



TRILETE: a randomised phase III study of modified FOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer

Beatrice Borelli,¹ Roberto Moretto,¹ Sara Lonardi,² Andrea Bonetti,³ Carlotta Antoniotti,¹ Filippo Pietrantonio,⁴ Gianluca Masi,¹ Valentina Burgio,⁵ Federica Marmorino,¹ Lisa Salvatore,⁶ Daniele Rossini,¹ Alberto Zaniboni,⁷ Gemma Zucchelli,¹ Angelo Martignetti,⁸ Monica Di Battista,⁹ Nicoletta Pella,¹⁰ Alessandro Passardi,¹¹ Alessandra Boccaccino,¹ Francesco Leone,^{12,13} Camilla Colombo,¹ Cristina Granetto,¹⁴ Francesca Vannini,¹ Valentina Angela Marsico,¹⁵ Erika Martinelli,¹⁶ Lorenzo Antonuzzo,^{17,18} Stefano Vitello,¹⁹ Laura Delliponti,¹ Luca Boni,²⁰ Chiara Cremolini,¹ Alfredo Falcone¹

To cite: Borelli B, Moretto R, Lonardi S, *et al.* TRILETE: a randomised phase III study of modified FOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer. *ESMO Open* 2018;3:e000403. doi:10.1136/esmoopen-2018-000403

Received 20 May 2018
Accepted 21 May 2018

For numbered affiliations see end of article.

Correspondence to
Dr Chiara Cremolini;
chiaracremolini@gmail.com

ABSTRACT

Background FOLFOXIRI plus bevacizumab is considered a standard option in the upfront treatment of clinically selected patients with metastatic colorectal cancer irrespective of *RAS* and *BRAF* molecular status. The randomised MACBETH and VOLFI studies showed that a modified FOLFOXIRI regimen in combination with cetuximab or panitumumab, respectively, achieved high therapeutic activity in *RAS* and *BRAF* wild-type patients with an acceptable toxicity profile. Drawing from these considerations, we designed TRILETE study aiming at comparing two different chemotherapy backbones (mFOLFOXIRI or mFOLFOX6) in combination with panitumumab in the first-line treatment of patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer.

Methods This is a prospective, open-label, multicentre phase III trial in which initially unresectable and previously untreated *RAS* and *BRAF* wild-type metastatic colorectal cancer patients are randomised to receive a standard treatment with mFOLFOX6 plus panitumumab or an experimental regimen with modified FOLFOXIRI (irinotecan 150 mg/m², oxaliplatin 85 mg/m², L-leucovorin 200 mg/m², 5-fluorouracil 2400 mg/m² 48-hour continuous infusion) plus panitumumab up to 12 cycles, followed by panitumumab plus 5-fluorouracil and L-leucovorin until disease progression. The primary endpoint is overall response rate according to RECIST 1.1 criteria.

Discussion The relative benefit of chemotherapy intensification when using an anti-EGFR-based regimen in molecularly selected patients is unknown; TRILETE study aims at filling this gap of knowledge. The study is sponsored by the Gruppo Oncologico Nord Ovest

Cooperative Group and is currently ongoing at 42 Italian centres.

Clinical trial information NCT03231722.

INTRODUCTION

Selecting the most appropriate first-line treatment is a challenging issue in the management of metastatic colorectal cancer (mCRC). The paramount importance of this choice lies in the role of the upfront treatment in achieving disease control, thus obtaining symptoms' relief, allowing further locoregional and systemic interventions and, even more relevantly, providing the unique opportunity to cure some metastatic patients.¹

A growing amount of drugs is indicated for the first-line treatment of mCRC and, in the absence of contraindications, the association of a biological agent to a chemotherapy doublet is a standard upfront choice. Nevertheless, emerging evidence highlights the possibility to further personalise the treatment by modulating the intensity of the chemotherapy backbone from one- drug to three- drug regimens according to treatment's objective, patient's characteristics and tumour biology.^{2,3}

To this regard, the phase III randomised TRIBE study evaluated the combination of bevacizumab with the three-drug regimen

Table 1 Trials with anti-EGFR plus triplet chemotherapy in patients with metastatic colorectal cancer

