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TOPIC HIGHLIGHT

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Evidence-based appraisal of the upfront treatment for unresectable metastatic colorectal cancer patients

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Abstract

Colorectal cancer (CRC) is a significant health problem, with around 1 million new cases and 500000 deaths every year worldwide. Over the last two decades, the use of novel therapies and more complex treatment strategies have contributed to progressively increase the median survival of patients with unresectable advanced CRC up to approximately 30 mo. The availability of additional therapeutic options, however, has created new challenges and generated more complicated treatment algorithms. Moreover, several clinically important points are still in debate in first-line, such as the optimal treatment intensity, the most appropriate maintenance strategy, the preferred biologic to be used upfront in patients with KRAS wild-type CRC, and the need for more detailed information on tumor biology. In this moving landscape, this review analyses why the first-line treatment decision is crucial and how the choice may impact on further treatment lines. In addition, it focuses on results of major phase Ⅲ randomized trials.

Key words: Colorectal cancer; Chemotherapy; Angiogenic inhibitors; Epidermal growth factor receptor inhibitors; Maintenance; First-line

Core tip: The choice of the first-line therapy is crucial for patients with advanced, unresectable colorectal cancer. The aim of this review is to critically focus on updated scientific data that medical oncologists need to interpret to make the most appropriate evidence-based choice among many possible treatment options.

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WHICH REASONING DOES LIE BENEATH THE CHOICE OF A FIRST-LINE TREATMENT?

Colorectal cancer (CRC) is currently the second most common cancer in Europe, with nearly 450000 new cases and approximately 215000 deaths occurred in 2012[1]. Half of those patients are either initially diagnosed at an advanced or metastatic stage or later develop distant metastases, and have a 5-year survival rate of 5%-10%[2]. While chemotherapy following resection of liver or lung

metastases has been reported to increase the chance of cure in selected patients, palliative systemic treatments may at least produce survival benefits for those presenting with diffuse unresectable disease. Over the last two decades, the median survival of patients with metastatic CRC has progressively improved, approaching 30 mo in recent reports. Notably, not only the widespread use of all available active agents (including 4 different chemotherapy drugs and 5 biologics) has shaped this clinical success, but also more patients have profited enhanced quality of life while receiving modified or less intensive maintenance treatments or while enjoying chemotherapy-free intervals. In fact, a smoother, more plastic concept embracing a "comprehensive treatment strategy" has substituted the rigid classical sequence of following structured treatment lines in the continuum of care. Notwithstanding those significant advances, the treatment landscape for unresectable advanced CRC has become increasingly complex. For all those incurable patients, mainstay of the treatment is to maximise survival while minimizing toxicities and maintaining optimal quality of life. The availability of more therapeutic options, however, has generated intricate algorithms of treatment decision-making and medical oncologists are often overwhelmed by a large number of trials providing unclear or conflicting results.

Unquestionably, when deciding the delivery of an optimally personalized treatment sequence, the ultimate treatment goal, outcome data from randomized clinical trials, different regimen-related toxicity profiles, molecular status of the disease, and patients' willingness should all be considered. However, while recent guidelines suggest to combine chemotherapy with targeted agents for the vast majority of those aged less than 75 years[3], it is much less clear which patients deserve a higher treatment intensity and which is the best biologic to use upfront for CRC patients with KRAS wild-type disease[4]. Moreover, it should be acknowledged that the proportion of patients receiving therapy diminishes with subsequent lines and that efficacy results are the greatest in untreated patients and usually reduce along with treatment course because of a growing degree of chemoresistance. The foundation of the upfront treatment is, therefore, crucial: in first-line setting the highest number of patients may benefit therapies with the highest response rates and the longest median progression-free survival (PFS). Moreover, there is still a chance for unexpected resection and even cure, and for all those who will not be cured, first-line therapy may impact on overall survival (OS).

Actually, whenever discussing with a previously untreated patient the different first-line treatment options, some clinical considerations should be made: (1) How long will the patient survive and how long will the patient benefit from first-line treatment? (2) Does the patient need (and agree on) an aggressive strategy? (3) Will a deeper knowledge of tumor molecular biology aid in the decision-making process? (4) May the patient benefit from maintaining an antiangiogenic strategy across treatment lines? and (5) Has the first-line choice potential impact on further treatment lines?

In addition, if the patients has previously received adjuvant chemotherapy (indeed, approximately 30% of metastatic CRC patients had), other questions arise: (1) How long have the patient lived without evidence of disease? (in other words, how long did the disease-free interval last?) and (2) May previous adjuvant treatments condition the first-line treatment choice?

Reporting as a springboard for discussion results from key randomized clinical trials (Table 1), aim of this viewpoint is to help clinicians making an evidence-based decision when choosing among possible first-line treatments for their medically-fit advanced unresectable CRC patients.

