





Tumour location and efficacy of first-line EGFR inhibitors in *KRAS/RAS* wild-type metastatic colorectal cancer: retrospective analyses of two phase II randomised Spanish TTD trials

Manuel Benavides ¹, Eduardo Díaz-Rubio,² Alfredo Carrato,³ Albert Abad,⁴ Carmen Guillén ^{5,6}, Pilar Garcia-Alfonso,⁷ Silvia Gil,¹ María Teresa Cano,⁸ María José Safont,⁹ Cristina Gravalos,¹⁰ José Luis Manzano,⁴ Antonio Sánchez,¹¹ Julia Alcaide,¹² Rafael López,¹³ Bartomeu Massutí,¹⁴ Javier Sastre,² Eva Martínez,¹⁵ Pilar Escudero,¹⁶ Miguel Méndez,¹⁷ Enrique Aranda,⁷ On behalf of Spanish Cooperative Group for the Treatment of Digestive Tumours

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For numbered affiliations see end of article.

Correspondence to Dr Manuel Benavides; manuel.benavides.sspa@juntadeandalucia.es

ABSTRACT

Purpose Metastatic colorectal cancer (mCRC) is a group of distinct diseases, with clinical and molecular differences between right-sided and left-sided tumours driving varying prognosis.

Methods Patients with *KRAS/RAS*-wild type (wt) mCRC treated in first line with epidermal growth factor receptor inhibitors (EGFR-Is) (cetuximab or panitumumab) plus oxaliplatin or irinotecan-based chemotherapy from two phase II randomised trials conducted by the Spanish Cooperative for the Treatment of Digestive Tumours group were included in this retrospective study. The main objective was to analyse the prognostic effect of primary tumour location on objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Results Patients with *KRAS*-wt right-sided tumours (n=52) had significantly lower efficacy as compared with patients with *KRAS*-wt left-sided tumours (n=209); confirmed ORR (25% vs 47%, respectively; OR 0.4, 95% CI 0.2 to 0.8, p=0.004); and shorter median PFS (7.2 vs 9.9 months; HR 0.6, 95% CI 0.4 to 0.9, p=0.0157) and OS (13.6 vs 27.7 months; HR 0.5, 95% CI 0.3 to 0.7, p<0.0001). Similar results were observed in the *RAS*-wt populations. The further classification of left-sided tumours as colon or rectum delivered similar survival outcomes, as well as a tendency to diminished ORR in patients with rectum tumours.

Conclusion We observed significantly improved efficacy outcomes in patients with *KRAS/RAS*-wt mCRC treated with first-line EGFR-I plus chemotherapy in left-sided primary tumours as compared with right-sided primary tumours.

Trial registration numbers NCT01161316 and NCT00885885.

INTRODUCTION

Primary tumour location has emerged as a potential prognostic and predictive factor in retrospective analyses of clinical trials in

Key questions

What is already known about this subject?

- Given the enormous complexity and heterogeneity of metastatic colorectal cancer (mCRC), primary tumour location has emerged as a potential prognostic and predictive factor in retrospective analyses of clinical trials in patients with *KRAS/RAS*-wild type (wt) mCRC treated with panitumumab-based or cetuximab-based therapies.
- Relevant differences have been described between right-sided and left-sided mCRCs in recent studies. Further, descending and sigmoid colon cancers present differences from rectal cancer in their molecular features, treatment approaches and prognosis. *BRAF* mutations have also been associated with poorer outcomes in mCRC and described to be gradually higher from the rectum (<2%) to the ascending colon (36%).

What does this study add?

- This study retrospectively evaluates the impact of primary tumour location on efficacy outcomes in 261 patients with *KRAS/RAS* wt mCRC treated with first-line epidermal growth factor receptor inhibitor (EGFR-I) (cetuximab or panitumumab) in combination with chemotherapy. Our results clearly show that patients with tumours up to the splenic flexure (right-sided) had a significantly higher risk of death and progression compared with patients with distal tumours (left-sided).

patients with *KRAS/RAS*-wild type (wt) metastatic colorectal cancer (mCRC) treated with panitumumab-based or cetuximab-based therapies. Better outcomes were shown in patients with left-sided tumours (those originating in the splenic flexure, descending



Key questions

How might this impact on clinical practice?

