



Single-arm phase II trial to evaluate efficacy and tolerance of regorafenib monotherapy in patients over 70 with previously treated metastatic colorectal adenocarcinoma FFCD 1404 - REGOLD

T. Aparicio, A. Darut-Jouve, F. Khemissa Akouz, C. Montérymard, P. Artru, L. Cany, O. Romano, B. Valenza, C. Le Foll, C. Delbaldo, et al.

► To cite this version:

T. Aparicio, A. Darut-Jouve, F. Khemissa Akouz, C. Montérymard, P. Artru, et al.. Single-arm phase II trial to evaluate efficacy and tolerance of regorafenib monotherapy in patients over 70 with previously treated metastatic colorectal adenocarcinoma FFCD 1404 - REGOLD. Journal of geriatric oncology, 2020, 10.1016/j.jgo.2020.04.001 . hal-02901884

HAL Id: hal-02901884

<https://hal.science/hal-02901884>

Submitted on 7 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Single-arm phase II trial to evaluate efficacy and tolerance of regorafenib monotherapy in patients over 70 with previously treated metastatic colorectal adenocarcinoma FFCD 1404 – REGOLD

Thomas Aparicio (1), Ariane Darut-Jouve (2), Faiza Khemissa Akouz (3), Carole Montérymard (4), Pascal Artru (5), Laurent Cany (6), Olivier Romano (7), Bruno Valenza (8), Christine Le Foll (9), Catherine Delbaldo (10), Claire Falandry (11), Emmanuelle Norguet Monnereau (12), Meher Ben Abdelghani (13), Denis Smith (14), Yves Rinaldi (15), Denis Père Verge (16), Nathalie Baize (17), Emmanuel Maillard (18), Anthony Dohan (19), Gaetan Des Guetz (20), Frédéric Pamoukdjian (21), Come Lepage (22).

(1) Gastroenterology and Digestive Oncology Department, CHU Saint Louis, APHP, Université de Paris, Paris, France.

(2) Oncology Department, Institut de Cancerologie de Bourgogne, Dijon, France.

(3) Hepatology-Gastroenterology Department, CH Perpignan, Hôpital Saint Jean, Perpignan, France.

(4) Biostatistic Department, Fédération Francophone de Cancérologie Digestive, Dijon, France.

(5) Oncology Department, Hôpital Jean Mermoz, Lyon, France.

(6) Radiotherapy and Oncology Department, Polyclinique Francheville, Perigueux, France.

(7) Oncology Département, Institut de Cancérologie Lille Métropole, Villeneuve d'Ascq, France.

(8) Oncology Department, CHI de Fréjus – Saint-Raphaël, Fréjus, France.

(9) Oncology Department, Grand Hôpital de l'Est Francilien - site de Marne la Vallée, Jossigny, France.

(10) Oncology Department, Hôpital des Diaconesses - Croix Saint Simon, Paris, France.

(11) Oncology Department, CH Lyon Sud, Pierre Bénite, France.

- (12) Hepato-Gastroenterology and Medical Oncology department, CHU La Timone, Marseille, France.
- (13) Oncology Department, Centre Paul Strauss, Strasbourg, France.
- (14) Digestive Oncology Department, CHU of Bordeaux, Bordeaux, France.
- (15) Hepato-Gastroenterology Department, Hôpital Européen de Marseille, Marseille, France.
- (16) Hepato-Gastroenterology Department, Hôpital Saint Joseph - Saint Luc, Lyon, France.
- (17) Oncology department, Hôtel Dieu, CHU of Angers, Angers, France.
- (18) Hepato-Gastroenterology Department, CH Annecy Genevois, Pringy, France.
- (19) Radiology Department, CHU Cochin, APHP, Paris, France.
- (20) Oncology Department, CHU Dupuytren, Limoges, France.
- (21) Geriatric Department, CHU Avicenne, APHP, Bobigny, France.
- (22) Gastroenterology and Digestive Oncology Department, University hospital Dijon ; EPICAD INSERM LNC-UMR 1231, Université de Bourgogne et Franche Comté, Dijon, FR.

Corresponding author: Thomas Aparicio, MD PhD
Gastroenterology Department
Saint Louis Hospital, AP-HP, University Paris Diderot, Sorbonne Paris Cité
1 avenue Claude Vellefaux
75010 Paris, France.
Tel: 33 1 42 49 95 97 Fax: 33 1 42 49 91 68
e-mail: thomas.aparicio@aphp.fr

Running head: Regorafenib for older patients with advanced colorectal cancer

Previous presentations: This work was presented at the annual ESMO meeting in 2018 and the SLOG meeting in 2018.

ABSTRACT

BACKGROUND Regorafenib significantly increases overall survival (OS) in patients with metastatic colorectal cancer previously treated but gives toxicities. .

OBJECTIVES to assess the efficacy and safety of regorafenib at it's approved dose in the older population.

PATIENTS AND METHODS This multicenter single-arm phase II enrolled patients ≥ 70 years old after the failure of fluoropyrimidine-based chemotherapy, anti-VEGF, and anti-EGFR treatment. The primary endpoint was disease control rate (DCR) 2 months after initiation of regorafenib (160 mg/day, 3 weeks on/1 week off).

RESULTS 43 patients were enrolled, with a median age of 77 years. The 2 months DCR was 31.4% in the 35 evaluable patients. For the 42 patients that received at least one dose of regorafenib, median progression-free survival and OS were 2.2 and 7.5 months. The median time to autonomy degradation and quality of life degradation was 3.1 and 3.2 months, respectively. A grade 3-4 treatment-related adverse events was observed in 35/42 patients, notably: fatigue (45.2%), hand-foot skin reaction (19.0%), hypertension (21.4%), and diarrhea (7.1%). There is a trend to achieve DCR in patients ≤ 80 years and a trend to discontinue the study due to toxicity in patients with ECOG ≥ 1 , over 80 years and with impaired baseline autonomy.