Author	n	Molecular selection	Schedule	RR (%)	R0 resection rate (%)	Grades 3–4 diarrhoea (%)	mPFS	mOS
Garufi <i>et al</i> ⁸	43	No molecular selection	Chrono-IFLO+ cetuximab	79	60	94–36	14 months	37 months
Assenat <i>et al</i> ⁹	42	KRAS exon 2 wt	FOLFIRINOX+ cetuximab	81	Not reported	52	9.5 months	24.7 months
Folprecht <i>et al</i> ¹⁰	20	No molecular selection	mFOLFOXIRI+ cetuximab	75	Not reported	25	16 months	33 months
Saridaki <i>et al</i> ¹¹	30	KRAS exon 2 wt	FOLFOXIRI+ cetuximab	70	37	53	10.2 months	30.3 months
Fornaro <i>et al</i> ¹²	37	KRAS, NRAS and BRAF wt	mFOLFOXIRI+ panitumumab	89	35	33	11.3 months	Not reached
Geissler <i>et al</i> ¹³	30	RAS wt	mFOLFOXIRI+ panitumumab	86	16	Not reported	10.8 months	Not reported
Cremolini <i>et al</i> ¹⁴	143	KRAS exon 2 then, RAS and BRAF wt	mFOLFOXIRI+ cetuximab	72	28	18	10.1 months	33.2 months

mPFS, median progression free survival; mOS, median overall survival; RR, response rate.

FOLFOXIRI (5-fluorouracil, oxaliplatin and irinotecan) or the doublet FOLFIRI (5-fluorouracil and irinotecan). The trial met its primary endpoint reporting significantly longer progression-free survival (PFS; 12.1 vs 9.7 months, HR: 0.75, $p=0.003$) in favour of the triplet. A significant advantage in terms of overall survival (OS; 29.8 vs 25.8 months, HR: 0.80, $p=0.030$) and objective response rate (ORR; 65% vs 53%, $p=0.006$) was also evident. The triplet was associated with increased grade 3 and 4 neutropaenia, diarrhoea and stomatitis but no higher incidences of febrile neutropaenia, serious adverse events or treatment-related deaths were reported.^{4,5} Other phase II randomised trials with the use of FOLFOXIRI plus bevacizumab were conducted, and consistent efficacy and safety results were achieved.⁶ Based on these results, the triplet FOLFOXIRI plus bevacizumab is now regarded by all major guidelines as a safe and efficacious first-line therapeutic option for selected patients with mCRC.^{2,3,7}

Also the combination of FOLFOXIRI with an anti-EGFR monoclonal antibody has been investigated in some phase II trials, pointing out remarkable activity results, translating into high secondary resection rates (table 1),^{8–14} at the price of a substantial increase in chemotherapy-related toxicities, in particular grades 3 and 4 diarrhoea. A single-arm phase II study by Gruppo Oncologico Nord Ovest (GONO) assessed the activity and safety of the combination of panitumumab with a modified schedule of FOLFOXIRI (irinotecan was administered at 150 instead of 165 mg/m²) in a highly molecularly selected population of 37 patients with unresectable KRAS/NRAS/HRAS/BRAF wild-type (wt) disease. Based on the occurrence of severe diarrhoea and mucositis in two of the first three patients enrolled, the study was amended to reduce the dosage of the 48-hour continuous infusion of 5-fluorouracil (5-FU) from 3200 mg/m² to 2400 mg/m². After the amendment, the most common grades 3–4

adverse events were neutropaenia (48%), diarrhoea (35%), asthenia (27%), stomatitis (14%) and skin rash (14%).¹² More recently, the phase II randomised MACBETH study tested the combination of cetuximab plus a modified FOLFOXIRI regimen (mFOLFOXIRI: irinotecan: 130 mg/m² day 1, oxaliplatin: 85 mg/m² day 1, L-Leucovorin (LV) 200 mg/m² day 1, 5-FU 2400 mg/m² 48-hour continuous infusion) in 116 patients with RAS/BRAF wt mCRC. The safety profile was acceptable (31% grades 3–4 neutropaenia, 18% grades 3–4 diarrhoea, 6% grades 3–4 stomatitis, 16% grades 3–4 skin rash and 3% febrile neutropaenia) and reassuring results about the feasibility of this combination were provided. Encouraging activity data emerged, with 72% and 91% ORR and disease control rate (DCR), respectively. In addition, 76% of patients achieved early tumour shrinkage (ETS), and the median depth of response (DoR) was 53%; R0 resection rate was 28% in the overall population and 50% in the liver-only subgroup. Four months of mFOLFOXIRI plus cetuximab followed by cetuximab maintenance achieved a median PFS of 10.1 months and an OS of 33.2 months.¹⁴ Therefore, data from MACBETH confirmed the feasibility of the modified triplet plus an anti-EGFR monoclonal antibody and remarked the notable activity of this treatment translating into a high secondary resection rate.

