Maintenance Therapy in Colorectal Cancer: Moving the Artillery Down While Keeping an Eye on the Enemy

Giuseppe Aprile,[1] Francesco Giuliani,[2] Stefania Eufemia Lutrino,[3] Caterina Fontanella,[1] Marta Bonotto,[1] Karim Rihawi,[1] Gianpiero Fasola[1]

Abstract

The survival improvement in metastatic colorectal cancer, achieved with more intensive chemotherapy regimens, has recently led clinicians to question the optimal duration of therapies and to consider the role of maintenance. Indeed, patients whose disease is controlled after induction chemotherapy may benefit from continuing a less intensive regimen in order to reinforce the results achieved with up-front treatment. In addition, the more favorable toxicity profile of maintenance approaches would ensure a better quality of life. After discussing the rationale and the difference of pursuing a maintenance strategy with chemotherapeutic and/or biologic agents, we present significant available data from the literature and comment on the current implications and future directions of maintenance therapy. The current roles of depotentiated treatment schedules, antiangiogenic compounds, epidermal growth factor receptor inhibitors, and novel targeted therapies are also reviewed. Finally, we address elements that may foster clinical and social debate on this topic, suggesting potential aspects that need to be further investigated.

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Introduction

Although curative rates remain low for patients with metastatic colorectal cancer (CRC), the median overall survival (OS) is now more than 30 months in molecularly selected cases.[1,2] The introduction of irinotecan and oxaliplatin, the widespread up-front use of biologic agents, and the milestone progress achieved in molecular biology[3] have all contributed to improve outcome results to unprecedented levels.[4] In addition, with the introduction of more intensive up-front combinations including drugs with potential cumulative toxicities, the common practice of continuing first-line chemotherapy until disease progression or unacceptable toxicity has changed, raising the question of optimal treatment duration.[5] Whether first-line treatment should be continued until disease progression or discontinued as soon as a response has been achieved is debated.[6] Indeed, there is limited evidence supporting the prolongation of first-line treatment beyond 4 to 6 months,[7] and modern trials suggest avoiding treatment continuance beyond 6 months.[8] At the time of tumor reassessment, oncologists may face 3 possible scenarios. If initially unresectable disease eventually becomes resectable, patients may be referred for salvage curative surgery.[9] Conversely, if the disease has progressed, the patient may undergo second-line systemic treatment.[3] Finally, if the disease is stable or it has even shrunk yet remains unresectable, patients might be considered for maintenance therapy.[5]

Although treatment discontinuation has been addressed with perplexity, especially for those patients with optimal performance status and who experience limited cumulative adverse effects, continuing chemotherapy may cause excessive toxicity with reduced quality of life and may potentially induce drug resistance. In this landscape, maintenance therapy represents a compelling alternative, which might keep the disease under control without the intensity of a full-regimen treatment. In the quest for the optimal maintenance strategy, 2 different strategies may be considered. The first is based on the concept of intermittency; it can involve either preplanned drug holidays or clinically driven treatment breaks. The second strategy is more focused on the intensity of the treatment. In such cases,

[1]Department of Oncology, University Hospital, Udine, Italy
[2]Department of Medical Oncology, National Cancer Institute "G. Paolo II", Bari, Italy
[3]Department of Medical Oncology, Antonio Perrino Hospital, Brindisi, Italy

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Address for correspondence: Giuseppe Aprile, MD, Department of Oncology, University and General Hospital, Piazzale S Maria della Misericordia, 15, 33100 Udine, Italy
Fax: +39 0432 559305; e-mail contact: aprile.giuseppe@aoud.sanita.fvg.it

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maintenance includes either a depotentiated combination of the up-front therapy or a completely different compound to which the patient has not previously been exposed (Figure 1). Finally, whenever medical oncologists decide whether patients need to continue to receive treatment or can take a drug holiday, the patients' desires should always be taken into account. We completed a narrative literature review on maintenance therapy for patients with metastatic CRC, searching for eligible studies using the Medline database.

Clinical Concept of Maintenance

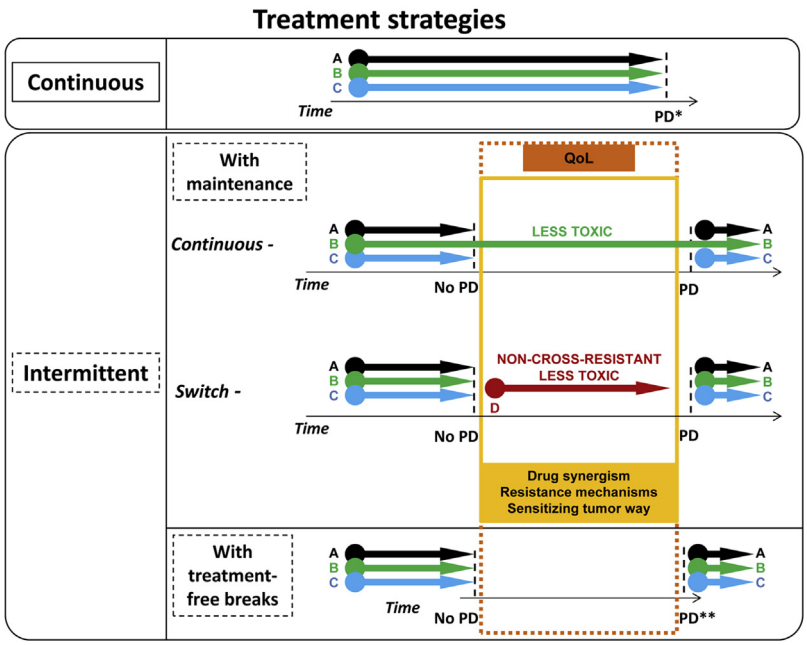
In patients with disease not amenable to salvage treatments, maintenance therapy aims at extending the favorable results obtained with the first-line induction therapy.[10] Drug holidays or less intensive treatments ensure less toxicity as well as fewer hospital visits with increased quality of life. Treatment breaks may also result in cost savings. Maintenance encompasses continuous maintenance, where a less-toxic part of the former regimen is used until disease progression, and switch maintenance, where patients are exposed to novel non—cross-resistant cytotoxic drugs or targeted agents that were not included in the previous induction treatment (Figure 1). Optimal candidates must have experienced disease control with the induction therapy—namely, a response, or at least disease stabilization. Consequently, the current availability of more active first-line treatments increases the number of potential candidates for maintenance therapy. Initial induction treatment followed by de-escalation of cytotoxic drugs and planned maintenance treatment is gaining credibility, and recent data in the literature suggest that maintenance treatment may play a key role in different cancer types such as lung,[11,12] breast,[13] and ovarian carcinomas.[14,15]

Cellular and Molecular Biology Underpinning Appropriateness of Maintenance Therapy

Most patients with metastatic disease experience progression, either while receiving chemotherapy as a result of intrinsic drug resistance or after an initial response as a result of an acquired drug resistance.[16-18] Understanding the cellular and molecular biology underpinning drug resistance permits improving outcomes of CRC patients and planning more effective treatment strategies. The administration of 5-fluorouracil (5-FU) with either irinotecan or oxaliplatin to fluoropyrimidine-resistant CRC cells modulates thymidylate synthase activity, implicated with the response to 5-FU treatment[19-23]; their reintroduction after disease progression is considered a rational strategy to overcome 5-FU resistance for patients initially treated with 5-FU—based combinations who had then received maintenance chemotherapy with 5-FU alone.[24,25] Accordingly, even if at the cost of higher rates of neutropenia or peripheral neuropathy, a significant response rate was observed with second-line combination regimens in clinical trials recruiting patients with 5-FU—refractory disease.[26-32]

