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EDITORIAL

# Angiogenic inhibitors for older patients with advanced colorectal cancer: Does the age hold the stage?

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## Abstract

Although major progress has been achieved in the treatment of advanced colorectal cancer (CRC) with the employment of antiangiogenic agents, several questions remain on the use of these drugs in older patients. Since cardiovascular, renal and other comorbidities are common in the elderly, an accurate assessment of the patients' conditions should be performed before a treatment decision is made. Since most CRC patients enrolled in clinical trials testing antiangiogenic drugs were aged < 65 years, the efficacy and tolerability of these agents in elderly patients has not been adequately explored. Data suggest that patients with advanced CRC derive similar benefit from bevacizumab treatment regardless of age, but the advantage of other antiangiogenic drugs in the same class of patients appears more blurred. Literature data suggest that specific antiangiogenic-related toxicities such as hypertension or arterial thromboembolic events may be higher in the elderly than in the younger patients. In addition, it should be emphasized that the patients included in the clinical studies discussed herein were selected and therefore may not be representative of the usual elderly population. Advanced age alone should not discourage the use of bevacizumab. However, a careful patients' selection and watchful monitoring of toxicities are required to optimize the use of antiangiogenics in this population.



**Key words:** Advanced colorectal cancer; Bevacizumab; Elderly; Antiangiogenesis; Chemotherapy

**Core tip:** Although promising, limited evidence supports the use of antiangiogenic drugs to treat elderly colorectal cancer patients, that also may have increased toxicities compared to younger subjects. However, advanced age *per-se* should not discourage the use of these drugs. Since older patients constitute a heterogeneous population in terms of overall health status and comorbid conditions, a careful patients' selection and a watchful monitoring of potential treatment-related side effects are recommended to optimize the use of angiogenesis inhibitors in this population.

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## INTRODUCTION

Whilst most of cancer diagnosis and deaths occur in older

subjects[1,2], three major factors are shaping the scenery in which the advanced colorectal cancer (CRC) is managed in all developed countries. Firstly, people are steadily aging and cancer incidence and prevalence are rising among senior citizens[3,4]. Secondly, the incorporation of new drugs within more complex treatment strategies has raised the median survival of CRC patients to unprecedented figures of 30 mo[5]. Lastly, more often than before, aggressive surgery and other regional approaches are performed with curative intent in older oligometastatic patients. As a result, the soaring demand for care of senior with CRC is likely to further increase. Although many elderly cancer patients have concurrent chronic disorders or morbidities requiring medical treatment and present with diminished organ functions, impairment of daily vital activities or minor cognitive deficits, the majority of them are treated with systemic chemotherapy and/or biologics[6,7]. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) inhibitor, has proven efficacy when added to systemic chemotherapy regardless CRC patients' age in first or subsequent lines of therapy[8]. Specific data regarding its use in the older population are limited. Nevertheless, one out of three patients receive bevacizumab beyond 65 years of age[9]. Chronological age is still a major barrier that limits the proposal of standard treatment options to the elderly and the harm-to-benefit risk is particularly challenging when treating with noncurative intent[10]. However, patients' chronologic age does not always reflect their overall health status and older patients are highly heterogeneous because of dissimilar types and grades of concurrent morbidities. All these reasons may increase the difficulty in choosing the most appropriate treatment. Besides, advanced age is a common exclusion criteria to be recruited in clinical trials so that elderly patients have been underrepresented in CRC studies and the few included, usually representing less than 15% of the whole trial population, are highly selected. Despite recent studies have demonstrated the usefulness of a comprehensive geriatric assessment, its adoption in the clinical practice is still limited. Herein, we present the latest data regarding the use of antiangiogenic drugs in older CRC patients, specifically focusing at safety issues and efficacy results of landmark clinical studies.

