First-line bevacizumab and capecitabine–oxaliplatin in elderly patients with mCRC: GEMCAD phase II BECOX study

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**Background:** Subgroup analyses of clinical studies suggest that bevacizumab plus XELOX is effective and tolerable in elderly patients with metastatic colorectal cancer (mCRC). The prospective BECOX study examined the efficacy and safety of bevacizumab plus XELOX, followed by bevacizumab plus capecitabine in elderly patients with mCRC.

**Methods:** Patients aged ≥ 70 years with Eastern Cooperative Oncology Group performance status 0 out of 1 and confirmed mCRC were included. Patients received bevacizumab 7.5 mg kg⁻¹ and oxaliplatin 130 mg m⁻² on day 1, plus capecitabine 1000 mg m⁻² bid orally on days 1–14 every 21 days; oxaliplatin was discontinued after 6 cycles. The primary end point was time to progression (TTP).

**Results:** The intent-to-treat population comprised 68 patients (65% male, median age 76 years). Median TTP was 11.1 months; median overall survival was 20.4 months; overall response rate was 46%. Grade 3 or 4 adverse events included diarrhoea (18%) and asthenia (16%). Grade 3 or 4 adverse events of special interest for bevacizumab included deep-vein thrombosis (6%) and pulmonary embolism (4%).

**Conclusions:** Bevacizumab plus XELOX was effective and well tolerated in elderly patients in the BECOX study. The adverse-event profile was similar to previous reports; no new safety concerns were identified. Fit elderly patients with mCRC should be considered for treatment with bevacizumab plus XELOX.

Treatment guidelines recommend that first-line treatment for patients with metastatic colorectal cancer (mCRC) should include doublet chemotherapy plus a targeted agent. The individual components of the regimen should be selected based on a number of factors including the patient’s potential for achieving resectability, number and location of metastases, and patient-related factors such as performance status and comorbidity (Schmoll et al, 2012).

In addition to performance status and comorbidities, age is one of the most important factors when deciding on a course of therapy.
for patients with mCRC. However, there is a paucity of robust evidence on which to base treatment decisions for older patients. The median age at presentation for patients with colorectal cancer is 72 years, whereas the median age of patients in clinical trials is 63 years (Schmoll et al, 2012). In addition, trials conducted specifically in older patients account for only a small proportion of all studies in patients with mCRC. This preferential selection of younger patients for clinical trials makes extrapolation of the resulting data to elderly patients difficult. As a result, many older patients’ risk being treated more conservatively than their younger counterparts. Studies have shown that older patients are more likely to receive monotherapy rather than combination therapy and are less likely to receive targeted agents compared with younger patients (McKibbin et al, 2008; Sorbye et al, 2009; Khattak et al, 2012).

We have previously shown that the combination of bevacizumab and capecitabine is an effective and well-tolerated first-line treatment option for elderly patients with mCRC (Feliu et al, 2010). Patients in that study, who were aged ≥70 years, had a median progression-free survival (PFS) of 10.8 months and a median overall survival (OS) of 18.0 months, with an overall response rate (ORR) of 34% and disease-control rate of 71% (Feliu et al, 2010). The combination of bevacizumab with capecitabine and oxaliplatin (XELOX) has also been investigated in patients with mCRC (Hochster et al, 2008; Saltz et al, 2008; Tebbutt et al, 2010; Wong et al, 2011; Diaz-Rubio et al, 2012; Cunningham et al, 2013). We therefore undertook the present multicentre phase II BECOX study (ClinicalTrials.gov Identifier: NCT01067053) to assess the efficacy and tolerability of this combination in elderly patients with mCRC.

MATERIALS AND METHODS

Study design and patients. Patients were eligible for inclusion in this multicentre phase II study if they were aged ≥70 years, had histologically or cytologically confirmed colorectal adenocarcinoma (at least one lesion measurable according to Response Evaluation in Solid Tumours (RECIST version 1.1; Eisenhauer et al, 2009)) that was not suitable for surgical resection and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Prior treatment for metastatic disease was not permitted and any prior adjuvant treatment had to be completed >12 months before the start of the study. Patients were required to have adequate renal function (creatinine ≤1.5 × the upper limit of normal (ULN) and calculated creatinine clearance ≥30 ml min⁻¹), liver function (alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN and ≤5 × ULN if liver metastases were present; total bilirubin ≤1.5 × ULN) and haematological function (haemoglobin ≥90 g l⁻¹, absolute neutrophil count ≥1.5 × 10⁹ l⁻¹ and platelet count ≥100 000 × 10⁹ l⁻¹).

