**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**

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**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 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...
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).

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

| Sex, n (%) | Right-sided tumour (n=52) | Left-sided tumour (n=209) | P value |
|-----------|---------------------------|---------------------------|---------|
| Male      | 29 (56)                   | 148 (71)                  | 0.047   |
| Female    | 23 (44)                   | 61 (29)                   |         |

| Median age, years (range) | Right-sided tumour | Left-sided tumour | P value |
|---------------------------|-------------------|------------------|---------|
| 62 (37–79)                | 61 (32–83)        | 0.89             |

| ECOG PS, n (%)* | Right-sided tumour | Left-sided tumour | P value |
|-----------------|-------------------|------------------|---------|
| 0               | 19 (45)           | 73 (52)          | 0.55    |
| 1               | 20 (48)           | 62 (44)          |         |
| 2               | 3 (7)             | 6 (4)            |         |

| Pathological T stage, n (%) | Right-sided tumour | Left-sided tumour | P value |
|-----------------------------|-------------------|------------------|---------|
| 2                           | 2 (4)             | 5 (2)            | 0.75    |
| 3                           | 19 (37)           | 84 (40)          |         |
| 4                           | 15 (29)           | 51 (24)          |         |
| x                           | 15 (29)           | 69 (33)          |         |
| Missing                     | 1 (2)             | 0                |         |

| Pathological N stage, n (%)| Right-sided tumour | Left-sided tumour | P value |
|----------------------------|-------------------|------------------|---------|
| 0                           | 8 (16)            | 33 (16)          | 0.86    |
| 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 (%)†‡ | Right-sided tumour | Left-sided tumour | P value |
|------------------------------------|-------------------|------------------|---------|
| 1                                  | 24 (47)           | 135 (65)         | 0.048   |
| 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 (%) | Right-sided tumour | Left-sided tumour | P value |
|----------------------------------------|-------------------|------------------|---------|
| Yes                                    | 32 (63)           | 122 (58)         | 0.64    |
| No                                     | 19 (37)           | 87 (42)          |         |
| Missing                                | 1 (2)             | 0                |         |

| Prior treatment, n (%) | Right-sided tumour | Left-sided tumour | P value |
|------------------------|-------------------|------------------|---------|
| 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.
Table 2  Efficacy results for KRAS and RAS wt populations according to tumour location

|         | KRAS wt (Right-sided (n=52) | Left-sided (n=209) | RAS wt (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 RASwt 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...
Table 3  Treatment effects by primary tumour location in KRAS/RAS wild-type patients in the main published studies

| Study                  | Treatment                          | Right-sided Median OS (months) | Right-sided Median PFS (months) | Left-sided Median OS (months) | Left-sided Median PFS (months) |
|------------------------|------------------------------------|-------------------------------|--------------------------------|-------------------------------|-------------------------------|
| CRYSTAL                | FOLFIRI                            | 15.0                          | 7.1                            | 21.7                          | 8.9                           |
|                        | FOLFIRI+cetuximab                  | 18.5                          | 8.1                            | 28.7†                         | 12.0†                         |
| PRIME                  | FOLFOX                             | 15.4                          | 7.0                            | 23.6                          | 9.2                           |
|                        | FOLFOX+panitumumab                 | 11.1                          | 7.5                            | 30.3†                         | 12.9*                         |
| CALGB/SWOG 804056      | FOLFOX or FOLFIRI+bevacizumab      | 24.5                          | 9.5                            | 32.1†                         | 11.1†                         |
|                        | FOLFOX or FOLFIRI+cetuximab        | 16.4                          | 7.7                            | 37.5†                         | 12.0†                         |
| FIRE-3                 | FOLFIRI+bevacizumab                | 23.0                          | 9.0                            | 28.0†                         | 10.7                          |
|                        | FOLFIRI+cetuximab                  | 18.3                          | 7.6                            | 38.3†                         | 10.7†                         |
| PEAK                   | FOLFOX+panitumumab                 | 17.5                          | 8.7                            | 43.4†                         | 14.6                          |
|                        | FOLFOX+bevacizumab                 | 21.0                          | 12.6                           | 32.0†                         | 11.5                          |
| Present study:         | FOLFOX or FOLFIRI+cetuximab or     | 13.5                          | 6.5                            | 32.7†                         | 10.0†                         |
|                       | panitumumab                        |                               |                                |                               |                               |

*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/RASwt 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 RASwt 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.24

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, Kohnie 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.2 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 RASwt 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

Loupakis et al8 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 RASwt mCRC treated with first-line EGFR-I plus chemotherapy. The benefit, if any, of EGFR-I in right-sided tumours remains controversial.