CONCLUSION Treatment with regorafenib in pretreated patients ≥ 70 years is feasible and demonstrate similar efficacy that was observed in previous studies in young patients. Fatigue is the most frequent severe adverse event. However,

caution should be taken for older patients with ECOG ≥ 1 , over 80 years, and with impaired baseline autonomy.

Introduction

More than half of colorectal cancer (CRC) cases are diagnosed in patients older than 70 years [1]. Nevertheless, new drugs evaluation and evidence-based medicine data is mainly derived from younger population due to poor enrollment of older patients in clinical trials. As a consequence, the treatment choice for older patients with CRC remains a challenge because of a number of unresolved issues with the evaluation of new drugs [2]. Treatment targeting neo-angiogenesis have demonstrated clinical activity in metastatic CRC (mCRC) in first [3] and second-line setting [4] [5] [6]. Two randomized trials dedicated to older patients, the AVEX [7] and the PRODIGE 20 trial [8], evaluated first-line bevacizumab in combination with chemotherapy and reported significant improvements in progression-free survival (PFS) [7], compared with chemotherapy alone and good tolerability [8] as well as the preservation of autonomy and quality of life [9].

Regorafenib is an oral multi-kinase inhibitor VEGFR-2 and 3, and tumour cell signalling kinases (RET, KIT, PDGFR, and Raf). In the phase III, CORRECT study, regorafenib demonstrated an improvement in overall survival (OS) compared with placebo in patients with mCRC who had received all currently approved standard therapies [10]. In this trial, the median age was 61 years, which is under the age observed of the majority of patients treated in routine practice. A sub-group analysis of patients <65 years compared with patients ≥ 65 years reported no significant interaction of age for OS but a trend to a decrease

magnitude of effect of regorafenib in older patients with a median OS of 6 months in the regorafenib group versus 5.6 months in the placebo group (Hazard Ratio (HR)=0.86 [95% Confidence Interval (CI) 0.61–1.19]) compared with the results observed in younger patients with a median OS of 6.7 months in the regorafenib group versus 5 months in the placebo group (HR=0.72 [95% CI 0.56–0.91]) [11]. The purpose of the FFCD 1404-REGOLD trial was to prospectively evaluate the antitumor activity and tolerability of regorafenib in older patients with mCRC. In addition, the evolution of quality of life and specific geriatric measurements were assessed.

Patients and Methods

Patient selection

The eligibility criteria were histologically confirmed: unresectable mCRC, age ≥ 70 years; Eastern Cooperative Oncology Group (ECOG) score ≤ 1 ; life expectancy ≥ 3 months; at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1); failure of fluoropyrimidine-based chemotherapy, anti-VEGF and anti-EGFR treatment; hemoglobin ≥ 9 g/dL, neutrophils $\geq 1500/\text{mm}^3$, platelets $\geq 100\,000/\text{mm}^3$, total bilirubin ≤ 1.5 upper limit of normal (ULN), aspartate transferase, alanine transferase, and alkaline phosphatase ≤ 2.5 ULN (≤ 5 ULN in cases of hepatic metastasis), lipase ≤ 1.5 ULN, prothrombin time $\geq 70\%$, creatinine clearance ≥ 30 mL/min, informed consent; and completed geriatric questionnaires at the time of enrollment.

Non-inclusion criteria were the inability to swallow oral tablets; prior treatment with regorafenib or another multi-kinase inhibitor; previous or concurrent other

cancer within 5 years prior to enrollment (except for curatively treated cervical *in situ* cancer, non-melanoma skin cancer, or superficial bladder tumor); extended field radiotherapy within 4 weeks or limited field radiotherapy within 2 weeks prior to the start of study drug. We also excluded unresolved toxicity higher than NCI-CTCAE v 4.0 Grade 1 attributed to any prior therapy/procedure; major surgical procedure, open biopsy, or significant traumatic injury within 28 days; congestive heart failure classified as New York Heart Association (NYHA) Class ≥ 2 ; unstable angina or new-onset angina within the last 3 months; myocardial infarction, uncontrolled hypertension, pheochromocytoma, arterial or venous thrombotic or embolic within the previous 6 months; active clinically serious infection, human immunodeficiency virus infection or hepatitis B or C requiring treatment with antiviral therapy; liver cirrhosis; brain metastases; hemorrhage \geq grade 3 within 4 weeks; non-healing wound, ulcer, or bone fracture; interstitial lung disease; proteinuria \geq grade 3; any malabsorption condition; medical, psychological or social condition that may interfere with participation in the study or evaluation of the study results; known hypersensitivity to the study drug; systemic anti-cancer therapy during this trial or within 4 weeks; and concomitant use of strong inhibitors or strong inducers of CYP3A4 activity and/or of strong UGT1A9 inhibitors.

The ethics committee (CPP Ile de France 10, protocol 23-2015) approved the study and the trial was registered at ClinicalTrials.gov (NCT02788006).

Study design

This multicenter, single-arm exploratory phase II trial evaluated regorafenib monotherapy at an initial dose of 160 mg once daily orally (21 days on, 7 days off treatment). Dose interruptions and/or dose reductions might be required based on individual safety and tolerability. The compliance of treatment was assessed with a patient-diary. Patients received the treatment until disease progression or death, regorafenib dose reduction by more than two dose levels (<80 mg/day) or regorafenib interruption for more than four consecutive weeks, consent withdrawal, investigator's opinion considering that continuation in the study was harmful to the patient's well-being. Radiological assessments were performed every 8 weeks (abdominal and thoracic computed tomography scan or MRI) and tumor response was evaluated by RECIST 1.1. The tumor *RAS* and *BRAF* mutation status was collected if available, but was not mandatory for enrollment and not specifically required for the study.

