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# Neutropenia and Febrile Neutropenia in Metastatic Colorectal Cancer Patients Receiving FOLFOXIRI plus Bevacizumab: Insights from a Pooled Analysis of the TRIBE and TRIBE2 Trials

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## Abstract

The TRIBE and TRIBE-2 trials established that first-line treatment with FOLFOXIRI combined with bevacizumab yields superior efficacy over FOLFIRI or FOLFOX plus bevacizumab in metastatic colorectal cancer, though it is associated with increased toxicity. In the present study, we investigated the occurrence and temporal patterns of neutropenia and febrile neutropenia (FN) in these trials, with the aim of determining their clinical impact, quantifying the effects attributable to FOLFOXIRI/bevacizumab, and evaluating predictive factors for their development. We investigated how often severe neutropenia (grade 3–4) and febrile neutropenia (FN) occurred, when these events typically developed, and the patterns of granulocyte colony-stimulating factor use. Analyses were performed for the full study population and separately by treatment regimen. FN episodes were further categorized using the (MASCC) risk score to evaluate their clinical severity. Out of 1,155 patients, 568 (49%) received FOLFOXIRI in combination with bevacizumab. Overall, severe neutropenia (grade 3–4) occurred in 410 patients (35%), while febrile neutropenia (FN) was observed in 70 patients (6%), with 21 (2%) classified as high risk. The FOLFOXIRI/bevacizumab regimen showed a markedly higher rate of neutropenia (51% vs. 21%, $P < 0.001$), FN (8% vs. 4%, $P = 0.02$), and high-risk FN [18 (3%) vs. 3 (1%), $P = 0.015$] compared with the alternative regimens, though no treatment-related deaths were reported. The majority of first G3–4 neutropenia and FN events occurred within the initial two months of therapy across all treatment arms. Temporal analysis across cycles indicated distinct patterns, with early cycles being particularly prone to G3–4 neutropenia in patients receiving FOLFOXIRI/bevacizumab ($P < 0.001$). Advanced age ($P = 0.01$) and female sex ($P < 0.001$) emerged as significant predictors of severe neutropenia, yet no meaningful interaction was found between treatment arm and these risk factors in terms of G3–4 neutropenia or FN occurrence. Notably, FN affected 12% of older female patients treated with FOLFOXIRI/bevacizumab. Despite the higher hematologic toxicity, neither severe neutropenia nor FN negatively influenced treatment outcomes, including overall response rate, progression-free survival, or overall survival. Treatment with FOLFOXIRI combined with bevacizumab carries a greater risk of grade 3–4 neutropenia and febrile neutropenia (FN) compared with doublet chemotherapy plus bevacizumab. FN was observed in fewer than 10% of patients and was predominantly classified as low risk. Enhanced monitoring during the initial two months of therapy is advisable, and prophylactic administration of granulocyte colony-stimulating factor could be considered for older female patients.

**Keywords:** Metastatic colorectal cancer, FOLFOXIRI, Febrile neutropenia, Neutropenia

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## Introduction

The combination of FOLFOXIRI—comprising fluorouracil, leucovorin, oxaliplatin, and irinotecan—with the anti-VEGF agent bevacizumab has emerged as an effective first-line approach for selected patients with metastatic colorectal cancer. The phase III TRIBE trial first demonstrated that this triplet regimen provides

superior outcomes compared with the doublet FOLFIRI plus bevacizumab [1, 2] while the subsequent TRIBE2 study showed that initiating treatment with FOLFOXIRI plus bevacizumab and reintroducing the same therapy upon disease progression offers prolonged clinical benefit relative to the sequential strategy of mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab.[3]

A recent pooled analysis of individual patient data from five randomized trials comparing FOLFOXIRI plus bevacizumab with doublet regimens (FOLFOX or FOLFIRI) confirmed a significant survival advantage for the intensified upfront therapy, albeit accompanied by an increased risk of treatment-related adverse events.[4] In particular, patients receiving FOLFOXIRI plus bevacizumab experienced higher rates of grade 3–4 diarrhoea, neutropenia, and febrile neutropenia (FN).[1, 3 ,4] Myelotoxicity is clinically relevant because FN and related complications can be severe or even life-threatening [5] and may necessitate dose reductions, treatment delays, or discontinuation, potentially undermining both treatment adherence and efficacy.[6] Consequently, the role of prophylactic granulocyte colony-stimulating factors (G-CSFs) in patients receiving FOLFOXIRI plus bevacizumab remains a topic of debate.

