Impact of age and gender on the safety and efficacy of chemotherapy plus bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies.

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Abstract

Background

The phase III TRIBE and TRIBE2 studies randomized metastatic colorectal cancer patients to receive first-line FOLFOXIRI/bevacizumab or a doublet (FOLFIRI or FOLFOX)/bevacizumab, demonstrating a significant benefit from the triplet at the price of an increased incidence of chemotherapy-related adverse events (AEs). In both trials males and females aged between 18 and 70 with ECOG PS≤2 and between 71 and 75 with ECOG PS=0 were eligible. We investigated the effect of FOLFOXIRI/bevacizumab versus doublets/bevacizumab according to age and gender.

Patients and Methods

Subgroup analyses according to age (<70 *versus* 70-75 years) and gender were performed for overall response rate (ORR), progression-free survival (PFS) and AEs rates.

Results

Out of 1187 patients, 1005 (85%) were aged <70 years and 182 (15%) 70-75 years; 693 (58%) were males and 494 (42%) females. There was no evidence of interaction between age or gender and the benefit provided by the intensification of the upfront chemotherapy in terms of ORR and PFS, or the increased risk of experiencing G3/4 AEs. Elderly patients and females experienced higher rates of overall G3/4 AEs (73% *versus* 60%, $p<0.01$ and 69% *versus* 57%, $p<0.01$, respectively). Notably, in the FOLFOXIRI/bevacizumab subgroup, G3/4 diarrhoea and febrile neutropenia occurred in the 27% and 16% of elderly patients, respectively, while females reported high incidences of any grade nausea (67%) and vomiting (50%).

Conclusions

The improvements in terms of ORR and PFS of FOLFOXIRI/bevacizumab versus doublets/bevacizumab are independent of gender and age, with a similar relative increase in AEs among elderly patients and females. Initial dose reductions and possibly primary G-CSF prophylaxis

should be recommended for patients between 70 and 75 years old candidate to FOLFOXIRI/bevacizumab, and a careful management of the antiemetic prophylaxis should be considered among females.

Key words

FOLFOXIRI/bevacizumab, age, gender, metastatic colorectal cancer.

Key message

Among patients aged 70-75 years treated with FOLFOXIRI/bevacizumab, G3/4 diarrhoea and febrile neutropenia occurred in the 27% and 16% of cases, respectively, suggesting the need for initial dose reduction and possibly primary G-CSF prophylaxis. Due to the high rates of nausea and vomiting among females, a careful management of the antiemetic prophylaxis should be considered.

Introduction

FOLFOXIRI/bevacizumab is recognized by all major international guidelines as a valuable upfront option for the treatment of mCRC patients. Two recent phase III randomized trials by GONO group, named TRIBE (NCT00719797)[1] and TRIBE2 (NCT02339116)[2], compared the three-drug regimen FOLFOXIRI (5-fluorouracil, oxaliplatin and irinotecan) plus bevacizumab with the doublets FOLFIRI (5-fluorouracil and irinotecan) or FOLFOX (5-fluorouracil and oxaliplatin) plus bevacizumab, and both trials met their primary and secondary endpoints reporting significantly higher response rates and longer survivals with the triplet plus bevacizumab. FOLFOXIRI/bevacizumab was associated with increased rates of grade 3 and 4 neutropenia, diarrhoea, stomatitis and febrile neutropenia, although higher incidences of serious adverse events (AEs) or treatment-related deaths were not reported. Only patients aged ≤ 70 with ECOG-PS ≤2 and those aged between 71–75 years with an ECOG-PS of 0 were eligible for both trials.

A careful cost/benefit balance, estimating the impact of the intensification of the upfront chemotherapy backbone in every single patient in terms of both efficacy and toxicity, would be of paramount importance to select the best candidates to FOLFOXIRI/bevacizumab in the daily clinical practice.

The individualization of treatment approaches according to the multidimensional evaluation of individual characteristics is highly relevant for elderly patients, in order to offer them the appropriate treatment intensity while limiting the occurrence of AEs and preventing treatment-related deterioration of quality of life[3–5]. The magnitude of the benefit from the intensification of the chemotherapy backbone from doublets to the triplet and the associated risk of AEs has never been estimated in the elderly population (i.e. in those patients aged >70 years in good general conditions) eligible for TRIBE and TRIBE2 studies.

Similarly, gender seems to influence cancer risk and survival, but also cancer treatments' safety and efficacy. Gender-specific drug metabolism and sensitivity as well as specific conditions that modify sex hormones levels (i.e. contraceptives, hormone cycle, menopause) play a major role in these differences [6]. In particular, a higher incidence of chemotherapy-related AEs is reported among females than males in many solid tumours [7–9]. Only a few retrospective data are currently available about the toxicity profile and outcome of standard systemic regimens in mCRC according to patients' gender [10].

Here we conducted an individual patient data-based pooled analysis of TRIBE and TRIBE2 studies in order to evaluate the effect of the intensification of the upfront chemotherapy backbone according to age (< 70 *versus* 70-75 years) and gender (males *versus* females) in terms of activity, efficacy and safety.

Methods:

Study design and procedures

TRIBE[1] and TRIBE2[2] are two phase III randomized, open-label, multicentre trials involving 1187 unresectable previously untreated mCRC patients. In the TRIBE study, patients were randomized in a 1:1 ratio to receive up to 12 cycles of FOLFIRI/bevacizumab or FOLFOXIRI/bevacizumab, both followed by maintenance with 5-fluorouracil plus bevacizumab until disease progression, unacceptable adverse events, or consent withdrawal in both arms. In the TRIBE2 trial, patients were randomized in a 1:1 ratio to FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab after disease progression or FOLFOXIRI/bevacizumab followed by the reintroduction of the same agents after disease progression; all treatments were administrated up to 8 cycles followed by 5-fluorouracil plus bevacizumab maintenance until disease progression, unacceptable adverse events, or consent withdrawal. Primary endpoints were progression-free survival (PFS) for TRIBE and progression-free survival 2 (defined as the time from the randomization to the disease progression on any treatment given after 1st progression) for TRIBE2 study.

Definition of endpoints

Overall response rate (ORR), defined as the proportion of patients achieving partial or complete response according to RECIST version 1.0 and version 1.1 in TRIBE and TRIBE2 trials, respectively, and PFS, defined as the time from randomization to the evidence of disease progression or death, whichever occurred first, were evaluated in the intention-to-treat (ITT) populations of the two studies, including all randomized patients. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 for TRIBE and version 4.0 for TRIBE2 and the safety analyses included all patients who had received at least one

dose of the study medication with available toxicity data. One patient received one cycle of treatment according to random assignment without available toxicity data and was not included.

Statistics

The chi-square test and Fisher's exact test were used, when appropriate, to compare clinical and biological features and ORR among different groups (< 70 *versus* 70-75 years and males *versus* females). PFS was determined according to the Kaplan-Meier estimates method and survival curves were compared using the log-rank test. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with a logistic-regression model, and hazard ratios (HR) and 95% CI were estimated with a Cox proportional hazards model. Subgroup analyses of FOLFOXIRI/bevacizumab versus doublets/bevacizumab for ORR, PFS, any grade and ≥G3 AEs rate were done using an interaction test. Firth's penalized likelihood approach was used when appropriate. The risk of experiencing treatment-related AEs was estimated according to gender and age at the time of randomization. In order to assess the weight of age and gender on the risk of developing AEs, significant toxicities ($p \leq 0.05$) were analysed in multivariable logistic regression models including age (≥ *versus* <70 years), gender (females *versus* males), treatment (triplet *versus* doublets), ECOG-PS (1-2 *versus* 0) and duration of the induction therapy (6 *versus* 4 months) as covariates. All statistical tests were two-sided, and *p*-values of 0.05 or less were deemed significant. No adjustment for multiple comparisons was made. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Study Population

1187 patients were included in this pooled analysis, 591 (50%) in the FOLFOXIRI/bevacizumab group, and 596 (50%) in the doublets/bevacizumab group (256 assigned to FOLFIRI/bevacizumab and 340 to FOLFOX/bevacizumab). 1175 patients were included in the safety analyses, 586 (50%) in the FOLFOXIRI/bevacizumab group, and 589 (50%) in the doublets/bevacizumab group (254 assigned to FOLFIRI/bevacizumab and 335 to FOLFOX/bevacizumab). The data cut-off for the present analysis was March 1, 2019.

Elderly versus younger patients

Overall, 1005 (85%) and 182 (15%) patients were aged <70 years or 70-75, respectively. Patients' characteristics are summarized in Table 1. Age subgroups were similar, although the elderly group included more patients with ECOG-PS=0 (p<0.001) as per inclusion criteria, metachronous disease (p=0.006) and males (p=0.008).

In the overall population, no differences were reported in terms of ORR (OR: 1.14, [95% CI: 0.83-1.56], p=0.43) and PFS (HR: 1.07, [95% CI: 0.90-1.27], p=0.42) (Table S1) between younger and elderly patients. There was no evidence of interaction between age and the benefit provided by the intensification of the upfront chemotherapy in terms of both ORR (p for interaction: 0.55) and PFS (p for interaction: 0.52) (Table S1 and Figure 1, panel A and B).