- ▶ We observed similar survival outcomes when patients with rectum primary tumour location were classified accordingly.
- ▶ According to other studies, our data also suggest that poorer efficacy outcomes might be achieved with EGFR-I in patients with right-sided tumours. The observed efficacy differences are likely related with the suggested EGFR-I -sensitive phenotype that might be more prevalent in left-sided tumours, presenting among other variables higher levels of expression of epiregulin and amphiregulin, which have been associated with enhanced response to EGFR-I. In addition, right-sided tumours have been associated with chemoresistance.
- ▶ Our results strongly support the prognostic effect of primary tumour location in patients with KRAS/RAS-wt mCRC treated with first-line EGFR-I plus chemotherapy.

colon, sigmoid colon or rectum) treated with epidermal growth factor receptor inhibitor (EGFR-I)-based therapies compared with chemotherapy-based or bevacizumab-based therapies.¹⁻⁸

Relevant differences have been described in the epidemiology, pathogenesis, genetic or epigenetic features, clinical presentation and outcomes between right-sided and left-sided mCRCs.⁹⁻¹³ Further, descending and sigmoid colon cancers present differences from rectal cancer in their molecular features, treatment approaches and prognosis.¹⁴⁻¹⁶ *BRAF* mutations have also been associated with poorer outcomes in mCRC¹⁷ and have been described to be gradually higher from the rectum (<2%) to the ascending colon (36%).¹³

Given the enormous complexity and heterogeneity of mCRC, the assessment of the impact of tumour location on efficacy outcomes of different populations and settings is a paramount step towards an optimally targeted therapy. However, the stratification of patients according to tumour location has not been regarded in clinical trials.

Our aim was to retrospectively evaluate the impact of primary tumour location on efficacy outcomes in patients with *KRAS/RAS* wt mCRC treated with first-line EGFR-I (cetuximab or panitumumab) in combination with chemotherapy included in two phase II randomised trials conducted by the Spanish Cooperative Treatment of Digestive Tumours group.¹⁸⁻²⁰

METHODS

Study design

This is a retrospective, pooled analysis of two phase II, randomised, open-label, multicentre trials MACRO-2 and PLANET. Their respective study designs and treatment regimens have been previously reported.¹⁸⁻²⁰

Patient population

This retrospective analysis included all patients with *KRAS*-wt (exon 2) and *RAS*-wt (exons 2, 3 and 4 of *KRAS/NRAS*) mCRC who were randomised in the

MACRO-2 trial and in the PLANET trial. All patients included in the PLANET trial had liver-limited disease. Patients were classified according to their primary tumour location as right-sided for patients whose tumours originated from the caecum, ascending and transverse colon up to the splenic flexure; or left-sided for patients whose tumours originated from the splenic flexure to the descending and sigmoid colon or rectum. Patients whose primary tumour locations were not available or were sited in both sides with an unknown origin were not included in the analysis. All studied variables were analysed for the pooled population according to the primary tumour location.

For the secondary analysis, patients with left-sided tumours were further classified into patients with primary tumours in the rectum and those with primary tumours from the splenic flexure to the descending and sigmoid colon.

Statistical analysis

The primary endpoint of MACRO-2 was a progression-free survival (PFS) rate at 9 months, whereas the primary endpoint of PLANET was the objective response rate (ORR) (complete response+partial response). Additionally, we analysed the following efficacy outcomes studied in the MACRO-2: overall survival (OS) and ORR. For the PLANET trial, the additional analysed outcomes were PFS and OS. Results of both confirmed and unconfirmed ORRs were reported, given that liver metastases resection was performed in some participants of the PLANET trial before radiological response confirmation.

Efficacy endpoints were analysed using descriptive statistics, 95% CIs and Kaplan-Meier plots. Survival functions were compared using the log-rank test. Cox proportional hazards model was carried out to estimate the HRs for prognostic significance for OS. Data analysis was performed using the SAS statistical package for Windows V.9.4. P values less than 0.05 were considered significant.

RESULTS

Patients' characteristics

A total of 270 patients were included for analysis from the MACRO-2 (n=193) and PLANET (n=77) studies. Nine patients from the MACRO-2 trial were excluded since their primary tumour location could not be determined.