In this context, the present study focuses on the incidence and timing of neutropenia and FN among participants in the TRIBE and TRIBE2 trials, aiming to identify patient characteristics that predispose to these toxicities and to characterize the use of G-CSF in clinical practice within these study populations.

## Materials and Methods

The TRIBE and TRIBE2 trials were multicenter, phase III, randomized, open-label studies designed for patients with unresectable, previously untreated metastatic colorectal cancer. Eligibility included adults aged 18–70 years with an ECOG performance status of 0–2, and a subset of patients aged 71–75 years with ECOG 0. In TRIBE, 508 patients were randomly assigned to receive either FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab for up to 12 induction cycles, followed by maintenance with 5-fluorouracil and bevacizumab until disease progression, unacceptable toxicity, or withdrawal of consent. TRIBE2 enrolled 679 patients, who were allocated to FOLFOX plus bevacizumab (arm A) or FOLFOXIRI plus bevacizumab (arm B) for up to eight induction cycles. After first progression, arm A transitioned to FOLFIRI plus bevacizumab, while arm B received FOLFOXIRI plus bevacizumab, with both groups continuing maintenance therapy until second progression, unacceptable adverse events, or consent withdrawal.

This analysis focused on the occurrence and timing of grade 3–4 neutropenia and febrile neutropenia (FN), as well as the use of granulocyte colony-stimulating factor (G-CSF). Assessments were conducted in the modified safety population, including patients who had received at least one dose of study treatment and had evaluable toxicity data, stratified by treatment arm. Patients who received G-CSF as primary prophylaxis were excluded; primary prophylaxis was defined as G-CSF administered from the first cycle and continued in subsequent cycles without prior G3–4 neutropenia or FN.

Adverse events were graded according to NCI CTCAE v3.0 in TRIBE and v4.0 in TRIBE2. Neutropenia was considered G3–4 if absolute neutrophil counts fell below 1,000/μL, and FN was defined by a fever >38.3°C or sustained ≥38°C in combination with neutrophil counts ≤1,000/μL. FN episodes were stratified using the MASCC risk score, which assigns points based on clinical parameters to classify patients as low risk (≥21) or high risk (<21).[7]. According to protocol, laboratory tests and clinical evaluations were conducted within 48 hours before each chemotherapy cycle.

Time to onset of neutropenia and FN was estimated using Kaplan–Meier methods and compared using the log-rank test, with hazard ratios and 95% confidence intervals calculated via Cox proportional hazards modeling. Longitudinal assessment of neutropenia during the first eight induction cycles employed the toxicity over time (ToxT) approach, as described by Thanarajasingam *et al.* [8].

Patient characteristics—including age, sex, ECOG performance status, prior adjuvant therapy, previous radiotherapy, and presence of bone metastases—were evaluated for associations with G3–4 neutropenia or FN using logistic regression, with older age defined as ≥65 years. Significant predictors were confirmed through multivariate analyses. Interaction tests compared the impact of FOLFOXIRI plus bevacizumab versus doublets on G3 or higher adverse events across subgroups. OS and PFS were estimated with Kaplan–Meier curves and compared with log-rank tests. Statistical analyses were performed using MedCalc

v14.8.1 (MedCalc Software Ltd, Ostend, Belgium) and SAS v9.4 (SAS Institute, Cary, NC).

All patient data were documented in electronic case report forms and monitored by study personnel. Written informed consent was obtained from all participants, and both studies were conducted in accordance with the Declaration of Helsinki. TRIBE2 and TRIBE are registered on ClinicalTrials.gov under NCT02339116 and NCT00719797, respectively.

## Results and Discussion

Among the modified safety population, 1,175 patients were initially considered, with roughly half assigned to FOLFOXIRI plus bevacizumab (n = 586) and half to a doublet regimen plus bevacizumab (n = 589; 254 FOLFIRI and 335 FOLFOX). Twenty patients who received G-CSF as primary prophylaxis per investigator discretion were excluded, leaving 1,155 patients for analysis. Of these, 568 received FOLFOXIRI plus bevacizumab, whereas 587 received a doublet plus bevacizumab as first-line therapy (333 FOLFOX, 254 FOLFIRI).

