Bevacizumab + chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: a randomized phase II trial - PRODIGE 20 study results


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Running head: Bevacizumab for elderly patients with advanced colorectal cancer

Previous presentation: this work was presented at the annual ASCO meeting in 2015 and ESMO 2016.
ABSTRACT

BACKGROUND Metastatic colorectal cancer frequently occurs in elderly patients. Bevacizumab in combination with front line chemotherapy is a standard treatment but some concern raised about tolerance of bevacizumab for these patients. The purpose of PRODIGE 20 was to evaluate tolerance and efficacy of bevacizumab according to specific endpoints in this population.

PATIENTS AND METHODS Patients aged 75 and over were randomly assigned to bevacizumab + chemotherapy (BEV) versus chemotherapy (CT). LV5FU2, FOLFOX and FOLFIRI regimen were prescribed according to investigator’s choice. The composite co-primary endpoint, assessed 4 months after randomization, was based on efficacy (tumor control and absence of decrease of the Spitzer QoL index) and safety (absence of severe cardiovascular toxicities and unexpected hospitalization). For each arm, the treatment will be consider as inefficient if 20% or less of the patients met the efficacy criteria and not safe if 40% or less met the safety criteria.

RESULTS 102 pts were randomized (51 BEV and 51 CT), median age was 80 years (range 75-91). Primary endpoint was met for efficacy in 50% and 58% and for safety in 61% and 71% of patients in BEV and CT respectively. Median progression-free survival was 9.7 months in BEV and 7.8 months in CT. Median overall survival (OS) was 21.7 months in BEV and 19.8 months in CT. The 36-months OS rate was 27% in BEV and 10.1% in CT. Severe toxicities grade 3/4 were mainly non hematologic toxicities (80.4% in BEV, 63.3% in CT).

CONCLUSION Bevacizumab combined with chemotherapy was safe and efficient. Both arms met the primary safety and efficacy criteria.

Key words
Key message

Tolerance and efficacy of antiangiogenic therapy for metastatic colorectal cancers remains a concern in older patients. The results of our phase II showed that bevacizumab combined with chemotherapy was safe and efficient according to the composite co-primary endpoint. A prolonged overall survival was observed in patient treated by bevacizumab combined with chemotherapy.
Introduction

Colorectal cancer (CRC) occurs mainly in elderly patients. Recent European evaluation reported that 38.5% of CRC patients were over 75 (1). Several concerns have risen about the care of elderly due to the age-related comorbidities and functional status (2). Moreover, elderly patients are underrepresented in clinical trials, thus the transposition for elderly of current guidelines established in younger patients should be taken with caution (3; 4).

In first line metastatic CRC (mCRC), bevacizumab combined with irinotecan has demonstrated an overall survival (OS) advantage compare to irinotecan based chemotherapy alone (5) and an improvement of progression-free survival (PFS) in combination with 5-fluorouracil (FU) compare to single FU regimen in patients considered unfit for a doublet chemotherapy regimen (6).

Two recent phase III trials comparing capecitabine alone or combined with bevacizumab have focused on elderly patients. Both studies reported a PFS improvement in the bevacizumab arm (7; 8) without significant OS improvement. Some concerns also raised for the use of usual oncologic endpoints as OS and PFS in elderly patients (9). It has been reported that if elderly patients have a good acceptance of chemotherapy they are less willing to have a toxicity than their younger counterparts (10). Moreover, unplanned hospitalization is a concern in elderly patients as it can delay scheduled treatment and result in functional decline (11). A recent guideline of the International Society of Geriatric Oncology (SIOG) recommends to the use of composite endpoint evaluating quality of life (QoL) and global toxicity for mCRC trials in elderly (12). According to these recommendations we built specifically for PRODIGE 20 trial a composite endpoint assessing efficacy.
(tumor control rate and QoL evaluation) and safety (unexpected hospitalization and severe cardiovascular toxicity).

Several studies have demonstrated that doublet chemotherapy have a limited effect on PFS and did not prolong OS compare to fluoropyrimidine alone in elderly patients (13; 14). Nevertheless, the SIOG guideline recommends doublet chemotherapy in fit elderly patients (12). Thus, it is important to allow chemotherapy choice according to investigator evaluation.

