Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013


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Received 29 April 2014; revised 19 June 2014; accepted 19 June 2014

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in Europe and worldwide, with the peak incidence in patients >70 years of age. However, as the treatment algorithms for the treatment of patients with CRC become ever more complex, it is clear that a significant percentage of older CRC patients (>70 years) are being less than optimally treated. This document provides a summary of an International Society of Geriatric Oncology (SIOG) task force meeting convened in Paris in 2013 to update the existing expert recommendations for the treatment of older (geriatric) CRC patients published in 2009 and includes overviews of the recent data on epidemiology, geriatric assessment as it relates to surgery and oncology, and the ability of older CRC patients to tolerate surgery, adjuvant chemotherapy, treatment of their metastatic disease including palliative chemotherapy with and without the use of the biologics, and finally the use of adjuvant and palliative radiotherapy in the treatment of older rectal cancer patients. An overview of each area was presented by one of the task force experts and comments invited from other task force members.

Key words: colorectal cancer, guidelines, geriatric assessment, older, SIOG, International Society of Geriatric Oncology

introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide [1]. There are marked differences in incidence trends between countries, with the total number of cases affected both by changes in individual risk at a given age (the age-standardized rate, ASR) and by the changing age demographic of the population.

In the USA, the ASR fell by over 30% between 1975 and 2010, perhaps reflecting lifestyle changes and the uptake of opportunistic screening [2], while rates in Canada, New Zealand and elsewhere were broadly stable [3]. However, over the same period the ASR in the UK, although remaining unchanged in women, rose by 30% in men [4]. Changes in ASRs do not, however,
represent the overall burden of disease. The age-specific risk rises markedly with age, and as mortality from heart disease and other non-cancer causes reduces, this leaves an elderly population at high risk of developing bowel cancer. This has major implications for the organization of cancer services: for example, in the UK, the number of new cases of bowel cancer diagnosed in patients >75 years rose by 30%, from 13,400 elderly patients in 1993 to 17,300 in 2010 [5]. And, even countries with a stable ASR may see a rising number of cases of CRC in the elderly.

Oncologists and surgeons managing patients with CRC must recognize that ~60% of their patients are >70 years of age and 43% >75 years [5], that these proportions may increase further, and that many of these older patients will have problems of frailty and comorbidity which demand careful patient assessment and, if necessary, individualized treatment approaches [6, 7].

Currently, the majority of patients with stage I or II CRC are treated and cured by surgery [8, 9]. For patients with stage III colon cancer, the standard treatment is surgery followed by adjuvant chemotherapy, whereas for those patients with metastatic CRC (mCRC) systemic chemotherapy alone or in combination with targeted biologics is usually the treatment of choice. Also, increasingly, patients with mCRC are managed within multidisciplinary teams (MDTs) and being considered for surgical resection of their metastatic disease wherever possible [10]. For patients with rectal cancer, treatment may involve surgery alone, preoperative short-course radiation therapy (SCRT), or chemoradiotherapy (CRT) with surgical resection followed by postoperative adjuvant chemotherapy in selected patients.

Comorbidity, functional dependency, and older age are associated with early postoperative mortality in patients with gastrointestinal malignancies, with 30-day postoperative mortality rates underestimating postoperative mortality in older patients [11]. The International Society of Geriatric Oncology (SIOG) previously recommended that CRC patients >65 years of age requiring surgery should undergo a preoperative whole patient evaluation of the most common physiological side-effects of aging, physical and mental ability, and social support [12]. Furthermore, for those patients assessed as having physical or psychological comorbidities, it was recommended that ‘a geriatrician was involved in patient management’ [12].

One of the major challenges is the physiological heterogeneity of the older patient population with frequent discrepancies between physiological and chronological age coupled with the additional complications of coexisting medical conditions and the potential psychological and social care issues alluded to above. Defining old or elderly patients is challenging. The patient’s biological age should ideally be established through a comprehensive geriatric assessment in order to aid therapeutic decisions. There is a paucity of clinical trial data for these patients in terms of their poor functional reserves, major comorbidities, and frailty. Indeed, there is a huge debate in the literature about how to define frail patients and how to differentiate frailty from comorbidity and disability [13–16]. Experts anticipate that, by distinguishing the fit from the more vulnerable older patients, treatment can be adjusted to maximize its effectiveness, avoid complications, and better meet the individual requirements of the older patient. It is against this backdrop that SIOG convened a task force meeting to review and update their existing recommendations for the treatment of older patients with CRC [12], based on recent publications and personal experience.

**methods**

The task force consists of 2 surgeons, 1 epidemiologist, 10 medical oncologists, 2 radiation oncologists, 1 geriatrician, and 1 statistician.

The key areas for discussion were structured under five headings:

- Patient assessment
- Surgery in older patients
- Adjuvant chemotherapy
- Palliative chemotherapy
- Rectal cancer

**patient assessment**

A geriatric assessment (GA) evaluates a patient’s functional status [activities of daily living (ADL), physical performance, and Eastern Cooperative Oncology Group/World Health Organization performance status], comorbidities, polypharmacy, nutritional status, cognitive function, emotional function (anxiety and depression), and social support. However, other key issues related to older patients are limited life expectancy, reduced treatment tolerance, and, in frail patients, different treatment goals. Regardless of objective measures of treatment toxicity, older patients, either frail or non-frail, may have different views about the acceptability of certain of the medical interventions proposed, and may arrive at different personal trade-offs in terms of the positive and negative impacts of such interventions. The question is how to address these issues in everyday clinical practice, with only limited evidence to aid decision-making.