Patients were not permitted to have received prior chemotherapy for metastatic disease. For those who had adjuvant chemotherapy (or neoadjuvant chemotherapy for patients with rectal cancer), this treatment had to be completed 12 months before study entry. Patients who had previously received bevacizumab treatment were excluded from the study, as were patients with clinical evidence of brain metastases and current or recent (within 10 days of starting the study) treatment with full-dose aspirin, anticoagulants or thrombolytics. Patients who were dependent in terms of basic or instrumental activities of daily living and those with more than three comorbidities were also excluded, as were those with clinically significant cardiovascular disease within 6 months before the start of the study and those with a history of arterial thromboembolic events or predisposition to bleeding or coagulopathy.

The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and was approved by local ethics committees. All patients provided written informed consent.

Treatment regimen. Treatment consisted of intravenous bevacizumab 7.5 mg kg⁻¹ and oxaliplatin 130 mg m⁻² on day 1 of each cycle, plus oral capecitabine 1000 mg m⁻² twice daily (bid) on days 1–14 of each cycle (patients with a baseline creatinine clearance of 30–50 ml min⁻¹ had a 25% reduction in their initial capecitabine dose to 750 mg m⁻² bid). Treatment was repeated every 3 weeks for 6 cycles. After 6 cycles, oxaliplatin was discontinued and patients continued to receive bevacizumab and capecitabine following the same regimen until progression or study discontinuation. This strategy has been used in other studies, including OPTIMOX1 (Tournigand et al, 2006) and CAIRO3 (Koopman et al, 2013), to minimise the toxicities associated with oxaliplatin and maximise the acceptability of treatment for patients and therefore the likelihood of continuing treatment.

Assessments. Tumour response was assessed using RECIST version 1.1 at baseline and after the administration of three and six cycles in the initial treatment phase, and every three cycles thereafter in the continuation phase. Assessment of overall tumour burden was performed using imaging of the thorax with computed tomography (CT), conventional helical CT, magnetic resonance imaging or chest radiography, resulting in documentation of target and non-target lesions. Subsequent assessments were performed using the imaging technique used at baseline. Adverse events, assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), were evaluated during the study period and until 28 days after the last dose of study treatment was administered.

Statistical analysis. The primary end point of the study was time to progression (TTP), defined as the time from the start of treatment until disease progression or death as a result of disease progression. Secondary end points included: OS, defined as the time from the start of treatment until the death of the patient; ORR, defined according to RECIST; confirmed response rate; and safety of the treatment. Exploratory post hoc end points included analyses of the effect on efficacy and tolerability of age (70–75 years, >75 years), performance status (ECOG performance status 0, 1), extent of disease (1, 2, ≥3 organs with metastases) and baseline creatinine clearance (>50 ml min⁻¹, ≤50 ml min⁻¹).

On the basis of an estimated median TTP of 10.6 months (s.d. of 2 months), a significance level of 95% and an α-error of 0.05, it was calculated that a sample size of 62 patients was required. Estimating a loss of up to 10% of the final sample, 69 patients would need to be recruited to achieve this number.

Analyses were performed on the intent-to-treat (ITT) population, which consisted of all patients who received at least one dose of study medication. Survival analyses were performed using the Kaplan–Meier method, which provided medians and 95% confidence intervals (CIs).

RESULTS

Patients. Between 19 November 2009 and 1 March 2012, 69 patients were entered into the study at 15 centres in Spain. One patient received no treatment and the ITT population therefore consisted of 68 patients. Patients’ baseline characteristics are summarised in Table 1. Prior or current comorbidities at baseline included hypertension (47%), diabetes (24%), atrial fibrillation (9%), gastrointestinal ulcers (9%), haematological disorders (7%) and thromboembolic disease (6%). The majority of patients (n = 53; 78%) had synchronous metastases. Liver metastases were
present in 55 patients (81%), 23 patients (34%) had lung metastases and 38 patients (56%) had metastases in other locations. Two-thirds of patients (n = 46; 68%) had lesions in >2 organs. The primary tumour had been resected in 41 patients (60%) and 6 patients (9%) had resection of metastases. Tumour KRAS status was known for 58 patients (85%): 33 patients (57%) had wild-type KRAS tumours and 25 patients (43%) had mutant KRAS tumours.