Geriatric questionnaire

A geriatric questionnaire was completed at inclusion either by the oncologist's team or during a geriatric assessment. In this study, the geriatric assessment did not result in additional planned medical interventions. Geriatric assessments investigated the Geriatric 8 (G8) score [12], quality of life (QoL) using the Spitzer index [13], co-morbidities according to the modified Charlson comorbidity scale [14], functional status by the Instrumental Activities of Daily Living (IADL) Lawtons scale adapted for sex-specific questions according to the patient and the

Activities of Daily Living (ADL) scale [15], mobility with one-leg balance [16], nutrition using the Mini-Nutritional Assessment Short-Form (MNA-SF) [17] and body mass index (BMI), cognition with the Mini-Cog scale [18], depression with the brief version of the Geriatric Depression Scale (Mini-GDS) [19], energy evaluated by the patient on a 1 to 10 scale [20], physical activity by the aging Risk Factor Questionnaire (RFQ) [21], social support evaluated by the presence or absence of a caregiver, along with questions on hearing and reading.

IADL and Spitzer QoL scores were repeated every 8 weeks to assess time to autonomy degradation and time to QoL degradation.

Statistical analysis

The primary objective of the REGOLD trial was to evaluate the disease control rate (DCR) under treatment, which was defined as the number of patients with a complete or partial response, or stable disease with regorafenib at 2 months post-initiation of study therapy. In the phase III CORRECT study, tumor control was achieved in 41% of the patients at least 6 weeks after randomization [10] but was not specifically reported for older patients. The sample size was calculated according to the following hypothesis: if at 2 months the DCR is $\leq 25\%$ the treatment should be considered to not have sufficient efficacy in the study population, whereas if the 2-months DCR is $>25\%$ the treatment is considered as having efficacy. With a single-sided α risk of 5% and a power of 90%, 42 patients were to be enrolled in the study.

Secondary endpoints included progression-free survival (PFS), OS, objective response rate, safety, survival without autonomy deterioration, and survival without QoL deterioration.

PFS was defined as the time from inclusion to first disease progression or death. OS was defined as the time between inclusion and all-cause death. Survival without autonomy deterioration was defined as the time from inclusion to the first decrease in IADL score ≥ 1 point or death compared to baseline score, or all-cause death. Survival without QoL deterioration was defined as the time from inclusion to the first decrease in Spitzer QoL index ≥ 2 points or death as compared with baseline, or all-cause death. Patients alive without disease progression or deteriorated autonomy or QoL were censored at the last follow-up. Survival analyses were done using the Kaplan–Meier method and described using median with 95% two-sided CI.

All patients with mCRC who were receiving at least one dose of treatment were included in the analysis of the safety population (SP). The primary endpoint was analyzed on a modified ITT (mITT) population defined as all patients who received at least one tablet of regorafenib and who had a clinical or radiological evaluation from 2 to 3 months after starting treatment. Patients who died before 3 months without any evaluation were included in the mITT.

Exploratory analyses to determine predictive factors of the primary endpoint, as well as on PFS and OS were performed. Odds ratios (OR) and 95% confidence intervals (95% CIs) were estimated. Univariate and multivariate Cox proportional-hazards models were used to explore potential prognostic factors, estimating

hazard ratios and 95% CIs. Variables with $p < 0.20$ on univariate analyses were used in multivariate analyses. For geriatric variables, the associated scores were calculated and considered missing when one of the items was not available.

Qualitative and continuous variables are described with numbers (%) or median (interquartile range, Q1-Q3). Analyses involved the use of SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient's characteristics

Between January 2016 to April 2017, 43 patients were enrolled in the trial. One patient did not receive any treatment and was not included in the SP. Thus, the SP was 42 patients. One patient with ECOG 2 was enrolled in the trial. Seven patients did not have clinical or radiological evaluation at 2 to 3 months and were not included in the mITT population for the primary endpoints analysis. The median follow-up was 23.1 months (95% CI 13.7-24.5). Baseline characteristics of the patients are presented in Table 1. The median age was 77 years (range 70 to 91) and 15 (35.7%) patients were ≥ 80 years. Most patients had previously received irinotecan, oxaliplatin, and an antiangiogenic monoclonal antibodies. Geriatric characteristics are presented in Table 2. The G8 score was ≤ 14 in 66.7% of the patients, the autonomy scores ADL was impaired in 38.5% and the IADL in 43.9% of the patients.

Efficacy

The 2-months DCR was 31.4% (90% CI 18.7%-46.6%) in the mITT population. The rules have been reviewed for 35 patients (with unilateral α risk of 5% and a power of 84%), if 14 or more patients were in complete or partial response or stable disease then the treatment should be considered as efficient. Among the 35 patients, only 11 had a DCR at 2 months. A centralized review was performed for 31 patients with an available CT scan at baseline and 2 months. Radiological tumor control was 48.4% (15 patients). No patient achieved an objective tumor response.

In exploratory analysis, no factor was significantly associated with a 2 months-DCR in a multivariate analysis (Table S1, supplementary). Nevertheless, there is a trend to achieve better DCR in patients ≤ 80 years. Indeed, 9/11 (81.8%) patients with DCR were ≤ 80 years and patients under 80 years had an odds ratio (OR) of 14.3 (OR >1 means higher disease control) for 2-months DCR ($p=0.0685$). Moreover, patients who received a mean daily dose of regorafenib of 160 mg during the first cycle had an OR of 11.8 for 2-months DCR ($p=0.0609$).

At the time of data cut-off (May 2018), all patients had progression and 36/42 (85.7%) patients had died. The median PFS in the SP was 2.2 months (95% CI 2.0-3.3) (Figure 1A). The 3-months PFS rate was 40.5% (95% CI 25.8-54.7). No factor was significantly associated with PFS in a multivariate analysis (Table S2, supplementary). The median OS in the SP was 7.5 months (95% CI 5.5-10.6) (Figure 1B). The 9-months OS rate was 42.9% (95% CI 27.8-57.1) and the 12-months OS rate was 35.7% (95% CI 21.7-49.9). The presence of a caregiver, <3 metastatic sites, and a tumour harbouring *RAS* mutation were significantly

associated with a better survival in multivariate analysis (Table S3, supplementary). As there is a trend for better 2-months DCR in the sub-group of patients ≤ 80 compare to patients >80 years, the PFS and OS curves are presented (Supplementary Figure S1).