Elderly patients were more likely to experience overall grade ≥3 AEs (73% *versus* 60%; p<0.01) and chemo-related ones, including diarrhoea and febrile neutropenia (Table 2). On the other hand, they showed a reduced risk of any grade nausea (p<0.01) and vomiting (p=0.02) (Table S2). No difference in bevacizumab-related AEs was observed according to age (Table 2). Significant age-related

differences in univariate models were confirmed in the multivariate logistic regression analyses (Table S3).

FOLFOXIRI/bevacizumab was associated with a higher risk of grade ≥3 chemo-related AEs when compared with doublets/bevacizumab independently of age (*p* for interaction=0.47), as well as to a higher risk of specific chemo-related toxicities (Table S4).

Notably, among patients aged 70-75 treated with FOLFOXIRI/bevacizumab, 27% and 16% experienced grade ≥3 diarrhoea and febrile neutropenia, respectively.

Males versus females

As shown in Table 1, the study population included 693 males (58%) and 494 females (42%). No relevant differences among subgroups were evident, except for a higher proportion of *BRAF* mutated tumours (*p*=0.001), a higher percentage of resected primary tumours (*p*=0.011) and a younger age at diagnosis (*p*=0.008) among females.

No differences were reported in terms of ORR (HR: 0.93, [95% CI: 0.73-1.17], *p*=0.53) and PFS (HR: 0.89, [95% CI: 0.78-1.00], *p*=0.053) (Table S1) between females and males. There was no evidence of interaction between gender and the benefit provided by the intensification of the upfront chemotherapy in terms of both ORR (*p* for interaction: 0.53) and PFS (*p* for interaction: 0.87) (Table S1 and Figure 1, panel C and D).

Overall, females had a significantly higher risk of experiencing grade ≥ 3 AEs (69% *versus* 57%; *p*<0.01), in particular grade ≥3 chemo-related AEs (63% *versus* 48%; 1.48-2.38; *p*<0.01), while no difference in bevacizumab-related AEs was observed between subgroups (Table 3 and Table S5).

Significant gender-related differences in univariate models were confirmed in the multivariate logistic regression analyses (Table S3).

FOLFOXIRI/bevacizumab was associated with a higher risk of grade ≥3 chemotherapy-related AEs when compared to doublets/bevacizumab independently of gender (*p* for interaction=0.32), as well as a higher risk of some chemo-related toxicities (Table S4). Notably, among females treated with FOLFOXIRI/bevacizumab, 67% and 50% experienced any grade of nausea and vomiting, respectively.

Combined evaluation of age and gender

Clinically meaningful AEs were grouped based on age and gender (figure 2). Overall, elderly females reported the highest rate of severe chemo-related-toxicity: all AEs were more frequently observed in elderly females, except for nausea and vomiting that were more common among young females.

Discussion

In the era of personalized medicine, many efforts have been made to identify the best treatment for each individual patient. While biomarkers tightly related to the mechanism of action of targeted agents play a role in treatments' selection and their contribution is expected to increase, clinical characteristics are still major drivers of therapeutic choices [11]. .

The present analysis addresses the impact of age and gender on the clinical outcomes and the safety of mCRC patients receiving first-line triplet or doublets plus bevacizumab. Overall survival was not taken into account as an efficacy measure, because the follow up of patients enrolled in the TRIBE2 study is still immature[12]. Although activity and efficacy did not differ according to gender or age, and the intensification of the chemotherapy backbone was equally effective in analysed subgroups, toxicities' incidence was quite different between females *versus* males and elderly *versus* younger patients, consistently with literature evidence about other regimens [3, 6, 8].

The increased toxicity in the elderly population may be explained by the progressive decline in the functional reserve of multiple organ systems that reduces the tolerance of normal tissues, thus increasing the incidence of adverse events [10]. On the other side, the higher occurrence of adverse events among females may be justified by the differences in the pharmacokinetic and pharmacogenomic profiles that may influence drug-metabolism and lead to increased side effects [6]. Furthermore, females generally have a higher baseline body mass index than men because of the higher proportion of body fat, and this is associated with decreased drugs' clearance and increased toxicity[13].

The increased toxicity observed among patients aged 70-75 and among females was independent of the first-line regimens (doublets or triplet), as well as the magnitude of the increase in toxicity with the triplet versus doublets. Notably, among elderly patients treated with FOLFOXIRI/bevacizumab, 27% and 16% experienced grade ≥3 diarrhoea and febrile neutropenia,

respectively. Therefore, in patients aged 70-75, with ECOG-PS 0, potentially candidate to first-line FOLFOXIRI/bevacizumab, the higher efficacy of the triplet should be carefully balanced with the higher risk of clinically relevant toxicities. If the triplet is preferred to a less toxic regimen based on patient's and disease's characteristics, we recommend an initial reduction of the doses of 5 - fluorouracil and irinotecan (2400 mg/m² and 150 mg/m², respectively) and the use of G-CSF as primary prophylaxis especially in the case of other risk factors (i.e. reduced bone marrow reserve due to previous therapies, high risk of infection-associated complications, previous history of neutropenia or other concomitant organic disorders). Though in the absence of specific toxicity data in elderly patients who started the treatment with reduced doses, they are close to those recommended in the case of G3 diarrhoea (75% reduction of both 5-FU and irinotecan) in patients treated at full dose.

Similarly, among females treated with FOLFOXIRI/bevacizumab, the 67% and the 50% experienced any grade of nausea and vomiting, respectively. Though acknowledging the lack of data about the antiemetic prophylaxis actually administered and the lack of a recommended prophylaxis in the study protocol as intrinsic limitations of our analysis, differences in the incidences of nausea and vomiting between males and females are hardly due to unbalances in the prophylactic schemes chosen by investigators in these subgroups. Therefore a particularly careful attention to the prophylaxis of nausea and vomiting in females should be recommended. In particular, in females treated with FOLFOXIRI/bevacizumab an appropriate antiemetic prophylaxis with corticosteroids and 5-HT3-receptor antagonists should be recommended. Neurokinin-1 receptor antagonists should be considered as primary prophylaxis in the presence of other risk factors for emesis (pregnancy associated nausea/vomiting, dietary intake, anxiety, young age, motion sickness), and as secondary prophylaxis in those patients who experienced nausea and vomiting despite an appropriate use of corticosteroids and 5-HT3 receptor antagonists.

In conclusion, FOLFOXIRI/bevacizumab is confirmed as a more efficacious option than doublets/bevacizumab, irrespective of age and gender, with an increased risk of chemo-related toxicity among elderly and female patients. Despite the retrospective nature of this analysis, the high number of included patients and the consistency of these data with the evidence from the literature strengthen the present observations as a tool to properly tailor preventive supportive measures in mCRC patients receiving first-line FOLFOXIRI plus bevacizumab.

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Disclosures

C.C. is a consultant/advisory board member for Roche, Amgen, Bayer, Merck Serono. Servier. A.F. is a consultant/advisory board member for Bayer, Roche, Amgen, Eli-Lilly, Merck Serono, Sanofi, Servier. All remaining authors have declared no conflicts of interest.

Figures' legend

Figure 1. Kaplan-Meier estimates of PFS according to treatment arm in younger (panel A), elderly (panel B), males (panel C) and females (panel D).

Figure 2. Histograms of AEs grouped for age and gender.

Reference

1. Loupakis F, Cremolini C, Masi G et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N. Engl. J. Med. 2014; 371(17):1609–1618.

2. Cremolini C, Antoniotti C, Lonardi S et al. LBA20TRIBE2: A phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts). Ann Oncol 2018. doi:10.1093/annonc/mdy424.021.

3. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 2001; 56(3):M146-156.

4. Balducci L, Yates J. General guidelines for the management of older patients with cancer. Oncology (Williston Park, N.Y.) 2000; 14(11A):221–227.

5. Hurria A, Levit LA, Dale W et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J. Clin. Oncol. 2015; 33(32):3826–3833.

6. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009; 48(3):143–157.

7. Davidson M, Cafferkey C, Goode EF et al. Survival in Advanced Esophagogastric Adenocarcinoma Improves With Use of Multiple Lines of Therapy: Results From an Analysis of More Than 500 Patients. Clin Colorectal Cancer 2018; 17(3):223–230.

8. Wheatley-Price P, Le Maître A, Ding K et al. The influence of sex on efficacy, adverse events, quality of life, and delivery of treatment in National Cancer Institute of Canada Clinical Trials Group non-small cell lung cancer chemotherapy trials. J Thorac Oncol 2010; 5(5):640–648.

9. Abdel-Rahman O. Impact of Sex on Chemotherapy Toxicity and Efficacy Among Patients With Metastatic Colorectal Cancer: Pooled Analysis of 5 Randomized Trials. Clin Colorectal Cancer 2018. doi:10.1016/j.clcc.2018.12.006.