**Treatment.** The median duration of treatment was 6.8 months (range, 0.2–25.2 months); the median number of treatment cycles administered was 8.5 (range, 1–33). In total, 646 cycles were administered. Eight patients (12%) are currently still on treatment. The median duration of treatment was 6.8 months (range, 0.2–25.2 months); the median number of treatment cycles administered was 8.5 (range, 1–33). In total, 646 cycles were administered. Eight patients (12%) are currently still on treatment.

Analysis of treatment in cycle 6 (final cycle of the initial treatment phase) revealed that 23 patients (34%) were receiving no treatment, 41 patients (60%) were receiving bevacizumab plus XELOX, 3 patients (4%) were receiving XELOX with no bevacizumab and 1 patient (1%) was receiving bevacizumab plus capecitabine.

Eleven patients (16%) had their dose of bevacizumab delayed because of hypertension (n = 2; 3%), proteinuria (n = 1; 1%), embolism/thromboembolism (n = 4; 6%) or other reasons (n = 4; 6%). Fifteen patients (22%) had their dose of bevacizumab reduced, 8 (12%) because of weight loss. One patient had their dose of oxaliplatin suspended (general deterioration) and 24 patients (35%) had their dose reduced. In total, 32 doses were reduced as a result of peripheral neuropathy (3 doses; 4%), neutropenia (4 doses; 6%), febrile neutropenia (1 dose; 1%), thrombocytopenia/anaemia (2 doses; 3%), cutaneous toxicity (1 dose; 1%), weight loss (3 doses; 4%) and other reasons (18 doses; 56%). A total of 112 capecitabine dose modifications were required by 47 patients (69%). The most common reasons for dose modification were nonhaematological adverse events (34 doses; 30%), diarrhoea (33 doses; 30%) and hand–foot syndrome (9 doses; 8%).

Median relative dose intensities were 94% for bevacizumab, 92% for oxaliplatin and 80% for capecitabine.

**Efficacy.** Response to treatment is summarised in Table 2. After a median follow-up of 14.5 months, the median TTP was 11.1 months (95% CI: 8.1–14.1 months) (Figure 1A). Median OS was 20.4 months (95% CI: 13.2–27.6 months) (Figure 1B). The mean duration of response in the 31 patients with a complete or partial response was 15.8 months (95% CI: 12.2–19.5 months); median duration of response was not reached at the time of the analyses. The mean duration of response in the 31 patients with a complete or partial response was 15.8 months (95% CI: 12.2–19.5 months); median duration of response was not reached at the time of the analyses.

Five patients had surgery after treatment (one patient each with liver salvage surgery; hepatectomy and ileostomy closure; resection of liver metastases; resection of liver injury; and radiofrequency ablation of left hepatic lesions, resection of the primary tumour, sigmoid resection and colorectal anastomosis).

Twenty-four patients (35%) received second-line therapy after disease progression. Seven of these patients (29%) received bevacizumab-containing regimens, 4 patients (17%) received cetuximab-containing regimens and 1 patient (4%) received panitumumab plus irinotecan; the remaining 12 patients (50%) received various chemotherapy regimens.

### Table 1. Patient characteristics at baseline

| Characteristics                  | BECOX population (n = 68) |
|----------------------------------|---------------------------|
| **Gender, n (%)**                |                           |
| Male                             | 44 (65)                   |
| Female                           | 24 (35)                   |
| **Age**                          |                           |
| Median, years                    | 75.6                      |
| Range, years                     | 70.5–85.4                 |
| >75 years, n (%)                 | 43 (63)                   |
| **ECOG performance status, n (%)**|                         |
| 0                                | 32 (47)                   |
| 1                                | 36 (53)                   |
| **No. of lesions, n (%)**        |                           |
| 1 or 2                           | 12 (18)                   |
| 3 or 4                           | 19 (28)                   |
| >5                               | 37 (54)                   |
| **Tumour location, n (%)**       |                           |
| Colon                            | 41 (60)                   |
| Rectum                           | 19 (28)                   |
| Colon and rectum                 | 8 (12)                    |
| **Prior adjuvant therapy, n (%)**|                           |
| Chemotherapy alone               | 5 (7)                     |
| Chemotherapy and radiotherapy    | 2 (3)                     |
| Radiotherapy alone               | 2 (3)                     |
| **Creatinine clearance, n (%)**  |                           |
| >50 ml min$^{-1}$                | 56 (82)                   |
| ≤50 ml min$^{-1}$                | 12 (18)                   |