In total, 410 patients (35%) experienced grade 3–4 neutropenia, with a markedly higher rate in the FOLFOXIRI/bevacizumab group compared with doublets (3.9, 95% CI 3.03–5.1, P < 0.001 OR 51% versus 21%). Seventy patients (6%) experienced at least one episode of febrile neutropenia (FN), amounting to 79 episodes overall. FN was more common in the FOLFOXIRI/bevacizumab arm than in the doublet arms (1.81, 95% CI 1.1–2.98, P = 0.02 OR 8% versus 4%) **(Table 1).**

**Table 1.** Occurrence of grade 3–4 neutropenia, febrile neutropenia, and high-risk FN episodes by treatment arm

| Adverse Event | Overall (N=1155) Events, N (%) | Doublets/bev (N=587) Events, N (%) | FOLFOXIRI/bev (N=568) Events, N (%) | OR (95% CI) | P |
|---|---|---|---|---|---|
| **Grade 3-4 neutropenia** | 410 (35) | 122 (21) | 288 (51) | 3.92 (3.03-5.08) | <0.001 |
| **Febrile neutropenia** | 70 (6) | 26 (4) | 44 (8) | 1.81 (1.10-2.98) | 0.02 |
| **High-risk febrile neutropenia** | 21 (2) | 3 (1) | 18 (3) | 5.31 (1.38-20.37) | 0.02 |

*Statistically significant P values are indicated in bold or italics.*

G, grade; CI, confidence interval; Bev, bevacizumab; OR, odds ratio; *N*, number

FN events were evaluated according to the MASCC risk scoring system. High-risk FN was relatively uncommon, occurring in 21 patients (2%) overall: 18 cases (3%) were reported in the FOLFOXIRI/bevacizumab arm, compared with 3 cases (1%) in the doublet plus bevacizumab arm (OR 5.31, 95% CI 1.38–20.37, P = 0.015) **(Table 1).** Treatment discontinuation due to prolonged neutropenia was rare, affecting only one patient, and no deaths related to FN were observed.

The onset of grade 3–4 neutropenia followed a similar pattern in both treatment groups, with the majority of first episodes occurring during the first two months (median time: 0.7 months for FOLFOXIRI/bevacizumab versus 1.0 month for doublets plus bevacizumab; HR 1.13, 95% CI0.91–1.39, P = 0.27). Most events (78.5%) took place within these initial two months, while 14.2% occurred during the third and fourth months, and only 7.3% appeared after the fourth month of treatment **(Figure 1).**