10. Vallet-Regí M, Manzano M, Rodriguez-Mañas L et al. Management of Cancer in the Older Age Person: An Approach to Complex Medical Decisions. Oncologist 2017; 22(3):335–342.

11. Cremolini C, Schirripa M, Antoniotti C et al. First-line chemotherapy for mCRC—a review and evidence-based algorithm. Nat Rev Clin Oncol 2015; 12(10):607–619.

12. Cremolini C, Antoniotti C, Lonardi S et al. Updated results of TRIBE2, a phase III, randomized strategy study by GONO in the first- and second-line treatment of unresectable mCRC. J Clin Oncol 37, 2019 (suppl; abstr 3508) .

13. Prado CMM, Baracos VE, McCargar LJ et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin. Cancer Res. 2007; 13(11):3264–3268.

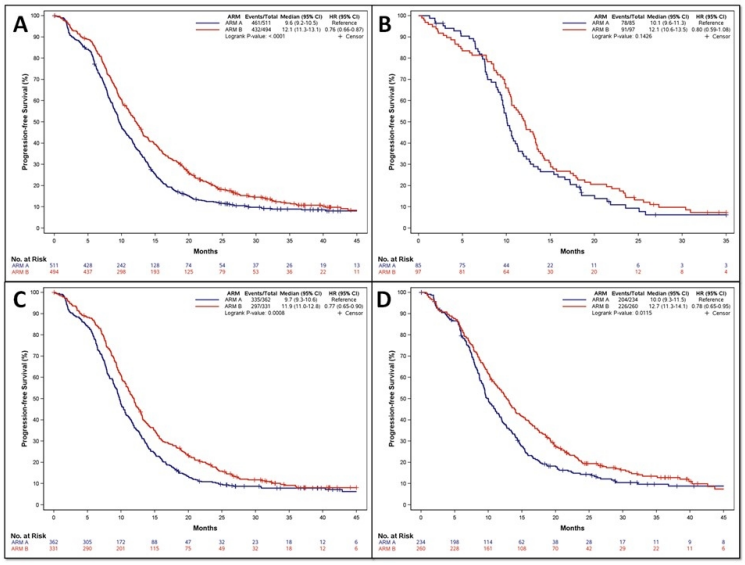

Figure 1

338x190mm (96 x 96 DPI)

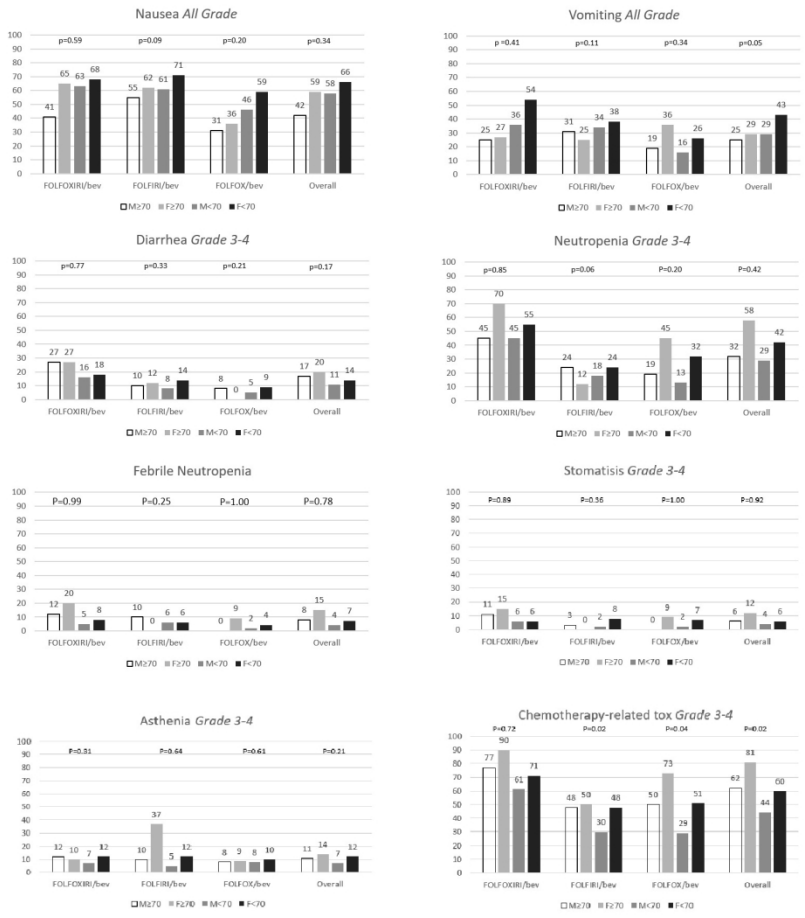

Figure 2

338x320mm (144 x 144 DPI)

Table 1. Patients' Characteristics						
ITT population N = 1187						
	< 70y N=1005 (85%)	**≥ 70y N=182 (15%)**	***p***	**M N=693 (58%)**	**F N=494 (42%)**	***p***
Site of Primary						
Right	351 (36)	57 (32)	0.445	223 (33)	185 (38)	0.071
Left and rectum	632 (64)	119 (68)		453 (67)	298 (62)	
NA	22	6		17	11	
Mutational Status						
RAS mut	563 (66)	108 (72)	0.221	382 (66)	289 (69)	***0.001***
BRAF mut	85 (10)	9 (6)		42 (7)	52 (12)	
All wt	204 (24)	33 (22)		156 (27)	81 (19)	
NA	153	32		113	72	
Resected Primary Tumor						
YES	576 (57)	111 (61)	0.408	379 (55)	308 (62)	***0.011***
NO	428 (43)	71 (39)		313 (45)	186 (38)	
NA	1	0		1	0	
Liver Only						
YES	261 (26)	49 (27)	0.871	185 (27)	125 (25)	0.617
NO	742 (74)	133 (73)		506 (73)	369 (75)	
NA	2	0		2	0	
Previous Adjuvant Therapy						
YES	59 (6)	20 (11)	***0.017***	41 (6)	38 (8)	0.275
NO	946 (94)	162 (89)		652 (94)	456 (92)	
Metastatic disease						
Synchronous	866 (86)	142 (78)	***0.006***	591 (85)	417 (84)	0.697
Metachronous	138 (14)	40 (22)		101 (15)	77 (16)	
NA	1	0		1	0	
ECOG-PS						
0	864 (86)	174 (96)	***<0.001***	618 (89)	420 (85)	***0.041***
1-2	141 (14)	8 (4)		75 (11)	74 (15)	
Gender						
M	570 (57)	123 (68)	***0.008***	/	/	/
F	435 (43)	59 (32)		/	/	
Age						
<70 y	/	/	/	570 (82)	435 (88)	***0.008***
≥ 70 y	/	/		123 (18)	59 (12)	

Legend Table 1. ITT= intention-to-treat; N=number; M= male; F= female; p= chi-square or Fisher's exact test when appropriate; y=years; ECOG-PS= Eastern Cooperative Oncology Group Performance Status; NA= not available.

