Optimal maintenance strategy following FOLFOX plus anti-EGFR induction therapy in patients with *RAS* wild type metastatic colorectal cancer: an individual patient data pooled analysis of randomized clinical trials

Alessandra Raimondi[a], Federico Nichetti[a,b], Arndt Stahler[c] , Harpreet S. Wasan[d], Enrique Aranda[e], Giovanni Randon[a], Annika Kurreck[c], Angela M. Meade[f], Eduardo Díaz-Rubio[g], Monica Niger[a], Sebastian Stintzing[c], Federica Palermo[a], Tanja Trarbach[h], Michele Prisciandaro[a], Greta Sommerhäuser[c], David Fisher[f], Federica Morano[a], Filippo Pietrantonio[a*], and Dominik P. Modest[c*].

List of affiliations:

[a] Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

[b] Computational Oncology Group, Molecular Precision Oncology Program, National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), Heidelberg, Germany.

[c] Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Tumor Immunology, Berlin, Germany and DKTK, German Cancer Consortium, German Cancer Research Centre (DKFZ), Heidelberg, Germany.

[d] Hammersmith Hospital, Imperial College London – London, United Kingdom.

[e] IMIBIC, Universidad de Córdoba, CIBERONC, Instituto de Salud Carlos III. Hospital Universitario Reina Sofía, Córdoba, Spain

[f] MRC Clinical Trials Unit, at University College London, Redhill, England – London, UK

[g] Hospital Clinico San Carlos, Madrid, Spain

[h] Reha-Zentrum am Meer, Bad Zwischenahn, Niedersachsen, Germany

*co-last authors

Correspondence to:

Filippo Pietrantonio, MD

Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, via

Giacomo Venezian 1, 20133 Milan, Italy. Phone: +39 02 23903807; Fax: + 39 0223902149;

Email: filippo.pietrantonio@istitutotumori.mi.it

Abstract

Background

Anti-EGFR antibodies plus doublet chemotherapy is standard of care in *RAS/BRAF* wild-type mCRC. No phase-3 level of evidence is available to guide treatment de-escalation after anti-EGFR-based first-line. Several randomized clinical trials investigated deintensification strategies with 5-fluorouracil/leucovorin (5-FU/LV) and/or anti-EGFR.

Methods

We performed an individual patient data pooled analysis of Valentino, Panama, MACRO-2, COIN-B trials including *RAS* wild-type mCRC patients who received first-line therapy with FOLFOX plus panitumumab or cetuximab followed by pre-specified maintenance strategy. Only patients who started maintenance according to assigned arm were included. Patients were categorized by type of maintenance (i.e. 5-FU/LV, anti-EGFR or 5-FU/LV+anti-EGFR). Progression-free (PFS) and overall survival (OS) were calculated from start of maintenance ; toxicity was evaluated for maintenance treatment period.

Results

A total of 518 patients were included in the pooled analysis. Overall, 123, 185, 210 patients received maintenance with 5-FU/LV, anti-EGFR, 5-FU/LV+anti-EGFR, respectively. Median PFS was 5.6, 6.0 and 9.0 (P=0.009) and OS was 25.7, 24.0 and 28.0 months (P=0.134) in 5-FU/LV, anti-EGFR and 5-FU/LV+anti-EGFR arms, respectively. Monotherapy maintenance (either 5-FU/LV or anti-EGFR) was inferior to combination in terms of PFS (HR 1.26, P=0.016) and non-significantly trending also in OS (HR 1.20, P=0.111). An increase of overall any grade and grade≥3 AEs and selected AEs was reported in combination compared to either 5-FU/LV or anti-EGFR arms.

Conclusions

This pooled analysis including four randomized phase II supports the use of 5-FU/LV plus anti-EGFR as preferred maintenance regimen. Data provide rational for a more individualized maintenance treatment approach based on tumor and patients features.

Keywords: Metastatic colorectal cancer; anti-EGFR therapy; maintenance treatment; *RAS* wild-type; meta-analysis.

Introduction

According to current guidelines, doublet chemotherapy plus an anti-EGFR agent is regarded as the optimal initial therapy in patients with *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC), especially with left-sided primary tumor location.[1]

In an oxaliplatin-based doublet/triplet first-line strategy, maintenance therapy with de-intensified regimens does not jeopardize survival outcomes compared to the continuation of intensive therapy until disease progression, with better tolerability and quality of life.[2-5] However, the optimal duration of first-line treatment should be based not only on the literature, but also on patient preferences, individual tolerability to specific drugs used in the induction phase and pharmacoeconomic considerations. Based on phase III studies, bevacizumab plus a fluoropyrimidine is the preferred maintenance option after a 4- to 6-month bevacizumab-based induction therapy, since maintenance treatment provided a significant benefit in PFS and a non-significant trend in terms of OS.[6-8] With anti-EGFR-targeted first-line treatment, several phase II randomized clinical trials (RCTs) investigated different de-intensification strategies varying from single-agent anti-EGFR antibody, fluoropyrimidine monotherapy or the combination of 5-fluorouracil/leucovorin (5-FU/LV) with an anti-EGFR antibody.[9-16]