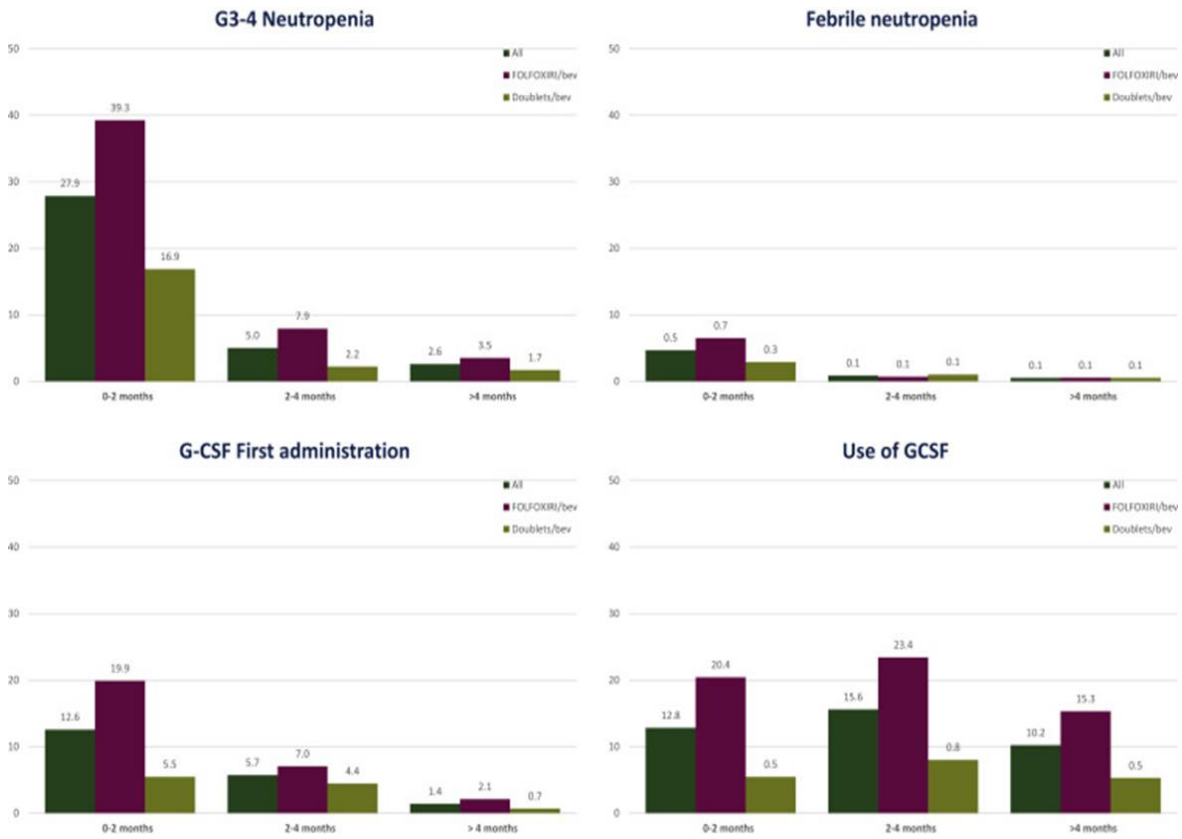



**Figure 1.** presents the distribution of grade 3–4 neutropenia, febrile neutropenia, and both initial and cumulative G-CSF administration over defined time intervals.

Analysis over successive treatment cycles demonstrated a distinct temporal profile between the two treatment arms ($P < 0.001$). Patients receiving FOLFOXIRI plus bevacizumab experienced higher average neutropenia levels throughout all time periods compared with those receiving doublet regimens (mean 0.64 versus 0.30, $P < 0.001$), highlighting the cumulative myelotoxic effect of the triplet combination **(Figure 2).**

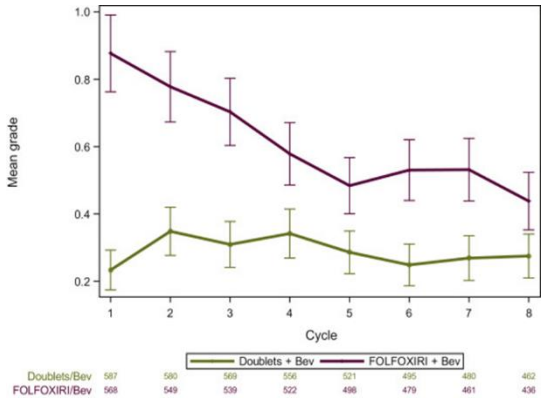



**Figure 2.** shows the changes in neutropenia grades over time, stratified by treatment arm.

The longitudinal analysis of neutropenia demonstrated notable differences between the two treatment arms. Patients receiving FOLFOXIRI plus bevacizumab experienced FN slightly earlier than those on doublet regimens, with median times of 0.6 and 1.6 months, respectively (HR 1.46, 95% CI 0.89–2.40, $P = 0.13$). The majority of FN events (77%) occurred within the first two months of therapy, while 14% emerged during months three and four, and fewer than 9% were reported beyond the fourth month **(Figure 1).** Among patients still undergoing treatment after four months (n = 1,018, 88.1%), the incidence of G3–4 neutropenia dropped to 2.9% (n = 30), and FN was observed in less than 1% of cases.

Survival outcomes were not significantly affected by the development of G3–4 neutropenia or FN. Patients experiencing G3–4 neutropenia had a median PFS of 11.7 months compared with 10.1 months for those without neutropenia (HR 0.91, 95% CI 0.80–1.03, $P = 0.13$), and median OS of 27.9 versus 24.5 months (HR 0.90, 95% CI 0.78–1.04, $P = 0.14$). Similarly, FN did not

significantly influence PFS (9.7 versus 10.8 months; HR 1.12, 95% CI 0.87–1.45, P = 0.38) or OS (22.3 versus 26.1 months; HR 1.26, 95% CI 0.96–1.66, P = 0.09). No interaction between treatment arm and either G3–4 neutropenia or FN was observed for survival endpoints.