Survival without autonomy deterioration and QoL deterioration

Twenty-eight patients (66.7%) patients had completed at least one IADL questionnaire after enrollment. The median survival without autonomy degradation was 3.1 months (95% CI 2.4-5.4) (Figure 2A). At 3 months, 51.7% (95% CI 35.2-65.9) of patients were alive without deteriorated autonomy. Twenty-six (61.9%) patients had completed at least one Spitzer QoL questionnaire during the planned evaluation after enrollment. The median survival without QoL degradation was 3.2 months (95% CI 2.0-5.5) (Figure 2B). At 3 months, 55.1% (95% CI 37.9-69.3) patients were alive without deteriorated QoL.

Treatment administration and tolerance

A total of 117 cycles were analyzed, the median duration of treatment was 45 days (range 5 to 440) and the median number of cycles per patient was 2 (range 1 to 16). Thirteen (31%) patients received a mean daily dose during the first cycle below the recommended dose of 160 mg per day. Among them, three patients started the treatment with a dose below 160 mg. Fifteen patients (36%) had at least one cycle delayed. A dose reduction was observed in 64 (55%) cycles for 28 (67%) patients. Forty-eight (41%) cycles were at dose of 160 mg, 39 (33%) at

dose of 120 mg, 14 (12%) at dose of 80 mg and 16 (14%) at other doses. The mean daily dose was 140.7 mg (standard deviation 19.9) and the median daily dose was 142.0 mg (range 95 to 160 mg). Among the 35 patients evaluable for DCR analysis at 2 months, the compliance was similar for patients with 2-months DCR and for those without DCR (compliance <50%: 1/11 (9%) vs 4/24 (17%), compliance from 50% to 80%: 5/11 (46%) vs 9/24 (38%) and compliance ≥80%: 5/11 (46%) vs 11/24 (46%). Causes of dose reduction were mainly asthenia, diarrhea, and hand-foot syndrome. The treatment was stopped due to toxicity without progression in 12 (28.6%) patients. Among them 10 (83.3%) were ECOG 1, 6 (50%) were >80 years and 6 (50%) had abnormal baseline ADL. Grade 3-4 treatment-related adverse events were observed in 35 (83.3%) patients, mainly: fatigue (45.2%), hand-foot skin reaction (19.0%), hypertension (21.4%) and diarrhea (7.1%) (Table 3). No toxic death was observed.

The 13 patients that have a dose reduction during the first cycle had a similar tolerance and QoL evolution compare to those of the 29 patients that have no dose reduction during the first cycle: 76.9% versus 65.5% of grade 3-4 adverse event during the first cycle and 50% versus 43.8% of patients with a decrease in Spitzer QoL index ≥2 points at the first evaluation respectively.

Eighteen (42.8%) patients received at least one systemic anti-cancer treatment after progression: chemotherapy only in 11 (26.2%) patients, chemotherapy + anti-angiogenic in 5 (11.9%) patients, anti-angiogenic alone in one patient, and anti-EGFR in one patient.

Discussion

Our study is the first phase II trial that specifically evaluated the tolerance and efficacy of regorafenib in older patients with mCRC at its registered approved dose and regimen. One subgroup analysis on patients over 65 derived from the pivotal study was reported in the poster of phase III CORRECT study [11]. In this study, the OS in the regorafenib group was not significantly improved compared with the placebo.

The 2-months DCR observed in our study was numerically lower than the DCR rate of 41% observed at 6 weeks in the CORRECT study [10]. The primary endpoint was not met in our study. Nevertheless, the DCR of 31.4% observed in our study is numerically higher than the DCR of 15% observed in the placebo group in the CORRECT study. Moreover, the PFS was 2.2 months and the median OS was 7.5 months in our study that is slightly longer than the PFS and OS observed in the CORRECT study that was 1.9 and 6.4 months respectively [10] but shorter than the PFS and OS observed in the Asian CONCUR study that was 3.2 and 8.8 months [22]. In the CONCUR study, a sub-group analysis suggests that prior exposure to targeted therapies is associated with worse OS of patient treated with regorafenib. It must be pointed out that in our study the majority of patients had received targeted therapy prior to enrollment (100% of patients with *RAS* wild type tumor had received anti-EGFR therapy and 83% of all the patients had received anti-angiogenic treatment) compared to 59% of the patient in the CONCUR study. In our study, the 12-months OS rate of 35.7% was higher than the 12-months OS rate observed in CORRECT trial (24.3%) [10] and

also observed in a large compassionate cohort of patient in the REBECCA study, treated with regorafenib (24%) [23] but near to the 33.8%, 12-months OS rate observed in a recent prospective international cohort CORRELATE study [24]. Altogether, the efficacy results in our study are similar to previous ones in younger patients.

In our study, the exploratory analysis found no prognostic factor for 2-months DCR but most patients achieving this endpoint were under 80 and have started regorafenib at 160 mg. No prognostic factor was identified for PFS. The presence of a caregiver, a number of metastatic sites <3 and a tumour *RAS* mutated were significantly associated with a better survival in multivariate analysis. *RAS* mutation status was previously reported as a pejorative prognostic factor for OS in one study [23] and have no prognostic value in other studies [10] [22]. Except for caregiver for OS, no geriatric parameter was identified in our study. In previous clinical trials assessing older patients treated in front line for mCRC, normal IADL [25] and high baseline QoL [9] were associated with better OS outcomes. The main limitation of our study is the small sample size and the failure to evaluate the primary endpoint in the pre-specified number of patient. The prognostic factors in advanced line in older patients deserve further evaluation with standardization across the trial. Recently, a core set of geriatric data to be methodically collected in clinical cancer trials of older adults has been proposed [26]. In our study, we have restricted the enrollment to patient with good performance status (0 or 1) as in the CORRECT [10] and CONCUR [22] trials. Our findings could not be generalized to the patients with ECOG >1.