The use of a GA is feasible in the oncology setting, with some domains associated with adverse outcomes [17]. Of four studies that examined the impact of such an assessment on treatment decisions [18–21], two [20, 21] judged the assessment to impact on 40%–50% of treatment decisions, mostly involving changes in the chemotherapy regimen. Components of the GA, such as age and functional status, are also associated with certain treatment modalities such as surgery alone [17]. However, a systematic review of seven frailty screening methods in older patients receiving surgery, radiotherapy (RT), or chemotherapy concluded that they had insufficient discriminatory power to refine patient selection [22]. The recommendation was that it might be beneficial for all older patients with cancer to receive a general GA [22], but that further research was required to elucidate the role of the GA in oncology [23].

Physical frailty increases the risk of major complications following surgery [odds ratio (OR) 4.1 (1.4–11.6)] in patients ≥75 (range 75–93) years [24], and is predictive for both complications and survival in patients ≥70 years following surgery [25, 26]. Older patients are also vulnerable to chemotherapy toxicity, and whereas frail patients are considered to be unfit to receive chemotherapy, non-frail patients with comorbidities may be considered for less intensive therapy. A prospective multicenter study showed at least 53% of older patients (mean age 73 years) receiving chemotherapy to experience at least one grade 3–5
toxicity, and that a risk stratification schema could be used to establish the risk of severe chemotherapy-induced toxicity in these patients [27]. Furthermore, changes in brain activation after chemotherapy have recently been linked to an increase in cognitive complaints in patients with breast cancer [28]. However, other issues that need to be addressed include remaining life expectancy and the impact of pretreatment optimization based on a GA. A Norwegian study which analyzed survival in all patients curatively resected for CRC over a 10-year period showed survival to increase substantially after the implementation of national management strategies. The improvements, however, were least for those patients with colon cancer and those >75 years of age with lymph node-positive disease; both possibly being a reflection of the age cut-off of 75 years for adjuvant chemotherapy in the previous Norwegian guidelines [29]. Current evidence supports evaluating elements of the GA, especially comorbidity, functional status, cognitive dysfunction, and frailty, which are consistently associated with adverse treatment outcomes in relation to both toxicity and mortality, in both the clinical trial and routine clinical practice settings. An assessment of cognitive function is essential in order to establish whether a patient is able to consent to and comply with, their treatment and follow-up.

The outcomes that need to be considered in relation to surgery and chemotherapy for older patients are presented in Table 1.

### Table 1. Treatment considerations for older patients with CRC

<table>
<thead>
<tr>
<th>Outcomes that need to be considered in relation to surgery</th>
<th>Outcomes that need to be considered in relation to chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Immediate postoperative morbidity</td>
<td>1) Toxicity (which can be divided into numerous subcategories)</td>
</tr>
<tr>
<td>2) Thirty-day postoperative morbidity and mortality</td>
<td>2) Completion of therapy</td>
</tr>
<tr>
<td>3) Length of stay</td>
<td>3) QoL</td>
</tr>
<tr>
<td>4) Discharge to nursing home</td>
<td>4) Functional status</td>
</tr>
<tr>
<td>5) One-year mortality</td>
<td>5) Progression</td>
</tr>
<tr>
<td>6) Short-term and long-term functional outcomes</td>
<td>6) Survival</td>
</tr>
<tr>
<td>7) QoL (short and long term)</td>
<td>7) Composite end points (overall treatment utility)</td>
</tr>
<tr>
<td>8) Survival</td>
<td></td>
</tr>
</tbody>
</table>

QoL, quality of life; CRC, colorectal cancer.

Surgery remains the cornerstone in the treatment of patients with CRC. The improvement in survival for patients with CRC over time has in large part been due to a decrease in postoperative mortality and, to a lesser degree, the resection of hepatic metastases in selected patients [30–35]. However, despite these improvements, the survival gain is smaller in older patients than in younger patients and the gap is widening [36–39]. Survival also varies substantially between countries [40, 41]. Not only do comorbidity and emergency surgery have a negative impact on survival, but age itself has been identified in several population-based studies as a negative prognostic factor [11, 42]. Malnourishment also impacts on outcome [43–45].

Decreased survival in older (≥75 years) patients post-surgery has mainly been attributed to differences in early mortality [46]. Older patients with CRC who survive the first year may have the same overall cancer-related survival as younger patients [47, 48]. Thus, the treatment of older patients with CRC should focus on perioperative care and the first postoperative year [48]. Indeed, if the data are corrected for the competitive risk of dying, older CRC patients respond well to different cancer treatments [48–50]. Manceau et al. concluded that older patients with rectal cancer undergoing surgery should receive the same treatment as their younger counterparts but with an adjustment of treatment strategy in the case of comorbidity, limited physiologic reserves, and emergency situations [50].

Currently, older patients undergoing surgery risk being undertreated, resulting in a worse oncological outcome [51], or overtreated, with the possibility of subsequent excess morbidity and mortality. Thus, it is important to optimize and individualize CRC surgery [52–54]. For example, a lower morbidity rate is seen if surgery is delayed following short-course RT [55, 56]. One of the specific requirements for achieving safe and effective surgical treatment is an explicit risk assessment as stated in the previous guidelines [12], with the specific recommendation that every older patient with CRC should be discussed by an MDT before the commencement of any therapy. Geriatricians are not typically members of MDTs [26, 54, 57]. However, there is clear evidence that the majority of older CRC patients can be safely treated in specialized centers where the expertise is available to provide the most favorable surgical treatment and care [57–61].

Also, where a GA is not feasible, quick screening tools for frailty can provide the most favorable surgical treatment and care [57–61].