Patients and Methods

Patient selection
The eligibility criteria were histologically confirmed unresectable mCRC, age ≥75 years, ECOG ≤2, ≥1 measurable lesion according RECIST 1.1, no previous chemotherapy for metastatic disease, adjuvant therapy if stopped at least 6 months before randomization, and geriatric questionnaires’ fulfilled. Uneligibility criteria were symptomatic bowel obstruction, brain metastasis, other malignant tumor, surgery in the previous 4 weeks, neutrophils <1500/mm³, platelets <100000/mm³ or proteinuria >1g/24h, wound or gastric ulcer and following disease during the last 12 months previous randomization: uncontrolled hypertension, myocardial infarction, cardiac insufficiency, stroke, arterial ischemia grade>2, pulmonary embolism. Written informed consent was obtained for each patient. The study was approved by the Ethics Committee (CPP EST I DIJON n°100109 in January 26, 2010) and registered in clinicaltrials.gov with the number NCT01900717.

Study design
This phase II trial was a randomized non-comparative phase II study evaluating bevacizumab combined with chemotherapy (BEV) and chemotherapy alone (CT) in patients with mCRC aged 75 or more. The chemotherapy regimen was chosen by the investigators before randomization according to their clinical evaluation. The following regimens were authorized: simplified LV5FU2, modified FOLFOX6 and modified FOLFIRI (13) (supplementary material). Randomization was stratified according to chemotherapy (FU monotherapy versus doublet), primary tumor (resection versus no resection), Spitzer QoL (0-3 versus 4-7 versus 8-10) (15). The recommended treatment duration was a minimum of 6 months, but investigators could decide to continue the treatment until progression. All toxicities were graded according to the US National Cancer Institute Common Toxicity Criteria (version 4.0). Serious adverse events were also reported. Radiological assessments were performed every 8 weeks (abdominal and thoracic CT scan or MRI) and tumor response was evaluated according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria (version 1.1). An ancillary geriatric study was planned. Statistical analysis are described in supplementary material.

**Primary endpoint and sample size**

This trial was designed to evaluate a composite co-criterion assessed 4 months after randomization and based on efficacy co-criterion: tumor control (stable disease or objective response) and no decrease ≥2 points of the Spitzer QoL index; and safety co-criterion: absence of severe cardiovascular toxicities defined by arterial hypertension grade 4 or thromboembolic event grade 3-4 or cardiac insufficiency grade 3-4 or an unexpected hospitalization whatever the cause at the exception of chemotherapy administration. To demonstrate an efficacy co-criterion for more than
20% of the patients (40% expected) and a safety co-criterion for more than 40% of the patients (70% expected), 92 evaluable patients was needed (one-sided alpha=5%, power=90%). All patients with a mCRC, receiving at least one dose of treatment and with at least one efficacy assessment and one Spitzer evaluation after treatment, were considered evaluable and included in the modified intent-to-treat population (mITT). Assuming for 10% non-evaluable patients, 102 patients were randomized in the trial. The decision rules applied only for BEV arm were: if ≥15 patients met the efficacy co-criterion and if ≥25 patients met the safety co-criterion, the treatment was considered efficient and well tolerated.

Secondary endpoints

Secondary endpoints were objective tumor response rate (ORR), PFS, OS, and tolerance. ORR was defined as complete or partial response. PFS was defined as the time from randomization to first progression or death (all causes). Patients alive without progression were censored at the last follow-up. OS was defined as the time between randomization and death (all causes). Toxicity was reported by the maximum toxicity grade per patient and per toxicity term during the treatment.

Results

Baseline characteristics

Between July 2011 and July 2013, 51 patients were randomly assigned to CT and 51 to BEV (figure 1). The median follow-up was of 20.4 (Q1-Q3: 11.8-31.2) months. Two patients died without receiving any treatment in CT. Four patients did not have tumor or QoL evaluation at M4 in each arm and one patient was enrolled without documented mCRC in BEV. Thus, the mITT population for the primary endpoint was
45 patients in CT and 46 in BEV. The two groups were well-balanced with regards to baseline characteristics except for the choice of doublet as there is more FOLFOX in CT and FOLFIRI in BEV (table 1). The median age was 80 years (range 75-90). RAS status was not determined upfront before enrollment.