WHEN TO TREAT PATIENTS WITH HIGHER INTENSITY? SEARCHING FOR THE OPTIMAL FINE-TUNING

The idea of combining all available drugs upfront with the aim to hit and immediately kill as many cancer cells as possible is certainly not new. In CRC, the combination of 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) was initially compared to 5-fluorouracil and irinotecan (FOLFIRI) in two independent studies[5,6]. Results from the phase Ⅲ randomized Italian trial showed significant advantage for the triplet in terms of RR (66% *vs* 41%, $P = 0.0002$), PFS (9.8 mo *vs* 6.9 mo, HR = 0.63), OS (22.6 mo *vs* 16.7 mo, HR = 0.70), and secondary resections for those with liver-limited disease (36% *vs* 12%, $P = 0.01$), thus presenting such an intensive upfront regimen among the potential choices to be used when a significant tumor shrinkage is needed. Oppositely, although based on an encouraging preclinical[7] and clinical[8] background, final results of combining doublet chemotherapy with both bevacizumab and Epidermal Growth Factor Receptor (EGFR)-inhibitors were vastly disappointing[9,10]. Overall, both the randomized phase Ⅲ CAIRO2 and PACCE studies showed significantly reduced PFS outcome results and increased toxicity profiles for the 4-drugs combination when compared to chemotherapy plus bevacizumab alone. The reasons for the unforeseen antagonism between the two biologic agents when combined with chemotherapy are still uncertain[11]. The issue regarding how much intense the chemotherapy backbone should be remains critical also in the era of targeted agents. Two randomized trials, phase Ⅲ TRIBE[12] and phase Ⅱ OLIVIA[13], investigated the combination of the FOLFOXIRI based-regimen with the antiangiogenic bevacizumab. In the first trial, 508 advanced CRC patients received upfront FOLFIRI or FOLFOXIRI plus bevacizumab. Patients in the experimental arm achieved a significantly longer PFS (12.1 mo *vs* 9.7 mo; HR = 0.77, 95%CI: 0.64-0.93, $P = 0.006$). The triplet also provided a significant increase in RR (65% *vs* 53%, $P = 0.006$), but not in radical resection rate (15% *vs* 12%, $P = 0.327$). Neverthe-

Table 1 Outcome results of major randomized phase Ⅲ trials in the first-line setting in metastatic colorectal cancer patients

Ref.	Regimen	*n*	Previous adjuvant treatment	ORR	Median PFS (mo)	Median OS (mo)	Post-study therapy
Hurwitz *et al*[80] Tebbutt *et al*[119]	IFL	411	28%	34.8%	6.2	15.6	50%
Hurwitz *et al*[80]	IFL+bevacizumab	402	24%	44.8%	10.6	20.3	50%
Cunningham *et al*[118]	Capecitabine	140	18.6%	10%	5.1	16.8	37%
	Capecitabine + bevacizumab	140	32.1%	19%	9.1	20.7	37%
Saltz *et al*[8]	XELOX/FOLFOX	701	25%[1]	38%	8	19.9	53%
	XELOX/FOLFOX + bevacizumab	699	24%[1]	38%	9.4	21.3	46%
Heinemann *et al*[81]	FOLFIRI + cetuximab	297	22.1%	62%	10	28.7	65.7%
	FOLFIRI + bevacizumab	295	18.9%	58%	10.3	25	61.7%
	Capecitabine	156	22%	30.3%	5.7	18.9	68%
Tebbutt *et al*[119]	Capecitabine + bevacizumab	157	28%	38.1%	8.5	18.9	62%
	Capecitabine + bevacizumab + MMC	158	16%	45.9%	8.4	16.4	61%
Falcone *et al*[12]	FOLFOXIRI + bevacizumab	252	12%	65%	12	31	NA[3]
	FOLFIRI + bevacizumab	256	12%	53%	9.7	25.8	NA[3]
Van Cutsem *et al*[82]	FOLFIRI	599	18.9%	39.7%	8.4	20	71.7%
	FOLFIRI + cetuximab	599	17.4%	57.3%	9.9	23.5	66%
Maughan *et al*[91]	XELOX/FOLFOX[2]	815	25%[1]	57%	8.6	17	62%
	XELOX/FOLFOX + cetuximab	815	25%[1]	64%	8.6	17.9	56%
Tveit *et al*[120]	FLOX	185	8%[1]	41%	7.9	20.4	73.5%
	FLOX + cetuximab	194	9%[1]	49%	8.3	19.7	75.8%
	FLOX intermittently + cetuximab	187	10%[1]	47%	7.3	20.3	64.2%
Douillard *et al*[90]	FOLFOX4	590	15%[1]	48%	8	19.7	63%
	FOLFOX4 + panitumumab	593	16.1%[1]	55%	9.6	23.9	53%
Schmoll *et al*[89]	FOLFOX + bevacizumab	713	19%	47.3%	10.3	21.3	23.8%
	FOLFOX + cediranib	709	17%	46.3%	9.9	22.8	28.2%
Díaz-Rubio *et al*[60]	XELOX + bevacizumab	239	13%[1]	47%	10.4	23.2	72%
	XELOX + bevacizumab→bevacizumab	241	17%[1]	49%	9.7	20	74%

[1]No previous oxaliplatin-based treatment allowed; [2]Both Arm A (continuously) and Arm B (intermittently) have been considered; [3]Data will be available in 2014. ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; IFL: Irinotecan, fluorouracil, leucovorin therapy; FOLFIRI: 5-fluorouracil and irinotecan; XELOX: Capecitabine/oxaliplatin.

less, the study population was unselected for conversion to surgical resectability, since only 20% of randomized patients had liver-limited disease. Preliminary data showed a trend toward improved OS in the FOLFOXIRI plus bevacizumab arm (31.0 mo *vs* 25.8 mo; HR = 0.83, 95%CI: 0.66-1.05). Phase Ⅱ OLIVIA trial allocated 80 advanced CRC patients with liver-only unresectable metastases to receive 5-fluorouracil and oxaliplatin (FOLFOX) or FOLFOXIRI plus bevacizumab. Overall resection rate, the primary endpoint, was numerically higher in the FOLFOXIRI plus bevacizumab arm (61.0% *vs* 48.7%, $P = 0.27$). The more intensive regimen provided both a higher RR (80.5% *vs* 61.5%, $P = 0.061$) and radical (R0) resection rate (48.8% *vs* 23.1%, $P = 0.017$), with longer PFS (18.8 mo *vs* 12.0 mo, $P = 0.0002$). Moreover, retrospective data suggest that the addition of bevacizumab to the FOLFOXIRI regimen does not impact on liver toxicity while enhancing the rate of pathologic response and tumor necrosis[14].

