Editorial Commentary



# First-line therapy of metastatic colorectal cancer: does one size fit all??

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*Comment on:* Maiello E, Di Maggio G, Cordio S, *et al.* Bevacizumab in Combination With Either FOLFOX-4 or XELOX-2 in First-line Treatment of Patients With Metastatic Colorectal Cancer: A Multicenter Randomized Phase II Trial of the Gruppo Oncologico dell'Italia Meridionale (GOIM 2802). Clin Colorectal Cancer 2020;19:109-15.

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In the study reported by Maiello and colleagues (Gruppo Oncologico dell'Italia Meridionale—GOIM 2802) and published in the January issue of *Clinical Colorectal Cancer*, the authors investigated the efficacy of bevacizumab combined with biweekly XELOX regimen (XELOX-2) and compared it to a more standard regimen of bevacizumab with FOLFOX-4. The authors had to be commended for doing this multicenter trial. They have concluded that the XELOX-2 with bevacizumab is an active regimen and is well tolerated. Accordingly, it might be suitable for elderly and frail patients with metastatic colorectal cancer. The trial was started in June 2011 and took 4 years and 4 months to recruit 132 patients from 8 Italian centers. Furthermore, it took the authors nearly 4 more years to publish the results.

The study asked a question in 2011 that probably is not very relevant in 2020. In the design of the trial the authors decided that fluoropyrimidines, oxaliplatin and bevacizumab are effective in all metastatic colorectal cancers regardless of the *KRAS* status, hence both *KRAS* mutant and wild-type tumors were included. They have also asked a question of maintenance therapy but this result was deferred for a latter publication.

The question of oral *vs.* intravenous fluoropyrimidines has been answered in multiple studies. The first was the N019669 trial where patients with metastatic colorectal cancer were randomized to FOLFOX *vs.* standard XELOX (given every 3 weeks) and to bevacizumab *vs.* placebo (1) (2×2 factorial design). The median progression-free survival (PFS) was equal in both XELOX and FOLFOX-4 groups [8.0 *vs.* 8.5 months respectively, hazard ratio (HR), 1.04; 97.5% confidence interval (CI), 0.93–1.16]. Similar results were observed for overall survival (OS) (19.8 months with XELOX *vs.* 19.6 months with FOLFOX-4, HR, 0.99; 97.5% CI, 0.88–1.12). Toxicity was different with more grade 3–4 neutropenia/granulocytopenia as well as febrile neutropenia in FOLFOX-4 group and more grade 3 diarrhea and hand-foot syndrome in the XELOX group. The FNCLCC (French national cancer centers) group also randomized patients to FOLFOX *vs.* XELOX (2) with similar results showing no statistical difference in the PFS (median 8.8 months with XELOX and 9.3 months with FOLFOX-6) and OS (median 19.9 and 20.5 months, respectively). There was more grade 3–4 thrombocytopenia (12% *vs.* 5%) and diarrhea (14% *vs.* 7%) in the XELOX group, but significantly less grade 3–4 neutropenia (5% *vs.* 47%), febrile neutropenia (0% *vs.* 6%) and neuropathy (11% *vs.* 26%). This comparison was also done in the second-line setting and confirmed non-inferiority of XELOX to FOLFOX in the NO16967 trial (3). In this trial XELOX was non-inferior to FOLFOX-4 for PFS (HR, 0.97; 95% CI, 0.83–1.14) and OS (HR, 1.02; 95% CI, 0.86–1.21). There were more grade 3–4 neutropenia in FOLFOX-4 (35% *vs.* 5% with XELOX) and febrile neutropenia (4% *vs.* <1%) while more grade 3–4 diarrhea with XELOX (19% *vs.* 5% with FOLFOX-4) and hand-foot syndrome (4% *vs.* <1%). An updated meta-analysis of all randomized

published trials (total of 8) comparing FOLFOX to XELOX was published in 2016 by Guo *et al.* (4). With 4,363 patients from eight randomized controlled trials, the pooled analysis showed no statistical differences between both arms in OS, and response rate. Thrombocytopenia, hand-foot syndrome, and diarrhea, where more common with the XELOX group while neutropenia was higher in the FOLFOX group.

The authors in the study by Maiello *et al.* however did not investigate the standard XELOX regimen given every 3 weeks, rather did investigate a 2-week regimen (XELOX-2) with a slightly higher oxaliplatin dose of 100 mg/m$^2$. There are two issues in this regard. First, they cited two previous phase II studies (one of them by the same group) with the XELOX-2 regimen (albeit lower oxaliplatin dose) with no signal indicating significantly higher efficacy or lower toxicity (5,6). The first phase II study enrolled 59 patients with metastatic colorectal cancer and is not yet published. The study reported 51% response rate and 76% disease control rate. The preliminary median time to progression was 6 months. Grade 3–4 reported toxicity were thrombocytopenia in 12%, nausea and vomiting, diarrhea and asthenia in 4%. The other trial enrolled 35 elderly patients (age >70 years) and reported a similar response rate of 49% with 86% rate for disease control. The median time to progression was 8.6 but the OS was disappointedly low at 15.5 months. Grade 3 side effects occurred in 17% of patients. The authors also reported on three trials investigating the efficacy and toxicity of XELOX-2 in combination with bevacizumab, 2 of which were randomized (7-9). The ORION was a randomized phase II trial in which the XELOX plus bevacizumab regimen given every 2 weeks was compared to the conventional XELOX plus bevacizumab given every 3rd week in the third/fourth-line setting as oxaliplatin re-introduction in 46 patients (8). The outcome was similar in both regimens, however, the biweekly regimen had a better safety profile with grade 3–4 fatigue of 21.7% *vs.* 27.3%, neuropathy and diarrhea 0% *vs.* 9.1%, compared to the triweekly regimen. The other randomized phase II trial reported by Hurwitz *et al.* (7). Four hundred and thirty-five untreated metastatic colorectal cancer patients were randomized to triweekly *vs.* biweekly XELOX plus bevacizumab. The author reported a median PFS of 9.6 *vs.* 9.1 months in favor of the triweekly regimen and similarly median OS of 28.4 *vs.* 22.1 months. The author concluded that the triweekly XELOX plus bevacizumab regimen remained the preferred regimen. Finally, the PHOENiX Japanese trial was a single arm phase II trial that accrued 51 patients treated with biweekly bevacizumab plus XELOX (9). Response rate was 51% and the median progression free survival was 11.3 months. Toxicity was mainly grade 3–4 neutropenia, peripheral neuropathy, and hypertension in 13.7% of treated patients.