**Treatment administration**

The median duration of the treatment was 6.0 months (Q1-Q3: 3.3-9.9) in CT and 7.7 months (Q1-Q3: 3.7-20.3) in BEV. Chemotherapy was given for a median number of 12 cycles (Q1-Q3: 8-18) in CT and 16 cycles (Q1-Q3: 7-29) in BEV. All patients have stopped the study treatment at time of evaluation. At least one chemotherapy dose reduction was observed for 57.1% patients in CT and 70.6% patients in BEV. A dose reduction was observed in CT for 38% patients treated with FU and for 78% patients treated with doublet and in BEV for 65% patients treated with FU and for 76% patients treated with doublet. Two third of doses for all the CT component was administered in 75.5% patients in CT and 66.7% patients in BEV during the first 4 months of treatment. FU bolus was the product mainly interrupted. Treatment interruption was mainly due to disease progression in both arms (supplementary table S1).

**Primary composite co-criterion**

According to the decisions rules, both efficacy and safety objectives for BEV were reached: 23 patients met the efficacy co-criterion (50.0% [90% CI: 37.1-62.9]) and 28 patients met the safety co-criterion (60.9% [90% CI: 47.7-73.0]). BEV arm was considered efficient and well tolerated (table 2). A trend of a better tumor control in BEV arm but more QoL degradation, more unexpected hospitalization and more grade 3-4 cardiovascular toxicity is observed. An exploratory analysis did not found differences for composite criterion according the type of doublet regimen.
Indeed, there is small number on each group and no definitive conclusion could be drawn.

**Response rate, progression-free and overall survival**

The following data are indicative as PRODIGE 20 trial was not designed to compare the differences in efficacy between the two arms. The best ORR was 37.2% in BEV and 32.6% in CT (supplementary table S3).

Forty nine (96.1%) patients in CT and 50 (98.0%) patients in BEV have progressed or died. The median PFS was 7.8 months [95% CI: 6.6-10.2] in CT and 9.7 months [95% CI: 8.2-12.0] in BEV (HR 0.79, 95% CI 0.53-1.17) (figure 2A). The 12-months PFS rate was 23.5% [95% CI: 13.0-35.8] in CT and 37.3% [95% CI: 24.3-50.2] in BEV.

Forty five (88.2%) patients in CT and 44 (86.3%) patients in BEV have died. Median OS was 19.8 months [95% CI: 13.9-23.7] in CT and 21.7 months [95% CI: 14.8-30.3] in BEV (HR 0.73, 95% CI: 0.48-1.11; figure 2B). The 36-months OS rate was 10.1% [95% CI: 3.1-22.0] in CT and 27.0% [95% CI: 15.7-39.7] in BEV.

**Prediction of PFS and OS by both and combined composite co-criterion**

An exploratory analysis was performed to assess the predictive value of both and combined composite co-criterion for PFS and OS (supplementary table S4). Efficacy, safety and combined composite co-criterion were associated with PFS and OS.

**Tolerance**

The main severe adverse events (grade 3-4) in CT and BEV arm were respectively neutropenia (12.2% versus 11.8%), diarrhea (10.2% versus 9.8%), and thromboembolic events (6.1% versus 9.8%). As expected with bevacizumab, Grade 3-4 arterial hypertension was more important in the BEV arm (13.7% versus 6.1%) (supplementary table S5).
Second and further lines of chemotherapy

Second-line chemotherapy was given in 31 (61%) patients in CT and 25 (49%) in BEV (supplementary table S6). A targeted therapy was given to 21 (41%) patients in CT and 13 (25%) patients in BEV. Third-line treatment was started for 16 (31%) patients in CT and for 8 (16%) in BEV. Altogether, a targeted therapy was given at least in one line across all treatment lines in 26 (51%) patients in CT. Only one patient had surgery of metastases in BEV. A second-line chemotherapy was given in 45% and 55% of the patients treated by FU or doublet respectively.