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

### Table 2. Efficacy outcomes

| Outcomes                          | BECOX population (n = 68) |
|-----------------------------------|---------------------------|
| **Time to progression, months**   |                           |
| Median (95% CI)                   | 11.1 (8.1–14.1)           |
| **Overall survival, months**      |                           |
| Median (95% CI)                   | 20.4 (13.2–27.6)          |
| **Best response, n (%)**          |                           |
| Complete                          | 2 (3)                     |
| Partial                           | 29 (43)                   |
| Stable disease                    | 23 (34)                   |
| Progressive disease               | 14 (21)                   |
| Overall response rate, % (95% CI)| 45.6 (33.6–68.1)          |
| Disease-control rate, % (95% CI)  | 79.4 (67.6–87.9)          |
| **Confirmed response, n (%)**     |                           |
| Complete                          | 2 (3)                     |
| Partial                           | 21 (31)                   |
| Stable disease                    | 31 (46)                   |
| Progressive disease               | 2 (3)                     |
| Overall response rate, % (95% CI)| 33.8 (23.1–46.4)          |
| Disease-control rate, % (95% CI)  | 79.4 (67.6–87.9)          |

Abbreviation: CI = confidence interval.
At the time of this analysis, 38 patients (56%) were 
tolerability. Similarly, there were no statistically significant differences in 
age, ECOG performance status and number of organs with metastases are shown in 
Table 3, and Kaplan–Meier curves for OS according to age and 
ECOG performance status are shown in Figure 2. Patients aged >75 years had comparable ORR, TTP and OS to those aged 70–75 
years. Similarly, there were no statistically significant differences in 
ecology outcomes according to ECOG performance status or 
number of organs with metastases (Table 3).

Tolerability. At the time of this analysis, 38 patients (56%) were 
still alive; 26 patients died as a result of disease progression, 1 as a 
result of an adverse event (gastrointestinal perforation) and 3 for 
other reasons (one each because of clinical deterioration, aspiration 
pneumonia and unknown reasons).

Adverse events are summarised in Table 4. Overall, 65 patients 
(96%) experienced any adverse event, 45 patients (66%) experi-
enced a grade 3 or 4 event and 1 had a grade 5 event (fatal 
gastrointestinal perforation). The most common all-grade events 
were diarrhoea (n = 42; 62%), asthenia (n = 42; 62%), neurotoxi-
city (n = 23; 34%), vomiting (n = 22; 32%) and mucositis (n = 22; 32%). The most common grade 3 or 4 events were asthenia 
(n = 11; 16%), diarrhoea (n = 12; 18%) and hand–foot syndrome 
(n = 5; 7%).

Adverse events of interest with bevacizumab are summarised in 
Table 5. The most common all-grade events were epistaxis (n = 9; 13%), hypertension (n = 8; 12%) and proteinuria (n = 8; 12%). Deep-vein thrombosis occurred in six patients (9%) and four 
patients (6%) had a pulmonary thromboembolism.

Exploratory post hoc subgroup analyses of adverse events did 
not provide any indication that the incidence of adverse events varied according to patient age (Table 6) or ECOG performance 
status (data not shown).

Analysis of adverse events (any grade) associated with 
capecitabine was analysed in patients with baseline creatinine 
clearance > 50 ml min⁻¹ and ≤50 ml min⁻¹. There were no 
significant differences between the two groups in terms of 
mucositis, vomiting, anorexia, nausea or hand–foot syndrome 
(data not shown); a trend towards a significant difference in 
asthenia was observed (66 vs 33% for patients with baseline 
creatinine clearance > 50 ml min⁻¹ and ≤50 ml min⁻¹, respecti-
v; P = 0.052) and there was a numerically higher incidence of 
diarrhoea in patients with creatinine clearance < 50 ml min⁻¹ 
(83 vs 57%; P = 0.112).