A higher rate of grade 3-4 related-adverse events was reported in our study (83.3%) compared to previous studies in younger patients, 54% in CORRECT [10] and CONCUR study [22] and 43.7% in REBECCA study [23]. Severe fatigue was reported more frequently in our trial than in previous studies not specifically conducted in older patients (45.2% compared to 10% [10], 3% [22] and 14.5% [23]). Severe fatigue was reported in 16% for patients over 75 in the sub-group analysis of CORRECT trial [11]. A sub-group analysis of patients ≥ 75 years enrolled in a prospective cohort of CONSIGN study reported 64% of grade ≥ 3 with 22% of grade ≥ 3 fatigue [27]. Even if the discrepancy between all these studies suggests heterogeneity of collected data, severe fatigue was the most frequent and limiting toxicity in older. The other frequent severe adverse event in our study was hand-foot skin reaction (19%). The frequency of grade 3-4 hand-foot skin reactions in our study was similar to CORRECT trial (17%) [10], in the sub-group analysis of patients over 75 in the CORRECT trial (18%) [11], and CONCUR trial (16%) [22] but higher compared to REBECCA study (9%) [23] and in the CORRELATE study (7%) [24]. Discontinuation of regorafenib for all types of adverse events without progression occurs in 28.6% compared to 32% in the CORRELATE [24] study but only 14% observed in CONCUR trial [22]. As to patient characteristics, ECOG >0 , age >80 years and abnormal ADL seems associated with more permanent drug discontinuations due to toxicity, however, this has to be considered cautiously and requires further evaluation, because of the small numbers in our study.

Despite the relatively high frequency of adverse events, QoL and autonomy was preserved during the treatment time in our study. This result is in accordance with previous observations in randomized trials showing no degradation of QoL in patients treated with regorafenib compared to patients receiving placebo [10] [22].

The mean daily dose of regorafenib of 140.7 mg observed in our study was similar to that in the CORRECT study (147.1 mg) [10] and CONCUR study (145.4 mg) [22]. Nevertheless, the incidence of adverse events related to regorafenib in patients over 80 years might require treatment adaptation. A recent alternative regimen of regorafenib 2 weeks-on treatment and one week off was evaluated in 23 fit older patients with mCRC who progressed after oxaliplatin and irinotecan based-chemotherapy [28]. The authors reported a DCR at 2 months of 52.2%, a PFS of 4.8 months and an OS of 8.9 months. Patients enrolled in the Petrioli et al. study were more strictly selected than in our study (most patients with a G8 score over 14) and only 39% of the patient previously treated by anti-angiogenic treatment. Nevertheless, these results suggest that the 2/1 schedule may be more adapted for older patients. Moreover, a recent randomized phase II ReDOS trial reported that an 80 mg starting dose with planned dose escalation of regorafenib compared to the conventional regimen using a 160 mg starting dose is associated with a higher number of patients starting cycle 3 and a trend to a better OS [29]. Thus, according to our results suggesting a higher drop-out rate in the more older and frail patients, an

alternative regimen with dose escalation would be interesting to evaluate in frail or patients over 80 years.

In conclusion, treatment with regorafenib in heavily pretreated older patients gave a tumor control at 2 months of around 30% of patients. The median PFS and OS were similar to those observed in the previous phase III and observational trials in younger patients. Fatigue was the most common severe adverse event observed. Overall, regorafenib therapy looks manageable in patients ≥ 70 years, however, even if no conclusion can be drawn due to the small sample size, the drop-out rate for treatment toxicity seems higher in patients with ECOG=1, age over 80 years, and impaired baseline ADL suggesting that in this population where QoL and toxicity are highly valued, alternative dosing, such as escalation schedule, should be strongly considered.

Acknowledgements:

We thank the operational team (statisticians, data manager and CRAs), with K.Le Malicot, C.Choine, C Fuchey, F.Guiliani, N.Lasmi, G.Arnould, N.Guiet, M.Maury-Negre, H.Fattouh, N.Le Provost, L Gaba, and C.Girault for editing support and Bayer France for financial support.

Funding:

This work was supported by a grant of Bayer.

Conflict of Interests statement

Thomas Aparicio declared Honoraria from Sanofi, Roche, Amgen, BMS, Servier and Ipsen Pharma; Consultancy / Advisory role for Ipsen Pharma, Pierre Fabre, BMS and HalioDX ; Travel accommodations from Novartis, Ipsen Pharma, Bayer and Roche.

Pascal Artru declared personal fees from Bayer (advisory board).

Ariane Darut-Jouve declared travel accommodations from Novartis.

Faiza Khemissa Azouk declared personal fees from Sanofi, Roche and Ipsen (general honoraria); non-financial support from Roche and Bayer (travel paid).

Olivier Romano declared grant and personal fees from Amgen, Roche and Pfizer.

All other authors declare no competing interests.

Author Contributions

Study design: T. Aparicio, G. Des Guetz, C. Montérymard, F. Pamoukdjian

Data acquisition: T. Aparicio, A. Darut-Jouve, F. Khemissa Akouz, P. Artru, L. Cany, O. Romano, B. Valenza, C. Le Foll, C. Delbaldo, C. Falandry, E. Norguet Monnereau, M. Ben Abdelghani, D Smith, Y. Rinaldi, D. Père Verge, N. Baize, E Maillard, C. Lepage.

Data analysis and interpretation: T. Aparicio, A Dohan, C Montérymard

Statistical analysis: C. Montérymard

Manuscript writing: T. Aparicio, C. Montérymard

All named authors have given final approval of the version to be published; and have agreed to be accountable for all aspects of the work.