Epidermal growth factor receptor (EGFR) signaling inhibition may resensitize tumor cells to irinotecan/SN38, leading to clinically significant effects in irinotecan-refractory CRC patients.[33-35] Similarly, cetuximab may increase the tumor response to oxaliplatin-based chemotherapy in oxaliplatin-resistant disease, reducing the activity of ERCC1, a DNA excision repair protein that mediates the removal of platinum adducts.[36,37] The use of up-front combinations including EGFR inhibitors should therefore be limited to patients with no mutations in *RAS* and possibly *BRAF* genes.[10,38-43]

Figure 1 Potential Treatment Strategies for Patients With Metastatic Disease After Up-Front Induction Treatment. *Stop After Evidence of Progressive Disease (PD), Severe Toxicity, or Patient Request. **Restart After Evidence of PD or Fixed Time



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Notably, EGFR inhibitors may not be optimal for maintenance therapy because of the early emergence of acquired resistance to EGFR inhibitors, which typically occurs within few months after starting the therapy.[44-46] Recent data indicate that different genetic alterations in the *EGFR-RAS-RAF-MEK* pathway or the amplification of receptor tyrosine kinases, including HER2 or MET,[47] may cause resistance. Specific target mutations in the extracellular domain, such as the novel missense *EGFR* mutation S492R, may also cause secondary resistance.[48] Preclinical studies suggest that the escape from anti-EGFR blockade tends to converge on the (re) activation of *MEK-ERK*[49] or *AKT*,[50] and the early identification of those underlying mechanisms via liquid biopsies may lead to a rational development of additional treatments.[51]

Instead, a more promising maintenance strategy involves the use of antiangiogenic drugs.[52] CRC cells have a delayed onset pattern of growth inhibition, and vascular endothelial growth factor (VEGF) blockade is not immediately reflected by a change in tumor growth.[53] Bevacizumab may induce reversible shrinkage in hypervascularized tissue,[54] but a pro-angiogenetic rebound after drug discontinuation has also been documented.[55] Similarly, rapid disease progression has been shown during treatment interruptions in patients with renal cell tumors treated with pazopanib or sunitinib.[56] Even if the mechanism underpinning the angiogenic rebound is still unclear, it appears to be related to the VEGF produced by the host stroma.[57] Thus, prolonged exposure to antiangiogenic drugs may block the paracrine production of pro-angiogenic factors and may ultimately control tumor growth.[58] Although antiangiogenic therapy reduces vascular permeability and delays disease progression, it may ultimately promote an aggressive treatment-resistant phenotype. In human CRC tumor cells, high hypoxia-induced factor VEGF signaling intensity due to autocrine VEGF signaling correlates to bevacizumab resistance.[59] Recently, nintedanib has demonstrated antitumor activity in CRC models with intrinsic bevacizumab-resistant cells,[60] showing that antiangiogenic-based maintenance strategies may be effective in preventing growth rebound in bevacizumab-resistant CRC cells. Whether the choice of chemotherapy modulates and induces acquired resistance to VEGF inhibitors remains to be investigated.[61] Also, preclinical data about hypoxia and oxaliplatin activity are interesting. The formation of platinum adducts was reduced in hypoxic cells exposed to oxaliplatin, and oxaliplatin was consequently less effective in hypoxic compared to aerobic CRC cells. However, when hypoxia-induced factor 1 is inhibited, oxaliplatin adducts formation was restored.[58,62]

Maintenance in CRC: Clinical Evidence

How Long Should CRC Patients Be Treated With First-Line Therapy?

Discontinuing chemotherapy after a preplanned number of cycles is now considered with less skepticism. Although this strategy may be disadvantageous for a few patients, continuing treatment indefinitely is not actually supported by any strong evidence. A pivotal phase 3 trial enrolled 354 patients with disease that responded to up-front 5-FU or raltitrexed, and randomized them to either continuing the same treatment or temporarily discontinuing chemotherapy that was resumed later at disease progression. Despite only 37% of the patients recommencing treatment, no survival difference was observed among treatment arms (median OS, 11.3 vs. 10.9 months; hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.69-1.09; $P = .23$; similar survival rates at 2 years).[63] The COIN study, a randomized controlled phase 3 trial, randomized 1630 previously untreated patients with advanced CRC to receive continuous versus intermittent oxaliplatin-based therapy.[64] The primary end point was the noninferiority between the 2 treatment arms, with a predefined noninferiority boundary of 1.162 for intention-to-treat and per-protocol analyses. In the intention-to-treat analysis, the median OS was longer for patients who received continuous treatment (15.8 vs. 14.4 months; HR, 1.08; 95% CI, 1.00-1.16), as it was in the per-protocol analysis (19.6 vs. 18 months; HR, 1.08; 95% CI, 0.98-1.19). The 2-year survival rate was 28.3% versus 26.1% in the intention-to-treat analysis, and 34.8% versus 31.1% in the per-protocol analysis. Although the trial formally failed to demonstrate its primary noninferiority end point, a detrimental effect greater than 2.3 months in the intermittent arm was excluded. Moreover, intermittent chemotherapy was associated with improved quality of life and with a reduced number of visits to the hospital.

A recent systematic review and meta-analysis of randomized controlled trials comparing continuous versus intermittent treatments has shown similar results with the 2 strategies.[65] Even when the analysis is restricted to those trials comparing continuous chemotherapy with no maintenance therapy at all, no survival difference was observed (HR, 1.03; 95% CI, 0.94-1.14; $P = .5$). The meta-analysis included a phase 3 Italian trial,[66] in which 337 patients were randomized to receive FOLFIRI every 2 weeks continuously or FOLFIRI on a 2 months on/2 months off schedule, until disease progression. No difference in median progression-free survival (PFS; 6 months in both arms) or in median OS (18 vs. 17 months; HR, 0.88) was reported, suggesting that both strategies can be used. Not surprisingly, the intermittent schedule may be less expensive and better tolerated. Unfortunately, the above-mentioned meta-analysis[65] included only 2 trials that tested modern treatment regimens. In this view, intermittent strategies should be discussed with the patient, but the noninferiority of a treatment break cannot be ruled out in patients exposed to first-line chemotherapy in combination with biologic agents. From another point of view, tumor shrinkage and disease control may be necessary to symptom control and consequently quality-of-life improvement. Because quality-of-life data from maintenance studies are limited, the potential advantages deriving from intermittent strategy in terms of safety have to be evaluated, considering the impact of tumor burden on global patient health.

Which Is the Best "Maintenance" Approach?