**DISCUSSION**

Although many studies have demonstrated that medically fit 
elderly patients have the potential to derive similar benefit from 
chemotherapy as younger patients, treatment of elderly patients 
with colorectal cancer remains conservative outside of clinical 
trials. This is in part because of the scarcity of reliable data from 
clinical trials performed in elderly populations to support a more 
active approach in older patients.

Treatment regimens initially explored in elderly patients focused 
on fluoropyrimidine monotherapy, resulting in median PFS of ~ 3 
months and median OS of 10–11 months (Daniele et al, 2003; Feliu 
et al, 2005; Tutsuimi et al, 2006). Efficacy was further improved by 
the addition of irinotecan (Sastre et al, 2005; Souglakos et al, 2005), 
oxaliplatin (Mattioi et al, 2005; Rosati et al, 2005; Feliu et al, 2006; 
Sastre et al, 2009) or both (Vamvakas et al, 2010) to the
fluoropyrimidine. Patients treated with doublet chemotherapy could be expected to achieve a median PFS of 7–8 months and OS of 14–17 months, whereas triplet regimens yielded a median PFS of 8.5 months and OS of 19.9 months. More recently, the addition of targeted agents, such as bevacizumab, to monotherapy or doublet regimens in elderly patients has resulted in reported median PFS of 9–11 months and OS of 16–24 months (Puthillath et al, 2009; Feliu et al, 2010; Vrdoljak et al, 2011; Wong et al, 2011; Price et al, 2012; Cunningham et al, 2013; Rosati et al, 2013).

Patients in our study had a median OS of 20.4 months and TTP of 11.1 months. These results appear to compare favourably with other studies in elderly patients treated with bevacizumab plus chemotherapy (Puthillath et al, 2009; Vrdoljak et al, 2011; Wong et al, 2011; Rosati et al, 2013) or cetuximab with or without chemotherapy (Sastre et al, 2011; Abdelwahab et al, 2012; Sastre et al, 2012). Furthermore, our survival data appear to compare well with those from studies in which elderly patients were treated with chemotherapy alone, although such comparisons are made with caution as patient characteristics, inclusion criteria and other variables may differ between trials (Sastre et al, 2009; Rosati et al, 2010; Berretta et al, 2011; Benavides et al, 2012). These and other data, however, suggest that the addition of bevacizumab to doublet chemotherapy can be beneficial for appropriate elderly patients with colorectal cancer. Second-line treatment rates were in line with previous studies (Cunningham et al, 2013; Rosati et al, 2013), which may reflect a desire among our older patients for a better quality of life rather than extended treatment and the possibility of extended survival.

Although this is not a randomised comparison of regimens, the results of the present study appear favourable compared with our previous studies of XELOX and capecitabine–bevacizumab combinations. The addition of oxaliplatin to capecitabine–bevacizumab appeared to improve disease-control rates, an important measure in elderly patients, compared with our previous studies of XELOX (Feliu et al, 2006) and capecitabine–bevacizumab (Feliu et al, 2010) in this patient group. We measured unconfirmed and confirmed response rates in the present study and although the confirmed response rate was lower than the
unconfirmed rate, the disease-control rates were identical. As the effect of bevacizumab is cytostatic rather than cytotoxic, assessment of tumour response using RECIST may not accurately reflect the efficacy of bevacizumab on tumours, and therefore disease-control rates are a more valuable measure of the efficacy of treatment.

The proportion of patients who had received adjuvant therapy was low in our study. Several studies have shown that the use of adjuvant chemotherapy is low in patients over the age of 70 who have had resected colon cancer. Data from Europe and Australia suggest that only 20–25% of elderly patients received adjuvant chemotherapy (Lemmens et al, 2005; Morris et al, 2007), although the corresponding rates in the United States are higher (Jessup et al, 2005; Cronin et al, 2006).