Table 2. Univariable safety results according to age and treatment group

Safety population N=1175

	FOLFOXIRI + Bevacizumab N= 586				FOLFIRI + Bevacizumab N= 254				FOLFOX + Bevacizumab N= 335				Overall N= 1175			
	<70y N= 490 (84%)	**≥70y N=96 (16%)**	**OR (95%CI)**	***p***	**<70y N=217 (85%)**	**≥70y N=37 (15%)**	**OR (95%CI)**	***p***	**<70y N=288 (86%)**	**≥70y N=47 (14%)**	**OR (95%CI)**	***p***	**<70y N= 995 (85%)**	**≥70y N= 180 (15%)**	**OR (95%CI)**	***p***
Diarrhea																
Any grade	358 (73)	69 (72)	0.94 (0.58-1.55)	0.81	128 (59)	22 (59)	1.02 (0.50-2.07)	0.96	139 (48)	23 (49)	1.02 (0.55-1.90)	0.93	625 (63)	114 (63)	1.02 (0.74-1.42)	0.89
Grade 3-4	81 (17)	26 (27)	1.88 (1.13-3.12)	**0.01**	23 (11)	4 (11)	1.02 (0.33-3.15)	0.97	19 (7)	3 (6)	0.97 (0.26-3.41)	0.96	123 (12)	33 (18)	1.60 (1.05-2.43)	**0.03**
Neutropenia																
Any grade	355 (72)	71 (74)	1.08 (0.66-1.78)	0.76	87 (40)	23 (62)	2.46 (1.20-5.03)	**0.01**	147 (51)	26 (55)	1.19 (0.64-2.22)	0.59	589 (59)	120 (67)	1.38 (0.97-1.88)	0.06
Grade 3-4	243 (50)	53 (55)	1.25 (0.81-1.94)	0.31	44 (20)	8 (22)	1.08 (0.46-2.54)	0.85	61 (21)	12 (25)	1.28 (0.63-2.21)	0.50	348 (35)	73 (41)	1.27 (0.99-1.93)	0.15
Febrile Neutropenia																
Any grade	31 (6)	15 (16)	2.74 (1.42-5.31)	**<0.01**	13 (6)	3 (8)	1.38 (0.37-5.12)	0.63	9 (3)	1 (2)	0.67 (0.08-5.45)	0.71	53 (5)	19 (11)	2.10 (1.21-3.64)	**<0.01**
CT-related tox																
Any grade	483 (99)	92 (96)	0.33 (0.10-1.16)	0.07	201 (93)	37 (100)	0.93 (0.89-0.96)	0.09	275 (96)	45 (96)	1.06 (0.23-4.87)	0.94	959 (96)	174 (97)	1.09 (0.45-2.62)	0.85
Grade 3-4	321 (66)	79 (82)	2.45 (1.40-4.27)	**<0.01**	81 (37)	18 (49)	1.59 (0.79-3.21)	0.19	109 (38)	26 (55)	2.03 (1.09-3.79)	**0.02**	411 (52)	123 (68)	2.04 (1.45-2.86)	**<0.01**
Bev-related tox																
Any grade	279 (57)	53 (55)	0.97 (0.63-1.51)	0.90	117 (54)	25 (68)	1,78 (0.85-3.73)	0.12	172 (60)	30 (64)	1.19 (0.63-2.26)	0.59	568 (97)	108 (60)	1.13 (0.82-1.56)	0.47
Grade 3-4	81 (17)	21 (22)	1.41 (0.82-2.42)	0.21	27 (12)	8 (22)	1.94 (0.81-4.68)	0.14	62 (21)	8 (17)	0.76 (0.33-1.68)	0.48	170 (17)	37 (21)	1.25 (0.84-1.86)	0.27
Overall tox																
Any grade	484 (99)	92 (96)	0.24 (0.06-0.90)	**0.02**	205 (94)	37 (100)	4.56 (0.26-78.72)	0.30	280 (97)	45 (98)	0.64 (0.13-3.13)	0.58	969 (97)	174 (97)	0.78 (0.32-1.92)	0.59
Grade 3-4	351 (72)	81 (84)	2.37 (1.32-2.46)	**<0.01**	96 (44)	21 (57)	0.94 (0.92-0.98)	0.14	147 (51)	29 (63)	1.55 (0.82-2.91)	0.18	594 (60)	131 (73)	2.04 (1.44-2.90)	**<0.01**

Legend Table 2. N= number; OR= Odds Ratio; CI= Confidence Interval; y= years; p= chi-square or Fisher's exact test when appropriate; tox= toxicity; bev= bevacizumab; CT= chemotherapy.

Table 3. Univariable safety results according to gender and treatment group

	Safety population N=1175															
	FOLFOXIRI + Bevacizumab N=586				FOLFIRI + Bevacizumab N=254				FOLFOX + Bevacizumab N=335				Overall N=1175			
	M N=326 (56%)	F N=260 (44%)	OR (95%CI)	*p*	M N=154 (61%)	F N=100 (39%)	OR (95%CI)	*p*	M N=204 (61%)	F N=131 (39%)	OR (95%CI)	*p*	M N=684 (58%)	F N=491 (42%)	OR (95%CI)	*p*
Nausea																
Any grade	194 (60)	175 (67)	1.40 (1.00-1.97)	***0.05***	92 (60)	70 (70)	1.57 (0.92-2.69)	0.10	89 (43)	75 (57)	1.73 (1.11-2.70)	***0.02***	375 (55)	320 (65)	1.54 (1.21-1.96)	***<0.01***
Grade 3-4	13 (4)	15 (6)	1.47 (0.69-3.16)	0.32	3 (2)	5 (5)	2.65 (0.62-11.34)	0.17	4 (2)	9 (7)	3.69 (1.11-12.24)	***0.02***	20 (3)	29 (6)	2.08 (1.16-3.73)	***0.01***
Vomiting																
Any grade	111 (34)	129 (50)	1.91 (1.37-2.66)	***<0.01***	51 (33)	37 (37)	1.19 (0.70-2.01)	0.53	34 (17)	36 (28)	1.90 (1.11-3.23)	***0.02***	196 (29)	202 (41)	1.74 (1.36-2.22)	***<0.01***
Grade 3-4	6 (2)	15 (6)	3.27 (1.25-8.54)	***0.01***	3 (2)	5 (5)	2.65 (0.62-11.34)	0.17	0	6 (5)	1.05 (1.01-1.09)	***<0.01***	9 (1)	26 (5)	4.19 (1.95-9.03)	***<0.01***
CT-related tox																
Any grade	315 (97)	260 (100)	0.97 (0.95-0.99)	**<0.01**	142 (92)	96 (96)	2.03 (0.64-6.48)	0.22	194 (95)	126 (96)	1.30 (0.43-3.89)	0.64	651 (95)	482 (98)	2.72 (1.29-5.73)	**<0.01**
Grade 3-4	208 (64)	192 (74)	1.60 (1.12-2.29)	**<0.01**	51 (33)	48 (48)	1.86 (1.11-3.12)	**0.02**	66 (32)	69 (53)	2.33 (1.48-3.65)	**<0.01**	325 (48)	309 (63)	1.88 (1.48-2.38)	**<0.01**
Bev-related tox																
Any grade	191 (59)	141 (54)	0.84 (0.60-1.16)	0.29	86 (56)	56 (56)	1.01 (0.61-1.67)	0.98	118 (58)	84 (64)	1.30 (0.83-2.05)	0.25	395 (58)	281 (57)	0.98 (0.77-1.24)	0.86
Grade 3-4	57 (17)	45 (17)	0.99 (0.64-1.52)	0.96	22 (14)	13 (13)	0.90 (0.43-1.87)	0.77	44 (22)	26 (20)	0.90 (0.52-1.55)	0.71	123 (18)	84 (17)	0.94 (0.69-1.28)	0.70
Overall tox																
Any grade	316 (97)	260 (100)	17.28 (1.01-296.37)	**0.05**	145 (94)	97 (97)	2.01 (0.53-7.60)	0.31	204 (100)	131 (100)	0.64 (0.01-32.61)	0.83	655 (96)	488 (99)	7.20 (2.18-23.78)	**<0.01**
Grade 3-4	229 (70)	203 (78)	1.51 (1.03-2.20)	**0.03**	65 (42)	52 (52)	1.48 (0.89-2.46)	0.13	93 (46)	83 (63)	2.06 (1.32-3.24)	**<0.01**	387 (57)	338 (69)	1.70 (1.33-2.16)	**<0.01**

Legend Table 3. N= number; OR= Odds Ratio; CI= Confidence Interval; M= male; F= female; p= chi-square or Fisher's exact test when appropriate; tox= toxicity; CT= chemotherapy; bev= bevacizumab.

Table S1. Efficacy according to treatment group, age and gender

ITT population
N=1187

	<70y N=1005		**70-75y N= 182**		***p***	**M N= 693**		**F N= 494**		***p***
ORR (%)	58.1		54.9		*0.43*	56.9		58.7		*0.53*
OR (95%CI)	1.14 (0.83-1.56)					0.93 (0.73-1.17)				
PFS	10.9		10.9		*0.42*	10.6		11.3		*0.053*
HR (95% CI)	1.07 (0.90-1.27)					0.89 (0.78-1.00)				
	Doublet/ Bev N= 511	**Triplet/ Bev N= 494**	**Doublet/ Bev N= 85**	**Triplet/ Bev N= 97**	***p* for interaction**	**Doublet/ Bev N= 362**	**Triplet/ Bev N= 331**	**Doublet/ Bev N= 234**	**Triplet/ Bev N= 260**	***p* for interaction**
ORR (%)	52.8	63.6	47.0	61.9	0.554	52.2	61.9	51.7	65.0	0.527
OR (95%CI)	1.54 (1.19-1.99)		1.86 (1.04-3.94)			1.49 (1.10-2.02)		1.73 (1.21-2.49)		
PFS (months)	9.6	12.1	10.1	12.1	0.520	9.7	11.9	10.0	12.7	0.870
HR (95%CI)	0.76 (0.66-0.87)		0.80 (0.59-1.08)			0.77 (0.65-0.90)		0.78 (0.65-0.95)		

Legend Table S1. N= number; y= years; M= male; F= female; bev= bevacizumab; ORR= Overall Response Rate; OR= Odds Ratio; CI= Confidence Interval; PFS= Progression Free Survival; HR= Hazard Ratio.