Thus, the updated recommendations for CRC patients undergoing surgery are that:

- A protocol should be devised to identify those patients for whom a geriatrician needs to be involved and for whom comorbidity and frailty are a hazard.
- A formal GA should be considered and if this is not feasible, rapid screening tools for frailty should be used.
- A prehabilitation program should be considered, where necessary, which should include correction of malnutrition, optimization of cardiovascular and pulmonary comorbidities, as well as medication use.
- For patients requiring prehabilitation, major resection should be postponed and emergency surgery avoided.
- Emergency surgery should be kept to a minimum and, in the case of obstructive disease, alternative procedures such as the construction of a diverting stoma or stenting, if cure is not the aim, must be considered [63–65].
- Careful consideration should also be given to the consequences of the construction and siting of the stoma [66].
- The combination of an emergency procedure with a major resection or multimodality treatment within too short a time frame should be avoided [63, 65].
- Patients (especially high-risk patients) and their families need to be informed about the risks, possible functional impairment, and oncological outcome before consenting to a treatment plan.
- High-risk patients should be offered alternative options, ranging from no tumor-controlling treatment at all, to palliative treatment, through to full treatment. Ideally, the preferences of patients if serious complications occur should be discussed.
adjuvant chemotherapy

The benefits of 5-fluorouracil (5-FU)-based adjuvant chemotherapy for patients with stage III colon cancer are well established for both younger and older patients [67-71], although its use in the management of patients with stage II disease remains controversial [72, 73]. An important question is: can these benefits be extended beyond 5-FU/leucovorin (LV) in older patients with high-risk stage II or stage III colon cancer? Also, does the convenience of administration achieved by replacing intravenous 5-FU with the oral fluoropyrimidine capecitabine outweigh the problems seen in elderly patients with poor renal function and the issues of under or over compliance? It is anticipated that findings from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) colon cancer prospective pooled analysis in >10 500 patients with stage III colon cancer, from six trials (SCOT, PRODIGE, CALGB/SWOG C80702, TOSCA, HORG, and ACHIEVE), will help address some of the issues surrounding the use of oxaliplatin-based adjuvant therapy in older colon cancer patients. However, these results are not expected to be available until 2015/2016 [74].

Today, based on the results of three adjuvant studies (MOSAIC, NSABP-C-07, and XELOXA), oxaliplatin-based combination chemotherapy is considered to be a standard of care in patients with stage III colon cancer [8, 67, 72, 75-77]. In the MOSAIC trial, which compared FOLFOX4 with 5-FU/LV in 2246 patients with resected stage II (40%, 25% high-risk) and III colon cancer [8], the 6-year overall survival (OS) rates were 78.5% and 76.0% [hazard ratio (HR) 0.84, 95% confidence interval (CI): 0.71–1.00, P = 0.046], respectively, in favor of FOLFOX4 [67], with the benefit, attributable almost entirely to patients with stage III disease (5-FU/LV 68.7%, FOLFOX4 72.9%, HR 0.80, 95% CI: 0.65–0.97, P = 0.023). Subgroup analyses showed there to be no statistically significant benefit conferred by the addition of oxaliplatin in terms of disease-free survival (DFS) or OS for either stage II or older patients (70–75 years), although female patients 70–75 years had the same oxaliplatin benefit as younger patients [72]. Interestingly, the DFS and OS benefits in patients 70–75 years were similar to those of younger patients for the first 3 years of follow-up, but were lost later on due to deaths from other causes.

In the NSABP-C-07 trial, the addition of oxaliplatin to bolus 5-FU/LV (FLOX) improved DFS in patients with stage II/III colon cancer with the benefit still apparent after 8 years of follow-up (HR 0.82, 95% CI: 0.72–0.93, P = 0.002). OS was also significantly improved for patients <70 years of age receiving FLOX, compared with 5-FU/LV (HR 0.80, 95% CI: 0.68–0.95, P = 0.013). Patients ≥70 years failed to derive a statistically significant DFS or OS benefit from the addition of oxaliplatin. Indeed, those patients receiving FLOX had a poorer survival, which was attributed to toxicity [77].

Oxaliplatin is at least equivalent to bolus 5-FU/LV in the treatment of patients with stage III colon cancer [78], with improved outcomes when compared with 5-FU/LV in the X-ACT trial in patients ≥70 years [79]. In the NO16968 (XELOXA trial), 1886 stage III colon cancer patients were randomly assigned to receive XELOX or bolus 5-FU/LV [75]. The trial met its primary end point with patients receiving XELOX showing a DFS benefit (HR 0.80, 95% CI: 0.69–0.93, P = 0.0045), which increased over time and was coupled with a trend toward improved OS: a 3.4% difference in OS at 5 years. Furthermore, the trial showed that the efficacy benefits observed for XELOX were maintained although to a lesser degree in patients ≥65 and ≥70 years of age in contrast to the results from the MOSAIC and NSABP-C-07 trials [72, 77].

Analyses of six of the newer adjuvant regimens in the ACCENT database (C89803, X-ACT, NSABP-C-06, PETACC3, and the oxaliplatin combinations from the MOSAIC and NSABP-C-07 trials) showed none to be associated with significant efficacy benefits versus 5-FU/LV in 2575 patients ≥70 years [80]. The 2012 update of the ACCENT database, which included the mature data from the XELOXA trial, again showed no benefit for adjuvant combination therapy or oral fluoropyrimidine therapy over 5-FU/LV in terms of time to recurrence (TTR), DFS, and OS in patients ≥70 years, while those aged <70 years showed statistically significant benefits for all three end points [81, 82]. Analysis of the data from the three oxaliplatin trials only again showed patients <70 years of age to benefit from the addition of oxaliplatin in terms of TTR, DFS, and OS, while those aged ≥70 years did not (Table 2). However, a significant interaction by age was not seen, although for OS the interaction