Because fluoropyrimidines are well tolerated, have limited cumulative toxicities, and may be given orally,[67] these agents are optimal candidates for maintenance. In the OPTIMOX1 trial, 620 patients with unresectable CRC were randomly assigned to receive FOLFOX4 until progression or a stop-and-go strategy encompassing 6 cycles of FOLFOX7 followed by infusional 5-FU and leucovorin (LV5FU2) maintenance for up to 12 cycles, which ultimately might be followed by the reintroduction of the initial regimen in patients with controlled disease.[68] Results showed no significant difference in median PFS (9.0 vs. 8.7 months), median OS (19.3 vs. 21.2 months), or overall response (58.5% vs. 59.2%) between treatment arms, with a more favorable toxicity profile for the intermittent arm. OPTIMOX2

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compared the fluoropyrimidine-based maintenance strategy with an intermittent approach and evaluated whether maintenance could be replaced by a "chemotherapy-free interval" after FOLFOX induction. More than 600 CRC patients were randomized to 6 cycles of modified FOLFOX7 (mFOLFOX7), followed by either maintenance with LV5FU2 or a treatment break. In both cases, the reintroduction of mFOLFOX7 was planned at disease progression. The primary end point was the duration of disease control, defined as the time sum of the initial PFS plus the PFS after reintroduction.[69] Although the study was prematurely closed because of the approval of bevacizumab in first-line treatment, patients who had actually received maintenance therapy had a significantly longer median duration of disease control (13.1 vs. 9.3 months; HR, 0.71; $P = .046$), longer median PFS (8.6 vs. 6.6 months), and longer median OS (23.8 vs. 19.5 months) compared to those who discontinued treatment.

The greatest experience of maintenance therapy achieved so far is with antiangiogenic agents because strong biologic and clinical rationales suggest the use of bevacizumab until (and perhaps beyond) disease progression.[53]

The first indirect demonstration of the benefit of the use of bevacizumab until disease progression came from the NO16966 study, in which PFS was longer when the antiangiogenic treatment was maintained until disease progression.[70] Although the general PFS differed by only 1.4 months between treatment arms (9.4 vs. 8.0 months; HR, 0.83), the difference in median PFS was remarkably greater when considering on-treatment patients (10.4 vs. 7.9 months; HR, 0.63). In the CONcePT trial, patients were randomized to receive mFOLFOX7 plus bevacizumab indefinitely until disease progression or 8 cycles of mFOLFOX7 plus bevacizumab followed by 8 cycles of maintenance LV5FU2 plus bevacizumab with the reintroduction of the initial regimen at progression. Patients enrolled onto the intermittent arm had a longer time to treatment failure (5.6 vs. 4.2 months; HR, 0.58) and a longer time to progression (12 vs. 7.5 months; HR, 0.53), suggesting, despite the very attenuated trial sample, that an intermittent schedule may produce a significant benefit versus continuous dosing.[71]

In the Spanish Macro-TTD trial, 408 advanced CRC patients were randomized to receive either XELOX and bevacizumab until progression or unacceptable toxicity, or 6 cycles of the same regimen followed by bevacizumab alone.[72] The primary study end point was PFS, with a noninferiority limit of 7.6 months (HR, 1.32), assuming a median PFS of 10 months in the control arm. Median PFS was similar among treatment arms (10.3 vs. 9.7 months; HR, 1.10), but because the HR interval crossed the preplanned noninferiority boundary (95% CI, 0.89-1.35), the study should be formally considered as negative, and noninferiority cannot be ruled out. However, we were confident in excluding a median detriment in PFS of more than 20 days, and we concluded that single-agent bevacizumab may be considered a maintenance therapy option.

More recently, CAIRO3 and AIO KRK 0207, 2 North European randomized studies, have set the standard for maintenance therapy with bevacizumab.[73,74] CAIRO3 was designed to investigate the efficacy of maintenance treatment with metronomic capecitabine and bevacizumab. Patients with advanced unresectable CRC with responsive or stable disease after 6 cycles of oxaliplatin, capecitabine, and bevacizumab were randomly assigned to capecitabine (625 mg/m^2 2 times a day continuously) plus bevacizumab (5.5 mg/kg every 3 weeks) or observation alone. The primary end point of the study was PFS2, defined as the time from randomization to progression upon reintroduction of the initial treatment. PFS2 corresponded to PFS1 in patients for whom bevacizumab and CAPOX were not reintroduced after progression. Patients were balanced between treatment arms, with 279 allocated to the maintenance arm and 279 to the observation arm. Notably, the induction treatment was reintroduced in only 60% of the patients assigned to the observation arm and in 47% assigned to the maintenance arm. PFS2 was longer in the maintenance arm (11.7 vs. 8.5 months; stratified HR, 0.67; 95% CI, 0.56-9.81; $P < .0001$; adjusted HR, 0.64; 95% CI, 0.53-0.76). An even greater difference was observed in PFS1 (8.5 vs. 4.1 months; stratified HR, 0.43; 95% CI, 0.36-0.52; $P < .0001$). Despite the advantage in PFS1 and PFS2, the OS was longer but the difference observed was not statistically significant (21.6 months in the maintenance arm vs. 18.1 months in the observation arm; stratified HR, 0.89; 95% CI, 0.73-1.07; $P = .22$). Interestingly, patients with a response after induction treatment had a greater benefit from maintenance treatment compared to those with stable disease. A higher incidence of severe neurotoxicity (10% vs. 5%) and hand—foot syndrome (22% vs. 0) was observed in patients who received maintenance therapy. Nevertheless, no difference in quality of life was reported between treatment arms. Despite a slightly higher incidence of hypertension in the maintenance arm (24% vs. 18%), the incidence of venous thromboembolic events (3% vs. 2%) and gastrointestinal perforations (1% vs. 0) was similar.[73]

In the AIO KRK 0207 trial,[74] a total of 476 patients with metastatic or unresectable CRC who had at least stable disease after 6 months of bevacizumab plus an oxaliplatin-based chemotherapy, were randomly allocated to bevacizumab with fluoropyrimidine (arm 1, considered as the standard arm), bevacizumab alone (arm 2), or observation (arm 3). The aim of the trial was to test the noninferiority of observation or bevacizumab alone compared to the combination arm, and a noninferiority HR limit was set at 1.43. Time to failure of the strategy was the primary end point of the study, defined as the time elapsed from randomization to either the second progression after maintenance and reintroduction or, in case of no reintroduction, the use of a second-line drug or no further treatment. Secondary end points included PFS, OS, and toxicity analysis during maintenance treatment with time-specific quality-of-life assessments. Maintenance treatment was continued until progression, unacceptable toxicity, or patient refusal, or until it was no longer considered to be in the interest of the patient's care. The noninferiority of bevacizumab alone compared to bevacizumab and 5-FU was demonstrated (median tumor-free survival, 6.5 vs. 6.8 months; HR, 0.98; 95% CI, 0.76-1.26; $P = .85$); conversely, the noninferiority was not reached for the observation alone arm because the HR confidence interval crossed the prespecified boundary of 1.43 (median tumor-free survival for observation, 6.1 months; HR, 1.22; 95% CI, 0.96-1.57; $P = .11$). Because the rate of full chemotherapy reintroduction was much lower than expected, the primary trial end point could be biased by the significant rate of dropouts usually reported in previous CRC trials investigating stop-and-go or maintenance strategies. Nevertheless, OS was similar among treatment arms (23.8 vs. 26.2 vs. 23.1 months). Consistent with the results of the CAIRO3 trial, the maintenance treatment was well tolerated and caused no excess toxicities.