Table S2. Univariable safety results according to age and treatment group

Safety population N=1175

	FOLFOXIRI + Bevacizumab N= 586				**FOLFIRI + Bevacizumab N= 254**				**FOLFOX + Bevacizumab N= 335**				**Overall N= 1175**			
	<70y N= 490 (84%)	**≥70y N=96 (16%)**	**OR (95%CI)**	***p***	**<70y N=217 (85%)**	**≥70y N=37 (15%)**	**OR (95%CI)**	***p***	**<70y N=288 (86%)**	**≥70y N=47 (14%)**	**OR (95%CI)**	***p***	**<70y N= 995 (85%)**	**≥70y N= 180 (15%)**	**OR (95%CI)**	***p***
Nausea																
Any grade	319 (65)	50 (51)	0.58 (0.36-0.91)	***0.02***	141 (65)	21 (57)	0.71 (0.35-1.44)	0.34	149 (51)	15 (32)	0.44 (0.23-0.84)	**0.01**	609 (61)	86 (48)	0.58 (0.42-0.80)	**<0.01**
Grade 3-4	25 (5)	3 (3)	0.60 (0.18-2.03)	0.41	6 (3)	2 (5)	2.01 (0.40-10.36)	0.40	12 (4)	1 (2)	0.50 (0.06-3.95)	0.50	43 (4)	6 (3)	0.76 (0.32-1.82)	0.54
Vomiting																
Any grade	215 (44)	25 (26)	0.45 (0.28-0.73)	***<0.01***	77 (35)	11 (30)	0.77 (0.36-1.64)	0.50	59 (20)	11 (23)	1.19 (0.57-2.48)	0.65	351 (35)	47 (26)	0.65 (0.45-0.93)	**0.02**
Grade 3-4	19 (4)	2 (2)	0.53 (0.12-2.30)	0.39	7 (3)	1 (3)	0.83 (0.10-6.98)	0.87	5 (2)	1 (2)	1.23 (0.14-10.81)	0.85	31 (3)	4 (2)	0.71 (0.25-2.03)	0.52
Any grade	31 (6)	15 (16)	2.74 (1.42-5.31)	**<0.01**	13 (6)	3 (8)	1.38 (0.37-5.12)	0.63	9 (3)	1 (2)	0.67 (0.08-5.45)	0.71	53 (5)	19 (11)	2.10 (1.21-3.64)	**<0.01**
Trombocytopenia																
Any grade	145 (30)	33 (34)	1.25 (0.78-1.98)	0.35	17 (8)	5 (14)	1.84 (0.63-5.33)	0.27	89 (30)	16 (34)	1.15 (0.60-2.22)	0.67	251 (25)	54 (30)	1.15 (0.82-1.63)	0.42
Grade 3-4	9 (2)	3 (3)	1.72 (0.46-6.49)	0.42	0	0	5.80 (0.11-296.82)	0.38	7 (2)	1 (2)	0.87 (0.11-7.28)	0.90	16 (2)	4 (2)	1.39 (0.46-4.21)	0.56
Anemia																
Any grade	281 (57)	57 (58)	1.09 (0.70-1.70)	0.71	96 (44)	21 (57)	1.65 (0.82-3.34)	0.16	138 (48)	23 (49)	1.04 (0.56-1.93)	0.90	515 (52)	101 (56)	1.19 (0.87-1.64)	0.28
Grade 3-4	10 (2)	5 (5)	2.64 (0.88-7.90)	0.07	0	0	5.80 (0.11-296.82)	0.38	5 (2)	0	0.98 (0.97-0.99)	0.36	15 (2)	5 (3)	1.87 (0.67-5.21)	0.23
Neurotoxicity																
Any grade	300 (61)	50 (52)	0.69 (0.44-1.07)	0.10	27 (12)	4 (11)	0.85 (0.28-2.60)	0.78	194 (67)	30 (64)	0.86 (0.45-1.64)	0.63	521 (52)	84 (47)	0.80 (0.58-1.10)	0.16
Grade 3-4	19 (4)	4 (4)	1.08 (0.36-3.24)	0.89	0	0	5.80 (0.11-296.82)	0.38	5 (2)	2 (4)	2.52 (0.47-13.36)	0.26	24 (2)	6 (3)	1.40 (0.56-3.47)	0.47
Alopecia																

Any grade	72 (15)	11 (11)	0.75 (0.38-1.48)	0.41	33 (15)	6 (16)	1.08 (0.42-2.79)	0.88	14 (5)	2 (4)	0.87 (0.19-3.96)	0.86	119 (12)	19 (11)	0.87 (0.52-1.45)	0.59
Asthenia																
Any grade	331 (68)	62 (65)	0.88 (0.55-1.39)	0.57	117 (54)	33 (89)	7.05 (2.42-20.59)	**<0.01**	167 (58)	29 (62)	1.17 (0.62-2.20)	0.63	616 (62)	124 (69)	1.37 (0.97-1.92)	0.07
Grade 3-4	46 (9)	11 (11)	1.25 (0.62-2.51)	0.53	17 (8)	6 (16)	2.28 (0.83-6.22)	0.10	26 (9)	4 (9)	0.94 (0.31-2.83)	0.91	89 (9)	21 (12)	1.35 (0.81-2.30)	0.25
Hand and Foot Syndrome																
Any grade	100 (20)	9 (9)	0.40 (0.20-0.83)	**0.01**	34 (16)	5 (14)	0.84 (0.31-2.31)	0.74	46 (16)	13 (28)	2.01 (0.99-4.10)	0.05	180 (18)	27 (15)	0.80 (0.51-1.24)	0.32
Grade 3-4	14 (3)	2 (2)	0.72 (0.16-3.24)	0.67	1 (0.4)	0	1.00 (0.97-1.00)	0.68	5 (2)	3 (6)	3.86 (0.89-16.72)	0.05	20 (2)	5 (3)	1.39 (0.52-3.76)	0.51
Hypertension																
Any grade	153 (31)	27 (27)	0.86 (0.53-1.40)	0.55	56 (26)	11 (30)	1.22 (0.56-2.62)	0.62	101 (35)	18 (38)	1.15 (0.61-2.17)	0.67	310 (30)	56 (31)	0.99 (0.70-1.41)	0.99
Grade 3-4	34 (7)	9 (9)	1.39 (0.64-3.00)	0.40	2 (1)	5 (14)	16.80 (3.13-90.25)	**<0.01**	35 (12)	6 (13)	1.06 (0.42-2.68)	0.91	71 (7)	20 (11%	1.62 (0.96-2.74)	0.07
Bleeding																
Any grade	116 (24)	21 (22)	0.90 (0.53-1.53)	0.70	59 (27)	14 (38)	1.63 (0.79-3.38)	0.19	52 (18)	14 (30)	0.98 (0.96-1.00)	0.32	227 (23)	49 (27)	1.27 (0.89-1.83)	0.20
Grade 3-4	2 (0.4)	1 (1)	2.57 (0.23-28.61)	0.43	1 (0.4)	1 (3)	6.00 (0.37-98.10)	0.15	2 (1)	0	0.99 (0.98-1.00)	0.57	5 (1)	2 (1)	2.25 (0.43-11.57)	0.33
Thromboembolic Events																
Any grade	60 (12)	11 (11)	0.92 (0.46-1.82)	0.81	20 (9)	2 (5)	0.56 (0.13-2.52)	0.45	38 (13)	5 (11)	0.79 (0.29-2.11)	0.63	118 (12)	18 (10)	0.83 (0.49-1.41)	0.48
Grade 3-4	34 (7)	6 (6)	0.89 (0.36-2.19)	0.81	18 (8)	1 (3)	0.31 (0.04-2.37)	0.27	21 (7)	2 (4)	0.57 (0.13-2.50)	0.45	73 (7)	9 (5)	0.67 (0.33-1.36)	0.26
Gastrointestinal Perforation																
Any grade	9 (2)	0	0.98 (0.97-0.99)	0.18	2 (1)	0	0.99 (0.97-1.00)	0.56	6 (2)	0	0.98 (0.96-1.00)	0.32	17 (2)	0	0.16 (0.00-2.59)	0.19
Grade 3-4	8 (2)	0	0.98 (0.97-1.00)	0.21	2 (1%)	0	1.15 (0.05-24.42)	0.93	5 (2)	0	0.98 (0.96-0.99)	0.36	15 (2)	0	0.98 (0.98-0.99)	0.10

Legend Table S2. N= number; OR= Odds Ratio; CI= Confidence Interval; y= years; p= chi-square or Fisher's exact test when appropriate; tox= toxicity; bev= bevacizumab; CT= chemotherapy.