<table>
<thead>
<tr>
<th>Table 2. Outcomes of experimental (combination or oral FU) versus control arm (IV 5-FU) by treatment and age [81]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
</tr>
<tr>
<td>HR</td>
</tr>
<tr>
<td>All trials</td>
</tr>
<tr>
<td>Age &lt;70 years (N = 11 953)</td>
</tr>
<tr>
<td>Age ≥70 years (N = 2575)</td>
</tr>
<tr>
<td>Interaction</td>
</tr>
<tr>
<td>Oxaliplatin-based</td>
</tr>
<tr>
<td>Age &lt;70 years (N = 5420)</td>
</tr>
<tr>
<td>Age ≥70 years (N = 1119)</td>
</tr>
<tr>
<td>Interaction</td>
</tr>
</tbody>
</table>

aValues <1 favor the experimental arm.
CI, confidence intervals; FU, fluorouracil; HR, hazard ratio; IV, intravenous.
had borderline statistical significance ($P = 0.05$). Overall, these findings suggest that the benefit of the addition of oxaliplatin to 5-FU/LV is restricted to patients aged <70 years. A more recent pooled analysis of individual patient data from four large, randomized, trials in patients with stage III colon cancer (X-ACT, XELOXA, NSABP-C-08, and AVANT), so far published only in abstract form, showed oxaliplatin-based therapy to provide a significant benefit over 5-FU/LV, regardless of age and comorbidity. However, even in this highly-selected, clinical trial patient population the benefit was modestly attenuated in patients ≥70 years of age [83]. In addition, there are potential concerns about the methodology used as it involves the indirect comparison of treatments that were not randomized against each other.

Another consideration that should be included in the decision-making is the potential for long-term toxicity from the use of oxaliplatin. Evidence in the literature shows that a significant number of patients report neuropathy-related symptoms for years after the cessation of therapy [84–86] (Table 3).

A number of studies coming from registries have also attempted to look at the use and outcomes of adjuvant chemotherapy in a ‘real-life’ setting. Overall, it becomes clear from these publications that older patients with CRC are undertreated in routine clinical practice, even though there is evidence that there is benefit to be had from adjuvant therapy in this setting [87–93].

Thus, based on the available data, it is difficult to arrive at a clear conclusion concerning the use of oxaliplatin-based adjuvant therapy in older patients. The assessment of remaining life expectancy without recurrence and its impact on cost/benefit ratio of adjuvant therapy in older patients needs to be considered. What is clear is that:

- XELOX and FOLFOX are considered to be standard treatment options for the adjuvant management of stage III colon cancer, but their use is of uncertain benefit in patients aged >70 years.
- In view of the potential for increased serious adverse events (AEs) associated with combination chemotherapy regimens, the choice of whether to treat older patients with oxaliplatin-containing combination therapy or fluoropyrimidine monotherapy should depend on the treating physician’s clinical judgment and the individual patient’s risk of recurrence. The gains from the addition of oxaliplatin are modest and most of the benefit is still conferred by the fluoropyrimidine.
- The use of fluoropyrimidine monotherapy, either 5-FU/LV or capecitabine, is an appropriate adjuvant treatment option for many patients ≥70 years.
- The benefit of adjuvant chemotherapy in the management of stage II colon cancer remains controversial for patients of all ages.

It should be emphasized that the adjuvant chemotherapy data discussed come from clinical trials in which the patients are not always representative of the older patients seen in everyday clinical practice.

**palliative chemotherapy**

Older patients with mCRC (median age 73–75) are grossly underrepresented in most chemotherapy trials, where the median age of patients is typically <65 years [94]. Furthermore, the improvement in OS for unselected patients with synchronous mCRC over time (from 1980–1985 to 2006–2008) is much more pronounced for younger patients [39]. Therefore, except for the few trials (FOCUS2, AVEX, and FFCD 2001–2002) that have specifically targeted older patients [95–97], statements such as ‘reasonably well tolerated’ and ‘effective’ are applicable only to the highly atypical older patients specifically selected for treatment with full-dose regimens in clinical trials. For example, both irinotecan and oxaliplatin in combination with fluoropyrimidines are well tolerated and effective in selected older patients [98]. Furthermore, a post hoc analysis of randomized trials comparing irinotecan and 5-FU showed that although

### Table 3. Univariate efficacy analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Patients, N</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI P (Wald test)</td>
<td>HR 95% CI P (Wald test)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>2418</td>
<td>0.68</td>
<td>0.61–0.76</td>
</tr>
<tr>
<td>≥70</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>480</td>
<td>0.77</td>
<td>0.62–0.95</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>1588</td>
<td>0.69</td>
<td>0.61–0.78</td>
</tr>
<tr>
<td>&gt;1</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>309</td>
<td>0.59</td>
<td>0.46–0.76</td>
</tr>
<tr>
<td>NCI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>1567</td>
<td>0.70</td>
<td>0.62–0.79</td>
</tr>
<tr>
<td>&gt;1</td>
<td>XELOX/FOLFOX versus 5-FU/LV</td>
<td>330</td>
<td>0.58</td>
<td>0.46–0.73</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; CCI, Charlson comorbidity index; CI, confidence intervals; HR, hazard ratio; LV, leucovorin; NCI, National Cancer Institute comorbidity index.
patients ≥70 years of age represented only 22.3% (range 16.8%–24.6%) of the trial populations, the benefit to risk was maintained in patients >70 years (Tables 4 and 5) [99]. A phase II trial in patients >70 years showed FOLFIRI to be well tolerated and effective in selected older patients with a performance status of 0 or 1, and with no evidence of geriatric syndrome [104]. Similar observations were made for oxaliplatin with only 20% (range 18%–22%) of patients ≥70 years (Table 6). The key question, however, is how and when do age and frailty tip the balance between longer survival and reduced symptoms, and death-hastened toxic effects and general interference with life in patients with mCRC receiving systemic chemotherapy?