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

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REFERENCES
1 Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017;3:194–201.
2 Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 2015;51:1405–14.
3 Loupakis F, Yang D, Yao L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107:duj427.
4 von Einem JC, Heinemann V, von Weikersthal LF, et al. Left-sided primary tumours are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial. J Cancer Res Clin Oncol 2014;140:1607–14.
5 Moretto R, Cremoni G, Rossini D, et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with Ras and BRAF wild-type metastatic colorectal cancer. Oncologist 2016;21:988–94.
6 Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1st) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (PTS) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34:3504.
7 Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol 2017;28:1862–8.
8 Arnold D, Lueza B, Douillard J-Y, et al. Prognostic and predictive value of primary tumour side in patients with Ras wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017:28:1713–29.
9 Lee GH, Maitzias G, Askari A, et al. Is right-sided colon cancer different to left-sided colorectal cancer? - a systematic review. Eur J Surg Oncol 2015;41:300–8.
10 Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med* 1990;113:779–88.

11 Missiaglia E, Jacobs B, D’Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann Oncol* 2014;25:1995–2001.

12 Maus MKH, Hanna DL, Stephens CL, et al. Distinct gene expression profiles of proximal and distal colorectal cancer: implications for cytotoxic and targeted therapy. *Pharmacogenomics J* 2015;15:354–62.

13 Yamauchi M, Morikawa T, Kuchiba A, et al. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. *Gut* 2012;61:847–54.

14 Lee Y-C, Lee Y-L, Chuang J-P, et al. Differences in survival between colon and rectal cancer from SEER data. *PLoS One* 2013;8:e78709.

15 Li F-ying, Lai M-de. Colorectal cancer, one entity or three. *J Zhejiang Univ Sci B* 2009;10:219–29.

16 Frattini M, Balestra D, Suardi S, et al. Different genetic features associated with colon and rectal carcinogenesis. *Clin Cancer Res* 2004;10:4015–21.

17 Yuan Z-X, Wang X-Y, Qin Q-Y, et al. The prognostic role of BRAF mutation in metastatic colorectal cancer receiving anti-EGFR monoclonal antibodies: a meta-analysis. *PLoS One* 2013;8:e65995.

18 Carrato A, Abad A, Massuti B, et al. First-Line panitumumab plus FOLFOX4 or FOLFIri in colorectal cancer with multiple or unresectable liver metastases: a randomised, phase II trial (PLANET-TTD). *Eur J Cancer* 2017;81:191–202.

19 Alfonso PG, Benavides M, Ruiz AS, et al. Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (S/A) C as maintenance therapy in patients (P) with metastatic colorectal cancer (mCRC): The MACRO-2 trial [Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)]. *Ann Oncol* 2014;25:v168.

20 Aranda E, Garcia-Alfonso P, Benavides M, et al. 2122 treatment outcomes according to extended Ras mutation testing in a phase II study of first-line mFOLFOX plus cetuximab followed by cetuximab in monotherapy as maintenance therapy or mFOLFOX plus cetuximab in patients with metastatic colorectal cancer: the MACRO-2 trial. *Eur J Cancer* 2015;51:S371–2.

21 Petrelli F, Tomassello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol* 2017;3:211–9.

22 Holch JW, Ricard I, Stintzing S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer* 2017;70:87–98.

23 Jacobs B, De Roock W, Piessevaux H, et al. Amphiregulin and epiiregulin mRNA expression in primary tumors predicts outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol* 2009;27:5068–74.

24 Lee MS, Advani SM, Morris J, et al. Association of primary (1°) site and molecular features with progression-free survival (pfs) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy. *J Clin Oncol* 2016;34:3506.