Table S3. Multivariable safety results of gender-related toxicities											
Safety population N= 1175											
		Gender		Age		Treatment		ECOG PS		Duration of induction treatment	
		M	F	<70y	≥70y	Doublet + bevacizumab	Triplet + bevacizumab	0	1-2	4 months	6 months
Nausea – *Any grade*	OR [95%CI]	1	1.53 [1.20 – 1.95]	1	0.56 [0.40 – 0.78]	1	1.39 [1.10 – 1.77]	1	0.79 [0.56 – 1.11]	1	1.87 [1.47 – 2.39]
	p	**0.001**		**0.001**		**0.007**		0.171		**<0.001**	
Nausea – *Grade 3/4*	OR [95%CI]	1	1.99 [1.11 – 3.58]	1	0.87 [0.36 – 2.10]	1	1.31 [0.73 – 2.35]	1	1.36 [0.68 – 2.75]	1	0.60 [0.32 – 1.11]
	p	**0.021**		0.755		0.359		0.386		0.104	
Vomiting – *Any grade*	OR [95%CI]	1	1.72 [1.34 – 2.18]	1	0.64 [0.44 – 0.92]	1	1.95 [1.51 – 2.51]	1	1.08 [0.76 – 1.54]	1	1.92 [1.49 – 2.47]
	p	**<0.001**		**0.018**		**<0.001**		0.671		**<0.001**	
Vomiting – *Grade 3/4*	OR [95%CI]	1	4.09 [1.89 – 8.85]	1	0.81 [0.28 – 2.38]	1	1.48 [0.74 – 2.96]	1	1.54 [0.68 – 3.49]	1	1.74 [0.88 – 3.44]
	p	**<0.001**		0.701		0.269		0.299		0.113	
Diarrhoea – *Grade 3/4*	OR [95%CI]	1	1.33 [0.94 – 1.88]	1	1.61 [1.04 – 2.49]	1	2.42 [1.68 – 3.47]	1	1.15 [0.71 – 1.86]	1	1.25 [0.89 – 1.76]
	p	0.106		**0.031**		**<0.001**		0.567		0.204	
Stomatitis – *Any grade*	OR [95%CI]	1	1.34 [1.06 – 1.69]	1	1.09 [0.79 – 1.50]	1	1.38 [1.10 – 1.74]	1	0.94 [0.67 – 1.31]	1	1.06 [0.84 – 1.34]
	p	**0.015**		0.613		**0.006**		0.698		0.601	
Stomatitis – *Grade 3/4*	OR [95%CI]	1	1.75 [1.05 – 2.93]	1	1.66 [0.89 – 3.12]	1	1.66 [0.98 – 2.80]	1	1.20 [0.59 – 2.42]	1	1.47 [0.88 – 2.45]
	p	**0.031**		0.114		0.057		0.614		0.137	
Neutropenia – *Any grade*	OR [95%CI]	1	1.89 [1.47 – 2.44]	1	1.44 [1.01 – 2.06]	1	2.82 [2.20 – 3.61]	1	0.75 [0.53 — 1.05]	1	0.75 [0.59 – 0.96]
	p	**<0.001**		**0.042**		**<0.001**		0.097		**0.022**	
Neutropenia – *Grade 3/4*	OR [95%CI]	1	1.90 [1.47 – 2.46]	1	1.26 [0.88– 1.79]	1	3.71 [2.87 – 4.81]	1	0.60 [0.41 — 0.89]	1	0.94 [0.73 – 1.22]
	p	**0.042**		0.198		**<0.001**		**0.011**		0.647	
Febrile Neutropenia –	OR [95%CI]	1	1.65 [1.02 – 2.69]	1	2.15 [1.22 – 3.79]	1	1.77 [1.07 — 2.91]	1	1.11 [0.55 – 2.24]	1	1.53 [0.95 – 2.49]

Any grade	**p**	**0.042**		**0.008**		**0.025**		0.766		0.082	
Anemia – ***Any grade***	**OR [95%CI]**	1	1.33 [1.05 – 1.69]	1	1.25 [0.91 – 1.74]	1	1.48 [1.18 – 1.87]	1	1.26 [0.90 – 1.76]	1	0.85 [0.68 – 1.08]
	p	**0.017**		**0.001**		**0.001**		0.178		0.185	
Anemia – ***Grade 3/4***	**OR [95%CI]**	1	2.55 [1.00 – 6.50]	1	2.33 [0.80 – 6.74]	1	2.87 [1.03 – 8.00]	1	2.18 [0.85 – 5.62]	1	0.59 [0.22 – 1.56]
	p	**0.051**		0.120		**0.044**		0.105		0.286	
Alopecia – ***Any grade***	**OR [95%CI]**	1	1.56 [1.09 – 2.25]	1	0.87 [0.52 – 1.48]	1	1.61 [1.11 – 2.32]	1	1.30 [0.79 – 2.12]	1	2.56 [1.77 – 3.71]
	p	**0.016**		0.613		0.301		0.301		**<0.001**	
Asthenia – ***Any grade***	**OR [95%CI]**	1	1.32 [1.04 – 1.69]	1	1.41 [1.00-2.00]	1	1.41 [1.11 – 1.79]	1	1.16 [0.82 – 1.65]	1	1.25 [0.98 – 1.59]
	p	**0.025**		**0.050**		**0.005**		0.391		**0.073**	
Asthenia – ***Grade 3/4***	**OR [95%CI]**	1	1.66 [1.11 – 2.47]	1	1.46 [0.87 – 2.45]	1	1.06 [0.71 – 1.57]	1	1.39 [0.83 – 2.33]	1	1.35 [0.91 – 2.00]
	p	**0.013**		0.148		0.789		0.207		0.139	
CT-related tox – ***Any grade***	**OR [95%CI]**	1	2.68 [1.26 – 5.70]	1	1.15 [0.47 – 2.81]	1	2.82 [1.40 – 5.69]	1	0.66 [0.30 – 1.47]	1	0.66 [0.35 – 1.23]
	p	**0.010**		0.763		**0.004**		0.312		0.186	
CT-related tox – ***Grade 3/4***	**OR [95%CI]**	1	1.98 [1.54 – 2.55]	1	2.28 [1.59 – 3.27]	1	3.22 [2.52 – 4.12]	1	0.90 [0.63 – 1.27]	1	0.99 [0.77 – 1.27]
	p	**<0.001**		**<0.001**		**<0.001**		0.541		0.930	
Overall tox – ***Any grade***	**OR [95%CI]**	1	7.13 [2.15 – 23.69]	1	0.84 [0.34 - 2.12]	1	2.14 [1.00 – 4.58]	1	0.53 [0.23 – 1.26]	1	0.63 [0.31 – 1.29]
	p	**0.001**		0.717		0.051		0.152		0.207	
Overall tox – ***Grade 3/4***	**OR [95%CI]**	1	1.73 [1.34 – 2.23]	1	1.93 [1.33 – 2.79]	1	2.80 [2.19 – 3.59]	1	0.94 [0.66 – 1.34]	1	0.89 [0.69 – 1.14]
	p	**<0.001**		**0.001**		**<0.001**		0.743		0.341	

Legend Table S3. OR= Odds Ratio; CI= Confidence Interval M= male; F= female; y=years; ECOG PS= Eastern Cooperative Oncology Group Performance Status.

Table S4. Safety profile according to treatment group, age and gender														
Safety population N=1175														
	<70y			70-75y				M			F			
	Doublet/Bev N= 505	Triplet/Bev N= 490	OR (95%CI)	Doublet/Bev N= 84	Triplet/Bev N= 96	OR (95%CI)	*p*	Doublet/Bev N= 358	Triplet/Bev N=326	OR (95%CI)	Doublet/Bev N= 231	Triplet/Bev N= 260	OR (95%CI)	*p*
Nausea														
Any Grade	290 (6)	319 (65)	1.39 (1.08–1.80)	36 (43)	50 (52)	1.51 (0.84 – 2.73)	0.801	181 (51)	194 (60)	1.47 (1.09-1.99)	145 (63)	175 (67)	1.22 (0.84-1.77)	0.445
Grade 3-4	18 (4)	25 (5)	1.45 (0.78-2.69)	3 (4)	3 (3)	0.89 (0.17-4.54)	0.585	7 (2)	13 (4)	2.08 (0.82-5.28)	14 (6)	15 (6)	0.95 (0.45-2.01)	0.198
Vomiting														
Any Grade	136 (27)	215 (44)	2.15 (1.65-2.80)	22 (26)	25 (26)	1.02 (0.53 – 1.99)	**0.043**	85 (24)	111 (34)	1.71 (1.22-2.39)	73 (32)	129 (50)	2.13 (1.47-3.08)	0.383
Grade 3-4	12 (2)	19 (4)	1.65 (0.79-3.44)	2 (2)	2 (2)	0.89 (0.12-6.48)	0.569	3 (1)	6 (2)	2.22 (0.55-8.94)	11 (5)	15 (6)	1.22 (0.55-1.72)	0.468
Diarrhea														
Any Grade	267 (53)	358 (73)	2.39 (1.83-3.11)	45 (54)	69 (72)	2.36 (1.27-4.39)	0.971	182 (51)	237 (73)	2.58 (1.87-3.55)	73 (32)	190 (73)	2.11 (1.45-3.08)	0.429
Grade 3-4	42 (8)	81 (17)	2.17 (1.46-3.23)	7 (8)	26 (27)	4.20 (1.72-10.28)	0.187	24 (7)	57 (18)	2.95 (1.78-4.88)	25 (11)	50 (19)	1.96 (1.17-3.29)	0.268
Stomatitis														
Any Grade	214 (42)	249 (51)	1.39 (1.09-1.79)	37 (44)	50 (52)	1.44 (0.80-2.60)	0.919	139 (39)	160 (49)	1.52 (1.12-2.06)	112 (48)	139 (54)	1.22 (0.86-1.74)	0.359
Grade 3-4	22 (4)	28 (6)	1.33 (1.75-2.35)	2 (2)	12 (13)	6.00 (1.30-27.64)	**0.070**	8 (2)	21 (6)	3.01 (1.32-6.90)	16 (7)	19 (7)	1.06 (0.53-2.11)	0.058
Neutropenia														
Any Grade	234 (46)	355 (72)	3.01 (2.13-3.92)	49 (58)	71 (74)	1.96 (1.05-3.68)	0.217	154 (43)	217 (67)	2.57 (2.89-3.51)	129 (56)	209 (80)	3.24 (2.17-4.84)	0.372
Grade 3-4	105 (21)	243 (50)	3.72 (2.82-4.92)	20 (24)	53 (55)	3.69 (1.95-6.97)	0.977	58 (16)	146 (45)	4.06 (2.85-5.79)	67 (29)	150 (58)	3.34 (2.29-4.86)	0.458
Febrile Neutropenia														
Any Grade	22 (4)	31 (6)	1.47 (0.84-2.58)	4 (5)	15 (16)	3.80 (1.21-11.94)	0.147	14 (4)	20 (6)	1.61 (0.80-3.23)	12 (5)	26 (10)	2.03 (1.00-4.11)	0.646
Thrombocytopenia														
Any Grade	106 (21)	145 (30)	1.57 (1.18-2.10)	21 (25)	33 (34)	1.46 (0.76-2.75)	0.828	86 (24)	105 (32)	1.46 (1.04-2.04)	41 (18)	73 (28)	1.81 (1.17-2.79)	0.441
Grade 3-4	7 (1)	9 (2)	1.33 (0.49-3.59)	1 (1)	3 (3)	2.74 (0.28-26.85)	0.568	5 (1)	5 (2)	1.10 (0.32-3.83)	3 (1)	7 (3)	2.10 (0.54-8.23)	0.492