Out of the evaluable *KRAS*-wt population (n=261), 52 patients (20%) presented with right-sided tumours and 209 patients (80%) presented with left-sided tumours, of which 68 (26%) were classified as rectum tumours (figure 1A). Overall, 32% of patients were female, with a mean age of 60 years, and 39% had more than one metastatic site. The baseline characteristics of right-sided and left-sided populations were similar, except for a higher proportion of women (p=0.047), a lower percentage of exposure to adjuvant radiotherapy (p=0.02) and a higher number of metastatic sites (p=0.048) in patients with right-sided tumours (table 1).

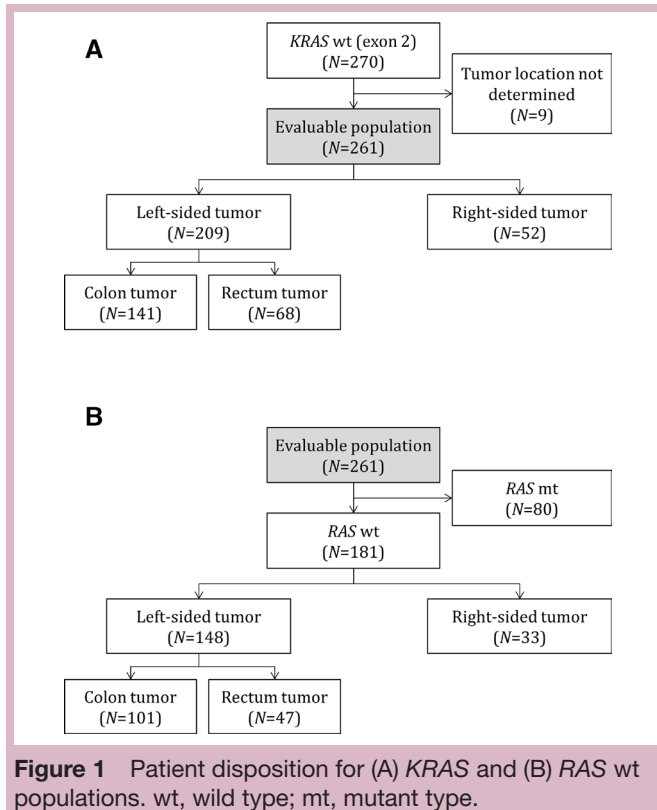


Figure 1 Patient disposition for (A) *KRAS* and (B) *RAS* wt populations. wt, wild type; mt, mutant type.

One hundred and eighty-one (69%) of the 261 *KRAS*-wt evaluable patients were *RAS* wt and 80 (31%) were *RAS* mutated. Thirty-three (18%) and 148 (82%) patients presented with right-sided and left-sided *RAS*-wt tumours, respectively. Forty-seven out of 68 rectum tumours presented with *RAS*-wt status (figure 1B).

Impact of primary tumour location on efficacy outcomes

ORR, median PFS and median OS were significantly greater in patients with left-sided versus right-sided tumours in both studied populations (*KRAS* and *RAS* wt) (table 2). In the *KRAS*-wt population, the median PFS was 7.2 months in the right-sided tumour group and 9.9 months in the left-sided tumour group (HR 0.6, 95% CI 0.4 to 0.9, $p=0.016$) (figure 2A). The median OS was also significantly prolonged in patients with left-sided tumours (13.6 vs 27.7 months; HR 0.5, 95% CI 0.3 to 0.7, $p<0.0001$) (figure 2C).

Similarly, in the *RAS*-wt population, the median PFS and OS were 6.5 vs 10.1 months and 13.6 vs 32.8 months for patients with right-sided versus left-sided tumours, respectively (HR (PFS) 0.6, 95% CI 0.4 to 1.0, $p=0.044$; HR (OS) 0.4, 95% CI 0.3 to 0.7, $p=0.0002$) (figure 2B,D).