Data are available from two randomized studies specifically designed to assess the impact of oxaliplatin- and irinotecan-based therapy in older mCRC patients in the first-line treatment setting. In the first of these, frail older patients entered into the prospective FOCUS2 trial [97] underwent a 117 item comprehensive health assessment (CHA) of their physical and nutritional status comprising four nurse-administered and four patient-completed modules [97]. A total of 459 patients (22% <70 years; 35% 70–75 years, and 43% >75 years) were randomized 1:1:1:1 to receive treatment with 5-FU/LV, simplified FOLFOX, capecitabine, or CAPOX (XELOX), at 80% of the standard drug doses [97]. Baseline clinical and CHA data were modeled against outcomes using a novel composite measure, overall treatment utility (OTU) at 3 months, which in patient terms was: with the benefit of hindsight, am I glad that I decided to receive this treatment. OTU was classified as good at 3 months if the clinician assessed the patient to have benefited from treatment, the patient was happy and there were no major toxicity issues, whereas OTU at 3 months was considered to be poor if the clinician assessed the treatment to be of no benefit, and the patient was unhappy, or was experiencing major toxicity or had died to their disease. The addition of oxaliplatin versus no oxaliplatin was associated with a non-significant improvement in PFS (median 5.8 versus 4.5 months; HR 0.84, 95% CI: 0.69–1.01, \( P = 0.07 \)). No difference in OS was observed. The risk of any grade ≥3 toxic effect was not significantly increased with oxaliplatin (38% versus 32%; \( P = 0.17 \)), but was higher for capecitabine than for 5-FU (40% versus 30%; \( P = 0.03 \)). A better OTU score at 3 months was strongly associated with improved PFS and OS (both \( P < 0.0001 \)). Univariate analyses showed one of the strongest predictors of OTU at 3 months to be allocation to treatment with oxaliplatin (all \( P < 0.01 \)). Overall, the data showed oxaliplatin-containing chemotherapy to be preferable to single-agent fluoropyrimidine therapy, although the primary (PFS) end point was not met. No advantage for capecitabine over 5-FU was observed in terms of patient quality of life (QoL). Thus, the FOCUS2 trial clearly showed that a baseline CHA holds promise as an objective predictor of treatment benefit in older patients.

The second of these studies, a phase III study of irinotecan-based first-line chemotherapy in mCRC patients ≥75 years

<table>
<thead>
<tr>
<th>Table 4. Patients according to age groups in pivotal randomized irinotecan-based combination chemotherapy trials [99]</th>
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</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Saltz et al. [100]</td>
</tr>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>% of all patients</td>
</tr>
<tr>
<td>Douillard [101]</td>
</tr>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>% of all patients</td>
</tr>
<tr>
<td>EORTC trial 40986 [102]</td>
</tr>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>% of all patients</td>
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<tr>
<td>FOCUS trial [103]</td>
</tr>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>% of all patients</td>
</tr>
<tr>
<td>All trials combined</td>
</tr>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>% of all patients</td>
</tr>
</tbody>
</table>

*Patients who received irinotecan monotherapy or no treatment were excluded.

| 5-FU bolus regimen.

| 5-FU infusional regimen.

5-FU, 5-fluorouracil; EORTC, European Organization for Research and Treatment of Cancer; IRI, irinotecan; LV, leucovorin.
(FFCD 2001–2002), prospectively demonstrated that geriatric characteristics are independent predictive factors of survival and toxicity. A total of 282 patients with mCRC were randomly assigned to receive 5-FU-based chemotherapy either alone or in combination with irinotecan [95]. Participating sites completed geriatric screening tools to perform prognostic factor analyses for treatment safety during the first 4 months of treatment. Patients who received irinotecan showed a significant benefit over those who received 5-FU/LV alone in terms of overall response rate (RR), 46.3% versus 27.4% (OR 2.3, 95% CI: 1.4–3.8, \(P = 0.001\)), a non-significant benefit in terms of PFS, 7.3 versus 5.2 months (HR 0.84, 95% CI: 0.66–1.07, \(P = 0.15\)), and no benefit in terms of OS [108]. The geriatric score was calculated for 123 patients (44%) with a median age of 80 years. Seventy-one patients (58%) had grade 3–4 toxicity, 41 (33%) had a dose reduction of >33%, and 54 (44%) had at least one unexpected hospitalization during the first 4 months of treatment. Multivariate analysis showed significant predictive factors for grade 3–4 toxicity to be the irinotecan arm, mini-mental state examination score ≤27/30, and impaired ADL. These data suggest that intensive chemotherapy should be used with caution in patients ≥75 years with low autonomy and cognitive impairment, and support the importance of the evaluation of risk factors for toxicity in older cancer patients being considered for chemotherapy [27].

Increasingly, combination chemotherapy plus a targeted agent (bevacizumab, cetuximab, and panitumumab) is being used to treat mCRC patients. Since the publication of the previous SIOG guidelines, more data on the efficacy and safety of the addition of bevacizumab and cetuximab to chemotherapy in older patients have been reported [109–117], including a prospective randomized study with bevacizumab [96] (Tables 7 and 8), and an efficacy and safety analysis of bevacizumab in 1462 patients ≥65 years and 426 patients ≥75 years using pooled data from seven randomized trials [119].