The question whether increasing oxaliplatin dose in the fluoropyrimidine-oxaliplatin combination increases the efficacy was tested in the OPTIMOX one trial where patients with metastatic colorectal cancer were randomized to the standard FOLFOX-4 (with 85 mg/m$^2$ of oxaliplatin) *vs.* FOLFOX-7 (with 130 mg/m$^2$ of oxaliplatin) (10). The response rate was similar in both arms (58% *vs.* 59% respectively), indicating that increasing the dose of oxaliplatin does not increase the efficacy.

The authors in the GOIM 2802 trial did not intend to test the XELOX-2 *vs.* FOLFOX-4 with bevacizumab in elderly patients, as it appears in their introduction and in the abstract conclusion. Hence, we are here evaluating the result of their work according to the trial objective. It is important to note that in 2020 we cannot accept one size fits all concept in the primary management of metastatic colorectal cancer. Except in very special circumstances, patients with metastatic colorectal cancer should have personalized therapy. Despite that age, performance status and co-morbidities are factors to be considered in personalizing therapy, other factors should also be taken into account including aim of therapy (conversion therapy *vs.* palliative), patient's attitude towards therapy, sidedness of the primary tumor, all RAS, BRAF, HER-2 mutational status and possibly microsatellite instability (MSI) (mismatch repair) status.

Data from CALGB 80405 (11) and FIRE-3 trials (12) indicate marked improved survival for left-sided RAS wild tumors when combined with anti-EGFR antibodies as compared to bevacizumab. This is not the case for right-sided tumors, where in fact adding anti-EGFR antibodies to the chemotherapy backbone resulted in numerically lower survival (though not statistically significant) than with bevacizumab. This has been confirmed in a meta-analysis performed by the European Society for Medical Oncology (13). In fact, regardless of the doublet chemotherapy used, right-sided colon cancer has poorer survival compared to left-side one (14). Patients with metastatic right-sided primary are best treated with triplet chemotherapy regimen with or without bevacizumab with significantly improved survival compared to doublets (15,16). It is important to remember that anti-EFGR therapy cannot be administered with capecitabine as it results in increased toxicity and hence lower dose intensity and lower efficacy as has been seen in

the COIN trial (17).

The incidence of *BRAF* mutation in metastatic colorectal cancer range from 2.5% to 15% (18,19). Patients with mutated *BRAF* have poor survival when treated with standard doublet regimens (20). Triplet chemotherapy combined with bevacizumab (FOLFOXIRI-Bevacizumab) and to a lesser extend with anti-EGFR (FOLFOXIRI-panitumumab) have shown improved response rate and OS in patients with *BRAF*-mutant colorectal cancer (16,21,22). HER-2 mutational status also may affect the choice of first-line therapy. Recent retrospective data have shown that patients with HER-2 over-expressive tumors and a wild type RAS status are less likely to respond to anti-EGFR therapy than those with HER-2 negative tumors (23). This data need to be confirmed in prospective studies. Finally, mismatch repair status (MSI) should always be known prior to starting upfront therapy in patients with metastatic colorectal cancer. The data for the benefit of checkpoint inhibitors in patients with MSI-high tumors (mismatch repair deficient, dMMR) is very encouraging, in the third, second and even in first-line setting. At this year's American Society of Clinical Oncology meeting, the result of the KEYNOTE-177 trial was presented. In this trial, patients with metastatic colorectal cancer and MSI-high tumors were randomized to standard chemotherapy (investigators choice) *vs.* the check-point inhibitor pembrolizumab. The preliminary data showed that pembrolizumab was superior to chemotherapy for PFS (median 16.5 *vs.* 8.2 months; HR, 0.60; 95% CI, 0.45–0.80; P=0.0002) (24). Furthermore, there are retrospective data indicating poorer response to anti-EGFR therapy in colorectal tumors with sporadic MSI than familial ones (25).

In summary, current first-line chemotherapy in patients with metastatic colorectal cancer cannot be one-size fits all. It should be personalized according to clinical, pathological and molecular factors. In the subset of patients that are not resectable, RAS mutant, microsatellite stable, left sided primary and frail or elderly, the XELOX-2 regimen might be an attractive option in the first-line setting.

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