Based on the results of single studies and the overall literature, the 2022 ESMO consensus guideline recommends the use of FU/LV plus an anti-EGFR agent as the preferred maintenance regimen after FOLFOX plus anti-EGFR initial therapy.[1] This recommendation was made without phase III study evidence and based on limited impact of such maintenance treatments on long-term survival.[9-16]

Based on all these considerations, we designed and conducted an international individual patient data (IPD) pooled analysis including the key RCTs on this topic, with the aim to

achieving more robust evidence on the optimal post-induction strategy after an anti-EGFR-based first-line treatment in patients with *RAS* wt mCRC.

Methods

Study design and trials population

We performed an IPD pooled analysis from four multicenter randomized phase II RCTs: Valentino, Panama, MACRO-2 and COIN-B trials. This pooled analysis was sponsored by GONO Foundation with the name GONO-AMM-1 study.

The Valentino study (NCT02476045) showed that 4-month induction with panitumumab plus FOLFOX followed by maintenance with single-agent panitumumab achieved inferior progression free survival (PFS) compared to the same induction regimen followed by panitumumab plus 5-FU/LV in patients with *RAS* wt mCRC, although with a slightly reduced toxicity burden during the maintenance phase.[12] The Panama study (NCT01991873) reported that, in patients with *RAS* wt mCRC achieving at least disease control after 6 cycles of panitumumab plus FOLFOX, maintenance therapy with panitumumab plus 5-FU/LV achieved significantly superior PFS as compared with 5-FU/LV alone.[14] The MACRO-2 study (NCT01161316) showed the potential non-inferiority in terms of 9-month PFS of 4-month induction with cetuximab plus FOLFOX followed by maintenance with cetuximab alone compared to continuation of first-line therapy until disease progression (PD) in patients with *KRAS* exon 2 wt mCRC, with subsequent re-analysis in the all-*RAS* wt subgroup.[11] The randomized COIN-B (ISRCTN38375681) study showed that, after 12 weeks of cetuximab plus FOLFOX induction, both a treatment break and maintenance with cetuximab alone followed by re-induction at PD may achieve acceptable failure-free survival in patients with *KRAS* exon 2 wt mCRC (with subsequent analysis of all *RAS* wt cases), though a treatment break may lead to inferior overall survival (OS) and post-induction PFS than single-agent maintenance.[9]

Eligibility criteria and complete results of each trial have been previously published.[9,11,12,14] The present analysis included patients with known and all wt *RAS* status who received the pre-planned induction therapy and started the assigned maintenance regimen.

Data gathering

Our analysis was designed in 2021 and trial management committees of all trials gave their approval, following their review of a formal protocol. The requested anonymized data consisted of patients' characteristics (including age, sex, ECOG performance status, primary tumor location, *RAS* and *BRAF* status, primary tumor resection and previous adjuvant treatment, number and site of metastases, first-line treatment start and stop date, number of cycles administered and best response to induction therapy), treatment arm (maintenance with anti-EGFR monotherapy either panitumumab or cetuximab, maintenance with 5-FU/LV monotherapy, maintenance with anti-EGFR plus 5-FU/LV) and details on treatment duration, outcome data (disease progression and survival) and toxicity reported. Patients with unknown/not assessed or mutated *RAS* status were excluded. A trial database was set up to include the information extrapolated from the four study datasets to ensure the collection of appropriately comparable data and to facilitate the planned IPD pooled analysis. All patients had given informed consent for trial participation and this study was approved by the ethical committee of Fondazione IRCCS Istituto Nazionale dei Tumori (Identifier: INT 99/22).

Statistical analysis

For trials which performed the randomization after successful induction treatment (PANAMA), the extraction of patients' data was performed according to an "intention-to-treat with maintenance therapy given" principle, whereas for trials with upfront randomization before induction therapy (Valentino, MACRO-2, COIN-B), data extraction was limited to a "per-protocol" population comprising only patients who received maintenance therapy in the respective trial. For trials allowing the enrollment of patients with *KRAS* exon 3-4 and *NRAS*

mutations, only patients with known *RAS* wt status were included into this analysis. Cases were grouped and compared according to the specific maintenance treatment received: 5-FU/LV+anti-EGFR versus anti-EGFR monotherapy versus 5-FU/LV alone. The outcome measures were PFS and OS in the overall study population and according to the main subgroups including *BRAF* status, primary tumor sidedness and RECIST response to induction therapy. PFS was defined as the time from start of maintenance treatment to PD or death from any cause, while OS was defined as the time from start of maintenance treatment to death from any cause. Moreover, to rule out a confounding effect of different induction regimen duration, a secondary analysis with PFS and OS calculated from the start of induction treatment was performed. In the absence of events, PFS and OS times were censored at the last date when patients were known to be free of progression and alive, respectively.