## THE IMPORTANCE OF ANGIOGENESIS IN COLORECTAL CANCERS

Angiogenesis is a cornerstone of tumor mass expansion. In response to hypoxia, the activation of hypoxia-inducible factor (HIF) triggers the expression of VEGF, one of the most important proangiogenic molecules[11], and its numerous isoforms[12]. In order to grow, CRCs need to continually acquire new blood supplies throughout the neoangiogenetic process, the formation of new capillaries rising from the splitting of existing ones. In the same way as in other solid tumors, angiogenesis plays an important role in CRC progression and metastatization, and its therapeutic inhibition has become a key component of anticancer treatment. Bevacizumab, the first Food and Drug Administration-labeled antiangiogenic antibody, was been approved for clinical use after showing efficacy in combination with chemotherapy in CRC patients. Still, many issues are unresolved, such as the lack of validated predictive biomarkers[13], the reasons for initial or acquired resistance to VEGF-inhibitors, and the uncertainty surrounding the opportunity for further antiangiogenic treatment beyond tumor progression. The study of non-endothelial cells involved in the neoangiogenesis through the production of growth factors or the modulation of cell-matrix interactions is of interest[14]. For example, pericyte recruitment, a key phenomenon in the neovascular formation that is regulated by platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and angiopoietin/Tie2, may be blocked by a number of novel antiangiogenic multitarget tyrosine kinase inhibitors (TKI), including sunitinib, sorafenib, and regorafenib.

## ANTIANGIOGENIC DRUGS IN OLDER CRC PATIENTS: FRIENDS OR FOES?

Elderly patients who received 5-FU either alone[15] or in combination with irinotecan[16] or oxaliplatin[17] had similar survival benefits when compared to younger patients, although they may suffer higher rates of specific toxicities[18]. Despite these reassuring data, clinicians tend to be conservative when considering systemic therapy in the elderly, either not proceeding or upfront reducing chemotherapy doses[19]. The use of antiangiogenic drugs in patients with advanced CRC is supported by strong scientific evidence and common bevacizumab-related side-effects have been extensively described. Although its treatment effect does not seem to be influenced by patients' age, specific outcome data on the use of bevacizumab in elderly patients derive from retrospective subpopulation analyses of large randomized controlled trials[20], small phase 2 studies[21-25], non-randomized community-based registries[26-29], or cohort studies[30,31], and have been summarized elsewhere[32].

In all, available data suggest that medically fit older CRC patients exposed to bevacizumab achieved the same benefits compared to younger patients[33,34], with a similar toxicity profile, except for a significant increase in arterial thrombosis[20].

More recently, the randomized phase Ⅲ AVEX study has prospectively evaluated the additive effect of bevacizumab in the older CRC population. In this trial, 280 elderly patients (median age 76 years, range 70-87 years) received either capecitabine alone (1000 mg/sqm *bid* days 1-14, q21) or combined with bevacizumab (7.5 mg/kg). Over 90% of the enrolled patients had ECOG PS $\leqslant$ 1. Clinically significant cardiovascular disease was among exclusion criteria. The simultaneous use of bevacizumab produced significant increase of median PFS (9.1 mo *vs* 5.1 mo, HR = 0.53). Interestingly, the RR was twice as high in the combination arm (19.3% *vs* 10.0%) while the safety profile was similar to that previously reported

when testing the combination of capecitabine and bevacizumab. Although the trial was underpowered to detect differences in survival, median OS was longer in the experimental arm (20.7 mo *vs* 16.8 mo, HR = 0.79)[35]. Nevertheless, senior patients are usually underrepresented in well-designed randomized clinical trials and those enrolled, with good PS and few comorbidities, may not represent the average elderly population. This is the main reason why although skilled in dealing with hypertension, proteinuria, vascular thromboembolic events, bleeding, congestive heart failure, gastrointestinal perforation, and wound-healing complications, most oncologists fear that frequency and intensity of those side-effects might be greater in older CRC patients and the benefit-to-risk ratio less favorable in the general practice.

## ANTIANGIOGENIC-INDUCED HYPERTENSION IN OLDER CRC PATIENTS

Epidemiological data collected over the last 30 years have demonstrated that the increasing prevalence of hypertension with age is linked to the combination of increased arterial stiffness, neurohormonal and autonomic dysregulation, and the progressive decline of renal function[36-38]. In the elderly, hypertension *per-se* is a significant risk factor for cardiovascular morbidity and mortality. The increase of blood pressure, the most frequent side-effect of systemic inhibition of VEGF signaling, may occur at any time during therapy and it is often associated with asymptomatic proteinuria that spontaneously resolves as soon as treatment ends[39-41]. According to a retrospective review that found an incidence of increased blood pressure of 29% in patients aged > 75 years *vs* 11% in those aged 65 to 75 years[42], advanced age has to be considered a risk factors for the development of bevacizumab-induced hypertension.

