

EXPERT OPINION

How to find the Ariadne's thread in the labyrinth of salvage treatment options for metastatic colorectal cancer?

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Since a chance for cure was found out in metastatic colorectal cancer (mCRC) patients undergoing a resection of liver and lung metastases, high tumor shrinkage by chemotherapy regimens and their combination with targeted agents have been addressed in potentially resectable mCRC. However, most mCRC patients cannot reach this opportunity because of tumor burden or metastatic sites. For these patients a salvage systemic therapy could be offered to prolong survival. To date, a huge number of clinical trials provided some evidences for the achievement of this goal. A lot of chemotherapeutic regimens in combination with biological therapies are now available. We tried to propose a simple way to choose the best options and to plan an optimal sequence of treatments. This tool could help the oncologists worldwide to better and easily manage mCRC patients who need salvage systemic therapy.

Keywords: algorithm, chemotherapy, metastatic colorectal cancer, salvage treatment, target therapy

Expert Opin. Biol. Ther. (2014) 14(6):743-748

Colorectal cancer (CRC) is one of the leading causes of cancer-related death. The development of metastases is the main event that impacts on survival in CRC patients. A chance of cure in stage IV CRC patients has arisen since the resection of liver and lung metastases induced the maintenance of prolonged disease-free interval in a consistent proportion of patients. Subsequently, the clinical development of chemotherapeutic regimens, alone or in combination with targeted agents, allowed the possibility of resection and cure also in those patients who were not resectable for liver and lung metastases at diagnosis time. For this reason, till now an increasing number of clinical trials have been designed and carried out to identify the best treatment option to achieve a high metastases resection rate and subsequent prolonged survival [1].

However, a relevant number of metastatic CRC (mCRC) patients show no ways to receive a resection for distant metastases. In these cases, only salvage therapy can be offered. Because cure is not possible in these patients, a prolongation of survival, with preservation or improvement of quality of life, is the main goal of the options available for these patients. Since a lot of clinical trials with various chemotherapeutic regimens and/or targeted drugs studied different end points, every oncologists need to choose the best option according to the real aim, which they would achieve for their patients. For all these reasons, a proper plan of the optimal sequence of treatments needs to be identified according to many patient- and tumor-related factors [2].

In the 2012 European Society of Medical Oncology guidelines, Schmoll *et al.* included the proposal of a sequence for salvage therapy in mCRC [3]. All the treatment options were included in a complicated algorithm, which would offer to the

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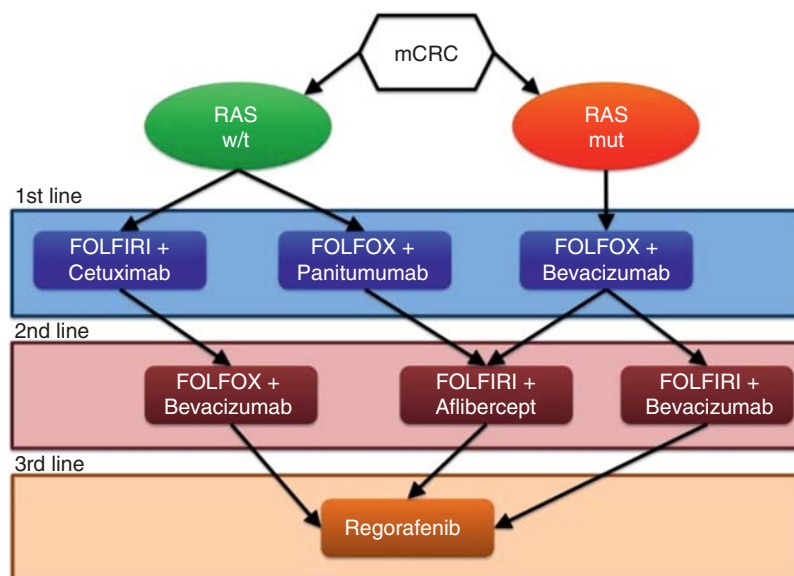


Figure 1. Algorithm for the optimal sequence of salvage treatment regimens in metastatic colorectal cancer.