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A smaller noninferiority phase 3 European study, the SWS-SAKK-41/06 trial,[75] compared maintenance bevacizumab (7.5 mg/kg every 3 weeks) versus observation in 262 CRC patients after 4 to 6 months of standard first-line chemotherapy plus bevacizumab. The primary end point was the median time to progression, which was assessed every 6 weeks. Secondary end points included PFS, OS, bevacizumab-related toxicities, and treatment costs. After a median follow-up of 30.1 months, the median time to progression for patients who received bevacizumab was 4.1 months (95% CI, 3.1-5.4) versus 2.9 months (95% CI, 2.8-3.8) for those enrolled onto the observation arm (HR, 0.74; 95% CI, 0.57-0.95; $P = .47$). Likewise, the median OS was also similar between trial arms (25.1 vs. 22.8 months; HR, 0.83; 95% CI, 0.61-1.12; $P = .218$). Overall, a combined analysis of the 3 trials[76] suggested that continuing bevacizumab is more advantageous in terms of PFS (HR, 0.56) than OS (HR, 0.89).

Regorafenib, a small multikinase inhibitor with a wide range of action,[77] was identified as a potential candidate for monotherapy maintenance treatment. A phase 3 randomized, double-blind, placebo-controlled study, RAVELLO, designed to evaluate the efficacy and safety of regorafenib as maintenance treatment after first-line therapy in 480 patients, is currently ongoing.[78]

Potential Role of EGFR Inhibitors in Maintenance Strategy

Cetuximab and panitumumab target the extracellular domain of EGFR, thus inhibiting cell proliferation and promoting tumor apoptosis in *RAS* wild-type patients.[79] Because of the potential development of acquired resistance after prolonged drug exposure and their specific safety profile, limited data on maintenance with EGFR inhibitors are available. The COIN-B study evaluated the safety and tolerability of cetuximab in combination with intermittent chemotherapy.[80] The randomized phase 2 trial enrolled metastatic CRC patients to intermittent oxaliplatin-based chemotherapy plus intermittent or continuous cetuximab. The primary study outcome was failure-free survival at 10 months that ultimately resulted similar among treatment arms (50% in the intermittent arm, 52% in the continuous arm).

Different mechanisms involving alternative pathways, such as the VEGF pathway, might be responsible for the emergence of acquired resistance to EGFR inhibitors. Although only preclinical evidence is currently available, there is a remarkably growing biologic rationale to further investigate the potential efficacy of the sequential administration of antiangiogenic agents after an up-front EGFR inhibitor exposure.[81-83] As a matter of fact, an innovative strategy for molecularly selected patients with advanced CRC could involve the exposure to the most active combinations followed by a less aggressive maintenance treatment to maintain tumor growth inhibition. A prospective randomized phase 2 trial, Macbeth,[84] is recruiting patients aged less than 75 years with adequate performance status and unresectable advanced *RAS* wild-type CRC to receive the triplet combination of FOLFOXIRI plus cetuximab for up to 8 cycles, followed by maintenance with either cetuximab or bevacizumab. In addition, 2 other Italian clinical studies (Ermes and Valentino) are testing the role of EGFR inhibitors in this setting.[85,*]

*EudraCT number 2015-000333-71 has been issued for the Sponsor's Protocol Code Number Valentino, according to the investigator's personal information.

Novel Molecules in Maintenance Strategy

The synergistic combination of erlotinib and bevacizumab was tested in preclinical models[86] and in pivotal clinical trials.[87] The aim of the GERCOR DREAM trial was to study the possible survival impact of the combination maintenance with erlotinib (150 mg/day orally, continuously) plus bevacizumab (7.5 mg/kg every 3 weeks) after induction treatment with chemotherapy and bevacizumab.[88] In this phase 3 study, patients with advanced CRC who received up-front chemotherapy plus bevacizumab for 6 months were randomly assigned to bevacizumab alone (n = 224) or bevacizumab plus erlotinib (n = 222). The trial met its primary end point: median PFS was 9.3 months for bevacizumab alone compared to 10.2 months for bevacizumab in combination with erlotinib (HR, 0.76; 95% CI, 0.61-0.94; $P = .009$), and such results were confirmed regardless of the *KRAS* mutational status. However, no difference in OS was observed (median OS, 27.9 vs. 28.5 months; HR, 0.89; $P = .312$), with higher frequency of severe diarrhea (9% vs. 1%) and skin toxicity (20% vs. 0) reported in the experimental arm.[88] Although the lack of OS benefit may be partially explained with the number of subsequent lines of therapy diluting the effect of front-line treatment, the median advantage in PFS (less than 1 month) was too limited to overweigh the increased toxicity and economic costs.

MGN1703 is a novel, dumbbell-shaped molecule that can potently stimulate the innate immune system through its action on the Toll-like receptor agonist. A small randomized, placebo-controlled phase 2 trial tested MGN1703 as maintenance treatment in 59 advanced CRC patients with disease control after standard first-line therapy with (88%) or without bevacizumab (22%).[89] The primary end point of the study was PFS, defined as the time elapsed from randomization to progression while receiving maintenance therapy. Although the median PFS while receiving maintenance therapy was similar (2.8 vs. 2.6 months), a clear advantage in HR was observed in favor of the experimental drug (HR, 0.55; 95% CI, 0.3-1.0; $P = .004$) as a result of the presence of a small subgroup of patients with a long PFS at 9 months (20% vs. 0; $P = .006$). MGN1703 was more active in patients with CRC that had previously achieved significant tumor shrinkage (median, 24.5 vs. 15.1 months; HR 0.40). Even if the very small trial sample size does not permit us to draw definitive conclusions, MGN1703 maintenance treatment might induce durable disease control in selected patients.[90] The phase 3 IMPALA study will further test this strategy and is currently recruiting patients.[91]

Efatutazone is a third-generation thiazolidinedione that acts as a highly selective peroxisome proliferator-activated receptor gamma agonist.[92] Preclinical studies have shown that efatutazone inhibits human CRX tumor xenograft growth, and early clinical studies have demonstrated an acceptable tolerability profile.[93] Recently, a placebo-controlled, multicenter phase 2 study randomized 84 CRC patients who had experienced disease control after standard first-line treatment with efatutazone (0.5 mg administered orally twice daily) or placebo.[94] The trial met its primary end point: the PFS rate at 18 weeks was 39.9% (95% CI, 23.5-55.7) in the efatutazone group and 25.0% (95% CI, 13.0-39.0) in the placebo group (HR, 0.66; $P < .0001$). Median PFS was 3.0 months in the efatutazone group and 2.7 months in the placebo group ($P = .03$); median OS was 22.9 months in the efatutazone group and 12.8 months in the placebo group ($P = .12$), although the study was not powered to

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demonstrate any difference in survival. Notably, the experimental treatment caused more hematologic toxicity and fluid retention.

Metronomic chemotherapy may also contribute to tumor control,[95,96] and this approach has recently gained renewed interest because of its possible synergistic association with molecular targeted agents.[97] Metronomic chemotherapy may mediate its action through angiogenesis inhibition, direct cytotoxic activity, and immunomodulation.[98] Several preclinical studies on human CRC xenografts have demonstrated that low-dose cyclophosphamide,[99] tegafur–uracil,[100,101] capecitabine,[102] and topotecan[103]; may all have antitumor activity. Small clinical trials have investigated metronomic schedules including capecitabine[104,105] or cyclophosphamide[106] and suggested their synergistic effect with bevacizumab.[107,108] The phase 2 MOMA trial is testing the role of metronomic chemotherapy in combination with bevacizumab after FOLFOXIRI and bevacizumab as induction treatment.[84]

Clinical trials investigating the role of maintenance therapy in CRC according to different strategies are summarized in Table 1.