Since hypertension-related disorders, such as stroke or myocardial infarction, have been reported with a higher incidence in older patients, a careful home-based daily blood pressure monitoring is suggested during the whole treatment period[43,44]. Older patients developing elevated systolic blood pressure may be at particular risk for complication, since this event is even more associated with cardiovascular morbidity and mortality than diastolic hypertension[45].

Management of antiangiogenic-induced hypertension in older patients usually requires standard treatment and should be promptly adopted[46]. An 1.5%-3.4% 60-d mortality rate has been reported for CRC patients older than 65 years who developed or worsened preexisting hypertension during exposure to bevacizumab in the BRITE trial[26]. How to manage this side-effect has been largely discussed. The upfront use of angiotensin-converting enzyme inhibitors is supported by their ability to counteract bevacizumab-induced plasminogen activator inhibitor-1 and this intervention is widely adopted in the general population[47]. However, the optimal treatment strategy in the elderly population is unconfirmed and the use of diuretics may be preferred. The JNC-7 hypertension guidelines suggested the use of thiazidic diuretics either alone or in combination as initial therapy for older patients[48]. Importantly, the Hypertension in the Very Elderly Trial study showed that the use of indapamide, either alone or combined with perindopril,significantly reduced the incidence of stroke and heart failure even in patients aged ≥ 80 years[49,50]. Although the long term benefits from antihypertensive drug treatment may be relevant for elderly subjects, fit octogenarians with bevacizumab-induced hypertension and a reduced life-expectancy should achieve benefits from intervention as soon as possible. Actually, immediate treatment compared with delayed treatment reduced the occurrence of stroke by 28% and cardiovascular complications by 15% in the Systolic Hypertension in Europe extension trial[51].

Interestingly, retrospective studies have consistently reported a better survival outcome for patients who had developed bevacizumab-induced hypertension[52,53]. Inhibition of VEGF signaling may induce a rapid increase in blood pressure, suggesting that hypertension could be a useful pharmacodynamic surrogate marker of VEGF activity[54]. However, a retrospective analysis of seven randomized phase Ⅲ trials with bevacizumab in different types of metastatic cancers, showed that the correlation between the vascular side-effect and the clinical outcome was shaggy, since the development of bevacizumab-induced hypertension inconsistently predicted longer PFS and OS[55].

## OTHER CARDIOVASCULAR SIDE-EFFECTS: VENOUS THROMBOEMBOLIC EVENTS, ARTERIAL THROMBOEMBOLIC EVENTS, BLEEDING, AND HEARTH FAILURE

Older cancer patients are at increased risk for vascular thrombosis[56-59], More specifically, placebo-controlled trials confirmed that the risk for venous thromboembolic events (VTE) is higher when the patient is aged ≥ 65, diagnosed with gastrointestinal malignancies, or receiving antiangiogenic drugs[60]. The average risk for VTE among ambulatory patients undergoing chemotherapy exceeds 12% over one year after treatment initiation, being the use of bevacizumab a potential risk factors[61,62]. Nevertheless, a pivotal randomized trial enrolling over 800 CRC patients showed similar VTE incidences (19.4% *vs* 16.2%) regardless of bevacizumab exposure[63]. In addition, a large pooled analysis showed similar incidence of all-grade VTE among CRC cancer patients exposed to bevacizumab (10.9%) compared to the control group (9.8%), with a similar median time to VTE of 2.2 mo *vs* 1.7 mo[64]. Moreover, a real-practice observational study enrolling 637

advanced CRC patients reported a VTE incidence rate of only 4% in those aged over 65 years[9]. Taking into account these data, it remains to be clarified if thromboprophylaxis should be considered for all cancer patients[65,66], or limited to older patients with limited mobility[67].

Some concerns surround the use of antiangiogenic drugs and the risk of arterial thromboembolic events (ATE) in elderly patients, many of whom may have preexisting cardiovascular risk factors or known cardiovascular disease. Although the event-related death rate remained low, the overall incidence of ATE is close to 4% for advanced CRC patients receiving bevacizumab, and less than 2% in those receiving chemotherapy alone. Significant risk factors for ATE are the history of previous VTE (HR = 2.17) and the older age (HR = 3.65)[43]. In the BRITE (Bevacizumab regimens: investigation of treatment effects and safety) study, the rate of ATE was identical in patients aged < 65 years old (1.4%) compared with those aged between 65-74 years (1.4%), but it was significantly higher in patients aged > 75 years (4.8%). The analysis of the MAX AGTGC showed that bevacizumab was associated with a modestly higher risk of ATE, but the safety profile was similar regardless of age, previous history of ATE or other vascular risk factors[68]. Whether the use of low-dose aspirin may be beneficial in reducing the rate of cardiovascular events in cancer patients as well as in the general population[69] is plausible but unproven.