Standard descriptive statistics were used to summarize clinical and biological patients' characteristics according to maintenance treatment arm in numbers and percentages, compared with P value at Person's Chi-squared test and reported in a dedicated table.

Median follow-up was quantified with the reverse Kaplan–Meier estimator, while PFS and OS curves were estimated with the Kaplan-Meier method. The impact of different maintenance regimens in the overall study cohort and in different subgroups was investigated with Cox proportional hazards regression models, with patient's clinical trial included as a random variable to account for inter-study differences. Exploratory analyses were performed in the main subgroups based on the following baseline characteristics: age (> *vs* ≤70 years old) and sex (male *vs* female), ECOG PS (0 *vs* >0), primary tumor resection (yes *vs* no), prior adjuvant therapy (yes *vs* no), synchronous or metachronous presentation of metastases, number of metastatic sites (1 *vs* >1), primary tumor sidedness (left- *vs* right-sided), *BRAF* mutational status (mutant *vs* wt), sites of metastases (liver-limited or not) and best response to first-line treatment (SD *vs* CR/PR).

Model results were summarized using hazard ratios (HR), together with the corresponding 95% confidence intervals (CI) and likelihood ratio test P values. The threshold for statistical significance was set to a p value (*P*) of 0.05 and all statistical tests were two-sided. Statistical analyses were performed using the R software [R version 4.2.0 (2022-04-22)].

Results

Study population

Among 1026 patients included in the initial pooled database, 435 patients were excluded as per pre-specified criteria (they did not receive the planned maintenance treatment, had a *RAS* mutated or not assessed tumor). As shown in **Figure 1,** a total of 591 patients were included in the dataset (164 patients from Valentino, 248 from Panama, 79 from MACRO-2 and 100 from the COIN-B trial, respectively). Of these, 73 patients were excluded: 23 patients in the MACRO-2 who continued first-line doublet chemotherapy plus anti-EGFR and 50 patients in the COIN-B trial who received treatment break Overall, 518 patients were included in the final analysis and, specifically, 210 (40%), 123 (24%) and 185 (36%) patients received maintenance treatment with 5-FU/LV+anti-EGFR, 5-FU/LV and anti-EGFR respectively. Overall 210 and 308 patients received combination or monotherapy maintenance, respectively.

Baseline patients and disease characteristics are illustrated in **Table 1**. Briefly, baseline characteristics were well balanced in the three maintenance treatment groups except for age, with a lower rate of elderly (>70 years old) in anti-EGFR monotherapy group.

Efficacy analysis

Median follow up was 49.3 months [interquartile range (IQR) 29.6-62.8] in the overall study population, and 54.1 (30.9-66.6), 35.1 (18.2-50.3) and 53.0 (36.1-60.8) in 5-FU/LV+anti-EGFR, 5-FU/LV, anti-EGFR arms, respectively. PFS and OS, both calculated from the start of

maintenance treatment, were 9.0, 5.6, 6.0 months and 28.0, 25.7, 24.0 months in 5FU/LV+anti-EGFR, 5FU/LV, anti-EGFR arms, respectively (**Figure 2A-B**). The efficacy outcomes with effect size are illustrated in **Table 2.** Monotherapy maintenance (either 5-FU/LV or anti-EGFR) was significantly inferior to combination in terms of PFS (median PFS 5.8 vs 9.0 months, HR 1.26 (95%CI, 1.04-1.53), P=0.016) and non-significantly in OS (median OS 24.1 vs 28.0 months, HR 1.20 (95%CI, 0.96-1.51), P=0.111) (**Figure 2C-D**). The survival outcomes calculated from the start of induction treatment demonstrated consistent results (**Supplementary Figure 1** and **Supplementary Table 1**). Monotherapy maintenance (either 5-FU/LV or anti-EGFR) confirmed the significant inferiority to combination in PFS (median PFS 9.7 vs 12.7 months, HR 1.31 (95%CI, 1.07-1.60), P=0.009) and non significant in OS (median OS 28.1 vs 31.6 months, HR 1.19 (95%CI, 0.95-1.50), P=0.139).

Pre-specified subgroup analyses were performed for both PFS and OS accounting for treatment effects of anti-EGFR+5-FU/LV versus anti-EGFR monotherapy (**Figure 3A-B**). Overall, the HRs favored the use of combination treatment in patients with right-sided or *BRAF* mutated tumors, and notably in patients achieving SD as best response to induction therapy. The forest plots for combination versus monotherapy and anti-EGFR+5-FU/LV versus 5-FU/LV monotherapy are shown in **Supplementary Figure 2A-B and C-D,** respectively.