Both *KRAS*-wt and *RAS*-wt patients with rectum tumours ($n=68$ (*KRAS*) and $n=47$ (*RAS*)) had similar efficacy results when compared with patients presenting with tumours in the descending and sigmoid colon ($n=141$ (*KRAS*) and $n=101$ (*RAS*)), both in terms of median PFS (*KRAS* wt: 9.7 vs 9.9 months, HR 0.9, 95% CI 0.6 to 1.3; *RAS* wt: 10.1 vs 10.1 months, HR 0.9, 95% CI 0.6 to 1.4) and OS (*KRAS* wt:

Table 1 Baseline characteristics in the MACRO-2 and PLANET *KRAS* wild-type pooled population according to tumour location

	Right-sided tumour (n=52)	Left-sided tumour (n=209)	P value
Sex, n (%)			0.047
Male	29 (56)	148 (71)	
Female	23 (44)	61 (29)	
Median age, years (range)	62 (37–79)	61 (32–83)	0.89
ECOG PS, n (%)*			0.55
0	19 (45)	73 (52)	
1	20 (48)	62 (44)	
2	3 (7)	6 (4)	
Pathological T stage, n (%)			0.75
2	2 (4)	5 (2)	
3	19 (37)	84 (40)	
4	15 (29)	51 (24)	
x	15 (29)	69 (33)	
Missing	1 (2)	0	
Pathological N stage, n (%)			0.86
0	8 (16)	33 (16)	
1	8 (16)	42 (20)	
1b	0 (0)	1 (0)	
2	18 (35)	61 (29)	
x	17 (33)	72 (34)	
Missing	1 (2)	0	
Number of affected organs, n (%)†‡			0.048
1	24 (47)	135 (65)	
2	17 (33)	50 (24)	
3	9 (18)	19 (13)	
>3	1 (2)	3 (1)	
Missing	1 (2)	2 (1)	
Prior surgery for primary tumour, n (%)			0.64
Yes	32 (63)	122 (58)	
No	19 (37)	87 (42)	
Missing	1 (2)	0	
Prior treatment, n (%)	6 (12)	27 (13)	1
Chemotherapy	6 (12)	22 (11)	0.80
Radiotherapy	0 (0)	19 (9)	0.02

*ECOG PS was not registered in PLANET study.

†All patients in the PLANET study presented liver-limited disease.

‡Missing data in two patients with left-sided tumour from the MACRO-2 study.

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

26.6 vs 31.5 months, HR 0.9, 95% CI 0.6 to 1.3; *RAS* wt: 32.5 vs 35.1 months, HR 1.0, 95% CI 0.6 to 1.5), respectively. Of note, a significantly lower not-confirmed ORR was observed

Table 2 Efficacy results for *KRAS* and *RAS* wt populations according to tumour location

	<i>KRAS</i> wt		<i>RAS</i> wt	
	Right-sided (n=52)	Left-sided (n=209)	Right-sided (n=33)	Left-sided (n=148)
ORR (confirmed)				
Rate, %	25.0	46.9	33.3	52.7
OR (95% CI)	0.4 (0.2 to 0.8)		0.5 (0.2 to 1.0)	
P value	0.004		0.044	
PFS				
Median (months) (95% CI)	7.2 (4.2 to 11.1)	9.9 (9.1 to 11.7)	6.5 (3.9 to 12.6)	10.1 (9.4 to 12.1)
HR (95% CI)	0.6 (0.4 to 0.9)		0.6 (0.4 to 1.0)	
P value	0.016		0.044	
OS				
Median (months) (95% CI)	13.6 (8.4 to 26.0)	27.7 (25.0 to 36.2)	13.6 (8.4 to 34.2)	32.8 (26.5 to 39.9)
HR (95% CI)	0.5 (0.3 to 0.7)		0.4 (0.3 to 0.7)	
P value	<0.0001		0.0002	

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; wt, wild type.

in the rectum *RAS*-wt population (64% vs 80%; OR 0.4, 95% CI 0.2% to 0.9%) and a trend to lower confirmed ORR (45% vs 56%; OR 0.6, 95% CI 0.3% to 1.3%).

Multivariate analysis identified the left-sided location of the primary tumour (HR 0.5, 95% CI 0.3 to 0.7, $p < 0.0001$), more than one affected organ (HR 1.9, 95% CI 1.4 to

