LINK TO ORIGINAL ARTICLE

# First-line therapy for mCRC — the influence of primary tumour location on the therapeutic algorithm

*Chiara Cremolini, Carlotta Antoniotti, Roberto Moretto, Gianluca Masi and Alfredo Falcone*

Many different factors influence the choice of upfront treatment for patients with metastatic colorectal cancer (mCRC). In a Perspectives article published in the October 2015 issue of this journal (First-line chemotherapy for mCRC — a review and evidence-based algorithm. *Nat. Rev. Clin. Oncol.* **12**, 607–619; 2015)[1], we presented an algorithm to facilitate the translation of results from clinical trials into daily practice, and to provide physicians with a useful tool to guide their routine treatment decisions. This algorithm summarized our evidence-based philosophy regarding the choice of both the 'most-appropriate' intensity of the chemotherapy backbone and the 'best' targeted agents to add to this backbone. Comprehensive assessment of patient characteristics was placed at the top of the therapeutic algorithm, emphasizing the importance of the patient's general health and condition in determining the intensity of the treatment; the same approach was subsequently endorsed in the 2016 updated ESMO clinical practice guidelines for the management of mCRC[2].

In the past few months, however, data highlighting the relevance of primary tumour location as both a prognostic factor and a predictor of benefit from treatment with anti-EGFR monoclonal antibodies have rapidly accumulated. In October 2016, results of a robust meta-analysis[3] confirmed previous evidence of a significantly worse patient prognosis associated with right-sided tumours (located up to the proximal two-thirds of the transverse colon) versus left-sided tumours (located within the distal third of the transverse colon or beyond), independent of disease stage — thus demonstrating the importance of including primary tumour location as a stratification factor in clinical trial design. With regard to predicting patient benefit from targeted agents, although findings indicate that no interaction exists between 'sidedness' and the efficacy of anti-VEGF therapy with bevacizumab[4], the location of the primary tumour does seem to affect sensitivity to anti-EGFR-antibodies[5,6]. In this respect, subgroup analyses of six international, randomized, controlled trials in large cohorts of patients with *RAS*-wild-type mCRC were also reported in October 2016 (REFS 7–9), and the results showed clear differences in the efficacy of anti-EGFR therapy in patients with left-sided and right-sided primary tumours (Supplementary information S1 (table)). Overall, the addition of anti-EGFR antibodies to a chemotherapy doublet is associated with a significant overall survival benefit for patients with left-sided tumours (hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.58–0.83), which is essentially absent in those with right-sided tumours (HR 0.96, 95% CI 0.68–1.35; $P_{interaction} = 0.10$)[10]. Consistent results were reported when comparing the addition of anti-EGFR antibodies versus bevacizumab to doublet chemotherapy according to tumour sidedness: a clear overall survival benefit from the combination with anti-EGFR antibodies was evident for patients with left-sided tumours (HR 0.71, 95% CI 0.58–0.85), whereas doublet chemotherapy plus bevacizumab seems to provide better results in those with right-sided tumours (HR 1.30, 95% CI 0.97–1.74; $P_{interaction} < 0.001$)[10].

The intrinsic methodological limitations of *post-hoc* subgroup analyses must be recognized, but the high intrastudy and interstudy consistency of these results cannot be disregarded, nor can the strong biological and molecular rationale underlying the reported findings. In fact, characteristics related to EGFR-dependency are more frequent in left-sided than in right-sided primary tumours, including *EGFR*-copy-number gain, high levels of the endogenous EGFR ligands AREG and/or EREG, and/or a 'canonical' phenotype according to the new classification of molecular CRC subtypes (CMS2)[11,12]. By contrast, molecular alterations potentially responsible for resistance to anti-EGFR therapy, such as $BRAF^{V600E}$ and/or *PIK3CA* mutation, low levels of AREG and EREG, and the 'BRAF-like', CpG-island methylator, or 'microsatellite instability immune' (CMS1) phenotypes, are clearly more highly represented in right-sided tumours[11,13,14]. Interestingly, however, consistent findings have been observed when limiting the analysis to patients with *RAS* and *BRAF* (RAS/BRAF)-wild-type tumours[8], suggesting that molecular alterations other than $BRAF^{V600E}$ mutation account for the poor prognosis and resistance to anti-EGFR therapy that is associated with right-sided tumours.