Table 1 Clinical Trials About Maintenance Therapy in Colorectal Cancer According to Different Strategies

Therapy Strategy	Study	Induction Regimen	Maintenance	OS (Months)	HR; *P*	Design; Primary End Point
Discontinuing chemotherapy	Maughan[63]	Single-agent 5-FU	Continuing	11.3	HR 0.87; $P = .23$	Superiority; OS
			Discontinuing	10.9		
	Adams COIN[64]	Oxaliplatin based	Continuing	15.8	HR 1.08; $P =$ NR	Noninferiority; OS
			Discontinuing	14.4		
On–off	Labianca[66]	FOLFIRI	Continuing	18.0	HR 0.88; $P =$ NR	Noninferiority; OS
			2 months on and 2 months off	17.0		
Maintenance with active agents	**Fluoropyrimidine Alone**					
	Tournigand OPTIMOX1[68]	FOLFOX	Continuing	19.3	HR 0.93; $P = .49$	Superiority; DDC
			Fluoropyrimidine alone	21.2		
	Chibaudel OPTIMOX2[69]	FOLFOX	Fluoropyrimidine alone	23.8	HR 0.88; $P = .42$	Superiority; DDC
			Discontinuing	19.5		
	Bevacizumab					
	Hochster CONcePT[71]	FOLFOX/Bev	Continuing	NR	NR	Superiority; TTF
			Intermittent oxaliplatin	NR		
	Díaz-Rubio Macro-TTD[72]	XELOX/Bev	Continuing	20.0	HR 1.05; $P = .38$	Noninferiority; PFS
			Bev	23.2		
	Simkens CAIRO3[73]	XELOX/Bev	Metronomic capecitabine/Bev	21.6	HR 0.89; $P = .22$	Noninferiority; PFS2
			Discontinuing	18.1		
	Arnold AIO KRK 0207[74]	Oxaliplatin-based CT/Bev	Bev without oxaliplatin	23.8	$P =$ NS for all comparisons	Noninferiority; TTF
			Bev alone	26.2		
			Discontinuing	23.1		
	Koeberle SWS-SAKK-41/06[75]	CT/Bev	Bev	25.1	HR 0.83; $P = .22$	Noninferiority; TTP
			Discontinuing	22.8		
	Cetuximab					
	Wasan COIN-B[80]	Oxaliplatin-based CT/cetuximab	Cetuximab	17.5	NR	Superiority; FFS
			Discontinuing	16		
	Erlotinib					
	Tournigand DREAM[88]	CT/Bev	Bev alone	27.9	HR 0.89; $P = .31$	Superiority; PFS
			Erlotinib/Bev	28.5		
	MGN1703					
	Schmoll IMPACT[90]	CT/±Bev	MGN1703	22.6	HR 0.63; $P = .30$	Superiority; PFS
			Discontinuing (placebo)	15.1		
	Efatutazone					
	Boucher PD-0008[94]	CT	Efatutazone	22.9	HR NR; $P = .12$	Superiority; PFS
			Discontinuing (placebo)	12.8		

Abbreviations: 5-FU = 5-fluorouracil; Bev = bevacizumab; CT = chemotherapy; DDC = duration of disease control; FFS = failure-free survival; HR = hazard ratio; NR = not reported; NS = not significant; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure; TTP = time to progression.

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Can We Afford the Cost of Maintenance?

In a time of growing costs for cancer care, the value of maintenance therapy and its sustainability should be carefully considered. Value is a composite ratio between benefits and costs, which includes price, toxicity, and time spent for each in-hospital treatment, although there is no consensus on its definition in cancer care.[109] Cost-effective analyses showed conflicting results on the up-front use of bevacizumab for CRC patients treated within clinical trials[110] or in a real-world setting,[111-114] and set for the use of the angiogenic inhibitor an incremental cost of around US$75,000 per life-year gained in older patients.[115] Recent clinical trials have demonstrated that the continuation of bevacizumab compared to observation alone may prolong the median PFS of approximately 1.5 months. This result, however, is achieved with significant additional health care expenditures. As expected, a cost analysis showed a significantly greater value for patients who received bevacizumab as maintenance therapy compared to those who did not, with an average value of US$37,596 and US$8180, respectively; this suggests that the usefulness of maintenance bevacizumab must be balanced by a careful cost analysis.[116] Interestingly, different studies showed that a cautious dose rounding of biologic drugs may be cost effective without any loss in efficacy,[117,118] and these observations may be transferred to maintenance treatment as well. An acceptable cost for quality-adjusted life-year has not been definitively established in Western countries, but it hardly deviates from a range between US$50,000 and US$150,000 per quality-adjusted life-year.[119] Therefore, we probably need to update our assessment tools, mainly by increasing the comparative effectiveness research[120] across different treatment strategies. In the meantime, we can reasonably expect that regulatory agencies may raise the bar of efficacy for drug approval.[121]

Conclusion

The treatment of patients with disease not amenable to cure should aim to achieve disease control, delay progression, and improve survival. These results should be pursued while avoiding cumulative toxicity, improving patients' quality of life, and maintaining sensitiveness to any given agent. On these premises, preclinical evidence and clinical trials have shown the importance of maintenance therapy in responsive or stable metastatic CRC patients. This approach may encompass either a less intensive treatment with more favorable toxicity profile or treatment breaks. In both cases, quality of life would be improved, and drug holidays may even result in health care savings. However, some key clinical issues remain unsolved, such as the optimal duration of first-line treatment and the value of maintenance therapy itself.

On the basis of the available results, it appears reasonable to start patients on an induction treatment with chemotherapy and targeted agents for periods no longer than 6 months and then offer maintenance therapy to selected candidates. In this landscape, bevacizumab, alone on in combination with fluoropyrimidines, is the most extensively investigated drug. Despite a growing amount of evidence from randomized trials supporting its efficacy in the maintenance setting, the widespread use of bevacizumab is still debated. A number of reasons account for this skepticism, including the lack of predictive factors for angiogenic inhibitors, the difficulties when evaluating drug efficacy with classic Response Evaluation Criteria in Solid Tumors, and the undefined frequency of the radiologic assessments during maintenance. Importantly, because the median gain in PFS achieved with maintenance is of a few months, we need to consider the costs that such a strategy would impose in a time of restricted financial resources. Although bevacizumab appears safe and effective in this setting, more cost-effective data are needed to further endorse its general use. The biologic rationale and the clinical evidence for using EGFR inhibitors as maintenance is less convincing. However, a more accurate molecular selection of patients with disease that has a greater chance of responding might support future studies. Novel compounds are currently tested as maintenance agents, thus enriching the future available options. For the time being, maintenance therapy should be considered a valuable option for selected patients rather than a standard of care. It remains unclear, however, which patients may benefit the most from continuing first-line treatment without drug holidays.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Venook AP, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with *KRAS* wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *J Clin Oncol* 2014; 32(suppl 5), abstract LBA3.
2. 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. pii: S1470-2045(15)00122-9.
3. Aprile G, Lutrino SE, Ferrari L, et al. Evidence-based appraisal of the upfront treatment for unresectable metastatic colorectal cancer patients. *World J Gastroenterol* 2013; 19:8474-88.
4. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; 383:1490-502.
5. Giuliani F, De Vita F, Colucci G, et al. Maintenance therapy in colon cancer. *Cancer Treat Rev* 2010; 36(suppl 3):S42-5.
6. Simkens LH, Koopman M, Punt CJ. Optimal duration of systemic treatment in metastatic colorectal cancer. *Curr Opin Oncol* 2014; 26:448-53.
7. Seymour M. Conceptual approaches to metastatic disease. *Ann Oncol* 2012; 23(suppl 10):x77-80.
8. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; 25:1670-6.
9. Marino D, Leone F, D'Avanzo F, et al. Potentially resectable metastatic colorectal cancer: an individualized approach to conversion therapy. *Crit Rev Oncol Hematol* 2014; 92:218-26.
10. Van Cutsem E, Cervantes A, Nordlinger B, et al, ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25(suppl 3):iii1-9.
11. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non—small-cell lung cancer. *J Clin Oncol* 2009; 27:591-8.
12. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non—small-cell lung cancer. *J Clin Oncol* 2013; 31:2895-902.
13. Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with *HER2*-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15:1351-60.
14. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; 365:2473-83.
15. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; 365:2484-96.
16. Troiani T, Martinelli E, Napolitano S, et al. Molecular aspects of resistance to biological and non-biological drugs and strategies to overcome resistance in colorectal cancer. *Curr Med Chem* 2014; 21:1639-53.
17. Sharp GS, Benefiel WW. 5-Fluorouracil in the treatment of inoperable carcinoma of the colon and rectum. *Cancer Chemother Rep* 1962; 20:97-101.
18. Sugimoto Y, Ohe Y, Nishio K, et al. In vitro enhancement of fluoropyrimidine-induced cytotoxicity by leucovorin in colorectal and gastric carcinoma cell lines