The combination of FOLFOXIRI with EGFR-inhibitors showed also interesting results in a phase Ⅱ trial, but a formal phase Ⅲ comparison of the added benefit of cetuximab or panitumumab to the triplet regimen is currently lacking. In the TRIP study, 37 highly molecularly selected patients (concomitant wild-type status for KRAS, BRAF, NRAS, and HRAS) received FOLFOXIRI plus panitumumab with a reported RR of 89%. Forty-three percent of them underwent secondary surgery of metastases, and R0 resection was achieved in 13 cases (35%). After a median follow-up of 17.7 mo, median PFS was 11.3 mo[15]. Another phase Ⅱ study enrolled 43 CRC patients with unresectable liver metastases to receive cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy[16]. After a median number of 6 cycles, RR was noted in 79% of patients, and median OS was of 37 mo.

Based on available results, when should we opt for a very intensive treatment? The use of triplet plus bevacizumab could be considered a possible treatment option for those who parallel the trial's inclusion criteria (*i.e.*, unresectable, metastatic disease, age < 75 years; optimal ECOG PS, no major comorbidities), but this appears to be a much more intriguing and logical option for patients with symptomatic, bulky or aggressive disease or when conversion from unresectable to resectable status is deemed possible (liver-limited unresectable metastases). In the first circumstance, patients may benefit from a fast disease shrinkage that while reducing the tumor burden may better control cancer-related symptoms or avoid their occurrence. In the second condition, the advantage of using this highly active combination is that it may exert its effect in few cycles, avoiding a sustained exposure to chemotherapy that might potentially increase liver toxicity just before hepatic surgery. Although phase Ⅱ studies results are promising, the use of a triplet regimen combined with EGFR-inhibitors outside of a clinical trial

should be currently discouraged, even in patients with optimal molecular selection. In order to ameliorate the tolerability, the intensification of the upfront therapy in never resectable patients usually requires to plan a short initial treatment period (induction phase) followed by a less intensive treatment (maintenance phase). To avoid excessive toxicity in a palliative setting, the strength of such an induction treatment should last no longer than 8 cycles. After that, patients are usually switched to an appropriate, more tolerable, maintenance regimen that may be continued for a long period. Ongoing studies are clarifying the role of the maintenance therapy and expounding which are the optimal agents to be used. Potential drawbacks of an intensive treatment include higher toxicity and more limited rescue options once the tumor has become resistant.

WHICH BIOLOGIC SHOULD BE PREFERRED IN THE UPFRONT TREATMENT OF KRAS WILD-TYPE CRC PATIENTS?

Although the predictive role of G13D mutation still remains a matter of discussion[17-19], having a KRAS mutation in codon 12 or 13 is a universally accepted marker for EGFR-inhibitor inefficacy[20,21]. Other germline mutations in *RAS* or *BRAF* genes also seem to predict unfavourable results[22,23], and acquired secondary mutations may cause resistance to EGFR-inhibitors[24-26]. Moreover, retrospective data confirmed that using a more adequate technique RAS or BRAF mutations were found in approximately 20% of cancers initially classified as wild-type[20], and this might help in refining the target population[27,28]. Current molecular selection has a negative predictive value, but it does not help in the clinical-decision process for patients with wild-type CRC. Actually, which targeted agent should be combined to first-line chemotherapy in KRAS wild-type patients is one of the hot-topics in colorectal oncology. Up today, the choice was essentially based on cross-trial comparisons and on meta-analyses estimating the magnitude of benefit provided by each targeted agent[29,30]. While EGFR-inhibitors were considered powerful shrinking agents, bevacizumab was preferred for its ability to delay tumor progression. FIRE-3, the first phase Ⅲ randomized trial to provide results on the head-to-head comparison, randomized 592 KRAS wild-type CRC patients to upfront FOLFIRI plus either cetuximab or bevacizumab, with the aim to detect a difference of 12% in RR induced by FOLFIRI plus cetuximab (62%) compared to FOLFIRI plus bevacizumab (50%)[31]. Though unusual for a randomized phase Ⅲ trial, RR was chosen as the primary endpoint of the study. Because of a higher than expected treatment activity reported for patients exposed to bevacizumab, RR resulted similar between treatment arms (62% in the FOLFIRI plus cetuximab arm *vs* 58% in the FOLFIRI plus bevacizumab arm, OR = 1.18, $P = 0.18$) and no differences in PFS were documented (HR = 1.06; 95%CI: 0.88-1.26, $P = 0.54$). Of note, in the cohort of patients assessable for response ($n = 526$, 89%), encompassing all those who had received a minimum of 3 cycles and had performed at least a CT-scan evaluation following baseline, RR was significantly higher in favour of cetuximab-containing arm (72.2% *vs* 63.1%, OR = 1.52, $P = 0.017$). Although, no significant differences in median PFS were reported (10 mo *vs* 10.3 mo, HR = 1.03; 95%CI: 0.88-1.26), a clinically meaningful 3.7-month median advantage in OS was evidenced in favour of the cetuximab arm (28.7 mo *vs* 25 mo, HR = 0.77; 95%CI: 0.62-0.96), confirmed in all exploratory subgroups analysed. Disparities in subsequent treatment lines may hardly explain this unforeseen survival difference, being the proportion of patients who crossed over or received treatment beyond progression similar between treatment arms (65.7% in the cetuximab arm *vs* 61.7% in the bevacizumab arm, $P = 0.34$). Oppositely, the association of both early tumor shrinkage (at least 20% decrease in the sum of the longest diameter compared with baseline at week 8) and the deepness of response (percentage of tumor shrinkage observed at the smallest tumor size compared to baseline) to EGFR-inhibitors with the post-progression survival were advocated as possible reasons for success[32]. According to this theoretical model, the higher tumour shrinkage may result in a lower tumour load, as per RECIST, at the time of disease progression so that the benefit achieved in terms of deepness of response may influence the following history of patients' disease. Likewise, a significant correlation of the early objective tumor response (EOTR) with survival was demonstrated by an individual patient data meta-analysis of 15 randomized first-line trials enrolling approximately 12000 patients from the ARCAD database[33]. In the analysis, median PFS and median OS were consistently longer in patients with an EOTR at 6, 8 or 12 wk compared to those without. Overall, these results support the hypothesis that the advantage in terms of activity of an intensive upfront regimen may translate into a significant survival gain regardless the opportunity to achieve secondary resections. While a confirmatory correlation analysis is being conducted in FIRE-3 trial, outcome results from a larger intergroup phase Ⅲ trial (CALGB 80405, NCT00265850) that aims to compare upfront chemotherapy with bevacizumab or cetuximab in over 1200 metastatic CRC patients are awaited. Differently from FIRE-3, OS is the primary endpoint of the CALGB and SWOG cooperative groups trial.