Figure legend

Figure 1A: Progression-free survival in safety population

Figure 1B: Overall survival in safety population

Figure 2A: Survival without autonomy degradation according instrumental activities of daily living (IADL)

Figure 2B: Survival without quality of life degradation

References

- 1 Holleczech B, Rossi S, Domenic A, *et al.* On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EURO CARE-5 study. *Eur J Cancer* 2015;**51**:2158–68. doi:10.1016/j.ejca.2015.07.024
- 2 Aparicio T, Pamoukdjian F, Quero L, *et al.* Colorectal cancer care in elderly patients: Unsolved issues. *Dig Liver Dis* 2016;**48**:1112–8. doi:10.1016/j.dld.2016.05.011

- 3 Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**:2335–42. doi:10.1056/NEJMoa032691
- 4 Bennouna J, Sastre J, Arnold D, *et al.* Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;**14**:29–37. doi:10.1016/S1470-2045(12)70477-1
- 5 Van Cutsem E, Tabernero J, Lakomy R, *et al.* Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;**30**:3499–506. doi:10.1200/JCO.2012.42.8201
- 6 Tabernero J, Yoshino T, Cohn AL, *et al.* Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015;**16**:499–508. doi:10.1016/S1470-2045(15)70127-0
- 7 Cunningham D, Lang I, Marcuello E, *et al.* Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;**14**:1077–85. doi:10.1016/S1470-2045(13)70154-2
- 8 Aparicio T, Bouché O, Taieb J, *et al.* Bevacizumab+chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: a randomized phase II trial-PRODIGE 20 study results. *Ann Oncol* 2018;**29**:133-38. doi:10.1093/annonc/mdx808
- 9 Aparicio T, Bouché O, Francois E, *et al.* Geriatric analysis from PRODIGE 20 randomized phase II trial evaluating bevacizumab + chemotherapy versus chemotherapy alone in older patients with untreated metastatic colorectal cancer. *Eur J Cancer* 2018;**97**:16–24. doi:10.1016/j.ejca.2018.03.030
- 10 Grothey A, Van Cutsem E, Sobrero A, *et al.* Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;**381**:303–12. doi:10.1016/S0140-6736(12)61900-X
- 11 Van Cutsem E, Sobrero A, Siena S, *et al.* Regorafenib in progressive metastatic colorectal cancer: Analysis of age subgroups in the phase III CORRECT trial. *J Clin Oncol* 2013; 31, (suppl; abstr 3636).
- 12 Bellera CA, Rainfray M, Mathoulin-Pélissier S, *et al.* Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012;**23**:2166–72. doi:10.1093/annonc/mdr587

- 13 Spitzer WO, Dobson AJ, Hall J, *et al.* Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. *J Chronic Dis* 1981;**34**:585–97.
- 14 Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;**173**:676–82. doi:10.1093/aje/kwq433
- 15 Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* 1983;**31**:721–7.
- 16 Vellas BJ, Wayne SJ, Romero L, *et al.* One-leg balance is an important predictor of injurious falls in older persons. *J Am Geriatr Soc* 1997;**45**:735–8.
- 17 Rubenstein LZ, Harker JO, Salvà A, *et al.* Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;**56**:M366-372.
- 18 Borson S, Scanlan JM, Watanabe J, *et al.* Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample. *J Am Geriatr Soc* 2005;**53**:871–4. doi:10.1111/j.1532-5415.2005.53269.x
- 19 Clément JP, Nassif RF, Léger JM, *et al.* [Development and contribution to the validation of a brief French version of the Yesavage Geriatric Depression Scale]. *L'Encephale* 1997;**23**:91–9.
- 20 Bandeen-Roche K, Xue Q-L, Ferrucci L, *et al.* Phenotype of frailty: characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci* 2006;**61**:262–6.
- 21 Davis HS, MacPherson K, Merry HR, *et al.* Reliability and validity of questions about exercise in the Canadian Study of Health and Aging. *Int Psychogeriatr* 2001;**13 Supp 1**:177–82.
- 22 Li J, Qin S, Xu R, *et al.* Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015;**16**:619–29. doi:10.1016/S1470-2045(15)70156-7
- 23 Adenis A, de la Fouchardiere C, Paule B, *et al.* Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBECCA) nested within a compassionate use program. *BMC Cancer* 2016;**16**:412. doi:10.1186/s12885-016-2440-9
- 24 Ducreux M, Petersen LN, Oehler L, *et al.* Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective,

observational CORRELATE study. *Eur J Cancer*. 2019;**123**:146-154. doi: 10.1016/j.ejca.2019.09.015.

25 Aparicio T, Gargot D, Teillet L, *et al*. Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderly metastatic colorectal cancer patients. *Eur J Cancer* 2017;**74**:98–108. doi:10.1016/j.ejca.2016.09.029.

26 Paillaud E, Soubeyran P, Caillet P, *et al*. Multidisciplinary development of the Geriatric Core Dataset for clinical research in older patients with cancer: A French initiative with international survey. *Eur J Cancer*. 2018; **103**:61-68. doi: 10.1016/j.ejca.2018.07.137.

27 Van Cutsem E, Martinelli E, Cascinu S, *et al*. Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: Results of the large, single-arm, open-label phase IIIb CONSIGN study. *The Oncologist* 2018. doi: 10.1634/theoncologist.2018-0072

28 Petrioli R, Chirra M, Messuti L, *et al*. Efficacy and Safety of Regorafenib With 2/1 Schedule for Patients ≥ 75 Years With Metastatic Colorectal Cancer (mCRC) After Failure of 2 Lines of Chemotherapy. *Clin Colorectal Cancer* 2018;**17**:307–12. doi:10.1016/j.clcc.2018.02.005

29 Bekaii-Saab T, Ou FS, Ahn DH, *et al*. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol* 2019;**20**(8):1070-1082. doi: 10.1016/S1470-2045(19)30272-4.

Table 1: Patient Characteristics

Characteristics	N=42 (%)
Age:	
Median, years (range)	77 (70-91)
Age >80 years	15 (35.7%)
Gender:	
Male	28 (66.7%)
ECOG:	
0	16 (38.1%)
1	25 (59.5%)
2	1 (2.4%)
Time from metastases diagnosis to enrollment:	27 months (4-107)
≤18 months	5 (11.9%)
≥18 months	37 (88.1%)
Primary (n=41) :	
Right colon	12 (29.2%)
Left colon	9 (22.0%)
Rectum	20 (48.8%)
Primary resected	36 (85.7%)
Liver metastases :	
Yes	31 (73.8%)
No	11 (26.2%)
Number of metastatic sites:	
<3	32 (76.2%)
≥3	10 (23.8%)
Carcinoembryonic antigen level [#] (n=38) :	
<40 µg/L	12 (31.6%)
≥40 to <130 µg/L	14 (36.8%)
≥130 µg/L	12 (31.6%)

Molecular tumor status:	
<i>RAS</i> (n=40): mutant	24 (60.0%)
<i>BRAF</i> (n=33): mutant	0 (0%)
Median number of previous lines	3 (1-8)
Previous treatment:	
Irinotecan	39 (92.9%)
Oxaliplatin	29 (69.0%)
Bevacizumab or aflibercept	35 (83.3%)
Cetuximab or panitumumab	17 (40.5%)

LN: limit of normal, BMI: body mass index, ECOG: Eastern Cooperative Oncology Group.