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but not in non—small-cell lung carcinoma cell lines. *Cancer Chemother Pharmacol* 1992; 30:417-22.
19. Salonga D, Danenberg KD, Johnson M, et al. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. *Clin Cancer Res* 2000; 6:1322-7.
20. Leichman L, Lenz HJ, Leichman CG, et al. Quantitation of intratumoral thymidylate synthase expression predicts for resistance to protracted infusion of 5-fluorouracil and weekly leucovorin in disseminated colorectal cancers: preliminary report from an ongoing trial. *Eur J Cancer* 1995; 31A:1306-10.
21. Leichman CG, Lenz HJ, Leichman L, et al. Quantitation of intratumoral thymidylate synthase expression predicts for disseminated colorectal cancer response and resistance to protracted-infusion fluorouracil and weekly leucovorin. *J Clin Oncol* 1997; 15:3223-9.
22. Qiu LX, Tang QY, Bai JL, et al. Predictive value of thymidylate synthase expression in advanced colorectal cancer patients receiving fluoropyrimidine based chemotherapy: evidence from 24 studies. *Int J Cancer* 2008; 123:2384-9.
23. Subbarayan PR, Sarkar M, Nelson G, et al. Chronic exposure of colorectal cancer cells in culture to fluoropyrimidine analogs induces thymidylate synthase and suppresses p53. A molecular explanation for the mechanism of 5-FU resistance. *Anticancer Res* 2010; 30:1149-56.
24. Fukushima M, Sakamoto K, Ohshimo H, et al. Irinotecan overcomes the resistance to 5-fluorouracil in human colon cancer xenografts by down-regulation of intratumoral thymidylate synthase. *Oncol Rep* 2010; 24:835-42.
25. Yeh KH, Cheng AL, Wan JP, et al. Down-regulation of thymidylate synthase expression and its steady-state mRNA by oxaliplatin in colon cancer cells. *Anticancer Drugs* 2004; 15:371-6.
26. Hofheinz R, Hartung G, Samel S, et al. Adding weekly irinotecan to high-dose 5-fluorouracil and folinic acid (HD-5-FU/FA) after failure for first-line HD-5-FU/FA in advanced colorectal cancer—a phase II study. *Anticancer Drugs* 2002; 13:999-1004.
27. Graeven U, Arnold D, Reinacher-Schick A, et al. A randomised phase II study of irinotecan in combination with 5-FU/FA compared with irinotecan alone as second-line treatment of patients with metastatic colorectal carcinoma. *Onkologie* 2007; 30:169-74.
28. de Gramont A, Vignoud J, Tournigand C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997; 33:214-9.
29. André T, Louvet C, Raymond E, et al. Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. *Ann Oncol* 1998; 9:1251-3.
30. André T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 1999; 17:3560-8.
31. Cassidy J, Clarke S, Díaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011; 105:58-64.
32. Montagnani F, Chiriatti A, Turrisi G, et al. A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity. *Colorectal Dis* 2011; 13:846-52.
33. Alagoz M, Gilbert DC, El-Khamisy S, et al. DNA repair and resistance to topoisomerase I inhibitors: mechanisms, biomarkers and therapeutic targets. *Curr Med Chem* 2012; 19:3874-85.
34. Petitprez A, Larsen AK. Irinotecan resistance is accompanied by upregulation of *EGFR* and *Src* signaling in human cancer models. *Curr Pharm Des* 2013; 19:958-64.
35. Cunningham D, Humblet Y, Siena S, et al. Cetuximab mono-therapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351:337-45.
36. Souglakos J, Kalykaki A, Vamvakas L, et al. Phase II trial of capecitabine and oxaliplatin (CAPOX) plus cetuximab in patients with metastatic colorectal cancer who progressed after oxaliplatin-based chemotherapy. *Ann Oncol* 2007; 18:305-10.
37. Balin-Gauthier D, Delord JP, Pillaire MJ, et al. Cetuximab potentiates oxaliplatin cytotoxic effect through a defect in NER and DNA replication initiation. *Br J Cancer* 2008; 98:120-8.
38. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al. Oncogenic activation of the *RAS/RAF* signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Cancer Res* 2007; 67:2643-8.
39. De Roock W, Claes B, Bernasconi D, et al. Effects of *KRAS, BRAF, NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; 11:753-62.
40. Perrone F, Lampis A, Orsenigo M, et al. PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients. *Ann Oncol* 2009; 20:84-90.
41. Bokemeyer C, Van Cutsem E, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for *KRAS* wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 2012; 48:1466-75.
42. Douillard JY, Rong A, Sidhu R. *RAS* mutations in colorectal cancer. *N Engl J Med* 2013; 369:2159-60.
43. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type *BRAF* is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; 26:5705-12.
44. Leto SM, Trusolino L. Primary and acquired resistance to *EGFR*-targeted therapies in colorectal cancer: impact on future treatment strategies. *J Mol Med (Berl)* 2014; 92:709-22.
45. Giampieri R, Scartozzi M, Del Prete M, et al. Molecular biomarkers of resistance to anti-*EGFR* treatment in metastatic colorectal cancer, from classical to innovation. *Crit Rev Oncol Hematol* 2013; 88:272-83.
46. Jeong WJ, Cha PH, Choi KY. Strategies to overcome resistance to epidermal growth factor receptor monoclonal antibody therapy in metastatic colorectal cancer. *World J Gastroenterol* 2014; 20:9862-71.
47. Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. *J Clin Oncol* 2010; 28:1254-61.
48. Montagut C, Dalmases A, Bellosillo B, et al. Identification of a mutation in the extracellular domain of the epidermal growth factor receptor conferring cetuximab resistance in colorectal cancer. *Nat Med* 2012; 18:221-3.
49. Troiani T, Napolitano S, Vitagliano D, et al. Primary and acquired resistance of colorectal cancer cells to anti-*EGFR* antibodies converge on MEK/ERK pathway activation and can be overcome by combined *MEK/EGFR* inhibition. *Clin Cancer Res* 2014; 20:3775-86.
50. Van Emburgh BO, Sartore-Bianchi A, Di Nicolantonio F, et al. Acquired resistance to *EGFR*-targeted therapies in colorectal cancer. *Mol Oncol* 2014; 8:1084-94.
51. Crowley E, Di Nicolantonio F, Loupakis F, et al. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol* 2013; 10:472-84.
52. Ciombor KK, Berlin J. Targeting metastatic colorectal cancer—present and emerging treatment options. *Pharmgenomics Pers Med* 2014; 7:137-44.
53. Bagri A, Berry L, Gunter B, et al. Effects of anti-VEGF treatment duration on tumor growth, tumor regrowth, and treatment efficacy. *Clin Cancer Res* 2010; 16: 3887-900.
54. Mautner VF, Nguyen R, Knecht R, et al. Radiographic regression of vestibular schwannomas induced by bevacizumab treatment: sustain under continuous drug application and rebound after drug discontinuation. *Ann Oncol* 2010; 21:2294-5.
55. Mancuso MR, Davis R, Norberg SM, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest* 2006; 116:2610-21.
56. Powles T, Kayani I, Sharpe K, et al. A prospective evaluation of VEGF-targeted treatment cessation in metastatic clear cell renal cancer. *Ann Oncol* 2013; 24: 2098-103.
57. Roberts DL, Williams KJ, Cowen RL, et al. Contribution of HIF-1 and drug penetrance to oxaliplatin resistance in hypoxic colorectal cancer cells. *Br J Cancer* 2009; 101:1290-7.
58. Han XX, Guo CM, Li Y, et al. Effects of bevacizumab on the neovascular membrane of proliferative diabetic retinopathy: reduction of endothelial cells and expressions of VEGF and HIF-1α. *Mol Vis* 2012; 18:1-9.
59. Mésange P, Poindessous V, Sabbah M, et al. Intrinsic bevacizumab resistance is associated with prolonged activation of autocrine VEGF signaling and hypoxia tolerance in colorectal cancer cells and can be overcome by nintedanib, a small molecule angiokinase inhibitor. *Oncotarget* 2014; 5:4709-21.
60. Capdevila J, Carrato A, Tabernero J, et al. What could nintedanib (BIBF 1120), a triple inhibitor of *VEGFR, PDGFR*, and *FGFR*, add to the current treatment options for patients with metastatic colorectal cancer? *Crit Rev Oncol Hematol* 2014; 92:83-106.
61. Bocci G, Loupakis F. The possible role of chemotherapy in antiangiogenic drug resistance. *Med Hypotheses* 2012; 78:646-8.
62. Wu Y, Lucia K, Lange M, et al. Hypoxia inducible factor-1 is involved in growth factor, glucocorticoid and hypoxia mediated regulation of vascular endothelial growth factor-A in human meningiomas. *J Neurooncol* 2014; 119:263-73.
63. Maughan TS, James RD, Kerr DJ, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicenter randomized trial. *Lancet* 2003; 361:457-64.
64. 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 III MRC COIN trial. *Lancet Oncol* 2011; 12:642-53.
65. Berry SR, Cosby R, Asmis T, et al. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 2015; 26:477-85.
66. Labianca R, Sobrero A, Isa L, et al. Intermittent versus continuous chemotherapy in advanced colorectal cancer : a randomized GISCAD trial. *Ann Oncol* 2011; 22: 1236-42.
67. Aprile G, Mazzer M, Moroso S, et al. Pharmacology and therapeutic efficacy of capecitabine: focus on breast and colorectal cancer. *Anticancer Drugs* 2009; 20: 217-29.
68. 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.
69. 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; 27:5727-33.
70. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; 26:2013-9.
71. Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. *Ann Oncol* 2014; 25:1172-8.
72. Díaz-Rubio E, Gómez-España A, Massutí B, et al. First-line XELOX plus bevacizumab followes 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; 17:15-25.