Another recent phase II study, VOLFI, that randomised 96 patients with RAS wt mCRC to receive FOLFOXIRI±panitumumab, reported high ORR (86% vs 61% with FOLFOLFOXIRI, $p=0.0096$) and DCR (97% vs 79%, $p=0.0071$) with the triplet plus the anti-EGFR. Secondary R0 resection rate was 16% in triplet plus anti-EGFR arm versus 9% in chemotherapy-only arm in the overall population and 50% vs 27% in the potentially resectable cohort.¹³

In spite of encouraging safety and activity results, it is not clear whether the intensification of the chemotherapy backbone in combination with the anti-EGFR

Figure 1. Study design

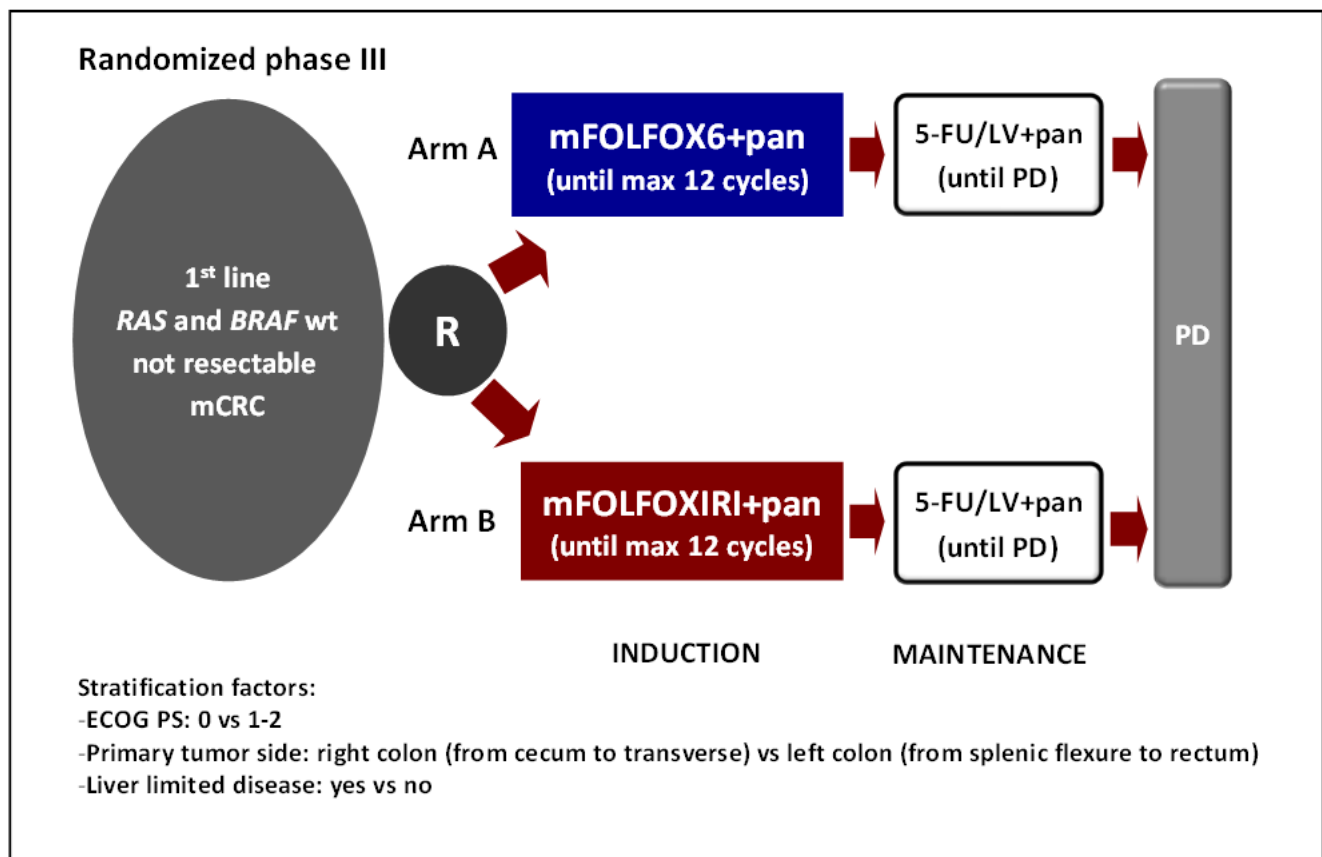


Figure 1 Study design. 5-FU, 5-fluorouracil; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LV, L-Leucovorin; PD, disease progression.

may be beneficial and to what extent in properly selected patients. This gap of knowledge might be filled only by a phase III study. Drawing from this evidence, we designed the TRIplete study, a phase III randomised trial of first-line mFOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab in patients with *RAS* and *BRAF* wt unresectable mCRC.