For what regards the main subgroups of interest, *BRAF* mutated tumors (n=37) had a poorer outcome in terms of PFS and OS calculated from the start of maintenance as compared to the overall population, but maintenance with anti-EGFR monotherapy showed the worst outcomes (median PFS 7.1, 5.3 and 2.3 months and median OS 18.8, 14.4 and 10.3 months in patients treated with anti-EGFR+5-FU/LV, 5-FU/LV and anti-EGFR, respectively, **Supplementary Figure 3** and **Supplementary Table 2**). Consistent results were reported in right-sided tumors (n=90): median PFS was 9.0, 5.4 and 3.5 months, and median OS was 21.9,

13.1 and 15.8 in patients treated with anti-EGFR+5-FU/LV, 5-FU/LV and anti-EGFR, respectively (**Supplementary Figure 4** and **Supplementary Table 3**). Conversely, in the subgroup of left-sided and *RAS-BRAF* wt tumors (n= 361), the outcomes of patients treated with anti-EGFR monotherapy or combined with 5-FU/LV were comparable, with worse results for 5-FU/LV single-agents (median PFS 9.0, 5.6 and 8.6 months and median OS 29.1, 26.6 and 30.9 months in patients treated with anti-EGFR+5-FU/LV, 5-FU/LV and anti-EGFR, respectively, **Supplementary Figure 5** and **Supplementary Table 4**). Finally, in patients stratified according to best response to induction treatment (SD vs PR/CR), the magnitude of benefit of the combination of 5-FU/LV+anti-EGFR over monotherapy with 5-FU/LV or anti-EGFR single-agent was higher in cases with SD as best response as compared to PR/CR, both in the overall population and in the left-sided/*BRAF* wt subgroup (**Supplementary Table 5 and Supplementary Table 6).** In particular, the outcomes of left-sided/*BRAF* wt patients with PR/CR to induction receiving maintenance with 5-FU/LV+anti-EGFR or single-agent anti-EGFR were superimposable.

The safety profile with incidence of overall, chemotherapy- and anti-EGFR-related AEs in the three maintenance arms is depicted in **Table 3**. Briefly, we reported a relevant increase of grade≥3 AEs in the combination arm as compared to monotherapy both 5-FU/LV and anti-EGFR, conditioning a slight consistent increase of any grade AEs and singular AEs. In details, we recorded rates of 86% and 42%, 76% and 25% and 81% and 21%of any grade and grade≥3 AEs in 5-FU/LV+anti-EGFR, 5-FU/LV monotherapy and anti-EGFR monotherapy arms, respectively.

Discussion

The balance between treatment effects on survival, toxicity and quality of life is a crucial consideration for patients with mCRC, especially in the maintenance setting.[1,17-19] There are

currently no validated factors to identify patients who may benefit from active maintenance after bevacizumab-based induction therapy, although the recommended regimen is 5-FU/LV plus bevacizumab, while bevacizumab monotherapy is not considered effective.[1] A recent network meta-analysis focused on bevacizumab showed no benefit of continuing bevacizumab-based induction therapy until PD, but a significant PFS benefit with the use of 5-FU/LV plus bevacizumab as maintenance therapy versus observation (HR 0.58; 95% CI, 0.43-0.77). A non-significant trend for OS favoring this guideline-recommended maintenance regimen was observed.[20] A secondary analysis of the CAIRO-3 trial, which explored maintenance treatment with capecitabine and bevacizumab in mCRC, showed a slight increase of quality-adjusted life-years at the price of a remarkably increased costs for maintenance treatment compared to observation.[21]

For several years, the differential toxicity profile of anti-EGFR agents and bevacizumab has raised concerns about the value of anti-EGFR-based maintenance therapy. Bevacizumab has a relatively low burden of side effects, whereas the skin toxicity of anti-EGFR agents may impair patients' quality of life and limit the long-term feasibility of maintenance strategies. Moreover, anti-EGFR-based induction therapy usually induces deep and rapid tumor responses in adequately selected patients without necessarily being a potent driver of progression-free survival, raising further doubts to the extent anti-EGFR antibodies might improve the outcome of patients in the maintenance setting.[22] However, a growing body of evidences from phase II RCTs led the updated ESMO guidelines to recommend 5-FU/LV plus anti-EGFR as the preferred maintenance option after an anti-EGFR- and oxaliplatin-based first-line therapy.[1,9-16]