Discussion

This randomized study was the first one evaluating bevacizumab treatment in mCRC patients aged of 75 or more according to geriatric guidelines. Our results showed that the addition of bevacizumab to chemotherapy was safe and efficient. This randomized phase II study was non comparative so not designed to demonstrate any difference or superiority of BEV arm over the CT arm for primary or secondary endpoints.

The efficacy co-criterion assessed 4 months after the randomization was reached in BEV. The separate analysis of the 2 efficacy criteria considered showed that the tumor control rate was higher in BEV arm but the QoL was less deteriorated in the CT arm. The trend observed in favor of CT for QoL could be explained by the slight difference existing in term of safety meaning that QoL and toxicities are correlated. The time to QoL degradation was similar in both arms (16).

Concerning the safety part, the majority of the patients had no unexpected hospitalization and there is few severe cardiovascular toxicity in both arms during the first 4 months. Considering all toxicities during the treatment duration there is an
increased of arterial hypertension and a 3.7% difference for thrombolytic events as expected with bevacizumab. This is in-line with what it was observed in previous study in elderly (7; 17). A careful monitoring of anti-hypertensive treatment is needed in elderly treated with bevacizumab.

Composite co-criterion assessing both tumor control, QoL and tolerance remains exploratory. The tumor control rate was in the same range for CT that those observed in our previous trial comparing 5-fluorouracil monotherapy to FOLFIRI (13). The prognostic value of Spitzer QoL score have been validate in oncology setting (18). Because of the lack of previous prospective data about the evolution of Spitzer QoL score under treatment in elderly patient treated for mCRC the hypothesis used in our trial design was exploratory. The optimal time of evaluation is also questionable as treatments are both well-tolerated. Unfortunately, QoL evaluations are exposed to a high drop-out rate. Around 10% of the patients in our study didn't have an evaluation at 4 months and this rate increased afterwards. Indeed, an intensive monitoring and investigators training is mandatory if QoL is part of primary endpoint. The safety co-criterion appears as poorly discriminant between both arms. Nevertheless, both criteria are predictive for PFS and OS but this observation is obtain on small number. It must be point out that our criteria was built specially to evaluate anti-angiogenic toxicity and could not be used for other purpose. Further research for optimal composite criteria is needed in geriatric oncology.

Our PFS results are in favor of BEV but are of less magnitude compared to the results of the two previous studies that have compared bevacizumab plus capecitabine to capecitabine monotherapy (HR= 0.53 (7) and 0.52 (8)). It must be pointed out that the median age was 80 years in our study but 76 (7) and 78 (8) in the previous studies. Others studies already suggested that the benefit for PFS of
treatment intensification was mainly observed in patients of 70-80 rather than over 80 (19; 20).

None previous study demonstrated a significant OS benefit of bevacizumab combined with chemotherapy compared to chemotherapy alone in elderly patients. Our OS results are consistent with previous observations in phase III randomized study that have addressed elderly patients (7; 8).

It must be pointed out that there is a trend in favor of BEV for usual endpoint as PFS and OS. At the contrary, QoL, unexpected hospitalization, cardiovascular toxicity and in result the primary safety co-criterion seems to be in favor of CT. This observation suggests that bevacizumab was associated with more toxicity even mild but is worthwhile given the longer PFS and OS.

We evaluated bevacizumab both in combination with FU monotherapy or with doublet chemotherapy which was never evaluated in previous randomized studies (7; 8). The investigators were allowed to choose between monotherapy or doublet according their evaluation of the patient. This pragmatic design minimize patient selection to enter the trial. Moreover, around 50% of patients received FU monotherapy or doublet, this proportion is close to those observed in a national cohort of elderly patient treated in front line for mCRC in France (21). Nevertheless, we could not rule out a part of patient selection for enter in a clinical trial. In our study, the effect of bevacizumab was similar whatever the doublet regimen delivered. It must be point out that doublet chemotherapy was not associated with an increase of PFS or OS in subgroup analyses that raise the question of the need for doublet therapy in front line (16). Nevertheless, our results confirm the possibility to combine bevacizumab with several chemotherapy regimens in elderly patients.
In our study, we observed a prolonged median duration of exposure to treatment despite advanced age. This could be explained by the pragmatic design of the trial that allow a tailored chemotherapy according to the investigator evaluation of the patient. Alternatively we can’t rule out a more stringent patient selection than in the previous trial that have evaluated bevacizumab in elderly (7; 8). Moreover, 55% of patients received a second-line therapy compared to 37% in the AVEX trial (7) and 10% in AGITG MAX trial (8). This high proportion of second-line treatment especially in the CT group could explain that the OS are close in both groups. It must be pointed out that more than 40% of patients were treated with a targeted therapy in second line in CT versus 25% in BEV.