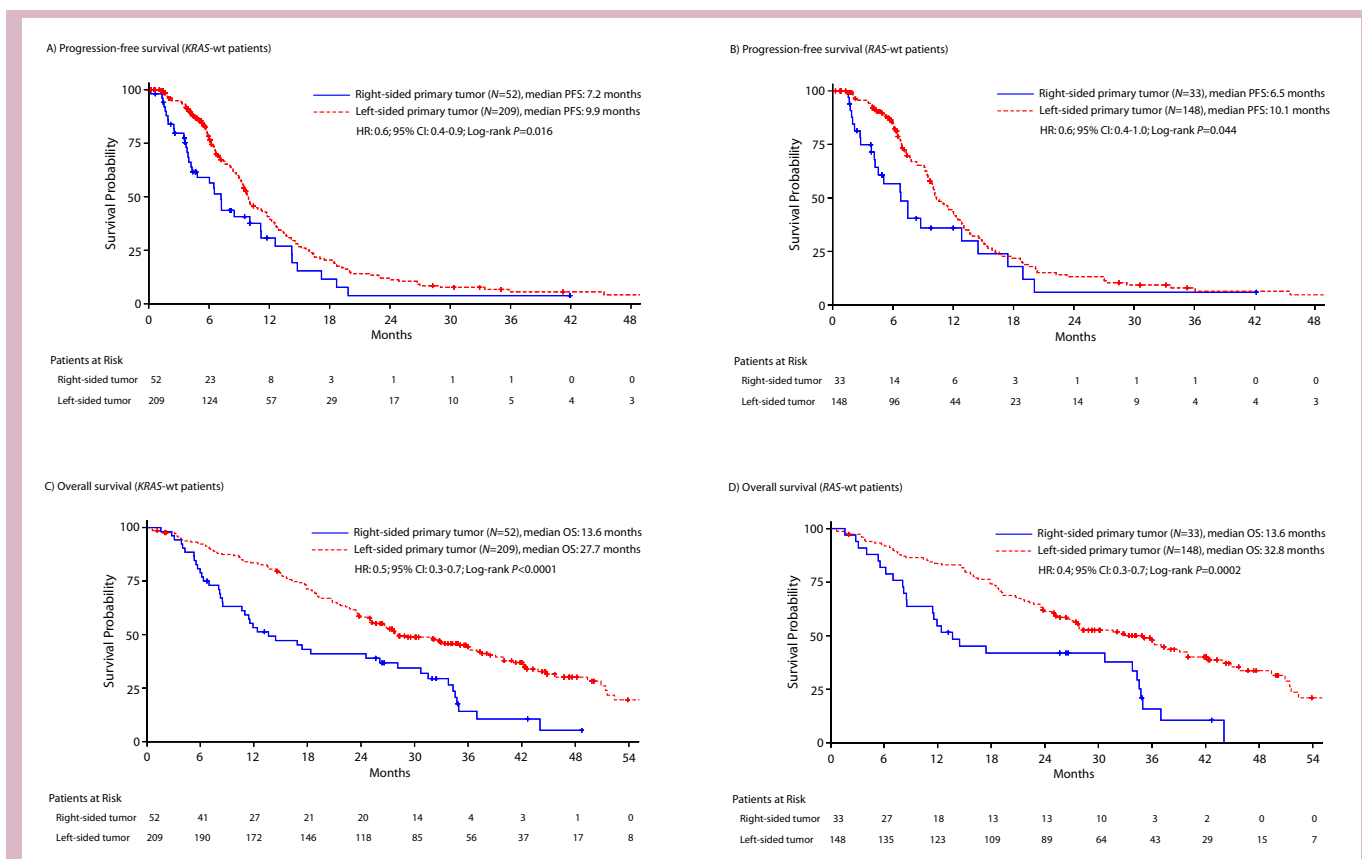


Figure 2 Analyses of survival by primary tumour location. (A,B) Kaplan-Meier estimates of the probability of PFS in the *KRAS* and *RAS* wt populations, respectively. (C,D) Kaplan-Meier estimates of the probability of OS in the *KRAS* and *RAS* wt populations, respectively, in patients with right-sided (blue line) and left-sided (red line) tumours. OS, overall survival; PFS, progression-free survival; wt, wild type.

Table 3 Treatment effects by primary tumour location in *KRAS/RAS* wild-type patients in the main published studies