In this scenario, while continuing FOLFOX plus an anti-EGFR agent is clearly not recommended based on the MACRO-2 and SAPPHIRE studies, [11-13] and also not with respect to the growing risk of severe neuropathy with continuous use of oxaliplatin[23], there is

uncertainty on the optimal maintenance strategy. In our pooled analysis, maintenance therapy with single-agent strategies was associated with inferior PFS compared to the ESMO guideline-recommended preferable option of 5-FU/LV+anti-EGFR, without a statistically significant effect on OS- despite a trend. However, the numerical increase of OS suggests that adequately powered studies or larger pooled analyses would be necessary to demonstrate the value of 5-FU/LV+anti-EGFR as the optimal maintenance therapy. Notably, we observed significantly different effects of specific strategies according to pre-specified subgroups. In fact, continuing lightened chemotherapy with 5-FU/LV added to anti-EGFR was beneficial in patients with primary resistance to EGFR inhibitions, such as those with *BRAF* mutations or right-sided cancers. However, these findings are less relevant for the current clinical practice since these patients are usually treated with upfront bevacizumab-based combinations[1,24]. Additionally, 5-FU/LV+anti-EGFR maintenance was beneficial in patients who achieved only SD as best response to induction therapy with FOLFOX plus anti-EGFR. The lack of tumor responses to EGFR inhibition is associated with significantly impaired outcome[25,26] and is usually considered as a surrogate and "in vivo" demonstration of primary resistance or reduced sensitivity to anti-EGFR agents. Consistently, potentially genomic correlates of worse outcomes have been shown in a preplanned analysis of the Valentino study [27]. On the contrary, in patients with EGFR-dependent disease, i.e. those with left-sided, *RAS* and *BRAF* wt mCRC, especially in case of PR/CR to induction therapy, there were no clear differences between anti-EGFR alone or in combination with 5-FU/LV in the maintenance setting.

The safety results were in line with the single trial reports and highlight an increase of toxicity in combination maintenance as compared to 5-FU/LV or anti-EGFR as single agents, with a specific profile mirroring the differential chemotherapy- and biologic agent-related side effects.[6,8] Therefore, when choosing active maintenance therapy after FOLFOX/anti-EGFR induction, several factors should be considered in light of the overall literature data, but also

based on patient preference, costs and healthcare resources, risk of toxicity and previous AEs to specific agents during induction, tumor response to induction and detailed molecular profiling.

Our study should be interpreted in light of the other valuable strategies that have been investigated in patients with mCRC. First, the evidence supporting maintenance therapy after initial therapy with FOLFIRI plus anti-EGFR is low and the current guidelines considered the continuation of treatment until disease progression, if well tolerated. Consistently, the recently presented ERMES trial failed to demonstrate the non-inferiority of maintenance with single-agent cetuximab versus continuation of FOLFIRI/cetuximab until disease progression, especially in right sided tumors.[15]

On the other hand, stop and go strategies may be valuable to improve quality of life and reduce financial toxicity. The COIN-B and PRODIGE-28 trials[9,10] showed a detrimental effect on PFS after a full treatment holiday compared to continuation of anti-EGFR as single agent. The use of reinduction therapy after off-treatment progression or the availability of subsequent lines of therapy may rescue most patients from a potential risk of death derived from chemotherapy breaks. The key point is that an intermittent anti-EGFR treatment, as compared with continuous anti-EGFR-based strategy, may potentially delay or avoid the onset of acquired resistance to EGFR inhibition. In fact, preclinical and clinical evidence showed the emergence of *RAS* mutated or resistant tumor clones during anti-EGFR therapy with a decline in off-therapy phases.[28] Consistently, the non-comparative phase II IMPROVE study has recently showed that FOLFIRI/panitumumab until PD conferred a higher benefit in the right-sided subgroup, whereas an intermittent regimen was more beneficial in the left-sided ones, potentially suggesting that secondary EGFR-antibody resistance might be delayed.[16]

Overall, the results of our pooled analysis added to the available studies may suggest that the continuation of chemotherapy is needed in tumors with lower predicted responsiveness to

anti-EGFR agents, whereas it might be spared in the subgroups with the highest benefit from anti-EGFR treatment. These intriguing findings should be prospectively validated by specific RCTs comparing stop and go and/or specific "continuation maintenance" regimens in patients with adequately selected highly EGFR-dependent mCRC.

This study is endowed with several limitations intrinsic to its design. The pooled analysis is on the four largest RCTs conducted on this topic. It is important to note that the heterogeneity of the studies in terms of design, conduction and historical period, has potentially influenced their outcome results and thus this analysis. Another limitation of this analysis is that the 5-FU/LV monotherapy arm was derived from a single trial. Finally, some studies with FOLFIRI-based induction such as ERMES and PRODIGE-28 were not included. Additionally, it should be noted that patients not progressing to induction and achieving the maintenance phase may be positively selected and thus may not represent the overall population, especially regarding *BRAF* mutated and right-sided primary tumors.

