone or in combination with chemotherapy in patients with mCRC.[33] However, only eight studies were involved in the previous meta-analysis and the pooled sample size was relatively small. Stratified analysis based on such as different study designs, line of treatment, and treatment protocols was not performed. Data concerning PFS and OS were also not available in the previous

meta-analysis. Since then, several additional studies with a larger sample size about this relationship have been reported; to address a more precise estimation of predictive and prognostic values of *KRAS* mutations in mCRC patients treated with cetuximab, we performed this meta-analysis.

A total of 22 studies were included in the final meta-analysis, consisting of 2188 mCRC patients, of whom 829 had *KRAS* mutations (38%). The overall RR of ORR indicated that mCRC patients with mutant *KRAS* were less sensitive to cetuximab than those with wild-type *KRAS*. Subgroup analyses were conducted on the basis of different study designs (retrospective design and prospective design), line of treatment (first-line treatment and second-line treatment or more) and treatment protocols (cetuximab monotherapy and cetuximab-based treatment), all the results were not materially altered and did not draw different conclusions, indicating that our results were robust.

Data concerning PFS and OS were available in only seven and four studies,respectively. Median of PFS and OS in *KRAS* mutant and wild-type patients was 3.0 versus 5.8 months, and 6.9 versus 13.5 months, respectively. The PFS was significantly shorter in mutant *KRAS* patients compared with that in wild-type *KRAS* patients (HR = 1.94; 95% CI: 1.62–2.33; $P < 0.01$). Similarly, the OS was significantly shorter in mutant *KRAS* patients compared with that in wild-type *KRAS* patients (HR = 2.17; 95% CI: 1.72–2.74; $P < 0.01$).

Heterogeneity is a potential problem that may affect the interpretation of the results of all meta-analyses. Significant between-study heterogeneity for RRs of ORR existed in overall comparisons. After subgroup analysis by line of treatment, the heterogeneity was effectively removed. When sensitivity analyses were performed by excluding studies evaluating the effect of *KRAS* mutation status in response to first-line cetuximab treatment, the heterogeneity was removed from overall comparisons and subgroup comparisons. One reason is that the ORR, PFS and OS of *KRAS* mutant patients in the first-line studies were significantly better than those in the second-line treatment or more studies. Another factor is that the line of treatment might have an influence on the relationship between *KRAS* mutation status and ORR.

Our studies had several limitations that need to be taken into consideration when interpreting the findings. First, only seven studies presented data on HR with 95% CI for PFS and only four studies presented data on HR with 95% CI for OS. The relatively small sample size might not have enough statistic power to detect the real association; second, our result was based on unadjusted estimates, while a more precise analysis should be conducted if a more detailed individual data were available, which would allow for an adjusted estimate by other factors such as age, sex, ethnicity, treatment protocols and other biomarkers.

Despite these limitations, our meta-analysis strongly suggests that *KRAS* mutations represent adverse predictive and prognostic biomarkers for tumour response and survival in mCRC patients treated with cetuximab. Patients with tumours that harbour mutant-type *KRAS* are more likely to have a worse response, PFS, and OS when treated with cetuximab. However, large prospective studies using standardised unbiased methods are needed, using homogeneous CRC patients, with assessors blinded to the clinical data. Moreover, other biomarkers such as *EGFR* gene amplification,[15,20] PTEN expression[17,34] and *BRAF* mutation[11,20] and biomarkers of side-effects should also be considered. Such studies taking the above mentioned factors into account may eventually lead to a comprehensive recommendation for individualisation and optimisation of chemotherapy for mCRC patients on the basis of *KRAS* mutations and other biomarkers' measurements.

Conflict of interest statement

None declared.

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