METHODS/DESIGN

Study design

The present study is a prospective, open-label, multi-centre phase III randomised trial in which initially unresectable and previously untreated patients with *RAS* and *BRAF* wt mCRC are randomised in a 1:1 ratio to receive panitumumab plus mFOLFOX6 (arm A, standard treatment) or panitumumab plus mFOLFOXIRI (arm B, experimental arm) every 14 days up to 12 cycles, followed by panitumumab plus 5-FU/LV as maintenance in both arms until disease progression, unacceptable adverse events or consent withdrawal (figure 1).

The feasibility of surgical radical resection of residual metastases in responsive patients is evaluated every 8

weeks. In the case of secondary resection of metastases, a postoperative therapy with the same chemotherapy regimen received before resection plus panitumumab is planned up to a total duration (preoperative plus postoperative treatment) of 12 cycles (figure 2). The postoperative treatment should start not earlier than 4 weeks after surgery.

Study objectives and endpoints

The primary objective of this trial is to compare the activity of panitumumab in combination with mFOLFOX6 or with mFOLFOXIRI in patients with *RAS* and *BRAF* wt mCRC in terms of ORR according to RECIST 1.1 criteria.¹⁵ ORR is defined as the percentage of patients achieving a complete response (CR) or partial response (PR) during the study treatment period.

Secondary objectives of this study are to compare the two proposed treatments in terms of safety profile, PFS, OS, centrally assessed ORR, ETS, DoR and R0 resection rate.

PFS is defined as the time from randomisation to the first disease progression or death, whichever occurs first;

Figure 2. Post-operative treatment in case of secondary resection of metastases

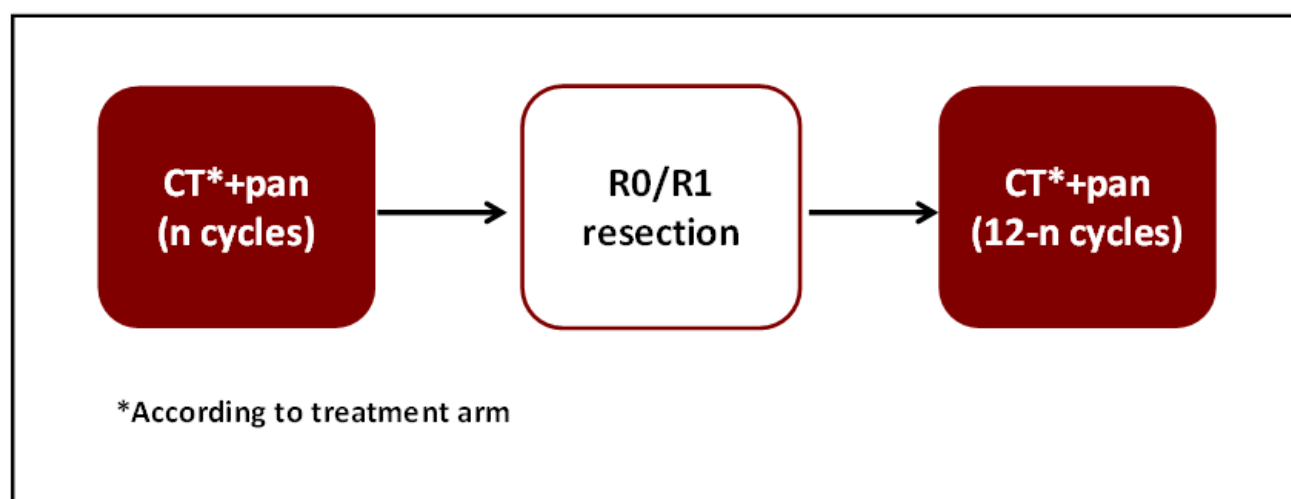


Figure 2 Postoperative treatment in case of secondary resection of metastases.

OS is defined as the time from randomisation to the date of death due to any cause; centrally assessed ORR is defined as the percentage of patients relative to the total of enrolled subjects, achieving a CR or PR based on central re-evaluation of CT scan images; ETS is defined as the rate of patients, relative to the total of the enrolled subjects, achieving a $\geq 20\%$ decrease in the sum of diameters of RECIST target lesions at week 8 compared with baseline; DoR is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, when compared with baseline; R0 resection rate is defined as the percentage of patients, relative to the total of enrolled subjects, undergoing secondary R0 resection of metastases.

Statistical design

The primary analysis of ORR will be performed in the intention-to-treat population. The proportion of patients with a best overall response of CR or PR with its 95% CI will be reported for each arm. The χ^2 test for heterogeneity and the OR will be used for comparing the distributions of best overall response among the treatment groups. Patients are stratified according to the following factors: ECOG Performance Status (ECOG PS) (0 vs 1–2), primary tumour location (right [from cecum to transverse colon] vs left [from splenic flexure to rectum]) and spread of metastatic disease (liver limited vs no liver limited). The stratified analysis in the intention-to-treat population will be presented as primary analysis.

