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ORIGINAL ARTICLE

# Re-evaluating the neutropenia–survival paradigm in irinotecan-based therapy for advanced gastric cancer: post-hoc analysis of the RINDBeRG trial

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## Abstract

**Background** Chemotherapy-induced neutropenia (CIN) has been considered a favorable prognostic marker across multiple cytotoxic regimens for gastrointestinal malignancies. However, its prognostic relevance in irinotecan (IRI)-based therapy for advanced gastric cancer (AGC) remains unclear.

**Methods** This post-hoc analysis used data from the phase III RINDBeRG trial comparing ramucirumab (RAM) plus IRI with IRI monotherapy as third- or later-line treatment for RAM-refractory AGC. Overall survival (OS) was evaluated according to the occurrence of grade 3 or higher neutropenia, defined as CIN. OS was also evaluated according to the baseline absolute neutrophil count (ANC), stratified by quartile-based cutoffs.

**Results** Among the 393 patients in the safety population, 44.5% and 28.5% in the RAM + IRI and IRI arms developed CIN, respectively. Baseline characteristics were generally comparable, with some imbalances across baseline ANC groups. In the RAM + IRI arm, those with and without CIN had a median OS of 9.7 and 8.9 months, respectively (HR = 0.84; 95% CI, 0.62–1.13; $p = 0.25$). In the IRI arm, those with and without CIN had a median OS of 8.4 and 8.6 months, respectively (HR = 0.85; 95% CI, 0.60–1.19; $p = 0.34$). Higher baseline ANC was associated with shorter OS, particularly in the RAM + IRI arm (7.3 vs. 10.9 months; HR = 1.83; 95% CI 1.14–2.94; $p = 0.01$).

**Conclusions** Unlike other cytotoxic regimens, CIN was not associated with survival in AGC patients receiving IRI with or without RAM. The clinical relevance of baseline ANC warrants further investigation.

**Trial registration** jRCT2031200106.

**Keywords** Chemotherapy-induced neutropenia · Irinotecan · Gastric cancer · later-line therapy

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## Introduction

Chemotherapy-induced neutropenia (CIN), one of the most common hematologic adverse events associated with cytotoxic chemotherapy, has traditionally been regarded as a dose-limiting toxicity requiring dose reduction or treatment delay. However, accumulating evidence suggests that CIN may reflect adequate systemic drug exposure to anticancer agents and, paradoxically, be associated with improved survival outcomes across various cancer types [1–9]. Indeed, retrospective analyses have shown that the occurrence of neutropenia during treatment with weekly paclitaxel or oral fluoropyrimidine S-1 has been associated with prolonged overall survival (OS) among patients with advanced gastric cancer (AGC) [3, 5]. Similar associations have also been reported in metastatic colorectal cancer treated with trifluridine/tipiracil or FOLFOX, further highlighting the potential prognostic relevance of CIN in selected chemotherapy settings [4, 6, 8, 9].

However, recent evidence has challenged the conventional interpretation of CIN as a surrogate marker of treatment efficacy. For instance, an exploratory biomarker analysis of the RAISE trial, which evaluated the effects of FOLFIRI with or without RAM in metastatic colorectal cancer, found that baseline absolute neutrophil count (ANC) was a stronger prognostic factor than was treatment-emergent neutropenia [7]; the apparent association between neutropenia and survival was thought to be confounded by the poorer prognosis of patients with a high baseline ANC, who were less likely to develop neutropenia during treatment.

The RINDBeRG trial was a multicenter, open-label, randomized phase III study that evaluated the efficacy and safety of ramucirumab (RAM) plus irinotecan (IRI) compared to IRI monotherapy as third- or later-line treatment for patients with RAM-refractory AGC [10]. In the primary analysis, RAM + IRI significantly improved progression-free survival and disease control rate compared with IRI monotherapy, and this was accompanied by a particularly high incidence of neutropenia in the RAM + IRI arm; however, this efficacy benefit did not translate into a significant improvement in OS. Although this discrepancy has been partly attributed to the substantial proportion of patients who received post-discontinuation treatment in both arms, potentially diluting any survival benefit conferred by ramucirumab, the underlying reasons remain incompletely understood. Notably, whether the neutropenia–survival paradigm described above applies in this treatment context has not previously been investigated.

Therefore, the present post-hoc exploratory analysis of the phase III RINDBeRG trial was conducted to primarily evaluate the prognostic significance of CIN among AGC patients receiving IRI with or without RAM. To further contextualize the findings, we also examined the association between baseline ANC and OS in this setting.

## Patients and methods

### Study design

This study was a post-hoc exploratory analysis of the phase III RINDBeRG trial, the design, eligibility criteria, treatment procedures, and primary results of which have been reported previously [10]. The present analysis, which was observational in nature, was designed to investigate the prognostic relevance of treatment-emergent CIN and baseline ANC by evaluating their association with survival outcomes among patients receiving IRI-based therapy.