In conclusion, bevacizumab in combination with both 5-fluorouracil monotherapy or doublet chemotherapy is well-tolerated and efficient in selected elderly patients. A trend for a longer tumor control is observed in BEV compare to CT. A phase III trial or with endpoint adapted to geriatric population would be of interest.

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Conflict of Interest:

T.Aparicio : Sanofi/Roche/Pfizer/Ipsen/Pierre Fabre/Novartis

O.Bouché : Novartis/Lilly/Bayer/Pierre Fabre/Roche/Merck/Amgen/Boehringer

J.Taieb: Roche /Merck/ Amgen/ Sanofi/ Lilly/ Celgene/ Baxalta Servier

S.Kirscher : Amgen

P.L Etienne : Sanofi/Merck/Roche/Ipsen Pharma/BMS/Novartis/Amgen

R.Faroux : Merck Serono/ Amgen

F.Khemissa Akouz :Roche/Sanofi/Bayer

C.Locher : Novartis/Ipsen/Roche/Celgene/Amgen/Sanofi

T.Lecomte : Amgen/Sanofi/Lilly

S.Lavau-Denes : Iceram/ medincell

F.Retornaz : Gilead/Teva

E.François : Roche/Merck/Sanofi
Reference List


Figure legends

Figure 1: Flow chart (CONSORT diagram)

Figure 2

A: Kaplan-Meier estimate of Progression-free survival

B: Kaplan-Meier estimate of Overall survival
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CT (N=51)</th>
<th>BEV (N=51)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>80.1 (75.0-90.6)</td>
<td>80.9 (75.2-88.3)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (58.8%)</td>
<td>26 (51.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (41.2%)</td>
<td>25 (49.0%)</td>
</tr>
<tr>
<td><strong>Primary localization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>19 (37.3%)</td>
<td>16 (31.4%)</td>
</tr>
<tr>
<td>Left colon</td>
<td>18 (35.3%)</td>
<td>21 (41.2%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>14 (27.5%)</td>
<td>14 (27.5%)</td>
</tr>
<tr>
<td><strong>Primary tumor resected</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (58.8%)</td>
<td>31 (60.8%)</td>
</tr>
<tr>
<td>No</td>
<td>21 (41.2%)</td>
<td>20 (39.2%)</td>
</tr>
<tr>
<td><strong>Chemotherapy regimen</strong></td>
<td></td>
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<tr>
<td>LV5FU2</td>
<td>26 (51.0%)</td>
<td>26 (51.0%)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>14 (27.5%)</td>
<td>9 (17.6%)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>9 (17.6%)</td>
<td>16 (31.4%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>2 (3.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m^2)</strong></td>
<td>(n=50)</td>
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<tr>
<td>&lt; 21</td>
<td>8 (16.0%)</td>
<td>9 (17.6%)</td>
</tr>
<tr>
<td>≥ 21</td>
<td>42 (84.0%)</td>
<td>42 (82.4%)</td>
</tr>
<tr>
<td><strong>Spitzer QoL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-7</td>
<td>16 (31.4%)</td>
<td>15 (29.4%)</td>
</tr>
<tr>
<td>8-10</td>
<td>35 (68.6%)</td>
<td>36 (70.6%)</td>
</tr>
<tr>
<td><strong>Biologics parameters</strong></td>
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<tr>
<td>Alkaline phosphatases</td>
<td>(n=48)</td>
<td>(n=48)</td>
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<tr>
<td>≤ 2 LN</td>
<td>37 (77.1%)</td>
<td>42 (82.3%)</td>
</tr>
<tr>
<td>&gt; 2 LN</td>
<td>11 (22.9%)</td>
<td>9 (17.7%)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
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<td>&lt; 10 (female), &lt; 11 (male)</td>
<td>11 (21.6%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>≥ 10 (female), ≥ 11 (male)</td>
<td>40 (78.4%)</td>
<td>46 (90.2%)</td>
</tr>
<tr>
<td>Albumin</td>
<td>(n=43)</td>
<td>(n=49)</td>
</tr>
<tr>
<td>≤ 35 g/L</td>
<td>20 (46.5%)</td>
<td>17 (34.7%)</td>
</tr>
<tr>
<td>&gt; 35 g/L</td>
<td>23 (53.5%)</td>
<td>32 (65.3%)</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>(n=48)</td>
<td>(n=50)</td>
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<tr>
<td>&gt; 45 mL/min</td>
<td>37 (77.1%)</td>
<td>36 (72.0%)</td>
</tr>
<tr>
<td>≤ 45 mL/min</td>
<td>11 (22.9%)</td>
<td>14 (28.0%)</td>
</tr>
<tr>
<td>CEA</td>
<td>(n=49)</td>
<td>(n=47)</td>
</tr>
<tr>
<td>≤ 2 LN</td>
<td>35 (71.4%)</td>
<td>40 (85.1%)</td>
</tr>
<tr>
<td>&gt; 2 LN</td>
<td>14 (28.6%)</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>(n=47)</td>
<td>(n=48)</td>
</tr>
<tr>
<td>≤ 2 LN</td>
<td>19 (40.4%)</td>
<td>29 (60.4%)</td>
</tr>
<tr>
<td>&gt; 2 LN</td>
<td>28 (59.6%)</td>
<td>19 (39.6%)</td>
</tr>
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Table 2: Primary endpoint assessed four months after randomization