Interestingly, G3–4 neutropenia was associated with higher overall response rates in the full cohort (OR 1.45, 95% CI 1.13–1.85, P = 0.003) and specifically within the FOLFOXIRI/bevacizumab group (OR 1.60, 95% CI 1.14–2.26, P = 0.007), whereas no difference was noted in the doublet arms (P = 0.84), with a borderline interaction by treatment (P = 0.06). Conversely, FN occurrence did not significantly affect response rates across any treatment groups.

G-CSF support was provided to 227 patients (20%), predominantly in the FOLFOXIRI arm (29%, n = 165) compared with the doublet arms (11%, n = 62). The timing of first G-CSF administration mirrored the early onset of neutropenia and FN, with 64% of initial administrations occurring within the first two months, declining to 29% during months three and four, and 7% beyond the fourth month **(Figure 1).** Secondary prophylaxis with G-CSF was given to 177 patients (15%) following a first G3–4 neutropenia episode, leading to a second neutropenia event in 40 patients (3%), most frequently in the FOLFOXIRI group (P = 0.30, 6% versus 1%). Among patients receiving G-CSF after an FN episode (n = 27), only two (<1%) experienced a subsequent FN event.

Treatment delays were common, affecting 62% of patients during induction therapy. G3–4 neutropenia accounted for FN for 7% and 39% of delays, with a higher frequency of delays in the FOLFOXIRI arm (G3–4 neutropenia: 35% versus 13%, P < 0.001; FN: P = 0.01, 6% versus 3%). Dose reductions following a first G3–4 neutropenia episode occurred in 14% of patients, more frequently in the FOLFOXIRI group (17% versus 10%), with 5% experiencing a second neutropenia event. Reductions after FN were less common (3%), and recurrence of FN was rare (<1%).

Risk factor analysis identified ECOG PS 0, older age (≥65 years), and female sex as significant predictors of G3–4 neutropenia (P = 0.01, and 0.01 and <0.001, respectively), findings confirmed by multivariate analysis. Prior exposure to adjuvant chemotherapy showed a trend toward increased risk (P = 0.054) **(Table 2).**

**Table 2.** Incidence of grade 3–4 neutropenia and febrile neutropenia according to patient-related risk factors

| Risk factors | Number of patients | G3-4 neutropenia Events, N (%) | OR (95% CI) | P | Febrile neutropenia Events, N (%) | OR (95% CI) | P |
|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | |
| **≥65 years** | 408 | 164 (40.2) | 1.37 (1.07-1.76) | 0.01 | 28 (6.86) | 1.24 (0.75-2.03) | 0.40 |
| **<65 years** | 747 | 246 (32.9) | 1 | | 42 (5.62) | 1 | |
| **ECOG PS** | | | | | | | |
| **1-2** | 144 | 38 (26.4) | 0.62 (0.42-0.91) | 0.01 | 10 (6.9) | 1.18 (0.59-2.37) | 0.64 |
| **0** | 1011 | 372 (36.8) | 1 | | 60 (5.9) | 1 | |
| **Sex** | | | | | | | |
| **Female** | 481 | 214 (44.5) | 1.95 (1.53-2.50) | <0.001 | 37 (7.7) | 1.62 (1.00-2.63) | 0.051 |
| **Male** | 674 | 196 (29.1) | 1 | | 33 (4.9) | 1 | |
| **Bone metastasis** | | | | | | | |
| **Yes** | 39 | 9 (23.1) | 0.54 (0.25-1.14) | 0.10 | 5 (12) | 2.38 (0.90-6.28) | 0.08 |
| **No** | 1116 | 401 (35.9) | 1 | | 65 (5.8) | 1 | |
| **Adjuvant chemotherapy** | | | | | | | |
| **Yes** | 79 | 36 (45.6) | 1.57 (0.99-2.49) | 0.054 | 3 (3.8) | 0.59 (0.18-1.93) | 0.39 |
| **No** | 1076 | 374 (34.8) | 1 | | 67 (6.2) | 1 | |