Anemia														
Any Grade	234 (46)	281 (57)	1.54 (1.20-1.98)	44 (52)	57 (59)	1.27 (0.71-2.30)	0.561	163 (46)	174 (53)	1.34 (0.99-1.81)	115 (50)	164 (63)	1.72 (1.20-2.47)	0.290
Grade 3-4	5 (1)	10 (2)	1.98 (0.70-5.61)	0 (0)	5 (5)	10.39 (0.58-194.07)	0.300	3 (1)	4 (1)	1.47 (0.33-6.62)	2 (1)	11 (4)	5.06 (1.11-23.07)	0.257
Neurotoxicity														
Any Grade	221 (44)	300 (61)	2.01 (1.56-2.59)	34 (40)	50 (52)	1.51 (0.84-2.73)	0.395	155 (43)	191 (59)	1.81 (1.33-2.45)	100 (43)	159 (61)	2.06 (1.44-2.96)	0.586
Grade 3-4	5 (2)	19 (4)	4.02 (1.49-10.85)	2 (2)	4 (4)	1.82 (0.33-10.22)	0.437	6 (2)	12 (4)	2.24 (0.83-6.04)	1 (0.4)	11 (4)	10.15 (1.30-79.15)	0.194
Alopecia														
Any Grade	47 (9)	72 (15)	1.67 (1.13-2.47)	8 (10)	11 (11)	1.26 (0.48-3.30)	0.595	28 (8)	39 (12)	1.60 (0.96-2.67)	27 (12)	44 (17)	1.54 (0.92-2.58)	0.915
Asthenia														
Any Grade	284 (56)	331 (68)	1.60 (1.24-2.07)	62 (74)	62 (65)	0.70 (0.37-1.32)	**0.018**	204 (57)	208 (64)	1.33 (0.98-1.81)	142 (61)	185 (71)	1.55 (1.06-2.25)	0.546
Grade 3-4	43 (9)	46 (9)	1.11 (0.72-1.71)	10 (12)	11 (12)	0.98 (0.40-2.44)	0.815	26 (7)	26 (8)	1.11 (0.63-1.95)	27 (12)	31 (12)	1.02 (0.59-1.77)	0.845
Hand and Foot Syndrome														
Any Grade	80 (16)	100 (20)	1.35 (0.98-1.88)	18 (21)	9 (9)	0.39 (1.17-0.92)	**0.008**	54 (15)	62 (19)	1.32 (0.89-1.97)	44 (19)	47 (18)	0.94 (0.60-1.48)	0.267
Grade 3-4	6 (1)	14 (3)	2.43 (0.93-6.39)	3 (4)	2 (2)	0.59 (0.10-3.61)	0.175	8 (2)	6 (2)	0.82 (0.28-2.40)	1 (0.4)	10 (4)	9.20 (1.17-72.38)	**0.042**
Hypertension														
Any Grade	157 (31)	153 (31)	1.00 (0.77-1.31)	29 (35)	27 (28)	0.77 (0.41-1.44)	0.448	112 (31)	97 (30)	0.93 (0.67-1.29)	74 (32)	83 (32)	0.10 (0.68-1.46)	0.793
Grade 3-4	37 (7)	34 (7)	0.94 (0.58-1.52)	11 (13)	9 (9)	0.70 (0.28-1.79)	0.591	26 (7)	21 (6)	0.88 (0.49-1.60)	22 (10)	22 (9)	0.88 (0.47-1.63)	0.997
Bleeding														
Any Grade	111 (22)	116 (24)	1.10 (0.81-1.47)	28 (33)	21 (22)	0.58 (0.30-1.12)	**0.084**	90 (25)	83 (26)	1.02 (0.72-1.44)	49 (21)	54 (21)	0.97 (0.63-1.50)	0.876
Grade 3-4	3 (0.6)	2 (0.4)	1.68 (0.11-4.11)	1 (1)	1 (1)	0.89 (0.06-14.51)	0.874	2 (1)	3 (1)	1.68 (0.11-4.11)	2 (1)	0 (0)	0.18 (0.01- 3.71)	0.219
Thromboembolic Events														
Any Grade	58 (11)	60 (12)	1.07 (0.73-1.57)	7 (8)	11 (11)	1.13 (0.43-3.02)	0.917	38 (11)	42 (13)	1.18 (0.74-1.88)	27 (12)	29 (11)	0.95 (0.54-1.88)	0.561
Grade 3-4	39 (8)	34 (7)	0.89 (0.55-1.43)	3 (4)	6 (6)	1.84 (0.45-7.61)	0.338	28 (8)	42 (13)	1.02 (0.57-1.81)	27 (12)	29 (11)	0.88 (0.43-1.81)	0.764

Gastrointestinal Perforation														
Any Grade	8 (2)	9 (2)	1.15 (0.45-2.93)	0 (0)	0 (0)	0.90 (0.02-46.62)	0.904	6 (2)	2 (1)	0.73 (0.20-2.60)	4 (1)	5 (2)	2.25 (0.43-11.68)	0.290
Grade 3-4	7 (1)	8 (2)	1.17 (0.43-3.14)	0 (0)	0 (0)	0.90 (0.02-45.60)	0.899	5 (1)	4 (1)	0.88 (0.23-3.29)	2 (1)	4 (2)	1.79 (0.33-9.86)	0.512
CT-related tox														
Any Grade	476 (94)	483 (99)	4.22 (1.83-9.73)	82 (98)	92 (96)	0.55 (0.10-3.07)	**0.037**	336 (94)	315 (97)	1.88 (0.90-3.93)	222 (96)	260 (100)	22.25 (1.28-386.48)	0.969
Grade 3-4	185 (37)	321 (66)	3.12 (2.41-4.04)	43 (51)	79 (82)	4.08 (2.08-8.02)	0.468	117 (33)	208 (64)	3.54 (2.58-4.85)	117 (51)	192 (74)	2.75 (1.89-4.02)	0.317
Bev-related tox														
Any Grade	289 (57)	279 (57)	0.98 (0.76-1.26)	55 (65)	53 (55)	0.63 (0.34-1.15)	0.180	204 (57)	191 (59)	1.04 (0.77-1.41)	140 (61)	141 (54)	0.77 (0.54-1.10)	0.207
Grade 3-4	89 (18)	81 (16)	0.92 (0.66-1.28)	16 (17)	21 (22)	1.22 (0.59-2.54)	0.486	66 (18)	57 (17)	0.94 (0.63-1.39)	39 (17)	45 (17)	1.03 (0.64-1.65)	0.762
Overall tox														
Any Grade	485 (96)	484 (99)	3.34 (1.33-8.39)	82 (98)	92 (96)	0.55 (0.10-3.07)	**0.070**	349 (97)	316 (97)	1.77 (0.81-3.87)	228 (99)	260 (110)	7.97 (0.40-155.92)	0.323
Grade 3-4	243 (48)	351 (72)	2.69 (2.07-3.50)	50 (60)	81 (84)	3.36 (1.76-7.17)	0.467	158 (44)	229 (70)	2.91 (2.12-3.99)	135 (58)	203 (78)	2.53 (1.71-3.75)	0.588

Legend Table S4. N= number; bev= bevacizumab; OR= Odds Ratio; CI= Confidence Interval; y= years; M= male; F= female; tox=toxicity; p= p for interaction; CT= chemotherapy.