Under the assumption of a ORR in the control group equal to 60%, based on the results of the registrative trial of panitumumab in association with FOLFOX,¹⁶ a

total sample size of 432 cases, randomised in a 1:1 ratio, provides approximately 90% power to a two-sided χ^2 test for heterogeneity at the 0.05 significance level, in order to detect a $\geq 15\%$ difference in ORR between the two treatment arm.

The Kaplan-Meier method will be used to performed survival analyses. Log-rank tests stratified by the same factors as used for randomisation will also be performed, as well as multivariable models including all the significant baseline variables. The median event times and corresponding two-sided 95% CIs for the median will be provided. A secondary analysis of all primary and secondary endpoints will be performed in the centrally assessed *RAS/BRAF* wt population.

Study population

The study has been approved by 58 ethics committees and is currently ongoing at 42 Italian oncology units. Consistent with previous FOLFOXIRI-based trials conducted by the GONO group, only patients aged < 70 years with ECOG PS ≤ 2 , or aged 71–75 years with ECOG PS 0, are eligible. Main inclusion criteria are: the availability of a tumour tissue sample (primary tumour and/or metastatic sites), *RAS* (codons 12, 13, 59, 61, 117 and 146 of *KRAS* and *NRAS* genes) and *BRAF* (V600E mutation) wt status of primary colorectal cancer or related metastasis, at least one measurable lesion according to RECIST 1.1, adequate liver, renal and bone marrow function. Previous oxaliplatin-based adjuvant chemotherapy is not permitted; adjuvant fluoropyrimidine monotherapy is allowed only if more than 6 months have elapsed between the end of adjuvant therapy and disease relapse. Other exclusion criteria are: previous treatment with anti-EGFR

inhibitors, symptomatic peripheral neuropathy >1 according to NCI-CTCAE V.4.0¹⁷ and contraindications to study drugs.

Study procedures

Patients randomised in arm A (standard arm) receive mFOLFOX6 plus panitumumab (panitumumab 6 mg/kg, oxaliplatin 85 mg/m², LV200 mg/m², 5-FU 400 mg/m² intravenous bolus, 5-FU 2400 mg/m² 48-hour continuous infusion) every 2 weeks for a maximum of 12 cycles.

Patients randomised in arm B (experimental arm) receive mFOLFOXIRI plus panitumumab (panitumumab 6 mg/kg, irinotecan 150 mg/m², oxaliplatin 85 mg/m², LV 200 mg/m², 5-FU 2400 mg/m² 48-hour continuous infusion) every 2 weeks for a maximum of 12 cycles. If no progression occurs, maintenance with 5-FU/LV plus panitumumab is administered biweekly in both arms at the same dose used at the last cycle of the induction treatment until disease progression, unacceptable toxicity or patient's refusal. The continuation of panitumumab until disease progression is recommended also if 5-FU is interrupted because of adverse events, patient's refusal or at investigator's choice.

The application of skin moisturisers, topical steroid (1% hydrocortison cream) and sunscreen protections is suggested in order to prevent skin acne-like rash. In addition, pre-emptive treatment with doxycycline 100 mg daily for 1 week starting from day 1 of cycle 1 and then in alternate cycles is recommended.

RAS and *BRAF* testing is locally or centrally performed at investigator's choice. The independent central reassessment of *RAS* and *BRAF* mutational status by means of MALDI-TOF MassArray (Sequenom) is planned.^{18 19} Disease assessment is performed every 8 weeks by means of CT-scan.

Safety

All adverse events observed during the study treatment period are properly registered in the subjects' medical records and in electronic case report forms. All serious adverse events (SAEs), that is, fatal or life-threatening adverse events or those requiring hospitalisation or resulting in persistent or significant disability/incapacity should be notified within 24 hours by the investigator to the sponsor according to local procedures, statutes and the European Clinical Trial Directive (when applicable). The sponsor will medically review all SAEs and is responsible for their notification to the appropriate ethics committees, competent authorities and participating Investigators.

Translational analyses

A wide programme of translational analyses is planned. The availability of tissue specimens (primary tumour or metastatic site) is mandatory for study entry. Tissue specimens are collected for the central assessment of *RAS* and *BRAF* status and for further molecular analyses. In the case of secondary resection of metastases, the collection

of newly available specimens is required. Also blood and plasma samples are collected at baseline, at every CT scan performed during induction and at first evidence of disease progression. In the case of secondary resection of metastases, plasma samples will be collected also within 1 month before and after surgery, respectively.

Ethics and regulatory considerations

The procedures set out in the present study respect the Good Clinical Practice guidelines and the guiding principles detailed in the Declaration of Helsinki. The study is also carried out in keeping with applicable local law(s) and regulation(s).