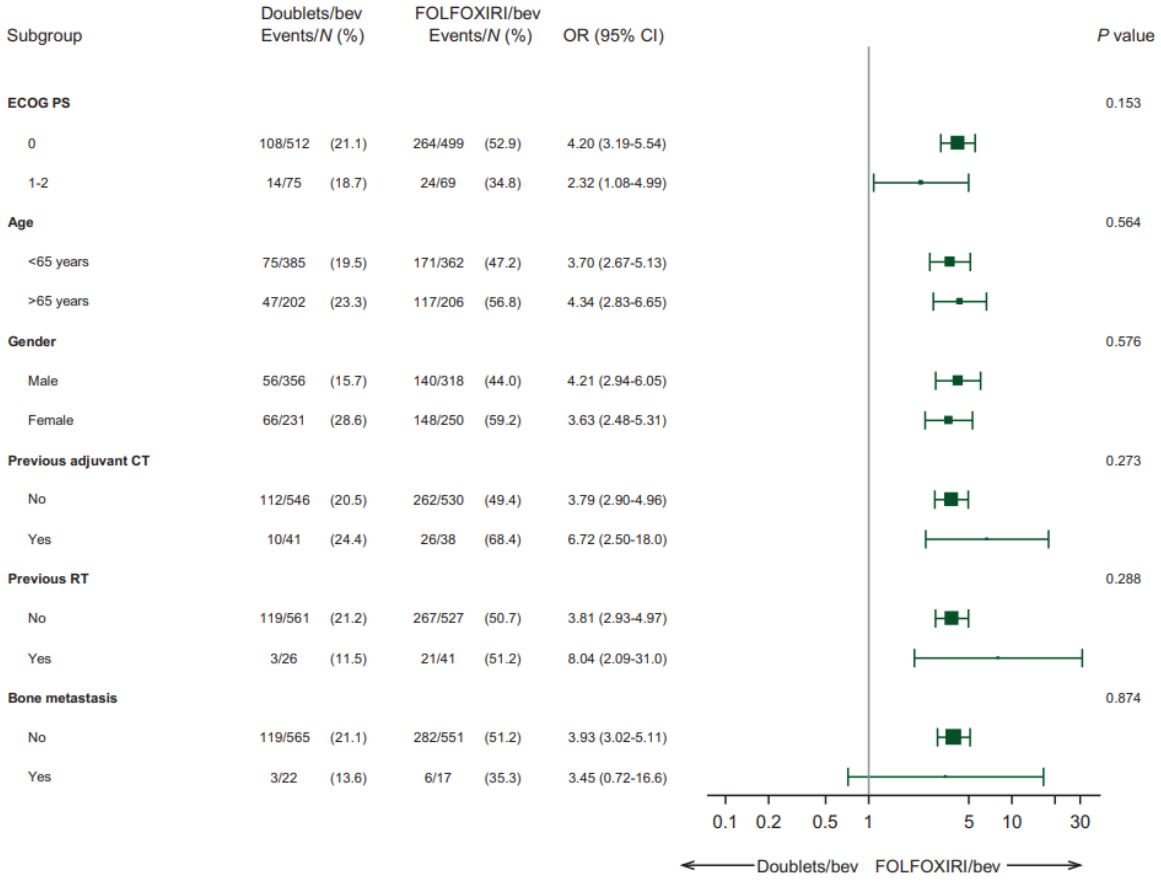
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Previous radiotherapy** | | | | | | | |
| **Yes** | 67 | 24 (35.8) | 1.02 (0.61-1.70) | 0.95 | 4 (6.0) | 0.98 (0.35-2.78) | 0.97 |
| **No** | 1088 | 386 (35.5) | 1 | | 66 (6.1) | 1 | |