Atrial fibrillation and coronary artery disease are prevalent with increasing age. Patients on antithrombotic treatment for those conditions should be carefully monitored since bleeding is another potentially severe bevacizumab-induced adverse event[70]. Whether patients on anticoagulant or antiplatelet therapy could be safely treated with bevacizumab is unclear[71]. Patients receiving full-dose anticoagulants have a limited risk of severe bleeding (< 1%) regardless concomitant antiangiogenic exposure[64] and advanced CRC patients treated with bevacizumab while on low-dose acetylsalicylic acid experienced similar rates of bleeding compared to the others (11% *vs* 14%, $P = 0.13$)[72]. Nonetheless, because of the retrospective nature of the data, a note of caution should be used in patients who are candidates for bevacizumab and are receiving full-dose anticoagulation or antiplatelet therapy.

A large population-based study evaluated the risk of cardiovascular events (ATE, cardiac death, cardiomiopathy or congestive hearth failure) among 6803 older CRC patients receiving bevacizumab and chemotherapy[73]. Median age of included patients 73 years and a fifth were 80 years or older. The cohort study confirmed that the cardiovascular risk of bevacizumab use is modest, reporting no clear association between bevacizumab use and cardiovascular events and a lower than expected increased risk for ATE (HR = 1.82). Accordingly, a large Surveillance, Epidemiology and End-Results Medicare analysis suggested that older CRC patients treated with bevacizumab do not experience an increased risk of cardiovascular adverse events compared with patients not treated with bevacizumab[74]. Nevertheless, in the presence of ECgraphic signs of asymptomatic ischemia or in the case of angina or myocardial infarction, antiangiogenic treatment should be immediately discontinued[75].

## ANTIANGIOGENIC-INDUCED PROTEINURIA AND THE AGING RENAL FUNCTION

Animal models showed that VEGF is critical in the regulation of renal vascular network and that perturbations of VEGF expression may damage cellular architecture and function, leading to hypertension and proteinuria[76]. Clinical data confirmed that bevacizumab may induce thrombotic microangiopathy by reducing glomerular VEGF, and the presence of podocyturia in patients treated with antiangiogenic drugs suggested that to quantify urinary podocyte excretion may be a highly sensitive indicator of glomerular damage[77]. A retrospective chart review showed that only 1.6% of patients developed severe proteinuria during bevacizumab administration; baseline chronic kidney disease and the development of hypertension significantly correlated with its occurrence ($P < 0.01$)[78]. Indeed, a number of factors may increase the chance for antiangiogenic-induced renal toxicity among elderly patients, including age-related renal structural changes and limited nephron reserve, baseline comorbid conditions such as hypertension, diabetes, or cardiovascular diseases, and the use of polypharmacy or potentially nephrotoxic agents[79]. Since renal failure is initially asymptomatic, a decreased glomerular filtration rate (GFR) or/and an increased albumin-to-creatinine ratio (albuminuria > 30 mg/g of creatinine) may suggest initial kidney damage and forecast later kidney failure[80]. Therefore, an accurate assessment of renal function is essential during antiangiogenic therapy, especially for elderly people at risk of developing renal dysfunctions. In the clinical practice, elderly CRC patients should be accurately screened for proteinuria before starting bevacizumab or other antiangiogenic drugs by dipstick urine analysis, and a 24-h urine collection is suggested when a 2+ or greater urine dipstick reading is detected. The frequency of the test during the course of therapy should be customized.