		Median OS (months)		Median PFS (months)	
		Right-sided	Left-sided	Right-sided	Left-sided
CRYSTAL ¹	FOLFIRI	15.0	21.7	7.1	8.9
	FOLFIRI+cetuximab	18.5	28.7*†	8.1	12.0*†
PRIME ⁷	FOLFOX	15.4	23.6	7.0	9.2
	FOLFOX+panitumumab	11.1	30.3*†	7.5	12.9*
CALGB/SWOG 80405 ⁶	FOLFOX or FOLFIRI+bevacizumab	24.5	32.1†	9.5	11.1†
	FOLFOX or FOLFIRI+cetuximab	16.4	37.5†	7.7	12.0†
FIRE-3 ¹	FOLFIRI+bevacizumab	23.0	28.0†	9.0	10.7
	FOLFIRI+cetuximab	18.3	38.3*†	7.6	10.7†
PEAK ⁷	FOLFOX+panitumumab	17.5	43.4†	8.7	14.6
	FOLFOX+bevacizumab	21.0	32.0†	12.6	11.5
Present study: MACRO-2+PLANET	FOLFOX or FOLFIRI+cetuximab or panitumumab	13.5	32.7†	6.5	10.0†

*P value statistically significant between treatments in the same tumour location.

†P value statistically significant between tumour locations (right vs left)

OS, overall survival; PFS, progression-free survival.

2.6, $p=0.0001$) and any prior surgery (HR 0.7, 95% CI 0.5 to 0.9, $p=0.022$) as independent prognostic factors of OS (online supplementary table 1). In the other hand, age ≥ 65 years, female sex and pathological n+stage were not identified as independent prognostic factors of OS (online supplementary table 1).

DISCUSSION

We retrospectively evaluated the effect of primary tumour location on the efficacy in 261 *KRAS/RAS*-wt mCRC patients treated with an EGFR-I plus chemotherapy as first line. Our results clearly show that patients with tumours up to the splenic flexure (right-sided) had a significantly higher risk of death and progression compared with patients with distal tumours (left-sided), consistent with the growing evidence reported in the literature showing the prognostic and predictive value of primary tumour location in patients with *RAS*-wt mCRC^{1-8 21 22} (table 3). This prognostic effect has been reported to be independent of stage, race, adjuvant chemotherapy, year of study, number of participants and quality of included studies in a recent meta-analysis of 66 studies.²¹

The negative prognostic impact of right-sided tumour location has also been demonstrated in patients treated with first-line bevacizumab, both in two retrospective cohorts and one prospective cohort, and has been found to be independent in multivariate analysis after adjusting for age, sex, race, Kohne score and prior adjuvant chemotherapy.³

The observed efficacy differences are likely related with the suggested EGFR-I-sensitive phenotype that might be more prevalent in left-sided tumours,¹¹ presenting among other variables higher levels of expression of epiregulin and amphiregulin, which have been associated with

enhanced response to EGFR-I.²³ In addition, right-sided tumours have been associated with chemoresistance.³ In our study, we also observed a higher proportion of women, a higher number of metastatic sites and locally advanced tumours among patients with right-sided tumours.

Our data also suggest that poorer efficacy outcomes might be achieved with EGFR-I in patients with right-sided tumours, questioning their value in this population. Similarly, this observation has been reported in several other studies.^{1 2 4-8}

Recently, a study analysing an extensive biomarker panel revealed that the primary tumour side's association with OS and PFS outcomes in patients receiving EGFR-I did not remain significant after multivariate analysis, suggesting that mutations in *BRAF* and *NRAS*, molecular subtypes and tumour methylation may provide a biological explanation for the association with anatomical location.²⁴

A predictive effect of tumour sidedness has been reported in several analyses, with improved results in patients with *RAS*-wt mCRC and left-sided primary tumours treated with EGFR-I as compared with those treated with chemotherapy alone or in combination with bevacizumab. In the meantime, the optimal treatment for patients with right-sided primary tumours is yet to be defined.^{1 2 4-8 22} Despite several molecular and genetic differences having been described between them,¹²⁻¹⁶ we observed similar survival outcomes when patients with rectum primary tumour location were grouped individually, compared with descending and sigmoid colon tumours, and these results are aligned with others.⁴ Loupakakis *et al*³ found similar survival functions in their retrospective analyses of the AVF2107g and NO16966 studies. As herein observed, the ORR was found to be

higher in patients with left-sided colon tumours than in patients with rectal tumours (49% vs 36%, $p=0.019$ in AVF2107g; and 55% vs 45% in NO16966, respectively, $p=0.005$).

In conclusion, the observed results, although limited by their retrospective nature and the study design, are aligned with previous works regarding the prognostic or predictive value of primary tumour sidedness in patients with RAS-wt mCRC treated with first-line EGFR-I plus chemotherapy. The benefit, if any, of EGFR-I in right-sided tumours remains controversial.