In conclusion, this pooled analysis including four phase II RCTs supports the recent guideline recommendation to maintenance with fluoropyrimidine plus anti-EGFR after an oxaliplatin- and anti-EGFR-based first line treatment in *RAS* wild-type mCRC patients. Comprehensive and dynamic evaluation of patients and tumor features may support more individualized maintenance treatment decisions in patients with *RAS* wild-type mCRC.

References

[1] A. Cervantes, R. Adam, S. Roselló, et al, Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis,treatment and follow-up. *Ann Oncol.* 2022, https://doi.org/10.1016/j.annonc.2022.10.003

[2] 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(3):394-400.

[3] Diaz-Rubio E, Gomez-Espana A, Massuti B, et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: The phase III MACRO TTD study. *Oncologist.* 2012;17(1):15-25.

[4] Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? the GERCOR OPTIMOX2 study. *J Clin Oncol.* 2009;27(34):5727-5733.

[5] Adams RA, Meade AM, Seymour MT, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial. *Lancet Oncol.* 2011;12(7):642-653.

[6] Hegewisch-Becker S, Graeven U, Lerchenmuller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): A randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol.* 2015;16(13):1355-1369.

[7] Koeberle D, Betticher DC, von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: A randomized phase III non-inferiority trial (SAKK 41/06). *Ann Oncol.* 2015;26(4):709-714.

[8] Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): A phase 3 randomised controlled trial of the dutch colorectal cancer group. *Lancet.* 2015;385(9980):1843-1852.

[9] 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(6):631-639

[10] Boige V, Francois E, Abdelghani MB, et al. Maintenance treatment with cetuximab versus observation in RAS wild-type metastatic colorectal cancer: Results of the randomized phase II PRODIGE 28-time UNICANCER study. DOI: 10.1200/JCO.2021.39.3_suppl.15 Journal of Clinical Oncology 39, no. 3_suppl (January 20, 2021) 15-15.

[11] Aranda E, Garcia-Alfonso P, Benavides M, et al. First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: Phase II randomised MACRO2 TTD study. *Eur J Cancer.* 2018;101:263-272.

[12] Pietrantonio F, Morano F, Corallo S, et al. Maintenance therapy with panitumumab alone vs panitumumab plus fluorouracil-leucovorin in patients with RAS wild-type metastatic colorectal cancer: a phase 2 randomized clinical trial. *JAMA Oncol.* 2019;5(9):1268-75.

[13] Munemoto Y, Nakamura M, Takahashi M, et al. SAPPHIRE: a randomised phase II study of planned discontinuation or continuous treatment of oxaliplatin after six cycles of modified FOLFOX6 plus panitumumab in patients with colorectal cancer. *Eur J Cancer.* 2019;119:158e167

[14] Modest DP, Karthaus M, Fruehauf S, et al. Panitumumab Plus Fluorouracil and Folinic Acid Versus Fluorouracil and Folinic Acid Alone as Maintenance Therapy in RAS Wild-Type

Metastatic Colorectal Cancer: The Randomized PANAMA Trial (AIO KRK 0212). *J Clin Oncol*. 2021;40:72-82.

[15] Pinto C, Orlandi A, Normanno N, et al. Phase III study with FOLFIRI/cetuximab versus FOLFIRI/cetuximab followed by cetuximab (Cet) alone in first-line therapy of *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC) patients: the ERMES Study, ESMO 2022.

[16] Avallone A, Giuliani F, Nasti G, et al. Randomized intermittent or continuous panitumumab plus FOLFIRI (FOLFIRI/PANI) for first-line treatment of patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): the IMPROVE study. ASCO 2022.

[17] Messersmith WA: NCCN guidelines updates: Management of metastatic colorectal cancer*. J Natl Compr Canc Netw*. 17:599-601, 2019

[18] Modest DP, Pant S, Sartore-Bianchi A: Treatment sequencing in metastatic colorectal cancer. *Eur J Cancer*. 2019;109:70-83

[19] Cremolini C, Schirripa M, Antoniotti C, et al: First-line chemotherapy for mCRC-a review and evidence-based algorithm. *Nat Rev Clin Oncol*. 2015;12:607-619

[20] Sonbol MB, Mountjoy LJ, Firwana B, Liu AJ, Almader-Douglas D, Mody K, Hubbard J, Borad M, Ahn DH, Murad MH, Bekaii-Saab T.The Role of Maintenance Strategies in Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis of Randomized Clinical Trials. *JAMA Oncol*. 2020;6(3):e194489.

[21] Scott K Sherman 1, Joel J Lange 2, Fadi S Dahdaleh 1, Rahul Rajeev 3, T Clark Gamblin 2, Blase N Polite 4, Kiran K Turaga 1 Cost-effectiveness of Maintenance Capecitabine and Bevacizumab for Metastatic Colorectal Cancer. *JAMA Oncol*. 2019;5(2):236-242.