On the basis of this new evidence, in our opinion, primary tumour location should be included together with other factors weighing on the choice of first-line treatment for a patient with newly diagnosed mCRC, as emphasized in the latest National Comprehensive Cancer Network (NCCN) clinical guidelines[15]. Considering this rapidly evolving scenario, we propose a revised version of our treatment algorithm that includes primary tumour location in the decision-making process (FIG. 1).

As we described previously[1], evaluation of a patient's suitability for a combination chemotherapy based on clinical assessment remains crucial to choosing the intensity of the upfront treatment. For patients who are not deemed to be appropriate candidates for combination regimens, fluoropyrimidine monochemotherapy plus bevacizumab should be the preferred treatment approach. In patients deemed fit for combination chemotherapy, doublet regimens (FOLFOX, XELOX, or FOLFIRI) and the FOLFOXIRI triplet can be feasible options.

Patients who are eligible for triplet chemotherapy — preferentially, those who have not previously received oxaliplatin-containing adjuvant therapy — can be treated with FOLFOXIRI plus bevacizumab, irrespective of their mutational status: in the presence of *RAS* or *BRAF* mutations, FOLFOXIRI plus bevacizumab remains a preferred option; in the *RAS/BRAF*-wild-type setting, no randomized comparison between doublet chemotherapy plus an anti-EGFR antibody and triplet chemotherapy plus bevacizumab is available, and this decision is mainly driven by the different toxicity profiles and the individual patient's preference. At present, we believe that the location of a primary *RAS/BRAF*-wild-type tumour can help guide this choice (FIG. 1). Specifically, both the intrinsic poor prognosis and the lack of benefit from anti-EGFR therapy for patients with right-sided tumours encourage intensive treatment with triplet chemotherapy plus bevacizumab, whereas a doublet regimen plus an anti-EGFR antibody might be the preferred choice in patients with left-sided tumours (although FOLFOXIRI plus bevacizumab is still an evidence-based option).

When a doublet is the preferred chemotherapy backbone, its combination with bevacizumab is the sole option for patients with *RAS*-mutant disease, and is the preferred option for those with *BRAF*-mutant disease.

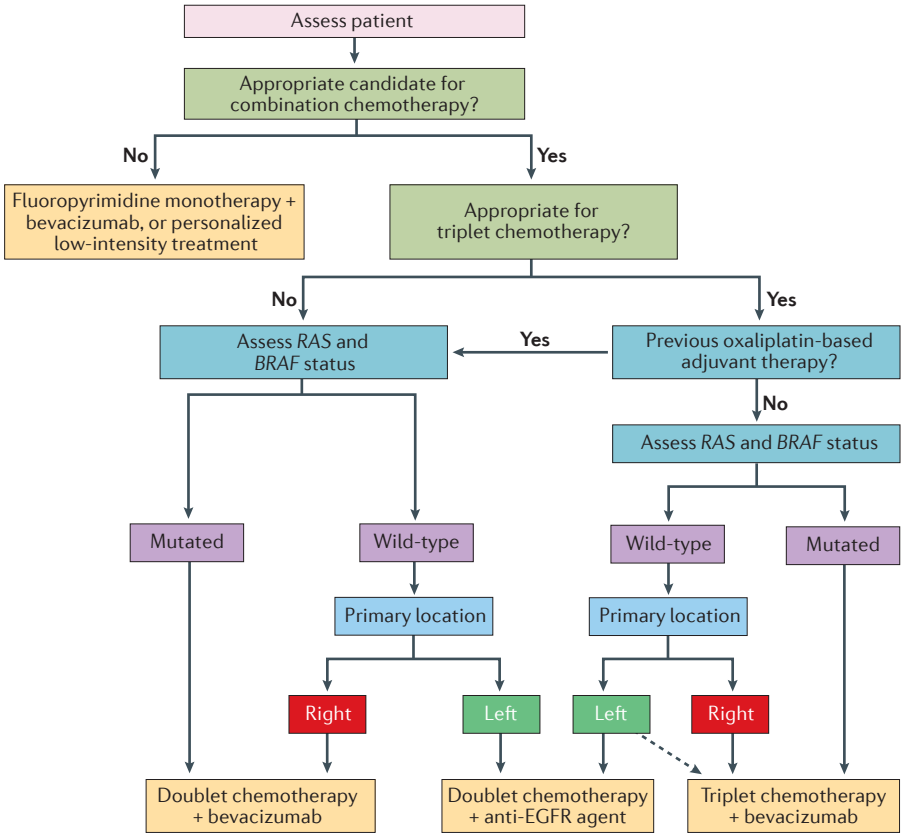


Figure caption | **Updated algorithm for personalized allocation of first-line treatments in patients with mCRC.** We propose this updated version of the algorithm originally presented in our 2015 Perspectives article in this journal[1], in order to reflect the importance of the primary tumour location — or 'sidedness' — to treatment decision-making.