Classes based on tertiles

Table 2: Geriatric characteristics

Geriatric characteristics	N=42 (%)
Hospitalisation <12 months (n=40)	13 (32.5%)
Modified Charlson Comorbidity (n=38) :	
6	35 (92.1%)
7	1 (2.6%)
8	1 (2.6%)
10	1 (2.6%)
Fail one-leg balance (n=39)	11 (28.2%)
Fall <6 months (n=41)	6 (14.6%)
ADL <6 (n=39)	15 (38.5%)
IADL* <14 (n=41)	18 (43.9%)
Body Mass Index <21 (n=42)	6 (14.3%)
MNA-SF \leq 11 (n=42)	30 (76.9%)
G8 \leq 14 (n=39)	26 (66.7%)
Abnormal Mini-Cog (n=38)	4 (10.5%)
Mini-GDS \geq 1 (n=39)	14 (35.9%)
Energy score <3 (n=40)	0 (0.0%)
Weak or no exercise (n=39)	21 (53.8%)
No caregiver (n=41)	7 (17.1%)
Spitzer QoL index <8 (n=40)	9 (22.5%)
Hearing impairment (n=39)	19 (48.7%)
Reading impairment (n=35)	3 (8.6%)

ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, MNA-SF: Mini-Nutritional Assessment Short-Form, Mini-Cog: Mini-Cognition evaluation, Mini-GDS: Mini-Geriatric Depression Scale,

* IADL adapted for sex-specific questions according to the patient.

Table 3: Treatment-related adverse events occurring in >5% of patients

Adverse event	N=42 (%)	
	Grade 1-2	Grade 3-4
Any event	41 (97.6)	35 (83.3)
Clinical events		
Anorexia	21 (50.0)	2 (4.8)
Fatigue	19 (45.2)	19 (45.2)
Hand-foot skin reaction	10 (23.8)	8 (19.0)
Diarrhea	14 (33.3)	3 (7.1)
Dysphonia	9 (21.4)	1 (2.4)
Hypothyroidism	9 (21.4)	0
Constipation	8 (19.0)	2 (4.8)
Oral mucositis	6 (14.3)	1 (2.4)
Abdominal pain	5 (11.9)	1 (2.4)
Muscle pain	5 (11.9)	0
Hypertension	5 (11.9)	9 (21.4)
Fever	5 (11.9)	0
Nausea	4 (9.5)	0
Headache	3 (7.1)	1 (2.4)
Dysgeusia	3 (7.1)	0
Biological events		
Hyperbilirubinemia	20 (47.6)	1 (2.4)
Thrombocytopenia	20 (47.6)	0
Elevated GGT	19 (45.2)	3 (7.1)
Elevated transaminase	16 (38.1)	1 (2.4)
Anemia	14 (33.3)	0
Hypocalcemia	14 (33.3)	0
Elevated alkaline phosphatase	13 (31.0)	1 (2.4)
Proteinuria	7 (16.7)	1 (2.4)

Hyponatremia	7 (16.7)	1 (2.4)
Elevated lipase	5 (11.9)	2 (4.8)
Neutropenia	4 (9.5)	0
Hypophosphatemia	4 (9.5)	3 (7.1)
Hypoalbuminemia	3 (7.1)	0
Hypokaliemia	3 (7.1)	0
Hypomagnesemia	3 (7.1)	0

GGT: gamma-glutamyl-transferase.