It was registered in the EUDRACT database (EUDRACT NUMBER 2016-004394-40) in October 2016 and at clinicaltrials.gov (NCT03231722) in July 2017. Written informed consent to study procedures must be provided by all candidate patients before the enrolment.

DISCUSSION

Doublets plus anti-EGFR are standard options for the upfront treatment of patients with *RAS*/*BRAF* wt mCRC. While phase II trials suggest interesting activity results with triple chemotherapy regimens plus an anti-EGFR, the added value of intensifying the chemotherapy backbone from doublets to the triplet, when using an anti-EGFR as upfront targeted agent, has never been estimated. TRIPLETE study aims at filling this current gap of knowledge.

Some key points of the trial design deserve consideration. First, with regard to patients' inclusion criteria, primary tumour location was chosen as a stratification factor, based on the clear negative prognostic impact of right-sidedness^{20 21} but not as a selection factor. In fact patients with right-sided primary tumours were not excluded from this trial. Although recognising the lower sensitivity to anti-EGFRs of right-sided versus left-sided tumours when using a chemotherapy doublet,^{22 23} the lack of regulatory restrictions to the use of anti-EGFRs in right-sided tumours, as well as the lack of evidence about the usefulness of an intensified chemotherapy backbone in combination with the anti-EGFR in this poor-prognosis subgroup, drove this choice. In addition, though acknowledging the small sample sizes, in the VOLFI study, right-sided tumours achieved an ORR of 60% with FOLFOXIRI plus panitumumab as compared with 38% with triplet alone.¹³

Second, in the TRIPLETE study, ORR was chosen as primary endpoint. While the choice of OS as primary endpoint would have substantially hampered the feasibility of this academic study, the reliability of PFS as a surrogate endpoint of OS appears weakened when using upfront anti-EGFR-based treatments. However, a significant improvement in ORR translating into OS benefit was observed in recent phase III trials investigating anti-EGFR-containing regimens.^{16 24} An emblematic example of how activity parameters predict OS better than PFS in

Table 2 Ongoing trials with anti-EGFR plus triplet chemotherapy in patients with metastatic colorectal cancer

Author	Phase	Estimated enrolment	Setting	Molecular selection	Experimental schedule	Endpoint
Deng <i>et al</i> ³³	Phase II	138	Unresectable liver metastases only	<i>RAS</i> wt	FOLFOXIRI± cetuximab	Complete curative liver treatment (surgery and/or RFA)
Nakajima <i>et al</i> ³⁴	Phase II	360	First line	<i>RAS</i> wt	FOLFOXIRI+ cetuximab or bevacizumab	DoR
Folprecht <i>et al</i> ³⁵	Phase II	256	Unresectable liver metastases only	<i>RAS/BRAF</i> wt	FOLFOXIRI+ cetuximab	ORR
Ychou <i>et al</i> ³⁶	Phase II	209	First line	<i>RAS/BRAF</i> wt selected by cDNA analysis	Panitumumab+ mFOLFOX6 or FOLFIRINOX	CRR

cDNA, circulating DNA; CRR, complete response rate; DoR, best deepness of response; ORR, overall response rate; RFA, radiofrequency ablation.

trials evaluating the efficacy of anti-EGFR agents is the FIRE-3 study. In this trial, a clear benefit was demonstrated in terms of OS in favour of FOLFIRI plus cetuximab with respect to FOLFIRI plus bevacizumab with no difference in terms of PFS. At the central independent radiological evaluation, significantly higher ORR, ETS and DoR were reported in *RAS* wt patients treated with cetuximab-based therapy. Also ETS and DoR correlated with survival.²⁵ Moreover, as clearly stated by European Society for Medical Oncology guidelines, achieving cytoreduction is a relevant clinical objective in different scenarios of mCRC, including those cases in which the secondary resection of metastases is a pursuable objective and those in which the high tumour burden makes response needed in order to improve symptoms or to prevent their occurrence.² To this purpose, the triplet plus an anti-EGFR might be a valuable option, as suggested by the choice of activity endpoints also in other currently ongoing trials evaluating similar regimens (table 2).