[22] Sebastian Stintzing, Dominik P Modest, Lisa Rossius, 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(10):1426-1434.

[23] André T, Meyerhardt J, Iveson T et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol*. 2020;21(12):1620-1629.

[24] Grothey A, Fakih M, Tabernero J. Management of BRAF-mutant metastatic colorectal cancer: a review of treatment options and evidence-based guidelines. *Ann Oncol*. 2021;32(8):959-967.

[25] Manca P, Corallo S, Randon G, et al. Impact of early tumor shrinkage and depth of response on the outcomes of panitumumab-based maintenance in patients with RAS wild-type metastatic colorectal cancer. *Eur J Cancer*. 2021;144:31-40.

[26] Sommerhäuser G, Kurreck A, Beck A, et al. Depth of response of induction therapy and consecutive maintenance treatment in patients with RAS wild-type metastatic colorectal cancer: An analysis of the PanaMa trial (AIO KRK 0212). *Eur J Cancer*. 2023;178:37-48.

[27] Morano F, Corallo S, Lonardi S, et al. Negative Hyperselection of Patients With *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer Who Received Panitumumab-Based Maintenance Therapy. *J Clin Oncol*. 2019;37(33):3099-3110.

[28] Siravegna G, Mussolin B, Buscarino M, et al. Clonal evolution and resi stance to EGFR blockade in the blood of colorectal cancer patients. *Nat Med*. 2015; 21(7):795-801.

Figures Legends

Figure 1: consort diagram

This figure depicts the patients' flow of the individual patient data pooled analysis.

Figure 2: Survival outcomes according to maintenance treatment arm

This figure shows the Kaplan-Meier curves for PFS (A) and OS (B) calculated from the start of maintenance according to the 3 maintenance treatment arms (5-FU/LV+anti-EGFR, 5-FU/LV and anti-EGFR); Kaplan-Meier curves for PFS (C) and OS (D) calculated from the start of maintenance according to maintenance with combination (anti-EGFR+5-FU/LV) or monotherapy (anti-EGFR or 5-FU/LV).

Figure 3: Subgroup analyses according to 5-FU/LV+anti-EGFR versus anti-EGFR monotherapy.

This figure shows the forest plots for PFS (A) and OS (B) of combination versus anti-EGFR therapy.

Authors contribution

Drs Pietrantonio, Modest and Raimondi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Pietrantonio, Modest

Acquisition, analysis, or interpretation of data: Raimondi, Nichetti, Pietrantonio, Modest.

Drafting of the manuscript: Raimondi, Nichetti, Stahler, Wasan, Aranda, Randon, Kurreck, Meade, Díaz-Rubio, Niger, Stintzing, Palermo, Trarbach, Prisciandaro, Sommerhäuser, Fisher, Morano, Pietrantonio, Modest.

Statistical analysis: Nichetti, Randon.

Administrative, technical, or material support: Palermo

Supervision: Pietrantonio, Modest.

Funding

Conflicts of interest

AR: Honoraria for lectures from Elma Academy and Servier. Travel support: Amgen.

HW: honoraria as a speaker and/or in an advisory role from Pierre Fabre, Merck KGaA, Incyte, Merck Sharp Dohme, Servier, Bayer, Roche Genentech and SIRTEX.

EA: Honoraria for advisory role from Amgen, Bayer, Bristol Myers Squibb, Merck, Roche, Sanofi.

FM: Honoraria from Servier, Lilly, Pierre-Fabre and received research grants from Incyte.

FP: Honoraria from Amgen, Bayer, Servier, Merck-Serono, Lilly, MSD, BMS, Astrazeneca, Astellas, Organon, Pierre-Fabre and received research grants from Bristol-Myers Squibb, Astrazeneca, Agenus, Incyte.

DPM: Honoraria for lectures and advisory boards: Merck, Amgen, Servier, Pierre Fabre, Sanofi, Lilly, BMS, MSD, AstraZeneca, G1, Cureteq, Takeda, Taiho, Onkowissen.de; GSK, Seagen, COR2ED. Travel support: Amgen, Servier. Research funding (inst): Amgen, Servier

All other authors declared no disclosures.