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>CT (N=45)</th>
<th>BEV (N=46)</th>
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<tbody>
<tr>
<td>Tumor controlled</td>
<td>33 (73.3%)</td>
<td>36 (78.3%)</td>
</tr>
<tr>
<td>No QoL degradation &gt;2</td>
<td>29 (64.4%)</td>
<td>27 (58.7%)</td>
</tr>
<tr>
<td>Efficacy co-criterion reached</td>
<td>26 (57.8%)</td>
<td>23 (50.0%)</td>
</tr>
<tr>
<td>No unexpected hospitalization</td>
<td>32 (71.1%)</td>
<td>30 (65.2%)</td>
</tr>
<tr>
<td>No Gr 3-4 cardiovascular toxicity</td>
<td>41 (91.1%)</td>
<td>40 (87.0%)</td>
</tr>
<tr>
<td>Safety co-criterion reached</td>
<td>32 (71.1%)</td>
<td>28 (60.9%)</td>
</tr>
<tr>
<td>Both efficacy and safety endpoint reached</td>
<td>21 (46.7%)</td>
<td>16 (34.8%)</td>
</tr>
</tbody>
</table>
**Figure 1: Flow chart (CONSORT diagram)**

- CT arm \( N=51 \)
  - \( N=49 \)
  - \( N=45 \)

- BEV arm \( N=51 \)
  - \( N=51 \)
  - \( N=46 \)

- ITT population \( N=102 \)
- Safety population \( N=100 \)
- mITT population \( N=91 \)

2 patients dead before M4 without treatment
4 patients without tumor or QoL evaluation at M4
4 patients without tumor or QoL evaluation at M4
1 patient without mCRC

**Figure 2A: Kaplan-Meier estimate of progression-free survival**

HR = 0.79 [95% CI: 0.53-1.17]

![Progression-free survival graph with HR and CI values](https://example.com/progression-free-survival-graph.png)

<table>
<thead>
<tr>
<th>N. at risk</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>51</td>
<td>39</td>
<td>24</td>
<td>12</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BEV</td>
<td>51</td>
<td>45</td>
<td>35</td>
<td>19</td>
<td>15</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Time (Months)
Figure 2B: Kaplan-Meier estimate of overall survival

HR = 0.73 [95% CI: 0.48-1.11]

Time (Months)

Overall survival

N. at risk
CT  51  46  42  37  31  25  18  12  7  3  2
BEV 51  46  41  39  31  28  23  22  18  11  5