Figure 1A: Progression free survival in safety population

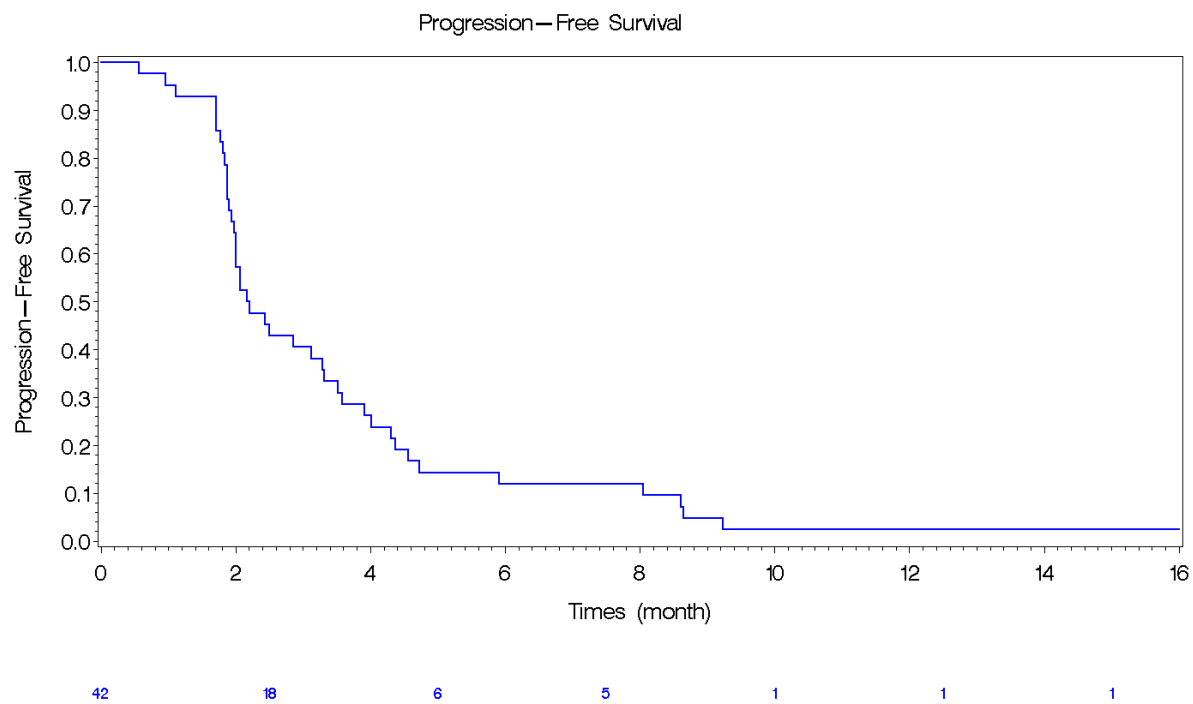


Figure 1B: Overall survival in the safety population

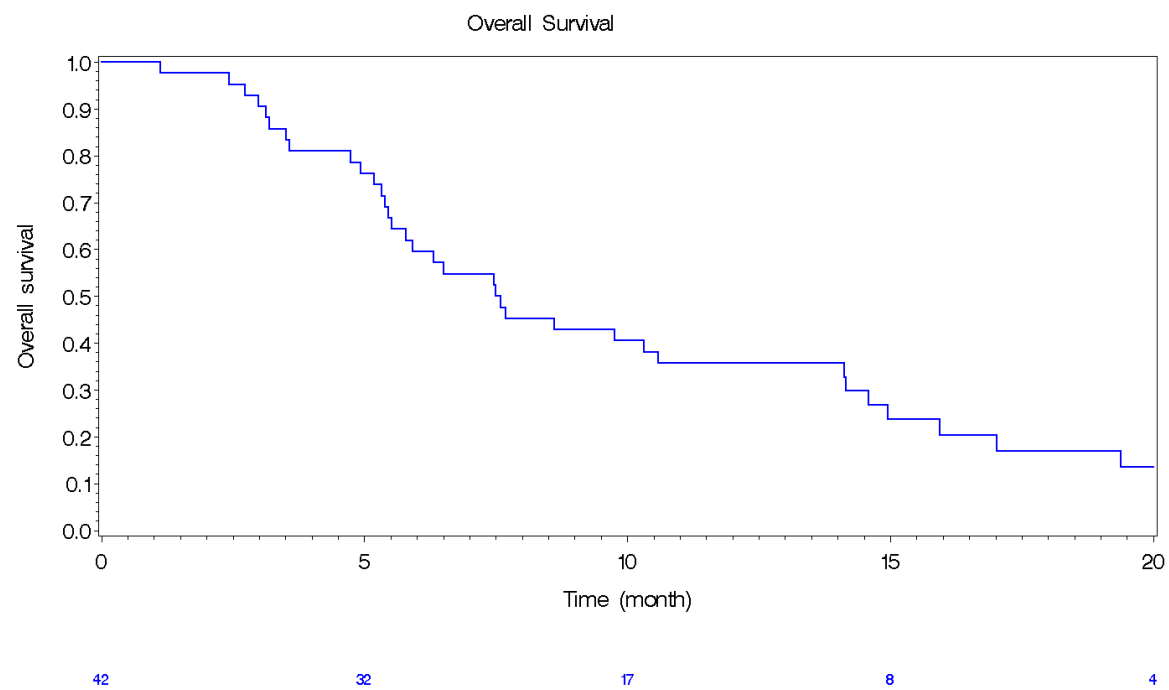


Figure 2A: Survival without autonomy degradation (IADL)

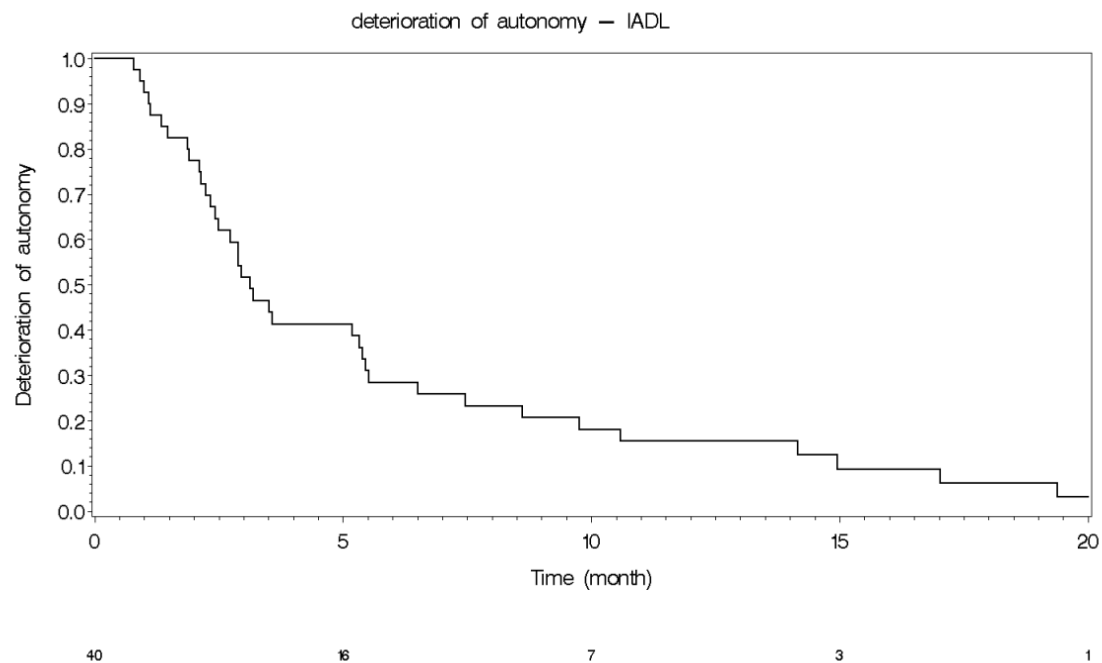


Figure 2B: Survival without quality of life degradation