Third, in the present study, a 6-month induction phase with chemotherapy plus panitumumab, followed by maintenance with 5-FU/LV plus panitumumab, is planned in both arms. Only a few data are currently available with regard to the role of maintenance after an anti-EGFR-based induction therapy and the 'best' maintenance to be administered. Our choice was driven by results of trials in the 'chemotherapy-alone era' underlining the possibility to de-potentiate the treatment without compromising patients' prognosis^{26,27} and by results of two phase II trials, respectively showing the non-inferiority of maintenance with cetuximab alone versus the full treatment until progression^{28,29} and the feasibility of cetuximab maintenance versus a 'stop&go' strategy.²⁹ This decision was also recently supported by the presentation of the Japanese phase II SAPPHERE trial where patients not progressing after six cycles of FOLFOX plus panitumumab were randomised to receive 5-FU/LV and panitumumab as maintenance therapy or to continue induction treatment. Preliminary data showed similar 9-months PFS (primary

endpoint of the study) in the two arms, thus supporting the use of anti-EGFR plus 5-FU/LV as maintenance in order to delay disease progression while preventing the occurrence of oxaliplatin-induced neuropathy.³⁰

Finally, in order to improve the adherence to the therapy, the administration of doxycycline is recommended in both arms to prevent anti-EGFR-induced skin rash. Based on clinical experiences demonstrating a reduced incidence of acneiform rash in the case of pre-emptive rather than reactive administration of a tetracycline during anti-EGFR-based therapy,³¹ Multinational Association of Supportive Care in Cancer guidelines actually recommend the pre-emptive use of oral doxycycline or minocycline.³²

CONCLUSIONS

In the era of personalised medicine, TRIPLETE study will throw light on the potential value of a modified schedule of FOLFOXIRI plus panitumumab as a valuable upfront option for some patients with mCRC, selected on the basis of a careful evaluation of patients' characteristics, molecular features and treatment's objective.

Author affiliations

¹Unit of Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy

²Department of Clinical and Experimental Oncology, SC Medical Oncology Unit 1, Istituto Oncologico Veneto – IRCCS, Padua, Italy

³Department of Oncology, "Mater Salutaris" Hospital, Legnago, Italy

⁴Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

⁵Department of Oncology, Division of Experimental Medicine, IRCCS San Raffaele, Milan, Italy

⁶Medical Oncology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

⁷Medical Oncology Unit, Fondazione Poliambulanza, Brescia, Italy

⁸Oncology Department, Azienda Usl Toscana Sud Est, Siena, Italy

⁹Department of Medical Oncology, Azienda USL, Bologna, Italy

¹⁰Department of Medical Oncology, Azienda Sanitaria Universitaria Integrata, Udine, Italy

- ¹¹Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Italy
- ¹²Department of Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy
- ¹³Department of Oncology, University of Turin, Turin, Italy
- ¹⁴Department of Medical Oncology, A.O. S. Croce and Carle Teaching Hospital, Cuneo, Italy
- ¹⁵Unit of Medical Oncology, Hospital San Giovanni Calibita Fatebenefratelli, Rome, Italy
- ¹⁶Department of Internal and Experimental Medicine "F. Magrassi e A. Lanzara", Institute of Medical Oncology, University of Campania Luigi Vanvitelli, Naples, Italy
- ¹⁷S.C. Oncologia Medica 1, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
- ¹⁸Medical Genetics, University of Siena, Siena, Italy
- ¹⁹Department of Medical Oncology, Sant'Elia Hospital, Caltanissetta, Italy
- ²⁰Clinical Trial Center, AOU Careggi, Firenze, Italy

Acknowledgements The study is sponsored by GONO Cooperative Group

Contributors RM, GM, ChC and AF contributed to the study design; all authors contributed to writing and revision of the paper.

Funding The study is supported by GONO Cooperative Group and partially funded by AMGEN s.r.l.

Competing interests None declared.

Patient consent Not required.

Ethics approval The study (protocol V. 1.2, 23 May 2017) was approved in June 2017 by the Ethics Committee of the Coordinating Center (Comitato Etico Area Vasta Nord Ovest) and then approved by the local ethics committees of participating centres.