Table S5. Univariable safety results according to gender and treatment group

	Safety population N=1175															
	FOLFOXIRI + Bevacizumab N=586				FOLFIRI + Bevacizumab N=254				FOLFOX + Bevacizumab N=335				Overall N=1175			
	M N=326 (56%)	F N=260 (44%)	OR (95%CI)	*p*	M N=154 (61%)	F N=100 (39%)	OR (95%CI)	*p*	M N=204 (61%)	F N=131 (39%)	OR (95%CI)	*p*	M N=684 (58%)	F N=491 (42%)	OR (95%CI)	*p*
Diarrhoea																
Any grade	237 (73)	190 (73)	1.02 (0.71-1.47)	0.92	91 (59)	59 (59)	1.00 (0.60-1.66)	0.99	91 (45)	71 (54)	1.47 (0.95-2.28)	0.09	419 (61)	320 (65)	1.18 (0.93-1.51)	0.17
Grade 3-4	57 (18)	50 (19)	1.12 (0.74-1.71)	0.59	13 (8)	14 (14)	1.77 (0.79-3.93)	0.16	11 (5)	11 (8)	1.61 (0.68-3.83)	0.28	81 (12)	75 (15)	1.34 (0.96-1.88)	0.09
Stomatitis																
Any grade	160 (49)	139 (54)	1.19 (0.86-1.65)	0.29	61 (40)	50 (50)	1.52 (0.92-2.53)	0.10	78 (38)	62 (47)	1.45 (0.93-2.26)	0.10	299 (44)	251 (51)	1.35 (1.07-1.70)	***0.01***
Grade 3-4	21 (6)	19 (7)	1.15 (0.60-2.18)	0.68	4 (3)	7 (7)	2.82 (0.80-9.91)	0.09	4 (2)	9 (7)	3.69 (1.11-12.24)	**0.02**	29 (4)	35 (7)	1.73 (1.05-2.88)	**0.03**
Neutropenia																
Any grade	217 (67)	209 (80)	2.06 (1.40-3.02)	***<0.01***	65 (42)	45 (45)	1.12 (0.67-1.86)	0.66	89 (44)	84 (64)	2.31 (1.47-3.63)	***<0.01***	371 (54)	338 (69)	1.86 (1.46-2.38)	***<0.01***
Grade 3-4	146 (45)	150 (58)	1.68 (1.21-2.34)	***<0.01***	29 (19)	23 (23)	1.29 (0.69-2.39)	0.42	29 (14)	44 (34)	3.05 (1.79-5.21)	***<0.01***	204 (30)	217 (44)	1.86 (1.46-2.37)	***<0.01***
Febrile Neutropenia																
Any grade	20 (6)	26 (10)	1.70 (0.93-3.12)	0.08	10 (7)	6 (6)	0.92 (0.32-2.61)	0.87	4 (2)	6 (5)	2.40 (0.66-8.67)	0.17	34 (5)	38 (8)	1.60 (0.99-2.59)	**0.05**
Trombocytopenia																
Any grade	105 (32)	73 (28)	0.82 (0.58-1.17)	0.28	17 (11)	5 (5)	0.42 (0.15-1.19)	0.10	69 (34)	36 (28)	0.74 (0.46-1.20)	0.22	191 (28)	114 (23)	0.78 (0.60-1.02)	0.07
Grade 3-4	5 (2)	7 (3)	1.78 (0.56-5.66)	0.33	0	0	1.54 (0.03-78.10)	0.83	5 (3)	3 (2)	0.93 (0.22-3.97)	0.93	10 (2)	10 (2)	1.40 (0.58-3.39)	0.45
Anemia																

Any grade	174 (53)	164 (63)	1.49 (1.07-2.08)	***0.02***	61 (40)	56 (56)	1.94 (1.17-3.23)	***0.01***	102 (50)	59 (45)	0.82 (0.53-1.27)	0.38	337 (49)	279 (57)	1.36 (1.07-1.61)	***0.01***
Grade 3-4	4 (1)	11 (4)	3.56 (1.12-11.30)	***0.02***	0	0	1.54 (0.03-78.10)	0.83	3 (2)	2 (2)	1.04 (0.17-6.30)	0.97	7 (1)	13 (3)	2.63 (1.04-6.64)	***0.03***
Neurotoxicity																
Any grade	191 (59)	159 (61)	1.11 (0.80-1.55)	0.53	17 (11)	14 (14)	1.31 (0.62-2.80)	0.48	138 (68)	86 (66)	0.91 (0.57-1.45)	0.71	346 (51)	259 (53)	1.09 (0.87-1.38)	0.46
Grade 3-4	12 (4)	11 (4)	1.16 (0.50-2.66)	0.73	0	0	1.54 (0.03-78.10)	0.83	6 (3)	1 (1)	0.25 (0.03-2.13)	0.17	18 (3)	12 (2)	0.93 (0.44-1.94)	0.84
Alopecia																
Any grade	39 (12)	44 (17)	1.50 (0.94-2.39)	0.09	20 (13)	19 (19)	1.57 (0.79-3.12)	0.19	8 (4)	8 (6)	1.59 (0.58-4.36)	0.36	67 (10)	71 (15)	1.56 (1.09-2.22)	***0.01***
Asthenia																
Any grade	208 (64)	185 (71)	1.40 (0.99-1.99)	0.06	90 (58)	60 (60)	1.07 (0.64-1.78)	0.81	114 (56)	82 (63)	1.32 (0.84-2.07)	0.22	412 (60)	327 (67)	1.32 (1.03-1.68)	***0.03***
Grade 3-4	26 (8)	31 (12)	1.56 (0.90-2.70)	0.11	9 (6)	14 (14)	2.62 (1.09-6.32)	***0.03***	17 (8)	13 (10)	1.21 (0.57-2.59)	0.62	52 (8)	58 (12)	1.63 (1.10-2.41)	***0.02***
Hand and Foot Syndrome																
Any grade	62 (19)	47 (18)	0.94 (0.62-1.43)	0.77	21 (14)	18 (18)	1.39 (0.70-2.76)	0.35	33 (16)	26 (20)	1.28 (0.73-2.27)	0.39	116 (17)	91 (19)	1.11 (0.82-1.51)	0.49
Grade 3-4	6 (2)	10 (4)	2.13 (0.77-5.95)	0.14	1 (1)	0	0.99 (0.98-1.00)	0.42	7 (3)	1 (1)	0.22 (0.03-1.78)	0.12	14 (2)	11 (2)	1.10 (0.49-2.44)	0.82
Hypertension																
Any grade	97 (30)	83 (32)	1.12 (0.78-1.58)	0.57	42 (27)	25 (25)	0.89 (0.50-1.58)	0.69	70 (34)	49 (37)	1.14 (0.72-1.81)	0.56	209 (31)	157 (32)	1.07 (0.83-1.37)	0.60
Grade 3-4	21 (6)	22 (9)	1.34 (0.72-2.50)	0.35	3 (2)	4 (4)	2.10 (0.46-9.58)	0.33	23 (11)	18 (14)	1.25 (0.65-2.43)	0.50	47 (7)	44 (9)	1.33 (0.87-2.05)	0.19
Bleeding																
Any grade	83 (26)	54 (21)	0.77 (0.52-1.13)	0.18	48 (31)	25 (25)	0.74 (0.42-1.30)	0.29	42 (21)	24 (18)	0.87 (0.50-1.51)	0.61	173 (25)	103 (21)	0.78 (0.59-1.04)	0.09
Grade 3-4	3 (1)	0	0.99 (0.98-1.00)	0.12	1 (1)	1 (1)	1.55 (0.10-24.99)	0.76	1 (1)	1 (1)	1.56 (0.10-25.18)	0.75	5 (1)	2 (0.4)	0.56 (0.11-2.88)	0.48
Thromboembolic Events																
Any grade	42 (13)	29 (11)	0.85 (0.51-1.41)	0.52	13 (8)	9 (9)	1.07 (0.44-2.61)	0.88	25 (12)	18 (14)	1.14 (0.60-2.18)	0.69	80 (12)	56 (11)	0.97 (0.68-1.40)	0.88

Grade 3-4	24 (7)	16 (6)	0.83 (0.43-1.59)	0.57	12 (8)	7 (7)	0.89 (0.34-2.35)	0.81	14 (7)	9 (7)	1.00 (0.42-2.38)	1.00	50 (7)	32 (7)	0.88 (0.56-1.40)	0.60
Gastrointestinal Perforation																
Any grade	4 (1)	5 (2)	1.58 (0.42-5.94)	0.50	1 (1)	1 (1)	1.55 (0.10-24.99)	0.76	5 (3)	1 (1)	0.31 (0.04-2.65)	0.26	10 (2)	7 (1)	0.98 (0.37-2.58)	0.96
Grade 3-4	4 (1)	4 (2)	1.26 (0.31-5.08)	0.75	1 (1)	1 (1)	1.55 (0.10-24.99)	0.76	4 (2)	1 (1)	0.39 (0.04-3.48)	0.38	9 (1)	6 (1)	0.93 (0.33-2.62)	0.89

Legend Table S5. N= number; OR= Odds Ratio; CI= Confidence Interval; M= male; F= female; p= chi-square or Fisher's exact test when appropriate; tox= toxicity; CT= chemotherapy; bev= bevacizumab.