## THE ISSUE OF THE INTACT PRIMARY TUMOR IN THE ELDERLY

Metastatic CRC patients with intact primary tumor seldom require palliative treatment while on systemic upfront chemotherapy[81,82]. Although bevacizumab has been associated with a 2% incidence of bowel perforation and a possible increased risk may exist in those with intact primary tumor, upfront noncurative intestinal resection of asymptomatic metastatic CRC patients may be avoided[83,84]. Among 1953 bevacizumab-treated patients included in the BRITE study, 37 (1.9%) developed gastrointestinal perforation[85]. Twenty-six of these cases (70%)

occurred within the first 6 mo since treatment start, with a median time to event of 3.5 mo. The presence of an intact primary tumor (HR = 2.0) or having received radiotherapy (HR = 2.1) were significant risk factors for perforation. Interestingly, the study failed to show higher rates of perforation in patients with history of peptic ulcer disease, diverticulosis, or in those who chronically used aspirin (≥ 325 mg/d) or other anti-inflammatory drugs. Moreover, the event was less frequently reported among those aged > 65 (1.1%) compared to those younger than 66 (2.6%) with an HR of 0.49. Similarly, in the MAX AGTGC trial, no gastrointestinal perforations were reported in CRC patients aged over 75 years exposed to bevacizumab, but 4 cases noted in the younger cohort[34]. Alongside, the rate of intestinal perforation was 3.6% among 223 patients with unresected primary tumor compared to 1.2% among 1373 patients who had been previously resected in the First BEAT study, although an age breakdown was not available[86].

## IS MAINTENANCE WITH BEVACIZUMAB USEFUL IN THE ELDERLY?

Showing a greater benefit if bevacizumab was given until disease progression, results of No. 19966 trial suggested a possible role of antiangiogenic drugs in the maintenance phase[87]. In addition, a number of randomized studies have been conducted to formally assess the role of bevacizumab as maintenance agent[88]. In the MACRO (Maintenance in Colorectal) trial, 480 CRC patients were randomly assigned to receive six cycles of bevacizumab, capecitabine, and oxaliplatin every 3 wk followed by bevacizumab either alone or combined with the same chemotherapy regimen until progression[89]. A slightly longer median PFS was reported in the combination arm (10.4 mo *vs* 9.7 mo), although burdened by a higher rate of severe sensory neuropathy (26% *vs* 8%) and HFS (13% *vs* 7%). Up today, the role of bevacizumab as maintenance therapy is still controversial[90] and additional randomized maintenance studies, such as the AIO KRK0207, the CAIRO-3, the FFCD Prodige 9, and the SAKK 41/06 trial, will soon clarify the point. Waiting for more substantial data, small non-randomized studies have investigated the role of bevacizumab as maintenance therapy. In the BOXE study, 44 elderly CRC patients with median age of 74 years (range 70-84 years) received XELOX and bevacizumab at the dose of 7.5 mg/kg every 3 wk for up to 8 cycles followed by maintenance with single-agent bevacizumab at the same dose[23]. The trial suggested that the combination is feasible and safe in the elderly population and a maintenance with bevacizumab may be offered to responding patients with the intent to prolong PFS.

## NOVEL ANTIANGIOGENIC ANTIBODIES: DO THEY FOSTER HOPE FOR OLDER PATIENTS?

Among the more promising novel drugs, aflibercept and ramucirumab deserve to be presented. Aflibercept, a humanized protein composed of the extracellular domains of VEGFR-1/2 fused onto the constant region of human IgG, was specifically designed to bind VEGF-A, VEGF-B, and PIGF. VELOUR is a phase Ⅲ placebo-controlled trial that tested the combination of FOLFIRI and aflibercept for advancer CRC patients that had failed an oxaliplatin-based first-line therapy[91]. The primary endpoint of the trial was OS; secondary endpoints included PFS, overall response rate, and safety. Median age of patients treated with aflibercept was 61 years (range 21-82 years). Patients exposed to aflibercept had longer median OS (13.5 mo *vs* 12 mo, HR = 0.81) and PFS (6.9 mo *vs* 4.6 mo, HR = 0.75) compared to those who were not. However, the toxicity profile was not negligible. While the increases in hypertension and proteinuria were expected as class side-effects, patients receiving aflibercept reported unforeseen significantly higher rates of severe diarrhea (19.3% *vs* 7.8%), fatigue (16.9% *vs* 10.6%), stomatitis (13.7% *vs* 5.0%), and neutropenia (36.7% *vs* 29.5%). This should be considered when offering the treatment to older subjects because they may have increased toxicity when treated with second-line FOLFIRI. Ramucirumab, a VEGFR-2 inhibitor that has shown efficacy in second line gastric cancer, is being studied combined with FOLFOX in the RAISE trial[92]. In this phase 3 study, over 1000 CRC patients that have previously failed first-line FOLFIRI and bevacizumab are randomized to FOLFOX or FOLFOX plus ramucirumab (8 mg/kg) every 2 wk. Results are eagerly awaited.