*Statistically significant P values are highlighted in bold or italic format.*

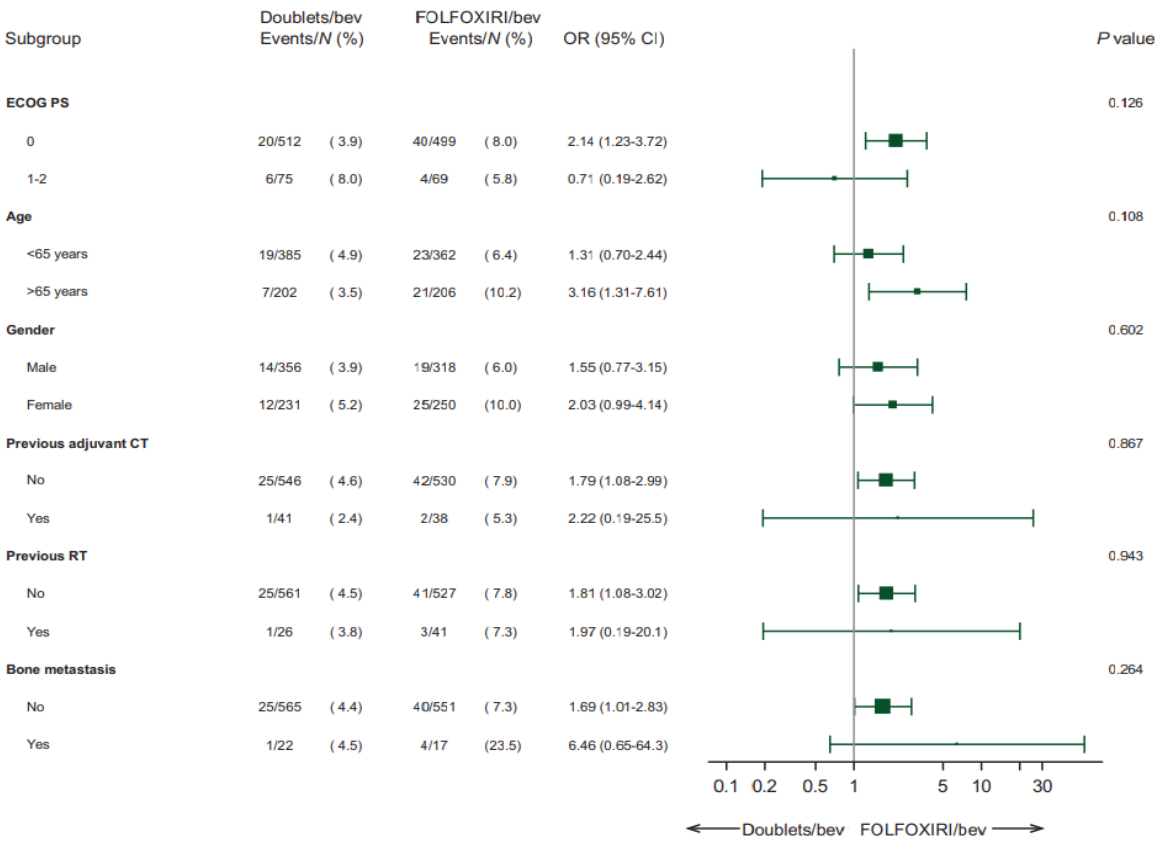
G, grade; ECOG PS, Eastern Cooperative Group Performance Status; CI, confidence interval; OR, odds ratio; N, number.

Although female patients (P = 0.051) and individuals with bone metastases (P = 0.08) displayed a greater tendency to develop febrile neutropenia (FN), these associations were not statistically significant **(Table 2).**

No notable interaction was detected between the treatment group and the evaluated risk factors regarding the occurrence of grade 3-4 neutropenia or FN **(Figures 3a and 3b**). That said, the heightened risk of FN linked to FOLFOXIRI plus bevacizumab relative to doublet chemotherapy plus bevacizumab was particularly noticeable in women and elderly patients. For instance, in a subgroup of 162 older women, 79 (49%) developed grade 3-4 neutropenia, including 59 (63%) in the FOLFOXIRI/bevacizumab group and 20 (29%) in the doublet/bevacizumab group (OR: 95% CI 2.18-8.31, 4.25, P < 0.001). When compared to the rest of the cohort, elderly female patients faced an increased likelihood of grade 3-4 neutropenia (OR: 95% CI 1.36-2.66, 1.90, P < 0.001).




a)




b)

**Figure 3.** presents forest plots illustrating the treatment effect on grade 3-4 neutropenia (panel a) and febrile neutropenia (panel b), stratified by various risk factors.

Among the elderly female patients, 13 (8%) developed febrile neutropenia (FN), with 11 (12%) occurring in the FOLFOXIRI plus bevacizumab group and 2 (3%) in the doublet chemotherapy plus bevacizumab group (OR: 95% CI 0.96-20.98, 4.49, P = 0.06). There were no statistically significant differences in the rate of FN when comparing older female patients to the remaining cohort (P = 0.26).