Provenance and peer review Not commissioned; internally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© European Society for Medical Oncology (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Cremolini C, Schirripa M, Antoniotti C, *et al.* First-line chemotherapy for mCRC—a review and evidence-based algorithm. *Nat Rev Clin Oncol* 2015;12:607–19.
- Van Cutsem E, Cervantes A, Adam R, *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386–422.
- Network NCC. *NCCN clinical practice guidelines in oncology, NCCN guidelines colon cancer (Version 2.2018)*, 2018.
- Loupakis F, Cremolini C, Masi G, *et al.* Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609–18.
- Cremolini C, Loupakis F, Antoniotti C, *et al.* FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015;16:1306–15.
- Masi G, Loupakis F, Salvatore L, *et al.* Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol* 2010;11:845–52.
- Salvatore L, Aprile G, Arnoldi E, *et al.* Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM). *ESMO Open* 2017;2:e000147.
- Garufi C, Torsello A, Tumolo S, *et al.* Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* 2010;103:1542–7.
- Assenat E, Desseigne F, Thezenas S, *et al.* Cetuximab plus FOLFIRINOX (ERBIRINOX) as first-line treatment for unresectable metastatic colorectal cancer: a phase II trial. *Oncologist* 2011;16:1557–64.
- Folprecht G, Hamann S, Schütte K, *et al.* Dose escalating study of cetuximab and 5-FU/folinic acid (FA)/oxaliplatin/irinotecan (FOLFOXIRI) in first line therapy of patients with metastatic colorectal cancer. *BMC Cancer* 2014;14:521.
- Saridaki Z, Androulakis N, Vardakis N, *et al.* A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in KRAS wt, metastatic colorectal cancer: a pilot phase II trial. *Br J Cancer* 2012;107:1932–7.
- Fornaro L, Lonardi S, Masi G, *et al.* FOLFOXIRI in combination with panitumumab as first-line treatment in quadruple wild-type (KRAS, NRAS, HRAS, BRAF) metastatic colorectal cancer patients: a phase II trial by the Gruppo Oncologico Nord Ovest (GONO). *Ann Oncol* 2013;24:2062–7.
- Geissler UMM M, Knorrnschield R. mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer m(CRC): a randomized phase II VOLFI trial of the AIO (AIO-KRK0109). *Ann Oncol* 2017;28(Suppl 5):159.
- Cremolini C, Antoniotti C, Lonardi S, *et al.* Activity and Safety of Cetuximab Plus Modified FOLFOXIRI Followed by Maintenance With Cetuximab or Bevacizumab for RAS and BRAF Wild-type Metastatic Colorectal Cancer: A Randomized Phase 2 Clinical Trial. *JAMA Oncol* 2018;4:529.
- Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- Douillard JY, Siena S, Cassidy J, *et al.* Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–705.
- National Cancer Institute. *Common terminology criteria for adverse events v4.0*, 2009.
- Arcila M, Lau C, Nafa K, *et al.* Detection of KRAS and BRAF mutations in colorectal carcinoma roles for high-sensitivity locked nucleic acid-PCR sequencing and broad-spectrum mass spectrometry genotyping. *J Mol Diagn* 2011;13:64–73.
- Fumagalli D, Gavin PG, Taniyama Y, *et al.* A rapid, sensitive, reproducible and cost-effective method for mutation profiling of colon cancer and metastatic lymph nodes. *BMC Cancer* 2010;10:101.
- Loupakis F, Yang D, Yau L, *et al.* Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015:107.
- Sunakawa Y, Ichikawa W, Tsuji A, *et al.* Prognostic Impact of Primary Tumor Location on Clinical Outcomes of Metastatic Colorectal Cancer Treated With Cetuximab Plus Oxaliplatin-Based Chemotherapy: A Subgroup Analysis of the JACCO CC-05/06 Trials. *Clin Colorectal Cancer* 2017;16:e171–e180.
- Arnold D, Lueza B, Douillard JY, *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.
- 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.
- Heinemann V, von Weikersthal LF, Decker T, *et al.* FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–75.
- Stintzing S, Modest DP, Rossius L, *et al.* FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol* 2016;17:1426–34.
- Tournigand C, Cervantes A, Figer A, *et al.* OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol* 2006;24:394–400.
- Chibaudel B, Maindault-Goebel F, Lledo G, *et al.* Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009;27:5727–33.
- García Alfonso P, Benavides M, Sánchez Ruiz A, *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) metastatic colorectal cancer (mCRC): The MACRO-2 trial (Spanish Cooperative Group for Treatment of Digestive Tumours [TTD]). *Ann Oncol* 2014;25(Suppl 4):iv167–iv209.

29. Wasan H, Meade AM, Adams R, *et al.* Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol* 2014;15:631–9.
30. Nakamura MMY, Takahashi M. SAPPHERE: A randomized phase II study of mFOLFOX6 + panitumumab versus 5-FU/LV + panitumumab after 6 cycles of frontline mFOLFOX6 + panitumumab in patients with colorectal cancer. *J Clin Oncol* 2018;36:729.
31. Lacouture ME, Mitchell EP, Piperdi B, *et al.* Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:1351–7.
32. Lacouture ME, Anadkat MJ, Bensadoun RJ, *et al.* Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* 2011;19:1079–95.
33. ClinicalTrials.gov. Medicine. UNLo. 2014 <https://clinicaltrials.gov/ct2/show/NCT02063529>
34. ClinicalTrials.gov. Medicine. UNLo. 2015 <https://clinicaltrials.gov/ct2/show/NCT02515734>
35. ClinicalTrials.gov. Medicine. UNLo. 2013 <https://clinicaltrials.gov/ct2/show/NCT01802645>
36. ClinicalTrials.gov. Medicine. UNLo. 2011 <https://clinicaltrials.gov/ct2/show/NCT01328171>