## IS THERE A ROLE FOR ORAL TKI IN CRC?

In the last few years a number of small molecule inhibiting the VEGF pathway have been tested for advanced CRC patients with disappointing results. A phase Ⅲ randomized trial compared FOLFIRI plus sunitinib (37.5 mg every 4 out of 6 wk) to FOLFIRI alone in 768 patients with advanced disease[93]. At the second planned interim analysis the trial was stopped because the data monitoring committee found that the futility boundary had been crossed and more toxicity events were reported in the experimental arm, including neutropenia and severe diarrhea. Final results confirmed no differences in median PFS (7.8 mo *vs* 8.4 mo, HR = 1.05) and a more severe toxic profile.

Vatalanib (PTK787/ZK222584) is an antiangiogenic TKI that blocks VEGFR-1, 2, and 3 by acting as a competitive inhibitor at the adenosine triphosphate–binding site of the receptor kinase. Two randomized, placebo-controlled, large phase 3 trials studied the role of vatalanib in CRC patients treated upfront or in second-line setting[94,95]. The CONFIRM-1 study showed that the addition of vatalanib to FOLFOX-4 had no impact on median PFS (7.7 mo *vs* 7.6 mo, HR = 0.88) or OS (21.4 mo *vs* 20.5 mo, HR = 1.08) compared with FOLFOX-4 alone as first-line treatment. Similarly, the CONFIRM-2 trial compared FOLFOX plus vatalanib or placebo in

855 advanced CRC patients after the failure of a first-line treatment. Again, marginal differences in terms of PFS (5.6 mo *vs* 4.2 mo, HR = 0.83) were registered with identical survival results (OS 13.1 mo *vs* 11.9 mo). In both trials, more gastrointestinal toxicities, dizziness, anorexia, pulmonary embolism and hypertension were reported in the vatalanib group. Taken together, the results of these trials suggested the uselessness of vatalanib for CRC patients, although a PFS advantage (HR = 0.65) was noted in those patients with higher lactate dehydrogenase baseline values.

The combination of oxaliplatin-based chemotherapy and cediranib, a potent inhibitor of the VEGF family receptor tyrosine kinases with multitarget TKI properties, has been extensively tested. The HORIZON Ⅲ trial compared FOLFOX plus cediranib (20 mg, daily) or bevacizumab in over 1400 advanced CRC patients in first-line setting[96]. The study did not meet its primary endpoint and the group exposed to cediranib experienced more toxicity. In addition, the randomized HORIZON Ⅱ trial showed a marginal improvement in median PFS (8.6 mo *vs* 8.3 mo) when cediranib was added to FOLFOX or XELOX (*vs* placebo), without overall survival differences[97]. A third randomized trial compared the outcome of advanced CRC patients receiving FOLFOX combined to bevacizumab or cediranib at two different daily doses (20 or 30 mg)[98]. The trial revealed reduced median PFS for the low-dose cediranib group compared to the standard arm (5.8 mo *vs* 7.2 mo). Similar outcome results and increased toxicity rates were noted when comparing the high-dose cediranib arm to the standard arm.

After all these unsatisfactory data, regorafenib renewed the interest in oral VEGF inhibitors for CRC patients. Regorafenib is an oral multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor TK[99]. In the randomized double-blind, placebo-controlled CORRECT study 760 advanced CRC patients received regorafenib or placebo plus best supportive care after progression to all approved standard therapies[100]. Overall survival, the primary endpoint, was significantly increased from 5 to 6.4 mo. The most common regorafenib-related AE included fatigue (47.4%), HFSR (46.6%), diarrhea (33.8%), anorexia (30.4%), voice alteration (29.4%), hypertension (27.8%), mucositis (27.2%), and rash/desquamation (26.0%).

Currently, there are no available data on the specific use of these new drugs in the elderly, and trials designed specifically for older patients are strongly desirable.

## CONCLUSION

There is strong evidence for efficacy of bevacizumab and other antiangiogenic drugs in the treatment of advanced CRC. Older age *per-se* should not represent a stringent limit for the employ of these agents. However, the widespread clinical use of antiangiogenetics to treat elderly CRC patients should be cautious and always deserves a personalized benefit-to-risk evaluation along with a careful monitoring of cardiovascular and renal potential side effects.

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