Neutropenia and febrile neutropenia (FN) are among the most commonly reported toxicities associated with cytotoxic chemotherapy, frequently resulting in treatment delays or dose adjustments, which can ultimately reduce dose intensity.[5, 9-13] The likelihood of developing neutropenia and FN increases with combination chemotherapy regimens.[9, 11] Prompt recognition and management of these complications are crucial to prevent severe adverse outcomes, which may affect 25–30% of patients, and potentially life-threatening events occurring in up to 11% of cases.[9, 13]

The TRIBE and TRIBE2 trials have demonstrated that FOLFOXIRI combined with bevacizumab is an effective and feasible first-line strategy, and also confers benefit when reintroduced after disease progression, albeit with a higher incidence of treatment-related toxicities, particularly myelosuppression.[1, 3] Our current analysis confirms that FOLFOXIRI plus bevacizumab is associated with a greater frequency of grade 3–4 (G3–4) neutropenia and FN compared with doublet regimens plus bevacizumab in the first-line treatment of advanced colorectal cancer. Despite the intensified regimen, the overall incidence of FN remained relatively low at 8%, and most FN episodes were classified as low-risk according to the MASCC score, with the majority of patients being managed as outpatients using G-CSF and/or oral antibiotics. Severe FN complications were rare, and no FN-related deaths were observed, supporting current guideline recommendations that routine primary prophylaxis with G-CSF is not required for the overall population. [9, 10, 14]

Longitudinal assessment of neutropenia provides a more detailed view of treatment-related toxicity than standard analyses. Over the course of therapy, FOLFOXIRI plus bevacizumab showed consistently higher neutropenia grades compared with doublet regimens, particularly during the early cycles. Most G3–4 neutropenia and FN events occurred within the first two months of treatment, irrespective of the regimen, consistent with observations in both solid tumors and hematologic malignancies treated with other chemotherapy protocols. Early clinical interventions, such as dose reductions and secondary prophylaxis with G-CSF, likely contributed to the reduced recurrence of severe neutropenia and FN in subsequent cycles. [12, 15, 16]

These findings emphasize the importance of close monitoring during the initial months of therapy to prevent FN and guide appropriate dose adjustments. In line with previous studies, older age and female sex were identified as significant risk factors for G3–4 neutropenia, with a trend toward increased FN risk in females and patients with bone metastases.[12, 16, 17] The apparent association of better ECOG performance status with higher neutropenia risk should be interpreted with caution, given the small number of patients with poorer ECOG scores in these trials and the fact that some received fewer cycles due to early progression or initiated chemotherapy at reduced doses at the investigators' discretion.

While the elevated risk of neutropenia and FN with FOLFOXIRI plus bevacizumab was largely independent of evaluated risk factors, older patients and females appeared particularly susceptible, highlighting the potential need for enhanced monitoring and consideration of primary G-CSF prophylaxis in selected cases when the triplet regimen is chosen upfront. Importantly, although G3–4 neutropenia and FN were associated with higher rates of treatment delays, they did not compromise overall response rate, progression-free survival (PFS), or overall survival (OS). G-CSF as primary prophylaxis may be considered in clinical scenarios where maintaining dose intensity is critical, such as in patients with potentially resectable metastatic disease, extensive or symptomatic metastases in vital organs, or in neoadjuvant settings. Alternative FOLFOXIRI schedules have been explored, particularly in Asian populations, although comparative efficacy data are currently lacking. [18-20]

At the time of study enrollment, pharmacogenomic screening for DPYD (dihydropyrimidine dehydrogenase) and UGT (uridine 5′-diphospho-glucuronosyltransferase) variants was not routinely performed. Previous analyses of the TRIBE cohort have shown that carriers of clinically relevant DPYD and/or UGT polymorphisms experienced higher rates of adverse events, particularly G3–4 hematologic toxicities including neutropenia and FN.21 These findings suggest that genotype-guided dose adjustments could potentially reduce toxicity without compromising therapeutic efficacy.[21,22]

## Conclusion

Treatment with FOLFOXIRI plus bevacizumab carries a greater likelihood of grade 3–4 neutropenia and febrile neutropenia compared with doublet regimens combined with bevacizumab. The majority of FN events were classified as low-risk by the MASCC score, and the overall incidence remained below 10%, indicating that routine primary prophylaxis with G-CSF is not warranted for the general population. Older patients and females were identified as independent risk factors for these toxicities, with the effect being particularly pronounced in those receiving FOLFOXIRI plus bevacizumab, supporting consideration of primary G-CSF prophylaxis in this higher-risk subgroup.

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**Conflict of Interest:** None

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