### Participants and data collection

Patients aged ≥ 20 years with histologically confirmed unresectable or recurrent gastric or gastroesophageal junction adenocarcinoma who experienced disease progression during prior RAM-based chemotherapy were eligible for inclusion. All patients had previously received fluoropyrimidine-, platinum-, and taxane-based chemotherapy and had no prior exposure to IRI. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 and adequate organ function, including bone marrow reserve, as defined in the original trial protocol.

Patients included in the present analysis were selected from the safety population of the RINDBeRG trial, defined as those who received at least one dose of IRI with or without RAM. Those without available post-baseline hematologic data were excluded.

Baseline demographic and clinical characteristics, including age, sex, ECOG PS, number of metastatic sites, liver metastasis, prior treatments, and laboratory results, were obtained from the trial case report forms. UGT1A1 genotyping was not mandated by the original trial protocol, although patients with known homozygous or doubly heterozygous UGT1A1 polymorphisms received a reduced starting dose of irinotecan (120 mg/m²). Hematologic laboratory data were collected at baseline and at each treatment cycle according to the study protocol. Tumor assessments were performed using computed tomography or magnetic resonance imaging at baseline and every 8 weeks, and tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events were prospectively recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

### Definition of CIN

The most severe grade of neutropenia was determined based on the lowest recorded neutrophil count for each patient. CIN was defined as grade 3 or higher neutropenia according to CTCAE version 5.0. OS was analyzed according to the presence or absence of CIN during the entire treatment period. Given that treatment-emergent adverse events are time-dependent variables that may introduce immortal time bias, a prespecified sensitivity analysis was conducted using CIN occurring during the first treatment cycle. Patients were then classified according to the presence or absence of grade 3 or higher neutropenia during cycle 1, and survival was analyzed from treatment initiation.

Baseline ANC, defined as the neutrophil count measured at enrollment prior to study treatment initiation, was evaluated as a potential prognostic factor. Patients with available baseline ANC data were categorized into low and high ANC ($2.7 \times 10^3$ /μL and $4.8 \times 10^3$ /μL, respectively) groups according to prespecified quartile-based cutoff values, consistent with prior biomarker analyses from the RAISE trial [7]; patients in the middle two quartiles were not included in this comparison. Baseline ANC was also analyzed as a continuous variable, with the hazard ratio expressed per 1,000/μL increase. Moreover, to assess the robustness of the quartile-based cutoff values, a sensitivity analysis was performed in which the cutoff values were varied by ± 5 percentile points around the prespecified quartiles.

### Statistical analysis

OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Multivariable Cox models were adjusted for stratification factors used in the RINDBeRG trial, including ECOG PS (0 vs. 1), duration of prior RAM treatment (<3 vs. ≥3 months), and presence of peritoneal metastasis (yes vs. no). All statistical tests were two-sided, with a P value of < 0.05 indicating statistical significance. To reduce potential confounding, multivariable models were adjusted for key prespecified clinical stratification factors. Given that all analyses were exploratory, no formal multiplicity adjustment was performed. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, United States).

### Ethics and registration

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation, the Japanese Clinical Trials Act, and the Helsinki Declaration. Informed consent for study participation, or an equivalent, was obtained from all patients. The RINDBeRG trial was registered with the Japan Registry of Clinical Trials (jRCT2031200106). ChatGPT (OpenAI, version 5.3) and Claude (version claude-sonnet-4.6; Anthropic) was used to assist with language editing and readability improvements during manuscript revision. The tool was not used for generating scientific content, data analysis, or interpretation.

## Results

### Patient characteristics

Patients with and without grade 3 or higher neutropenia were compared according to treatment arm. Accordingly, grade 3 or higher neutropenia occurred in 89 (44.5%) of the 200 patients in the RAM plus IRI arm and 55 (28.5%) of the 193 patients in the IRI arm. The remaining patients did not develop grade 3 or higher neutropenia. Table 1 summarizes the baseline demographic and disease characteristics of the patients with and without CIN after study treatment initiation.

In both treatment arms, age and ECOG performance status were generally comparable between patients with and without CIN. In the IRI arm, the proportion of patients with ECOG PS 0 tended to be lower and the frequency of peritoneal metastasis tended to be higher among those who developed CIN than among those who did not. However, these differences were less pronounced in the RAM + IRI arm. In both treatment arms, the proportion of male patients was slightly lower among those who developed CIN than among those who did not. UGT1A1 genotyping was performed in 61% (122/200) of patients in the RAM + IRI arm and 60% (116/193) in the IRI arm; among tested patients, the distribution of UGT1A1 status (wild-type vs. any variant) did not differ significantly between patients with and without CIN in either arm. Other baseline characteristics, including age, number of metastatic sites, and modified Glasgow Prognostic Score (GPS), were generally balanced between patients with and without CIN.