Exploratory post hoc subgroup analyses of outcomes according to age indicated that younger (age, 70–75 years) and older (age, ≥75 years) patients derived similar benefit from the treatment with bevacizumab plus XELOX in the present study, although the number of patients included in the older age group was small. This is in line with the age-specific analysis of CAIRO and CAIRO2 (Venderbosch et al, 2012) and the pooled analysis of four randomised trials by Cassidy et al (2010), both of which indicated that elderly and younger patients benefit from the addition of bevacizumab to chemotherapy. The study was not powered to explore the effect of age, performance status or number of metastases on outcome, and further studies in larger groups of patients are required to confirm our observations.

Treatment with bevacizumab and XELOX was generally well tolerated, with the most common toxicities – diarrhoea, vomiting, neutropenia and neurotoxicity – being as expected for the chemotherapy agents used. Hand–foot syndrome occurred in 19% of patients (all grades) and 7% of patients had grade 3 symptoms. We previously reported all-grade hand–foot syndrome in 46% of patients treated with bevacizumab plus capecitabine 1250 mg m\(^{-2}\) bid (Feliu et al, 2010) and others have reported incidences ranging from 16% in patients who received capecitabine 1000 mg m\(^{-2}\) bid as part of bevacizumab plus XELOX (Rosati et al, 2013) to 80% in patients treated with bevacizumab plus capecitabine 1000 mg m\(^{-2}\) bid (Vrdoljak et al, 2011). There were no statistically significant differences in the incidences of adverse events in our older patients, although the incidences of vomiting, anorexia and hypertension were numerically higher in this subgroup. Hypertension is more common in older vs younger patients as a result of age-related increases in arterial stiffness, neurohormonal and autonomic dysregulation, and progressive decline in renal function ( Kearney et al, 2005; Lionakis et al, 2012).

The incidence of grade 3 or 4 diarrhoea was higher in the present study than in our previous study of bevacizumab plus capcitabine (18 vs 9%, respectively; Feliu et al, 2010), despite the lower capcitabine dose used in the present study. Comparison of our previous studies of capecitabine monotherapy (Feliu et al, 2005) and XELOX (Feliu et al, 2006) in elderly patients suggests that the addition of oxaliplatin to capcitabine increases the incidence of diarrhoea. The incidence of diarrhoea in the present study was, however, lower than that observed for standard-dose XELOX plus bevacizumab in the XELOX-A-DVS study, despite that study having used a lower dose of capcitabine and a similar dose of oxaliplatin (Hurwitz et al, 2012). Diarrhoea was numerically – but not statistically significantly – more common in patients with low creatinine clearance at baseline, in line with our previous observation of a relationship between renal function before administration of treatment and subsequent grade 3 or 4 adverse events (Feliu et al, 2010). The findings of the present study support our proposal that creatinine clearance should be taken into consideration when determining the suitability of an elderly patient for chemotherapy and that patients with a baseline creatinine clearance of 30–50 ml min\(^{-1}\) should have a 25% reduction in their initial capcitabine dose.

Bevacizumab-related adverse events were also as expected and included proteinuria and thromboembolic events. The incidences of adverse events of special interest with bevacizumab were similar to those reported by others in elderly patients treated with bevacizumab plus chemotherapy (Feliu et al, 2010; Rosati et al, 2010; Wong et al, 2011; Rosati et al, 2013). Arterial thromboembolic events were uncommon in this study, which excluded patients with a history of these events. This was in contrast to other studies in which an increase in the incidence of thromboembolic events was observed in older patients (Scappaticci et al, 2007; Cassidy et al, 2010).

Our study has some limitations. The patients included in this study were selected on the basis of good performance status and adequate organ function. As a result, they may not be representative of those seen in clinical practice. In fact, patients were only included in the study if they were independent with regard to the basic or instrumental activities of daily living. Despite this, a large proportion of our patients had a range of comorbidities typical of those that would be observed in an elderly patient presenting in the clinic, increasing the generalisability of the results of the study.

In conclusion, chronological age is not a reliable indicator of an elderly patient’s ability to tolerate treatment for mCRC nor is it a predictor of the likelihood of response to therapy. The results of the present study indicate that the combination of bevacizumab plus XELOX is an effective and tolerable regimen for treating medically fit older patients. Comprehensive assessment of the patient’s functional and psychological ability is required to determine the potential benefit from treatment in individual patients.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.
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