To simultaneously explore the head-to-head comparison and the treatment strategy, the GERCOR is sponsoring the phase Ⅲ STRATEGIC-1 trial[34] that is designed to provide information on the optimal treatment sequence, with two different strategies each including all the currently available agents (oxaliplatin, irinotecan, fluoropyrimidines, bevacizumab, and EGFR-inhibitors), but in a different order. With disease control rate of the full strategy as the primary endpoint, nearly 500 patients with unresectable wild-type KRAS metastatic CRC will be

randomized to FOLFIRI-cetuximab, followed by an oxaliplatin-based chemotherapy with bevacizumab (Strategy A) or OPTIMOX-bevacizumab, followed by irinotecan-based chemotherapy with bevacizumab, followed by an EGFR-inhibitor with or without irinotecan (Strategy B). The study is starting soon the target recruitment.

TOWARD A BETTER MOLECULAR SELECTION? BROADENING CRC BIOLOGIC KNOWLEDGE BEYOND KRAS

Since the acknowledgment that CRC is a highly heterogeneous disease with regards to clinical evolution and response to treatments and the fact that it may change over time or evolve under treatment pressure[35], a more profound molecular knowledge of this cancer has been promoted[36]. Actually, a deeper understanding of the disease pathobiology and its molecular underpinnings allow clinicians to take advantage of a more detailed disease classification[37] and more robust information on predictive and prognostic biomarkers as well as resistance bioindicators for both antiangiogenic[38] and EGFR-inhibitors[39]. Whether serial tumor biopsies and repeated mutation testing may be useful to better capture the CRC heterogeneity and to systemically track its genomic evolution is a matter of debate[40,41], but the application of innovative, low-invasive techniques may find acceptance from both scientific and ethical standpoints[42,43]. Specifically focusing on the treatment tailoring, the landscape has rapidly evolved beyond KRAS codon 12 and 13 mutational status[44]. For example, rare mutation occurring in other KRAS codons, such as mutation in codons 61 or 146, may result in reduced EGFR-inhibitor efficacy[22]. As well, V600E BRAF mutations occurring in approximately 10% of all KRAS wild-type CRC tumors[45] or more rare KRAS amplifications[46] seem to limit the benefit from EGFR-inhibitors[47-49]. However, while there is total agreement on its negative prognostic value, the negative predictive role of BRAF mutations with regards to EGFR-inhibitor therapy is not universally accepted[50-52] and loss of PTEN expression or activity[53,54] have also been associated to inferior benefit from EGFR-inhibitors, but the small sample size of the cohort analysed linked to the relatively rare events prevent to draw strong definitive conclusions.

Importantly, the use of EGFR-inhibitors in the clinical practice should be based on a deep molecular analysis with further refinement of tumor-specific genetic markers in order to simultaneously allow: (1) identification of a wider patient population that does not benefit from the target treatment or may have detrimental effect; and (2) selection of patients who may achieve a maximized survival improvement. A prospective-retrospective analyses of phase Ⅲ PRIME trial[55] that randomized 1083 patients to upfront FOLFOX plus or minus panitumumaband a preplanned analysis of phase Ⅱ PEAK study that assigned in first-line 285 patients to FOLFOX plus either bevacizumab or panitumumab[56] consistently show that patients harbouring rare KRAS mutations in exon 3 (codons 59/61) and 4 (codons 117/146), or NRAS mutations in exon 2 (codons 12/13), 3 (codons 59/61), and 4 (codons 117/146) may not benefit from the EGFR-inhibitor. In the first analysis, patients without RAS mutations had a 2.2 mo median advantage in median PFS (10.1 mo *vs* 7.9 mo, HR = 0.72, 95%CI: 0.58-0.9, $P = 0.004$), and a 5.8 median advantage in OS (26 mo *vs* 20.2 mo, HR = 0.78, 95%CI: 0.62-0.99, $P = 0.04$). Impressively, patients with no RAS or BRAF mutations ($n = 446$) derived a 7.6 median survival benefit (28.3 mo *vs* 20.9 mo, HR = 0.74, 95%CI: 0.57-0.96, $P = 0.02$) if exposed to FOLFOX and panitumumab in first-line. An exploratory biomarker tumor analysis[57] of patients enrolled in the panitumumab *vs* BSC randomized phase Ⅲ study[58] reported similar results. Importantly, the addition of panitumumab to first-line FOLFOX might be even detrimental in patients with less common RAS mutations and should be cautiously avoided. On the basis of these data, marketing authorization for panitumumab has been amended, including the analysis of NRAS status before prescription, and restraining its use to RAS wild-type CRC patients. Since it has been highlighted how a more detailed molecular profile may impact on the evidence-based decision making process, a more accurate selection of candidates to upfront EGFR-inhibitors is warranted. Results of a similar deeper molecular analysis in patients exposed to upfront cetuximab or bevacizumab combined with FOLFIRI in the FIRE-3 trial will be soon presented.