Table 1. Patients and disease characteristics according to the specific maintenance therapy

	5-FU/LV (n = 123)	Anti-EGFR (n = 185)	Anti-EGFR plus 5-FU/LV (n = 210)	P value
Median age (years old, IQR)	65 (57-70)	61 (54-67)	65 (58-72)	<0.001
Age (years old)				<0.001
>70	29 (24%)	24 (13%)	59 (28%)	
≤70	94 (76%)	161 (87%)	151 (72%)	
Sex				0.158
Male	78 (63%)	113 (61%)	147 (70%)	
Female	45 (37%)	72 (39%)	63 (30%)	
ECOG performance status				0.922
0	74 (61%)	115 (62%)	133 (63%)	
1-2	47 (39%)	70 (38%)	77 (37%)	
NA	2	0	0	
Prior adjuvant treatment				0.872
Yes	16 (13%)	27 (15%)	27 (13%)	
No	107 (87%)	158 (85%)	182 (87%)	
NA	0	0	1	
Primary tumor resected				0.057
Yes	83 (67%)	109 (59%)	146 (70%)	
No	40 (33%)	76 (41%)	63 (30%)	
NA	0	0	1	
Liver-limited disease				0.201
Yes	49 (40%)	60 (32%)	85 (41%)	
No	74 (60%)	125 (68%)	124 (59%)	
NA	0	0	1	
Synchronous metastases				0.591
Yes	99 (80%)	143 (78%)	171 (82%)	
No	24 (20%)	41 (22%)	38 (18%)	
NA	0	1	1	
Number of metastatic sites				0.533
1	63 (51%)	94 (51%)	117 (56%)	
> 1	60 (49%)	91 (49%)	92 (44%)	
NA	0	0	1	
Primary tumor location				0.170
Right	19 (16%)	40 (22%)	31 (15%)	
Left-rectum	100 (84%)	140 (78%)	172 (85%)	
NA or multifocal	4	5	7	
BRAF status				0.602
Wild type	113 (92%)	121 (90%)	195 (93%)	
Mutated	10 (8%)	13 (10%)	14 (7%)	
NA	0	51	1	
Best Response to induction				0.608
PR/CR	91 (75%)	137 (79%)	161 (80%)	
SD	30 (25%)	36 (21%)	41 (20%)	
NA	2	12	8	

* P value at Person's Chi-squared test.
Data are presented as number (%).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; 5-FU/LV, 5-fluorouracil/leucovorin; NA, not assessed; CR, complete response; PR, partial response; SD, stable disease; IQR, intrequartile range.

Table 2: Efficacy measures in the study population

	Progression-Free Survival Median, months (95% CI)	*Effect size HR (95% CI)	p value	Overall Survival Median, months (95% CI)	*Effect size HR (95% CI)	p value
Anti-EGFR+ 5-FU/LV **(n = 210)**	**9.0 (7.7 - 10.3)**	ref	0.009	28.0 (25.3 - 35.0)	ref	0.134
Anti-EGFR **(n = 185)**	6.0 (5.5 - 8.2)	1.15 (0.93 - 1.43)		24.0 (20.3 - 29.5)	1.25 (0.96 - 1.62)	
5-FU/LV **(n = 123)**	5.6 (5.2 - 6.8)	1.47 (1.15-1.86)		25.7 (22.4 – 30.2)	1.15 (0.84 – 1.56)	

*The effect size is calculated considering as reference anti-EGFR+5-FU/LV
Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin. CI: confidence interval. HR: hazard ratio estimate (95% CI)

Table 3. Safety profile

Adverse event	Maintenance					
	5-FU/LV (n = 123)		Anti-EGFR (n = 178)*		5-FU/LV + anti-EGFR (n = 210)	
	Any Grade N (%)	Grade ≥ 3 N (%)	Any Grade N (%)	Grade ≥ 3 N (%)	Any Grade N (%)	Grade ≥ 3 N (%)
Any adverse event	93 (76)	31 (25)	144 (81)	38 (21)	181 (86)	89 (42)
Stomatitis/Oral mucositis	13 (11)	1 (1)	31 (17)	3 (2)	55 (26)	8 (4)
Nausea	12 (10)	2 (2)	23 (13)	0	24 (11)	1 (1)
Vomiting	7 (6)	2 (2)	11 (6)	0	8 (4)	1 (1)
Diarrhea	16 (13)	1 (1)	34 (19)	9 (5)	41 (20)	6 (3)
Hand-foot syndrome	7 (6)	0	43 (24)	5 (3)	23 (11)	4 (2)
Peripheral Neuropathy	33 (27)	2 (2)	53 (30)	2 (1)	51 (24)	1 (1)
Anemia	92 (75)	0	31 (17)	2 (1)	106 (51)	3 (1)
Thrombocytopenia	54 (44)	0	17 (10)	0	58 (28)	1 (1)
Neutropenia	36 (29)	5 (4)	24 (13)	5 (3)	44 (21)	7 (3)
Febrile Neutropenia	0	0	0	0	0	0
Fatigue	13 (11)	1 (1)	46 (26)	7 (4)	38 (18)	2 (1)
Skin rash	8 (7)	0	91 (51)	18 (10)	85 (40)	31 (15)
Hypomagnesemia	1 (1)	0	43 (24)	2 (1)	44 (21)	11 (5)

*missing data on safety for 7 patients in anti-EGFR single-agent arm