FOLFIRI: Fluorouracil, folinic acid, irinotecan; FOLFOX: Fluorouracil, folinic acid, oxaliplatin; mCRC: Metastatic colorectal cancer.

oncologists a way to treat each patient in agreement with his/her own characteristics. First-line treatment is usually chosen after the evaluation of some patient-related factors, such as age, performance status and comorbidity; tumor-related factors, such as tumor burden and presence of symptoms; and drug-related factors, such as the availability of drugs and the predictive markers of efficacy. Anyway the algorithm proposed there is not enough easy to be used. In fact, even though it includes the most up-to-date treatment options in agreement with evidence-based medicine, it does not let the oncologists find the optimal sequence easily.

This algorithm starts with a stratification of patients for first-line treatment in four clinical groups, from 0 to 3, according to metastatic sites, resectability, potential of the patient to tolerate systemic therapy. For Group 3 patients, who do not need primarily a maximal shrinkage of metastases, fluoropyrimidine alone or in combination with bevacizumab is proposed as first-line treatment. For the other patients, a sequence of treatment options is developed starting with oxaliplatin- or irinotecan-based regimens. The subsequent regimens used after progression are addressed by the previous combination with specific targeted drugs, including the anti-EGFR monoclonal antibodies (moAbs) and bevacizumab. However, among the treatment options included in this algorithm, which were studied in various clinical trials, just few achieved a benefit in overall survival.

In particular, to date no randomized Phase III trials are available for the comparison between fluorouracil, folinic acid, irinotecan (FOLFIRI) + bevacizumab versus FOLFIRI, so that the influence of bevacizumab on response rate, progression-free survival (PFS) and OS by this combination regimen has not been known yet. Furthermore, the combination of

oxaliplatin-based regimens with cetuximab showed no additional benefit in OS and some studies prompted some concerns about safety of this option, as reported in NORDIC VII and COIN trial [4,5]. The algorithm proposed by Schmoll *et al.* allows the development of some sequences composed by four lines of treatment by the delay of targeted agents delivery. Anyway no evidences of long-term benefit are documented by the increase of the number of treatment lines.

All these reasons induced us to propose a different way to identify the optimal sequence for salvage therapy in mCRC patients (Figure 1). To achieve this goal, we selected only those Phase III trials that obtained a clear benefit in PFS and/or OS by the addition of targeted agents to standard doublet chemotherapeutic regimens (i.e., fluorouracil, folinic acid, oxaliplatin [FOLFOX] and FOLFIRI) and regorafenib alone, when chemotherapy may not give further benefit. Since irinotecan- and oxaliplatin-based doublets are similar in terms of survival end points, a classification of the treatment sequences according to first-line chemotherapeutic backbone drug is not really useful [6]. To date, the main factor conditioning the first-line treatment decision-making is KRAS and NRAS mutation status. Even BRAF mutation seems to have a role as a predictive factor for the efficacy to anti-EGFR moAbs, but its prognostic role appears predominant. After the detection of somatic RAS gene mutations, each oncologist is able to know if a mCRC patient could have a benefit from the combination of the anti-EGFR moAbs with standard chemotherapy doublets [7]. In fact for RAS wild-type patients the benefit in OS was observed for both these two combinations: FOLFIRI + cetuximab, as showed in the CRYSTAL trial [8], and FOLFOX + panitumumab, as reported in the PRIME trial after the specific evaluation of both KRAS and NRAS