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73. 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; 385:1843-52.
74. Hegewisch-Becker S, Graeven U, Lerchenmüller 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. pii: S1470-2045(15)00042-X.
75. Koeberle D, Betticher DC, Von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: a randomized phase III non inferiority trial (SAKK 41/06). *J Clin Oncol* 2013;(suppl), abstract 3503.
76. Pereira AAL, Rego JFM, Hoff PM, et al. The effect of chemotherapy delivered until progression versus complete stop on the overall survival of patients with metastatic colorectal cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2014; 32(suppl 5):3542.
77. Aprile G, Macerelli M, Giuliani F. Regorafenib for gastrointestinal malignancies: from preclinical data to clinical results of a novel multi-target inhibitor. *BioDrugs* 2013; 27:213-24.
78. Martinelli E, Troiani T, Venturini F, et al. Phase III study of regorafenib versus placebo as maintenance therapy in *RAS* wild type metastatic colorectal cancer (RAVELLO trial). *J Clin Oncol* 2015; 33(suppl 3), abstract TPS789.
79. Mendelsohn J, Baselga J. Epidermal growth factor receptor targeting in cancer. *Semin Oncol* 2006; 33:369-85.
80. 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.
81. Bianco R, Garofalo S, Rosa R, et al. Inhibition of mTOR pathway by everolimus cooperates with *EGFR* inhibitors in human tumours sensitive and resistant to anti-*EGFR* drugs. *Br J Cancer* 2008; 98:923-30.
82. Loupakis F, Cremolini C, Fontanini G, et al. Beyond *KRAS*: perspectives on new potential markers of intrinsic and acquired resistance to epidermal growth factor receptor inhibitors in metastatic colorectal cancer. *Ther Adv Med Oncol* 2009; 1: 167-81.
83. Giampieri R, Aprile G, Del Prete M, et al. Beyond *RAS*: the role of epidermal growth factor receptor (*EGFR*) and its network in the prediction of clinical outcome during anti-*EGFR* treatment in colorectal cancer patients. *Curr Drug Targets* 2014; 15:1225-30.
84. Salvatore L, Loupakis F, Cremolini C, et al. Phase II randomized study of induction FOLFOXIRI plus bevacizumab (Bev) followed by maintenance with Bev alone or Bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): the MOMA trial. *J Clin Oncol* 2014; 32(suppl 5), abstract TPS3664.
85. ERbitux MEtastatic colorectal cancer Strategy Study: a phase III randomized two arm study with FOLFIRI + cetuximab until disease progression compared to FOLFIRI + cetuximab for 8 cycles followed by cetuximab alone until disease progression in first line treatment of patients with *RAS* and *BRAF* wild type metastatic colorectal cancer [EudraCT no. 2014-004299-41]. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014−004299−41/IT. Accessed: April 12, 2015.
86. Naumov GN, Nilsson MB, Cascone T, et al. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (*EGFR*) blockade inhibits tumor growth in xenograft models of *EGFR* inhibitor resistance. *Clin Cancer Res* 2009; 15:3484-94.
87. Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared to cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. *J Clin Oncol* 2007; 25:4557-61.
88. Tournigand C, Chibaudel B, Samson B, et al. Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer (mCRC) according to *k-ras* status: results of the GERCOR DREAM phase III trial. *J Clin Oncol* 2013;(suppl), abstract 3515.
89. Schmoll HJ, Wittig B, Arnold D, et al. Maintenance treatment with the immunomodulator MGN1703, a Toll-like receptor 9 (TLR9) agonist, in patients with metastatic colorectal carcinoma and disease control after chemotherapy: a randomised, double-blind, placebo-controlled trial. *J Cancer Res Clin Oncol* 2014; 140:1615-24.
90. Schmoll HJ, Riera-Knorrenschild J, Kopp HG, et al. Maintenance therapy with the TLR-9 agonist MGN1703 in the phase II IMPACT study of metastatic colorectal cancer patients: a subgroup with improved overall survival. *J Clin Oncol* 2015; 33(suppl 3), abstract 680.
91. Cunningham D, Zurlo A, Salazar R, et al. IMPALA, a randomized phase III study in patients with metastatic colorectal carcinoma: immunomodulatory maintenance therapy with TLR-9 agonist MGN1703. *J Clin Oncol* 2015; 33(suppl 3), abstract TPS791.
92. Zou B, Qiao L,Wong BC. Current understanding of the role of PPARγ in gastrointestinal cancers. *PPAR Res* 2009; 2009:816957.
93. Komatsu Y, Yoshino T, Yamazaki K, et al. Phase 1 study of efatutazone, a novel oral peroxisome proliferator-activated receptor gamma agonist, in combination with FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. *Invest New Drugs* 2014; 32:473-80.
94. Boucher E, Davidenko I, Hadler I, et al. *Randomised, placebo-controlled, phase 2 study of efatutazone maintenance therapy in patients with advanced colorectal cancer who have achieved disease control following first-line chemotherapy*. Barcelona, Spain: Paper presented at: World Congress on Gastrointestinal Cancers; 25-28 June, 2014.