ANGIOGENIC INHIBITORS UPFRONT AND IN THE FOLLOWING TREATMENT LINES? THE ISSUE OF MAINTENANCE AND TREATMENT BEYOND PROGRESSION

The choice of an upfront bevacizumab-based combination is considered a widely accepted standard treatment option for the majority of advanced CRC patients. Although supported by limited evidence, to continue the angiogenic inhibitor until disease progression is not uncommon in the clinical practice, especially for those patients who partially or entirely withhold the associated chemotherapy because of toxicity or towering cumulative doses of oxaliplatin[59]. Actually, results of randomized trials such as MACRO[60], DREAM[61], and COIN-B[62] suggest to continue bevacizumab as maintenance therapy until disease progression. In the MACRO trial, 480 CRC patients were randomly assigned to receive six cycles of bevacizumab, capecitabine, and oxaliplatin followed by bevacizumab either alone or combined with the same chemotherapy regimen until progression. A slightly longer median PFS was reported in the combination arm (10.4 mo *vs* 9.7 mo, HR = 1.1, $P = 0.38$), although burdened by a higher rate of severe sensory neuropathy (26% *vs* 8%, $P = 0.0001$) and HFS (13% *vs* 7%, $P = 0.03$). The primary analysis of DREAM demonstrated that a maintenance

therapy with bevacizumab and erlotinib may significantly prolong median PFS (10.2 mo *vs* 9.3 mo, HR = 0.76; 95%CI: 0.61-0.94, *P* = 0.009) but not median OS (28.5 mo *vs* 27.0 mo, HR = 0.89; 95%CI: 0.7-1.12, *P* = 0.31) after a first-line bevacizumab-based induction therapy[63]. The additive value of erlotinib to bevacizumab in this setting is however unconfirmed[64]. Yet, the issue regarding the role of bevacizumab in the maintenance phase was not formally addressed until recently. SAKK 41/06[65] and CAIRO-3[66] phase Ⅲ trials compared observation to a maintenance strategy following an induction phase of chemotherapy plus bevacizumab. In the non-inferiority Swiss study, 262 CRC patients without disease progression at 4-6 mo since treatment start were randomized to continue on single-agent bevacizumab until disease progression or observation. Even though median PFS (+ 1.2 mo) and OS (+ 3.3 mo) were both longer for patients who continued on bevacizumab, the trial formally failed to meet its primary endpoint, since the median time to progression did not differ sufficiently between treatment arms (17.9 wk *vs* 12.6 wk; HR = 0.74; 95%CI: 0.57-0.94, *P* = 0.47; with a non-inferiority limit for HR = 0.727). In CAIRO-3 trial, patients without disease progression after 6 cycles of capecitabine, oxaliplatin (CAPOX regimen) and bevacizumab were randomized to observation or continuing with capecitabine and bevacizumab. Upon the first disease progression, CAPOX plus bevacizumab was reintroduced and maintained until the second evidence of progression. The primary endpoint was the PFS2, defined as the time from randomization to progression upon treatment re-introduction. Patients in the maintenance arm achieved a significantly longer PFS2 (11.8 mo *vs* 10.5 mo, HR = 0.81; 95%CI: 0.67-0.98, *P* = 0.028), PFS (8.5 mo *vs* 4.1 mo, HR = 0.44; 95%CI: 0.36-0.53, *P* < 0.00001) and a non-significant advantage in OS (21.7 mo *vs* 18.2 mo, HR = 0.87; 95%CI: 0.71-1.06, *P* = 0.156), that became significant in the adjusted analysis (HR = 0.80). AIO KRK0207, a phase Ⅲ randomized trial comparing observation to maintenance with either bevacizumab alone or bevacizumab plus capecitabine, will clarify if a maintenance treatment, instead of a full holiday period, is actually needed for all patients. In conclusion, while reasonable, safe, and clinically feasible, whether a maintenance therapy is needed for all patients is still an open question.

The role of cetuximab in the maintenance therapy is also being investigated. The two-arm phase Ⅱ COIN-B study randomized 169 patients with unresectable KRAS wild-type CRC to intermittent chemotherapy plus continuous or intermittent cetuximab as first-line treatment. Continuous cetuximab was associated with a longer failure free survival (FFS), chemotherapy-free interval (3.7 mo *vs* 5.1 mo) and time to progression (20.1 mo *vs* 18.4 mo). Median FFS was 12.0 and 13.7 mo, respectively[62]. The phase Ⅲ Macbeth trial (EUDRACT 2011-000840-70) is an ongoing multicenter, randomized, open-label study designed to evaluate the efficacy and safety of eight cycles of FOLFOXIRI plus cetuximab followed by maintenance with cetuximab or bevacizumab as first-line treatment for unresectable KRAS wild-type metastatic CRC patients.