Another important choice is available, however, to those with *RAS*/*BRAF*-wild-type tumours. To this end, primary tumour location becomes crucial: independently of the goal of the treatment, the addition of bevacizumab should be preferred for patients with right-sided tumours, and the use of an anti-EGFR antibody seems highly recommendable for those with left-sided tumours (FIG. 1).

In conclusion, on the basis of the current evidence, consideration of the primary tumour location can help in tailoring the choice of frontline treatment for patients with mCRC and, particularly, in selecting the best candidates to receive an anti-EGFR-antibody-based regimen. Nevertheless, identifying the pattern of molecular alterations responsible for resistance or sensitivity to the available treatments is the real challenge for translational research, and will be a crucial step towards understanding why a few patients with right-sided tumours derive benefit from anti-EGFR therapy, while some with left-sided tumours do not. For example, although HER2 is emerging as a clinically relevant target in mCRC, *HER2*-amplified tumours do not seem to respond to anti-EGFR antibodies and are more frequently left-sided; thus, incorporating analysis of this target in the laboratory work-up of every patient with *RAS*/*BRAF*-wild-type mCRC will be of utmost importance.

*Chiara Cremolini, Carlotta Antoniotti, Roberto Moretto, Gianluca Masi and Alfredo Falcone are at the Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana; and at the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, 67, 56126 Pisa, Italy.*

*Correspondence to C.C.*
*chiaracremolini@gmail.com*

doi:10.1038/nrclinonc.2016.219
Published online 17 Jan 2017

1. Cremolini, C. *et al.* First-line chemotherapy for mCRC — a review and evidence-based algorithm. *Nat. Rev. Clin. Oncol.* **12**, 607–619 (2015).
2. Van Cutsem, E. *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann. Oncol.* **27**, 1386–1422 (2016).
3. Petrelli, F. *et al.* Prognostic survival associated with left-sided versus right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol.* http://dx.doi.org/10.1001/jamaoncol.2016.4227 (2016).
4. Loupakis, F. *et al.* Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J. Natl Cancer Inst.* **107**, dju427 (2015).
5. Brule, S. Y. *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* **51**, 1405–1414 (2015).
6. Moretto, R. *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* **21**, 988–994 (2016).
7. Tejpar, S. *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.* http://dx.doi.org/10.1001/jamaoncol.2016.3797 (2016).
8. Boeckx, N. *et al.* Primary tumor sidedness impacts on prognosis and treatment outcome: results from three randomized studies of panitumumab plus chemotherapy versus chemotherapy or chemotherapy plus bevacizumab in 1st and 2nd line *RAS/BRAF* WT mCRC. *Ann. Oncol.* **27** (Suppl. 6), abstr 89P (2016).
9. Lenz, H. Outcome in the CALGB 80405. Presented at the ESMO 2016 Congress, Copenhagen, Denmark.
10. Holch, J. W., Ricard, I., Stintzing, S., Modest, D. P. & Heinemann, V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur. J. Cancer* **70**, 87–98 (2016).
11. Guinney, J. *et al.* The consensus molecular subtypes of colorectal cancer. *Nat. Med.* **21**, 1350–1356 (2015).
12. Algars, A. *et al. EGFR* gene copy number predicts response to anti-EGFR treatment in *RAS* wild type and *RAS/BRAF/PIK3CA* wild type metastatic colorectal cancer. *Int. J. Cancer* **140**, 922–929 (2016).
13. Missiaglia, E. *et al.* Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann. Oncol.* **25**, 1995–2001 (2014).
14. Lee, M. S. *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 [abstract]. *J. Clin. Oncol.* **34** (Suppl.), 3506 (2016).
15. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology — Colon Cancer; Version 2.2016. NCCN* https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (2016).

**Competing interests statement**
C.C. has received payment for consultancy and honoraria for speaking from Amgen, Bayer, Eli-Lilly, Merck Serono, and Roche. A.F. has received payment for consultancy and honoraria for speaking from Amgen, Bayer, Celgene, Eli-Lilly, Merck Serono, and Roche. The other authors declare no competing interests.

**SUPPLEMENTARY INFORMATION**
**See online article:** S1 (table)
**ALL LINKS ARE ACTIVE IN THE ONLINE PDF**