95. Lien K, Georgsdottir S, Sivanathan L, et al. Low-dose metronomic chemotherapy: a systematic literature analysis. *Eur J Cancer* 2013; 49:3387-95.
96. Hao YB, Yi SY, Ruan J, et al. New insights into metronomic chemotherapy−induced immunoregulation. *Cancer Lett* 2014; 354:220-6.
97. André N, Carré M, Pasquier E. Metronomics: towards personalized chemotherapy? *Nat Rev Clin Oncol* 2014; 11:413-31.
98. Gnoni A, Silvestris N, Licchetta A, et al. Metronomic chemotherapy from rationale to clinical studies: a dream or reality? *Crit Rev Oncol Hematol* 2015; 95:46-61.
99. Bocci G, Nicolaou KC, Kerbel RS. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs. *Cancer Res* 2002; 62:6938-43.
100. Louvet C, Coudray AM, Tournigand C, et al. Synergistic antitumoral activity of combined UFT, folinic acid and oxaliplatin against human colorectal HT29 cell xenografts in athymic nude mice. *Anticancer Drugs* 2000; 11:579-82.
101. Tsujimoto H, Tsukioka S, Ono S, et al. Effect of leucovorin on the antitumor efficacy of the 5-FU prodrug, tegafur−uracil, in human colorectal cancer xenografts with various expression levels of thymidylate synthase. *Oncol Lett* 2010; 1: 973-80.
102. Kolinsky K, Shen BQ, Zhang YE, et al. In vivo activity of novel capecitabine regimens alone and with bevacizumab and oxaliplatin in colorectal cancer-xenograft models. *Mol Cancer Ther* 2009; 8:75-82.
103. Hackl C, Man S, Francia G, et al. Metronomic oral topotecan prolongs survival and reduces liver metastasis in improved preclinical orthotopic and adjuvant therapy colon cancer models. *Gut* 2013; 62:259-71.
104. Petrioli R, Pascucci A, Francini E, et al. Continuous oral capecitabine at fixed dose in patients older than 75 years with metastatic colorectal and gastric cancer: a study of the Multidisciplinary Oncology Group on Gastrointestinal Tumors. *Anticancer Drugs* 2008; 19:91-6.
105. Nannini M, Nobili E, Di Cicilia R, et al. To widen the setting of cancer patients who could benefit from metronomic capecitabine. *Cancer Chemother Pharmacol* 2009; 64:189-93.
106. Kelley RK, Hwang J, Magbanua MJ, et al. A phase 1 trial of imatinib, bevacizumab, and metronomic cyclophosphamide in advanced colorectal cancer. *Br J Cancer* 2013; 109:1725-34.
107. Pietrantonio F, Biondani P, Pellegrinelli A, et al. Hepatic colorectal cancer metastases showing a distinctive pattern of pathological response after metronomic capecitabine and bevacizumab. *Med Oncol* 2012; 29:2838-41.
108. Norrby K. Metronomic chemotherapy and anti-angiogenesis: can upgraded pre-clinical assays improve clinical trials aimed at controlling tumor growth? *APMIS* 2014; 122:565-79.
109. Jagsi R, Sulmasy DP, Moy B. Value of cancer care: ethical considerations for the practicing oncologist. *Am Soc Clin Oncol Educ Book* 2014:e146-9.
110. Carter HE, Zannino D, John Simes R, et al. The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study. *Eur J Cancer* 2014; 50:535-43.
111. Whyte S, Pandor A, Stevenson M. Bevacizumab for metastatic colorectal cancer: a NICE single technology appraisal. *Pharmacoeconomics* 2012; 30:1119-32.
112. Lange A, Prenzler A, Frank M, et al. A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer. *Eur J Cancer* 2014; 50:40-9.
113. Lawrence D, Maschio M, Leahy KJ, et al. Economic analysis of bevacizumab, cetuximab, and panitumumab with fluoropyrimidine-based chemotherapy in the first-line treatment of *KRAS* wild-type metastatic colorectal cancer (mCRC). *J Med Econ* 2013; 16:1387-98.
114. Ewara EM, Zaric GS, Welch S, et al. Cost-effectiveness of first-line treatments for patients with *KRAS* wild-type metastatic colorectal cancer. *Curr Oncol* 2014; 21: e541-50.
115. Shankaran V, Mummy D, Koepl L, et al. Survival and lifetime costs associated with first-line bevacizumab use in older patients with metastatic colorectal cancer. *Oncologist* 2014; 19:892-9.
116. Díaz-Rubio E, Pietrantonio F, de Braud F. Continuing single-agent bevacizumab as maintenance therapy after induction XELOX (or FOLFOX) plus bevacizumab in first-line treatment of metastatic colorectal cancer. *Oncologist* 2012; 17:1426-8.
117. Fasola G, Aprile G, Marini L, et al. Drug waste minimization as an effective strategy of cost-containment in oncology. *BMC Health Serv Res* 2014; 14:57.
118. Francis SM, Heyliger A, Miyares MA, et al. Potential cost savings associated with dose rounding antineoplastic monoclonal agents. *J Oncol Pharm Practice* 2015; 21:280-4.
119. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014; 371: 796-7.
120. Lipscomb J, Yabroff KR, Hornbrook MC, et al. Comparing cancer care, outcomes, and costs across health systems: charting the course. *J Natl Cancer Inst Monogr* 2013; 2013:124-30.
121. Sobrero A, Bruzzi P. Incremental advance or seismic shift? The need to raise the bar of efficacy for drug approval. *J Clin Oncol* 2009; 27:5868-73.

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