Another point of discussion is the use of antiangiogenics beyond disease progression. Data from retrospective registries such as BRITE[67] or ARIES[68] suggested a survival benefit with the use of bevacizumab beyond disease progression. More recently, the randomized phase Ⅲ ML18147 trial prospectively tested the efficacy of maintaining bevacizumab beyond disease progression[69]. After the failure of a bevacizumab-containing first-line treatment, 820 patients were randomized to receive a different second-line chemotherapy with or without bevacizumab. Those that continued on the antiangiogenic agent reported significantly longer OS (11.2 mo *vs* 9.8 mo; HR = 0.81; 95%CI: 0.69-0.94, *P* = 0.0062) and PFS (5.7 mo *vs* 4.1 mo, HR = 0.68; 95%CI: 0.59-0.78, *P* < 0.0001). Toxicity profiles were similar between the two arms, although more bleedings (2% *vs* 1%), venous thromboembolic events (5% *vs* 3%), and gastrointestinal perforations (2% *vs* < 1%) were noted among those receiving bevacizumab. In the phase Ⅲ BEBYP trial[70], 184 patients who had failed a bevacizumab-based first-line treatment were randomized to receive second-line chemotherapy with or without bevacizumab. The trial was stopped early, as soon as the positive results of the ML18147 were diffused. Performance status (ECOG PS 0 *vs* 1-2), length of the chemotherapy-free interval (< or > 3 mo), and type of second-line chemotherapy were considered as stratification factors. Two thirds of the patients received oxaliplatin-based combinations in both treatment arms. After a median follow-up of 22 mo, the results confirmed the benefit in PFS (6.8 mo *vs* 5 mo, HR = 0.72; 95%CI: 0.54-0.97, *P* = 0.029) for those maintained on bevacizumab, while OS data are still immature to be analyzed.

Indirect evidence supports how CRC patients may benefit from further angiogenic treatments after disease progression while on bevacizumab. The phase Ⅲ VELOUR trial showed the efficacy of aflibercept (a fusion protein with high affinity to all VEGF-A isoforms, VEGF-B, PlGF-1, and PIGF-2) in combination with FOLFIRI in 1,266 CRC patients who had failed a first-line oxaliplatin-based therapy[71]. Both median OS (13.5 mo *vs* 12.06 mo, HR = 0.817; 95%CI: 0.71-0.94, *P* = 0.0032) and PFS (6.9 mo *vs* 4.67 mo, HR = 0.76) were significantly longer in those who received FOLFIRI and aflibercept. Importantly, prior exposition to antiangiogenics did not reduced the outcome effect. Actually, a similar benefit in PFS (6.7 mo *vs* 3.9 mo, HR = 0.66; 95%CI: 0.51-0.85) and OS (12.5 mo *vs* 11.7 mo, HR = 0.86; 95%CI: 0.67-1.10) was reported for the use of aflibercept in those who had received bevacizumab as part of their upfront treatment (approximately 28% in both treatment arms). Regorafenib is another agent with broad antiangiogenic properties[72]. In the CORRECT trial, 760 chemorefractory CRC patients were randomized 2:1 to regorafenib (160 mg daily in a 3-wk-on, 1-week-off schedule) or placebo[73]. All patients had previously re-

ceived bevacizumab. Median OS was 6.4 mo in the regorafenib group *vs* 5.0 mo in the placebo group (HR = 0.77; 95%CI: 0.64-0.94).

Large, international efforts have tried to define who are the patients more likely to benefit from the antiangiogenic strategy. Unfortunately, given the complexity of cancer-related angiogenesis, conflicting results have been reported both at molecular[74] or clinical levels[75,76]. The prospective validation of other single predictive biomarkers such as baseline LDH value[75], number of circulating endothelial cells[77], or level of miRNA[78] are still pending, but will unlikely succeed.

WILL THE FIRST-LINE CHOICE IMPACT ON FOLLOWING TREATMENT LINES?

If and how the first-line therapy may influence further treatment is a matter of debate at many levels (molecular, clinical, regulatory). Nevertheless, how oncologists decide the sequence of treatment to use should be always based on a solid mainstay. The following reasoning is founded on a critical analysis of major phase Ⅲ randomized studies.

Accordingly to the results of a pivotal phase Ⅲ trial that compared FOLFOX6 followed by FOLFIRI to FOLFIRI followed by FOLFOX6 and showed similar outcomes regardless of the treatment sequence[79], the backbone treatment used after first disease progression of disease is currently based on a crossover from an irinotecan- to an oxaliplatin-based regimen or vice-versa. In that trial, 220 patients were randomized to receive initially either FOLFIRI or FOLFOX6 and to switch to the other regimen at disease progression. Neither first-line RR (56% *vs* 54%), nor first-line median PFS (8.5 mo *vs* 8 mo, P = 0.26), nor median OS (21.5 mo *vs* 20.6 mo, P = 0.99) were statistically different between treatment arms.

Ten years after the widespread use of biologics has begun in the clinical practice, the scenario has become much more complicated, particularly in patients with KRAS wild-type tumors that may benefit from a scope of different treatments. The initial choice of the upfront chemotherapy regimen, however, retains its value.