Bevacizumab in particular has a side-effect profile that needs careful consideration when treating elderly patients. However, the AGITG MAX 3-arm study of capecitabine versus capcitabine plus bevacizumab ± mitomycin C undertaken in 471 patients stratified according to age (< or >65 years) reported a significant improvement in PFS (8.5 versus 5.7 months, HR 0.63, 95% CI: 0.50–0.79; \(P = 0.001\)) in favor of bevacizumab combination treatment in the absence of significant additional toxicity [120]. QoL was similar for all groups [120]. A subgroup analysis (\(n = 99\)) showed the addition of bevacizumab to capcitabine to significantly improve PFS in patients >75 (range 75–86) years of age (8.8 versus 5.8 months, HR 0.52, 95% CI: 0.32–0.86; \(P = 0.01\)) [115]. The interaction test for OS, RR, and PFS revealed no impact of age. Treatment was well tolerated with no signs of increased toxicity (including thromboembolism) when compared with those patients aged <75 years. Similarly, the prospective randomized AVEX trial in patients ≥70 years (median age 76 years, range 70–87) also showed the addition of bevacizumab to capcitabine to significantly improve PFS (9.1 versus 5.1 months, HR 0.53, \(P < 0.001\)). In a subgroup analysis, all patients benefitted from the addition of bevacizumab including an essentially equal benefit for those <75

### Table 5. Efficacy according to age groups [99]

<table>
<thead>
<tr>
<th>Response</th>
<th>Overall response rate, %</th>
<th>&lt;70</th>
<th>≥70</th>
<th>&gt;75</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRI/5-FU</td>
<td>5-FU/FA</td>
<td>IRI/5-FU</td>
<td>5-FU/FA</td>
<td>IRI/5-FU</td>
</tr>
<tr>
<td>No. of patients</td>
<td>745</td>
<td>1218</td>
<td>208</td>
<td>346</td>
<td>60</td>
</tr>
<tr>
<td>95% CI</td>
<td>42.9–50.2</td>
<td>26.4–31.6</td>
<td>43.5–57.5</td>
<td>25.5–35.5</td>
<td>38.3–64.8</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression-free survival</th>
<th>No. of patients</th>
<th>Median, months</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>776</td>
<td>1307</td>
<td>220</td>
<td>376</td>
<td>64</td>
</tr>
<tr>
<td>Median, months</td>
<td>8.2</td>
<td>6.3</td>
<td>9.2</td>
<td>7.0</td>
<td>9.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.7–8.7</td>
<td>5.9–6.7</td>
<td>8.5–9.9</td>
<td>6.2–7.9</td>
<td>8.0–10.4</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.0026</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>No. of patients</th>
<th>Median, months</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>765</td>
<td>1308</td>
<td>219</td>
<td>375</td>
<td>64</td>
</tr>
<tr>
<td>Median, months</td>
<td>17.1</td>
<td>14.7</td>
<td>17.6</td>
<td>14.2</td>
<td>14.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.9–18.3</td>
<td>13.9–15.6</td>
<td>15.5–19.7</td>
<td>12.7–15.7</td>
<td>11.1–17.9</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0003</td>
<td>0.15</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values reflect the \(\chi^2\) or log-rank test of difference between treatment arms within the age groups. The test of interaction between age (<70 versus ≥70 years) and treatment arm was not significant for each parameter.

*Subgroup analysis.

CI, confidence interval; 5-FU, 5-fluorouracil; FA, folinic acid; IRI, irinotecan.
years and those ≥75 years. Grade ≥3 AEs and AEs leading to dose modification or discontinuation were all higher in the bevacizumab-containing arm. In older patients, there was a small to modest increased risk of arterial thrombotic events. In the recent pooled analysis [119], the addition of bevacizumab to chemotherapy was associated with statistically significant increases in both OS (HR 0.80, 95% CI: 0.71–0.90) and PFS (HR 0.57, 95% CI: 0.46–0.71), which were maintained across all age groups (<65 or ≥65 years; ≥75 years). It is striking that the HR is consistently around 0.5 for PFS across the different

### Table 6. Patients according to age groups in oxaliplatin-based first-line combination chemotherapy trials [99]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment by age group (years)</th>
<th>&lt;70</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxali/5-FU/LV</td>
<td>5-FU/LV</td>
<td>Oxali/5-FU/LV</td>
</tr>
<tr>
<td>de Gramont et al. [105]</td>
<td>No. of patients</td>
<td>167</td>
<td>334</td>
</tr>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>334</td>
<td>79.5</td>
</tr>
<tr>
<td>Rothenberg et al. [106]</td>
<td>No. of patients</td>
<td>224</td>
<td>448</td>
</tr>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>448</td>
<td>82.0</td>
</tr>
<tr>
<td>Goldberg et al. [107]</td>
<td>No. of patients</td>
<td>208</td>
<td>416</td>
</tr>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>416</td>
<td>78.3</td>
</tr>
<tr>
<td>All trials combined</td>
<td>No. of patients</td>
<td>599</td>
<td>1198</td>
</tr>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>1198</td>
<td>80.0</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; LV, leucovorin; Oxali, oxaliplatin.

### Table 7. Analysis of outcomes with bevacizumab in older patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVEX [96]</td>
<td>Capecitabine + BV versus capcitabine</td>
<td>9.1 versus 5.1</td>
<td>16.8 versus 16.8</td>
<td>0.53 (0.41–0.69)</td>
<td>0.79 (0.57–1.09)</td>
</tr>
<tr>
<td>AGITG MAX ≥75 subgroup [115]</td>
<td>Capecitabine + BV versus capcitabine</td>
<td>8.8 versus 5.6</td>
<td>13.4 versus 13.4</td>
<td>0.52 (0.32–0.86)</td>
<td>0.80 (0.47–1.36)</td>
</tr>
<tr>
<td>AVF2107 and AVF2192 pooled analysis [112]</td>
<td>CT + BV versus CT</td>
<td>9.2 versus 6.2</td>
<td>14.3 versus 14.3</td>
<td>0.52 (0.40–0.67)</td>
<td>0.70 (0.5–0.9)</td>
</tr>
<tr>
<td>NO16966, AVF2107, AVF2192 and E3200 pooled analysis [110]</td>
<td>5-FU-based CTa + BV versus CT</td>
<td>9.2 versus 6.4</td>
<td>14.1 versus 14.1</td>
<td>0.54 (0.44–0.66)</td>
<td>0.79 (0.66–0.93)</td>
</tr>
<tr>
<td>BRITE [114]</td>
<td>CTb + BV</td>
<td>10.0</td>
<td>20.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ARIES [113]</td>
<td>CT + BV</td>
<td>9.9</td>
<td>19.6</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

aThe IFL regimen in study 1 comprised irinotecan, bolus 5-FU, and bolus LV. The 5-FU/LV regimen in study 2 comprised weekly LV with bolus 5-FU.
bChemotherapy was physicians’ choice and regimens used included FOLFOX, FOLFIRI, IFL, XELOX, and capcitabine.