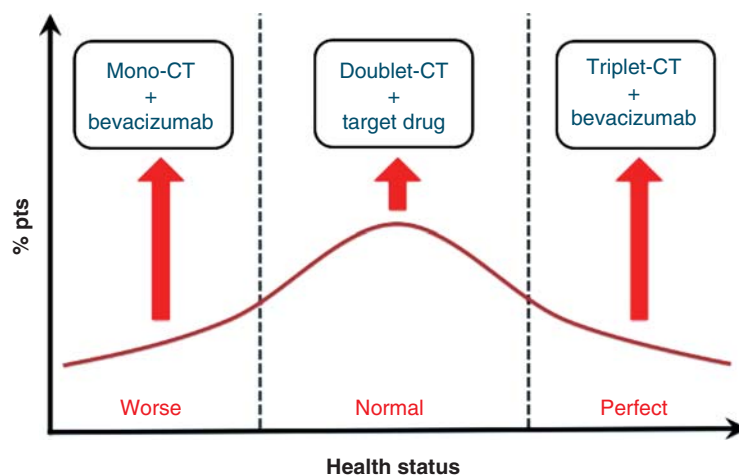


Figure 2. Perspectives for salvage first-line treatment options according to the general health status.

gene mutations [9]. These clear efficacy results are supported by the lack of consistent crossover in these anti-EGFR-based trials, since a minority of patients in the control arm received cetuximab or panitumumab as subsequent treatment.

Conversely, the FOLFOX/XELOX + bevacizumab regimen showed an improvement of PFS only, not of OS [10]. Moreover, FOLFIRI + bevacizumab has not been compared yet with FOLFIRI alone in a Phase III trial. For this reason in KRAS or NRAS-mutated mCRC patients, who cannot receive anti-EGFR moAbs, FOLFOX + Bevacizumab represents the best option, instead of FOLFOX or FOLFIRI alone, because it can delay progression even though it cannot reduce the risk of death.

The choice of the second-line treatment is mainly influenced by the scant evidences about a re-challenge with the same chemotherapeutic regimen. The re-challenge with Bevacizumab has been showed to give further benefit [11]. For the re-challenge with Cetuximab some intriguing results have been reported till now, but strong evidences are not still available [12]. On these bases, we propose FOLFOX + bevacizumab for those RAS wild-type patients who received FOLFIRI + cetuximab as first-line treatment, and FOLFIRI + aflibercept after first-line treatment with FOLFOX + panitumumab. The first second-line option is supported by the results from E3200 trial, which obtained survival benefit through the addition of bevacizumab to oxaliplatin-based treatment in those patients who did not receive bevacizumab before [13]. The latter option finds a support in the VELOUR trial, which reported an OS benefit when aflibercept was added to FOLFIRI after a previous treatment with an oxaliplatin-based regimen [14].

In RAS-mutated mCRC patients, who received an oxaliplatin-based regimen plus bevacizumab as first-line treatment, two options are available on the basis of evidence-based findings from Phase III trials with OS benefit. These chances include both FOLFIRI + aflibercept according to the VELOUR trial's results and FOLFIRI + bevacizumab as highlighted by the

ML18147 trial [11,14]. However, in ML18147 trial the use of bevacizumab together with FOLFIRI achieved a benefit in OS. Conversely, in VELOUR trial the aflibercept did not add benefit in OS in the subgroup of those patients treated previously with bevacizumab, since the HR for death was 0.862 (95% CI: 0.673 – 1.104). HR for progression showed significant improvement through aflibercept in the same subgroup of patients (HR: 0.661 [95% CI: 0.512 – 0.852]). For this reason, in patients with RAS mutation the difference of results according with the previous treatment with bevacizumab must be taken into account. Recently an update of VELOUR trial has been published reporting the results of prespecified subgroup analysis. The combination of aflibercept with FOLFIRI in patients with mCRC treated with oxaliplatin induces benefit across the specified patient subgroups, including both the subgroups of patients treated with or without prior bevacizumab [15].