When opting for an irinotecan-based first-line regimen, either bevacizumab[80] or cetuximab[81,82] could be used as optimal biologic partners. Either way the patient is started, survival results of the ECOG E3200 phase Ⅲ trial[83] would suggest to use FOLFOX plus bevacizumab as second-line treatment after an irinotecan-based first-line failure. Later on, following on the treatment route, the choice of third-line may become critical. In this setting, while strong data support the use of EGFR-inhibitors either alone[84,58] or combined to irinotecan[85],evidence suggesting potential benefit from retreating patients with EGFR-inhibitors is more shaggy[86,87] or under investigation[88]. Regorafenib, indeed, would be an appropriate choice for all highly pretreated patients[73]. Consequently, the treatment algorithm would offer 4 potential lines of treatment if the patient receive upfront an irinotecan-based chemotherapy plus bevacizumab, but one treatment line would be lost if the patient starts with an irinotecan-based therapy plus cetuximab. This hypothetical reasoning may be revised (and even reversed) if the outcome results of CALGB 80405 trial will confirm the unexpected 3.7-mo median survival advantage reported in FIRE-3 for KRAS wild-type CRC patients receiving FOLFIRI and cetuximab in first-line.

When opting for a first-line treatment including oxaliplatin, antiangiogenic drugs[60,89] or EGFR-inhibitor[90,91] may be used in combination, although the upfront use of bevacizumab seems to be preferable because it may better fit in the maintenance strategy[92,93] for its convenience and safety when combined to capecitabine[94]. Moreover, the upfront combination of oxaliplatin with an EGFR-inhibitor requires more detailed molecular biology data (see paragraph 4) and increased watchfulness if using an oral fluoropyrimidine[91]. At disease progression, many reasons strongly support the choice of switching to an irinotecan-based regimen, including the potential cumulative neurotoxicity of prolonged oxaliplatin use. Since in second-line setting many alternative options exist, to establish which is the optimal biologic to be delivered is challenging and depends on the previous use of targeted agents. A number of second-line randomized trials have investigated the role of biological agents in the treatment of CRC patients not previously exposed to EGFR-inhibitors. Tested agents included bevacizumab[69], aflibercept[71], cetuximab[95], or panitumumab[96,97]. Of note, in all those trials patients may have been upfront treated with bevacizumab, but the proportion of those who did receive the angiogenic inhibitors in first-line vastly varied, ranging from 2%[97] to 100%[69]. Results of ML18147 and VELOUR have been already discussed (see before). In the phase Ⅲ EPIC study[92], 1298 patients who had prior failed a first-line oxaliplatin-based regimen, were randomized to receive irinotecan plus cetuximab or irinotecan alone. The addition of cetuximab to irinotecan resulted in a significant improvement of PFS (4.0 mo *vs* 2.6 mo, HR = 0.69; 95%CI: 0.617-0.776, P < 0.0001), but no OS advantage was reported (10.7 mo *vs* 10.0 mo, HR = 0.97). Panitumumab was tested in another randomized phase Ⅲ trial, comparing in 1,186 pretreated metastatic CRC patients, the addition of panitumumab itself to FOLFIRI, to placebo. A significant improvement in PFS was observed (5.9 mo *vs* 3.9 mo, HR = 0.73; 95%CI: 0.59-0.90, P = 0.004), with a trend for longer OS (14.5 mo *vs* 12.5 mo, HR = 0.85; 95%CI: 0.70-1.04, P = 0.12). Similarly, the PICCOLO study[97] reported higher RR (34% *vs* 12%, P < 0.001), longer PFS (HR = 0.78; 95%CI: 0.64-0.95, P = 0.015), but no survival advantage (10.9 mo *vs* 10.4 mo; HR = 1.01; 95%CI: 0.83-1.23, P = 0.91) for the use of panitumumab and irinotecan-based chemotherapy compared to irinotecan alone. If the upfront biologic was the EGFR-inhibitor, less options are permitted (see point A). Again, regorafenib may be considered as salvage treatment for all pretreated patients. As discussed before, if the patient is started with a EGFR-inhibitor, the number

of therapeutic options seems narrowed.

CHOOSING A FIRST-LINE TREATMENT FOR CRC PATIENTS WHO HAVE FAILED ADJUVANT OXALIPLATIN - IS THERE ANY DIFFERENCE?

Since approximately 50% of stage Ⅲ and 20% of stage Ⅱ CRC patients do eventually recur, one third of patients present with metachronous metastatic disease, which is currently defined as more than 1 year between the occurrence of the primitive tumor and metastasis. Not surprisingly, a significant proportion of those patients may have already received an oxaliplatin-based chemotherapy, a universally confirmed standard regimen in the adjuvant setting[98-100]. Indeed, patients enrolled in first-line phase Ⅲ randomized trials which had already been exposed to adjuvant chemotherapy ranged from 8% to 32% (Table 1). However, having received a previous treatment with oxaliplatin was sometimes included among the exclusion criteria, and even when it was permitted, how many of those pretreated patients had actually received an oxaliplatin-based regimen was rarely specified in the publication.

To fully understand the importance of this point, some data should be further discussed. The analysis of over 20000 CRC patients included in the ACCENT database showed that the risk of recurrence peaks between 18 and 24 mo after radical surgery, and then decreases over time[101]. Most patients who recur, therefore, develop metastatic disease within 18 mo since the end of postoperative chemotherapy.

The use of oxaliplatin is burdened by the frequent occurrence of chronic peripheral sensory neuropathy[102,103], a dose-dependent disturbing toxicity characterized by dysesthesia and distal paresthesia, that often negatively impacts on patients' quality of life[104]. In addition, acute neuropathy (oral-facial and peripheral), which in some cases is induced or exacerbated by exposure to cold, was also reported. This neurological side-effect, quite unusual in the initial chemotherapy cycles, frequently appears during the treatment course as long as the cumulative dose of oxaliplatin increases.