BV, bevacizumab; 5-FU, 5-fluorouracil; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; NA, not available; OS, overall survival; CI, confidence interval.
studies including the pooled analysis (Table 7). Thus, bevacizu-
mab in combination with single-agent capcitabine should be
considered as an alternative first-line treatment option to
the combination of chemotherapy ± bevacizumab, for fit older
patients (≥70 years) with mCRC where surgical resection is
unlikely. It can also be used as maintenance therapy after
initial oxaliplatin-based induction therapy, with capcitabine
administered at a lower dose [121, 122]. Indeed, further data on
this approach as well as the previously described ‘stop and go’
strategy [121] would be very welcome in this group of patients.

Information is also available for the use of cetuximab in
older patients with KRAS wild-type mCRC from the TTD 04/01
[cetuximab alone] and 06/01 trials (cetuximab plus cap-
citabine), first-line in patients ≥70 years [117], a pooled analysis
of CRYSTAL and OPUS according to age [111] (Table 8), and a
subgroup analysis of the NCIC CTG CO.17 trial according to age
[109] (data not shown), suggesting that, for patients with good
performance status, restricting cetuximab use in older patients or
in patients with significant comorbidities is unjustified, although
diabetes was higher in some of these studies. There is an ongoing,
randomized, EORTC phase II study testing infusional 5-
FU ± cetuximab in older patients which should help to resolve
this issue. The results of a recent phase II trial in frail, older
patients with poor prognostic factors who were not candidates for
chemotherapy, support panitumumab as a treatment option in
patients with KRAS/RAS wild-type tumors [123].

In conclusion, the survival gains seen for the various drugs
and drug combinations in older mCRC patients have been
modest (median at best a few months). However, the cumulative
survival benefit of the various agents in combination, and even
in a specific sequence, is as important for older patients as it is
for younger patients. Treatment with a fluoropyrimidine (5-FU/
LV or capcitabine) clearly contributes to OS in older patients.
The added value of irinotecan, oxaliplatin, and targeted agents
may well be more limited due to the lower achievable dose
intensities and poorer benefit/risk ratio. Furthermore, these
limited incremental gains when explored in subgroup analyses
are restricted to older patients with good performance status.
Thus, it needs to be remembered that the gains from the addi-
tion of any drugs come with increased toxicity, restricting the
patients that can be treated. Thus, these data show that:

- Fit older patients can benefit from systemic cytotoxic combination
  therapy.
- Age alone should not be an exclusion criterion for the use of newer tar-
ged agents in the treatment of patients with mCRC.
- Those fit older patients selected for inclusion in clinical trials appear to
derive a similar benefit to younger patients in terms of RR and PFS from
the use of bevacizumab or cetuximab plus full-dose combination chemo-
therapy. However, the data are lacking as to whether this leads to signif-
cant patient-relevant gains such as improved survival with an acceptable QoL.
- For those older patients for whom such therapy would be inappropriate,
less intensive regimens, such as reduced-dose oxaliplatin plus 5-FU or
lower dose capcitabine plus bevacizumab, may be used.

**rectal cancer: preoperative and palliative RT in older patients**

Approximately one-third of CRC patients present with rectal
disease. However, the data show large variations in patient man-
gement with a lower use in older patients (compared with their
younger counterparts) of RT either alone or in conjunction with
surgery, while chemotherapy is rarely administered [12].
Population-based studies clearly show that older patients with
rectal cancer are treated less often with RT [49, 124–129].

Preoperative CRT and SCPRT are both standard components of
the treatment of intermediate or locally advanced rectal
cancer before surgery, and may be followed by adjuvant chemo-
otherapy in selected patients, although this remains more contro-
versial than in colon cancer. To date, the median ages of

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Table 8. Analysis of outcomes with cetuximab in older patients

<table>
<thead>
<tr>
<th>Trial/treatment</th>
<th>Age (years)</th>
<th>N</th>
<th>Median PFS (95% CI) (months)</th>
<th>Median OS (95% CI) (months)</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastre et al. [116]</td>
<td>≥70</td>
<td>41</td>
<td>2.9 (5.3–8.4)</td>
<td>11.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cetuximab/capcitabine</td>
<td>≥70</td>
<td>66</td>
<td>7.1 (5.3–8.4)</td>
<td>16.1 (12.0–18.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Folprecht 2010 ESMO [111]</td>
<td>&lt;70</td>
<td>700</td>
<td>Cet + CT: 10 (9.0–11.5)</td>
<td>Cet + CT: 23.6 (20.7–26.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>145</td>
<td>Cet + CT: 8.9 (7.2–16.1)</td>
<td>Cet + CT: 23.3 (16.8–25.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jonker et al. [118]*</td>
<td>NA</td>
<td>572</td>
<td>(41% ≥65 years)</td>
<td>Cet + BSC: 1.9</td>
<td>0.68 (0.57–0.80)</td>
<td>0.64–0.90</td>
</tr>
</tbody>
</table>

*Age <65/≥65 years was shown not to be associated with OS (P = 0.13) [109].
BSC, best standard of care; cet, cetuximab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; NA, not available; OS, overall survival.
patients in the preoperative CRT and SCPRT trials are ~63 and 68 years, respectively [130–134], well below the age of presentation in the general population. Data from the UK National Bowel Cancer Audit Project suggest that radical surgery is carried out in only 21% of patients ≥85 years compared with 60% in the overall population. As a consequence, fewer older patients are likely to receive preoperative RT with proportionally more receiving palliative RT as an alternative. Preoperative RT has been shown to improve local control in patients >70 years when compared with no or postoperative RT [135], although Swedish data suggest that the benefit is small in patients >75 years [49].