Author affiliations

¹Medical Oncology Service, Hospital Universitario Regional y Virgen de la Victoria. IBIMA, Malaga, Spain

²Medical Oncology Service, Hospital Clínico San Carlos, Madrid, Spain

³Ramón y Cajal University Hospital, IRYCIS, CIBERONIC, Alcalá University, Madrid, Spain

⁴Medical Oncology Service, Hospital Germans Trias i Pujol, Badalona, Spain

⁵Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Madrid, Spain

⁶Medical Oncology Service, IRYCIS, Madrid, Comunidad de Madrid, Spain

⁷Medical Oncology Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain

⁸Medical Oncology Service, Hospital Universitario Reina Sofía, Córdoba, Spain

⁹Medical Oncology Service, Hospital General Universitario de Valencia, Valencia, Spain

¹⁰Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain

¹¹Medical Oncology Service, Hospital Universitario Puerta del Hierro Majadahonda, Madrid, Spain

¹²Medical Oncology Service, Hospital Costa del Sol, Málaga, Spain

¹³Medical Oncology Service, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain

¹⁴Medical Oncology Service, Hospital General Universitario de Alicante, Alicante, Spain

¹⁵Medical Oncology Service, Hospital Universitario Marqués de Valdecilla, Santander, Spain

¹⁶Medical Oncology Service, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

¹⁷Medical Oncology Service, Hospital Universitario de Móstoles, Madrid, Spain

Collaborators Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD): Alfredo Carrato, Carmen Guillén (Hospital Ramón y Cajal); Pilar García Alfonso (Hospital General Universitario Gregorio Marañón); Manuel Benavides, Silvia Gil (Hospital Universitario Regional y Virgen Victoria); Enrique Aranda Aguilar, María Teresa Cano (Hospital Universitario Reina Sofía); María José Safont (Hospital General Universitario de Valencia); Cristina Grávalos (Hospital 12 de Octubre); Albert Abad, José Luis Manzano (ICO, Hospital Germans Trias i Pujol); Antonio Sánchez (Hospital Universitario Puerta del Hierro); Julia Alcaide (Hospital Costa del Sol); Rafael López (Hospital Clínico Universitario de Santiago de Compostela); Bartomeu Massutí (Hospital General Universitario de Alicante); Eduardo Díaz-Rubio, Javier Sastre (Hospital Universitario Clínico San Carlos); Fernando Rivera, Eva Martínez (Hospital Universitario Marqués de Valdecilla); Pilar Escudero (Hospital Clínico Universitario Lozano Blesa); Miguel Méndez (Hospital de Móstoles); Esther Falcó (Hospital Son Llàtzer); Encarna González Flores (Hospital Virgen de las Nieves); Teresa García García (Hospital Morales Meseguer); José Ignacio Martín Valadés (Hospital Universitario Fundación F. Jiménez Díaz); Javier Gallego (Hospital General Universitario de Elche); Margarita Reboredo, Manuel Valladares (Complejo Hospitalario Universitario A Coruña); Carlos García-Girón (Hospital Universitario de Burgos); Nuria Cárdenas, Rosario Dueñas (Complejo Hospitalario Universitario de Jaén); Ana Ma García Tapiador (Complejo Hospitalario La Mancha Centro); Carles Pericay (Hospital de Sabadell Corporació Sanitària Parc Taulí); Ferran Losa (Hospital de Sant Joan Despi Moisés Broggi); Antonio Viúdez (Complejo Hospitalario de Navarra); Paula García Tejjido (Hospital San Agustín). TTD Data Centre: Inma Ruiz de Mena and Susana Rodriguez; Statistics and Data Management: Trial Form Support (TFS): Mercè Viladrich; Medical Writing: TFS: Juan Martín.

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Ethics approval The study was conducted according to the principles of good clinical practice, applicable laws and regulations and the Declaration of Helsinki. Each institution's review board approved the study and all patients signed an informed consent document before study participation. MACRO-2 and PLANET studies were approved by independent ethics committees at each trial centre and were conducted in accordance with the ethical principles of the Declaration of Helsinki.

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Data availability statement Data may be obtained from a third party and are not publicly available.

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ORCID iDs

Manuel Benavides <http://orcid.org/0000-0002-9817-1291>

Carmen Guillén <http://orcid.org/0000-0002-3594-1084>

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