The vast majority of the patients enrolled in randomized clinical trials that tested oxaliplatin in the adjuvant setting developed peripheral sensory neuropathy. In MOSAIC trial, any grade peripheral neurotoxicity was observed in 92% of patients, while grade 2 (moderate) or grade 3 (severe) was reported in 44%. Often, however, the symptoms ameliorated or resolved over time: one and four years after treatment, 30% and 15% of patients had minimal residual toxicity, respectively. In NSABP C-07 trial, grade 3-4 peripheral neuropathy was reported in 8.4% of patients. At 1 year from random assignment, the rate of severe neurotoxicity was 0.6%. The inferior rate of neurotoxicity may be due to the lower cumulative dose of oxaliplatin in NSABP C-07 (9 planned doses of 85 mg/m^2) compared to MOSAIC (12 planned doses of 85 mg/m^2).

In NO16968 study, any grade peripheral neuropathy occurred in 78% of patients exposed to oxaliplatin, and grade 3-4 in 11%. At the end of adjuvant treatment, residual neurotoxicity was still present in 68% of patients.

Toxicity data were confirmed in another randomized trial that tested the efficacy of bevacizumab combined to oxaliplatin-based chemotherapy in the adjuvant setting[105]. Grade 2 or grade 3 sensory neuropathy was reported in 43.7% of patients treated with FOLFOX6 and in 48.9 % of those treated with FOLFOX6 + bevacizumab, with the delivery of similar median doses of oxaliplatin. Notably, about 10%-20% of patients developed severe neurotoxicity after cumulative oxaliplatin dose of 750-850 mg/m^2[106].

Recently, a number of studies reported on a long-lasting oxaliplatin-induced peripheral neurotoxicity[107,108]. Those studies showed that a not-negligible proportion of patients (5%-15%) still suffer from chronic neurotoxicity many years after treatment end, and refer troublesome numbness or tingling of hands and feet. Than, it is conceivable that a proportion of oxaliplatin-exposed patients may still have neurological symptoms at the time of recurrence. In order to prevent or reduce the incidence and intensity of this toxicity in the adjuvant setting, several strategies are being studied, including a reduced exposition to oxaliplatin[109] or the potential use of neuroprotectants such as glutathione[110], oxcarbazepine[111], or venlafaxine[112], but no preventive treatment has been recognized as a standard. Moreover, retrospective studies suggested that the *iv* supplementation with calcium and magnesium may be useful[113]. However, a randomized phase Ⅲ trial enrolling 362 radically resected CRC patients with no pre-existing peripheral neuropathy to compare calcium/magnesium supplementation *vs* placebo failed to show any significant difference among treatment arms in the rate of moderate or severe neuropathy[114].

For all these reasons, whether the clinical outcome of an oxaliplatin-based first-line therapy is maintained in patients who had been already exposed to the drug in the adjuvant setting is unclear and few data are available on this regard. Recently, a retrospective study assessed the first-line RR to either FOLFIRI or FOLFOX in 32 patients with advanced CRC who had previously received adjuvant FOLFOX after radical surgery[115]. The median time between the beginning of adjuvant chemotherapy and disease recurrence was 1.7 years. The overall RR was 17% in the FOLFOX group *vs* 36% in the FOLFIRI group. Despite a trend in favor of FOLFIRI, the difference was not statistically significant ($P = 0.22$).

For patients with residual neurotoxicity at the time of disease recurrence, the stop-and-go strategy may be an appropriate option to avoid the side-effect worsening while still using an active agent. Two different randomized trials showed a clinically significant reduction in the rate of severe neurotoxicity with the use of this strategy[116,117]. In conclusion, an oxaliplatin-based regimen could still be an option for patients without or with minimal residual neurotoxicity that become metastatic

after at least 12 mo since the end of an oxaliplatin-based adjuvant therapy. Oppositely, for those who relapse early (within 12 mo) or still have clinically significant neurotoxicity, it is reasonable to choose a regimen without oxaliplatin and delay as much as possible the reintroduction of the neurotoxic drug.

CONCLUSION

The landscape of CRC treatment is changing very fast, and the availability of new therapeutic options has created new challenges and generated more complicated treatment algorithms. In conclusion, we would like to suggest the reader short possible answers to the initial questions. Undoubtedly, the optimal choice of the first-line treatment is still of great importance. When considering this choice, patients' performance status, comorbidities and desires should be considered as well as the ultimate goal of the treatment and the molecular features of the tumor. An highly intensive regimen is particularly indicated for younger patients without comorbid conditions or for those patients with aggressive colorectal carcinomas (symptomatic, bulky disease or BRAF mutant tumors). The application of a deeper molecular analysis not only helps identifying those patients who may benefit the most from EGFR-inhibitors but also has a prognostic value. In the majority of cases with RAS and BRAF wild-type status, a first-line combination with an EGFR-inhibitor seems to be the preferred treatment option, while the antiangiogenic strategy should be pursued in those with RAS mutated tumors or when a less aggressive treatment is favoured. The exposition to oxaliplatin in the adjuvant setting may somehow limit its use in the advanced phases of the disease due to possible cumulative neurotoxicity. Randomized trials, however, are verifying if a shorter oxaliplatin-based adjuvant treatment may be equally protecting and less toxic. Notably, many other new molecules are being studied in randomized trials and, hopefully, results of those studies will help clinicians further refining the current treatment paradigms.

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