The overwhelming desire of surgeons to avoid local pelvic recurrence at all costs drives most decisions in younger patients. However, in older rectal cancer patients, the aim is not only to avoid local recurrence, but also to maintain health and function in these patients with a view to optimizing their chances of coping with their treatment. Older patients are understandably keen to avoid a permanent stoma and may accept a higher risk of local recurrence to achieve this [136–142]. Acute and long-term toxicity, fitness to undergo radical surgery, ultimate life expectancy, and the risk of metastasis also need to be considered.

Certainly, intensity-modulated RT or volumetric-modulated therapy is associated with a reduction in the acute toxicity associated with standard RT. They may also facilitate the safer integration of chemotherapy. Locally applied endocavity contact RT is associated with standard RT. They may also facilitate the safer integration of chemotherapy. Locally applied endocavity contact RT is also a well-accepted method of radical treatment of clinically staged T1 and T2 tumors in the mid and distal rectum [143], and is associated with minimal late morbidity and long-term local disease control rates of ≥80%. High-dose rate intraluminal brachytherapy (HDR-ILBT) allows a high dose of radiation to be delivered to the mucosal surface of the rectum, reducing the exposure of the surrounding normal structures. Publications are sparse on the use of intraluminal RT for more advanced, resectable rectal cancer. However, a team in Montreal has reported significant tumor regression in >300 patients with >29% achieving a complete pathologic response at surgery [61, 144, 145]. Limited data are also available evaluating the advantages of HDR-ILBT with external beam RT (EBRT) versus EBRT alone. A small randomized study suggests that RT dose escalation with an endoluminal boost is feasible, and may offer a higher rate of complete clinical response, and hence increase the chance of sphincter preservation [146]. Thus, HD-ILBT could offer an alternative to surgery and be useful in the palliative setting. However if radical surgery is planned the following should be considered:

- **RT (5 × 5 Gy) and immediate surgery (2–3 days) or long-course CRT with an interval of 6–8 weeks before surgery for cancers with no MRI-predicted threat to the mesorectal fascia (MRF) (<1 mm), based on three-dimensional imaging reconstructions.**
- **Preoperative long-course RT alone, although less effective for local control than long-course CRT, can be used as an alternative if there are concerns over the safety of chemotherapy.**
- **In locally inextirpable tumors, or where MRI predicts a threat to the MRF, long-course CRT is the treatment of choice in older patients who are fit enough for this therapy.**
- **If shrinkage of the tumor away from the MRF is required following CRT, a sufficient interval is required to allow an adequate response. Although the optimum interval has not been determined, most consider a delay of 6–12 weeks reasonable.**
- **Treatment with 5 × 5 Gy with a delay of 6–8 weeks (or longer) before surgery is an alternative option in very old and/or frail patients.**
- **EBRT can be used to manage inoperable patients with low rectal tumors (all stages) and in the palliative advanced disease setting.**
- **HDR brachytherapy or contact therapy are promising techniques for older patients with rectal cancer, but should not be used in the anal canal.**

**overall conclusions and recommendations**

The SIOG task force’s view on and recommendations for the management of older patients with CRC going forward based on the updated data presented in this document are that:

- **Embracing the concept of individualized treatment is an absolute requirement for further improvements in the management of these patients.**
- **MDTs are the key to individualized treatment in older patients.**
- **The treatment challenges presented by many older patients with CRC make it important to use some form of comprehensive GA to inform our clinical decision-making.**
- **Guidelines are urgently needed to support surgeons, medical and radiation oncologists in the treatment of older patients including formal assessments of the benefit/risk ratios of the various treatment interventions.**
- **Patients also need to be provided with tailored information in an acceptable format to support their involvement in the initial decision-making process with regard to optimal treatment, whenever possible.**
- **The potential for morbidities and the choices if serious complications do occur or treatments fail should be discussed in advance.**
- **Investigators should be encouraged to design not only trials using low-toxicity treatments that maintain most of the efficacy of full-dose treatments, but patient-centered assessments to expand the evidence base in the treatment of older patients with CRC.**

**acknowledgements**

Mr Satvinder Mudan, FRCS, The Royal Marsden, Fulham Road, London SW3 6JJ, UK, and Dr Charles Akle, BSc, MS, FRCS, The London Clinic Cancer Centre—B2 22 Devonshire Place, London W1G 6JA, UK, attended as observers. Medical writing support was provided by Anne Kinsella, PhD, Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, UK.

**funding**

This work was supported by an unrestricted grant from Roche.

**disclosure**

MA is a consultant for Amgen, BMS, Celgene, GSK, Helsinn, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Teva, and Vifor and has received honoraria for lectures at symposia of Amgen, Bayer Schering, Cephalon, Chugai, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Teva, and Vifor. AG has advisory board activities with Roche.
and Sanofi. RG-J has given invited lectures for Roche, Sanofi, Pfizer, and Merck Serono and has advisory board activities with Roche, Sanofi, Eli Lilly, Merck Serono, and Nucletron. EM has advisory board activities and received research funding from Pfizer and Roche. EVC has received research funding from Sanofi, Roche, Bayer, and Merck Serono. RAA, BG, DH, CHK, SR, VL, DP, HR, DS, JS, MS, and NS declare no conflicts of interest.

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