Anyway the choice between these two second-line options in RAS-mutated patients could be properly addressed by the time of progression from first-line treatment with bevacizumab. In fact, if an early progression arises during the treatment with an oxaliplatin-based regimen with bevacizumab, a switch to FOLFIRI + aflibercept is a reasonably more appropriate option than bevacizumab continuation.

If these possible sequences of first- and second-line treatments could be carried out, a further effective treatment opportunity with a targeted drug is now possible. In fact regorafenib, a BRAF inhibitor, showed an OS benefit over placebo in the Phase III CORRECT trial for unselected patients who previously were treated with irinotecan- and oxaliplatin-based regimens. Till now no other Phase III trials provided an OS benefit in these different settings [16].

This new simplified algorithm we propose here does not eliminate the previous one proposed by Schmoll *et al.* In fact, while that one includes all the options available now for the sequence of salvage chemotherapy, our flow chart

provides a tool for the identification of the optimal sequential strategy of targeted agents and chemotherapy to achieve the goal of an OS prolongation in mCRC patients. To obtain this purpose, only those Phase III trials with strong evidence of survival benefit were taken into account. However, the plan of the optimal sequence does not exclude that alternative suboptimal treatment options are searched if particular conditions arise. Moreover, it could be useful to design a new clinical trial for comparison of the different sequences of treatment strategy.

In the next future, the perspective for the choice of first-line treatment in the overall population of mCRC patients includes the evaluation of the general health status (Figure 2). Those patients with worse health status or advanced age (> 70 years) could benefit from a combination of fluoropyrimidine-based monochemotherapy plus bevacizumab. This combination was showed to be more effective in term of PFS compared with fluoropyrimidine alone, as reported in MAX and AVEX trials [17,18].

For patients with normal health status, the first-line treatment should include an oxaliplatin- or irinotecan-based doublet in combination with a target agent such as anti-EGFR or anti-VEGF, taking into account the RAS mutation status. In this case, the sequence of treatment should follow the flow chart proposed here.

Finally young patients in perfect health status could have a further benefit in term of PFS from a triplet chemotherapy, such as FOLFOXIRI + bevacizumab. Indeed this combination was showed to reach longer PFS than that achieved with FOLFIRI + bevacizumab, according to the results of TRIBE trial [19]. This trial provides interesting results, above all for the long duration of induction treatment, that is, 12 cycles, and the possibility of continuation of maintenance treatment with 5-FU and bevacizumab.

A further support to this proposal derives from the recent published data about FIRE-3 trial, which compares the combination of chemotherapy and bevacizumab with the same chemotherapy and cetuximab in KRAS wild-type mCRC patients [20]. Although these results have not reached

a high level of evidence yet, the use of cetuximab confers a better OS compared to bevacizumab without difference in PFS. These findings are controversial and should be better clarified with further studies, since PFS and OS were not the primary end points in this trial. Further trials are ongoing to explore the comparison between anti-EGFR and anti-VEGF moAbs, such as PEAK and CALGB trial. When the results from these trials will be definitively published we could have a further confirmation about the pertinence of our proposal. The actual decision-making of first-line treatment in RAS wild-type patients should be only based on CRYSTAL and PRIME trial with respect to NO16966 trial results.

In conclusion, for mCRC patients who do not have a clear perspective for a resection of distant metastases, an optimal sequence of salvage therapy could be planned, including chemotherapy and targeted agents. An accurate evaluation of the general health status and age is the fundamental factor to lead the choice of the most proper combination of chemotherapeutic regimens and moAbs for first-line treatment. mCRC patients with normal health status could receive doublet chemotherapy in combination with anti-EGFR or anti-VEGF moAbs according to RAS mutation status. We previously stated that the choice among drugs addressing these two targets, EGFR and VEGF, depends on various clinical and molecular factors [21]. However, the most recent evidences about the selection of patients by KRAS and NRAS mutations allowed us to propose a new simplified algorithm to find the optimal sequence of salvage therapy as well as we tried to get the Ariadne's thread in a labyrinth.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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