Baseline characteristics were also compared according to baseline ANC within each treatment arm. In the RAM + IRI arm, 55 and 44 patients were classified into the low (lowest quartile) and high ANC groups (highest quartile), whereas in the IRI arm, 42 and 54 patients were classified into the low and high ANC groups, respectively. The remaining 96 and 95 patients of the middle two quartiles in the RAM + IRI and IRI arms, respectively, were not included in this comparison. Across both treatment arms, an ECOG PS of 1, no history of primary tumor resection, and a modified GPS of

**Table 1** Baseline characteristics according to chemotherapy-induced neutropenia

| Factors | IRI + RAM | | IRI | |
|---|---|---|---|---|
| | CIN(+) *N* = 89 | CIN(−) *N* = 111 | CIN(+) *N* = 55 | CIN(−) *N* = 138 |
| Age, median (range) | 69 (41–87) | 67 (40–82) | 68 (32–81) | 67 (31–82) |
| Sex, male, % | 70.8 | 82.0 | 74.5 | 81.2 |
| ECOG PS 0, % | 49.4 | 51.4 | 38.2 | 55.1 |
| No. of metastatic sites, median (range) | 2 (1–5) | 2 (1–4) | 2 (1–5) | 2 (1–5) |
| Prior gastrectomy, % | 53.9 | 44.1 | 52.7 | 47.8 |
| ALP, median (range) | 111 (51–527) | 107 (0–1458) | 105 (18–684) | 107 (18–828) |
| Liver metastasis, % | 39.3 | 46.8 | 40.0 | 42.0 |
| Peritoneal metastasis, % | 36.0 | 40.5 | 43.6 | 34.1 |
| Prior nivolumab, % | 42.7 | 45.9 | 41.8 | 41.3 |
| Modified GPS 0/1/2, % | 48.3/31.5/20.2 | 48.1/32.7/19.2 | 44.4/33.3/22.2 | 45.6/31.6/22.8 |
| Histology, diffuse, % | 46.1 | 39.6 | 40.0 | 45.7 |
| Histology, intestinal, % | 47.2 | 54.1 | 50.9 | 52.9 |
| Histology, other, % | 6.7 | 6.3 | 9.1 | 1.4 |
| HER2 positive, % | 16.9 | 18.9 | 21.8 | 20.4 |
| *UGT1A1* *28/*6 polymorphism, wild-type, %† | 83.1 | 87.7 | 75.0 | 75.0 |

*CIN* Chemotherapy-induced neutropenia, *IRI* Irinotecan, *RAM* Ramucirumab, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ALP* Alkaline phosphatase, *GPS* Glasgow Prognostic Score, *HER2* Human epidermal growth factor receptor 2

† Percentages are calculated among tested patients only; UGT1A1 genotyping was not mandated by the protocol and was performed in 65 of 89, 57 of 111, 32 of 55, and 84 of 138 patients in the respective columns

1 or 2 were more frequent among patients in the high baseline ANC group than among those in the low ANC group (Supplementary Table 1).

## Overall survival according to chemotherapy-induced neutropenia

During the entire treatment period and during the first treatment cycle, OS was analyzed according to the occurrence of grade 3 or higher CIN. During the entire treatment period, OS did not differ significantly between patients who did and did not develop CIN in either treatment arm. In the RAM + IRI arm, median OS was 9.7 and 8.9 months among patients with and without CIN, respectively (HR = 0.84; 95% CI, 0.62–1.13; $P = 0.25$). In the IRI arm, median OS was 8.4 and 8.6 months among patients with and without CIN, respectively (HR = 0.85; 95% CI, 0.60–1.19; $P = 0.34$). Kaplan–Meier curves for OS according to CIN status during the entire treatment period are presented in Fig. 1.

Consistent results were observed when CIN was defined as grade 3 or higher neutropenia occurring during the first treatment cycle. In the RAM + IRI arm, median OS was 9.4 months in both patients with and without CIN (HR = 1.08; 95% CI, 0.77–1.51; $P = 0.65$). In the IRI arm, median OS was 7.1 and 8.8 months in patients with and without CIN, respectively (HR = 0.97; 95% CI, 0.67–1.40; $P = 0.87$). Kaplan–Meier curves for OS according to first-cycle CIN are presented in Fig. 2.

## Overall survival according to baseline absolute neutrophil count

OS was evaluated according to baseline ANC. In the RAM + IRI arm, median OS was 10.9 and 7.3 months in the low and high baseline ANC groups, respectively (HR = 1.83; 95% CI, 1.14–2.94; $P = 0.01$). In the IRI arm, median OS was 8.9 and 7.7 months in the low and high baseline ANC groups, respectively (HR = 1.37; 95% CI, 0.87–2.16; $P = 0.17$). Kaplan–Meier curves for OS according to baseline ANC category are shown in Fig. 3. When baseline ANC was analyzed as a continuous variable, higher ANC remained significantly associated with shorter OS in the RAM + IRI arm (adjusted HR = 1.12 per 1000/μL increase; 95% CI, 1.04–1.20; $P = 0.002$), whereas this association did not reach statistical significance in the IRI arm (adjusted HR = 1.07; 95% CI, 0.99–1.16; $P = 0.11$). The sensitivity analysis also showed that the association between higher baseline ANC and shorter OS remained statistically significant (stratified log-rank $P < 0.05$) across the entire range of cutoff combinations tested in the RAM + IRI arm. In contrast, in the IRI arm, this association did not reach statistical significance across the tested cutoff combinations, consistent with the primary quartile-based analysis (Supplementary Fig. 1).

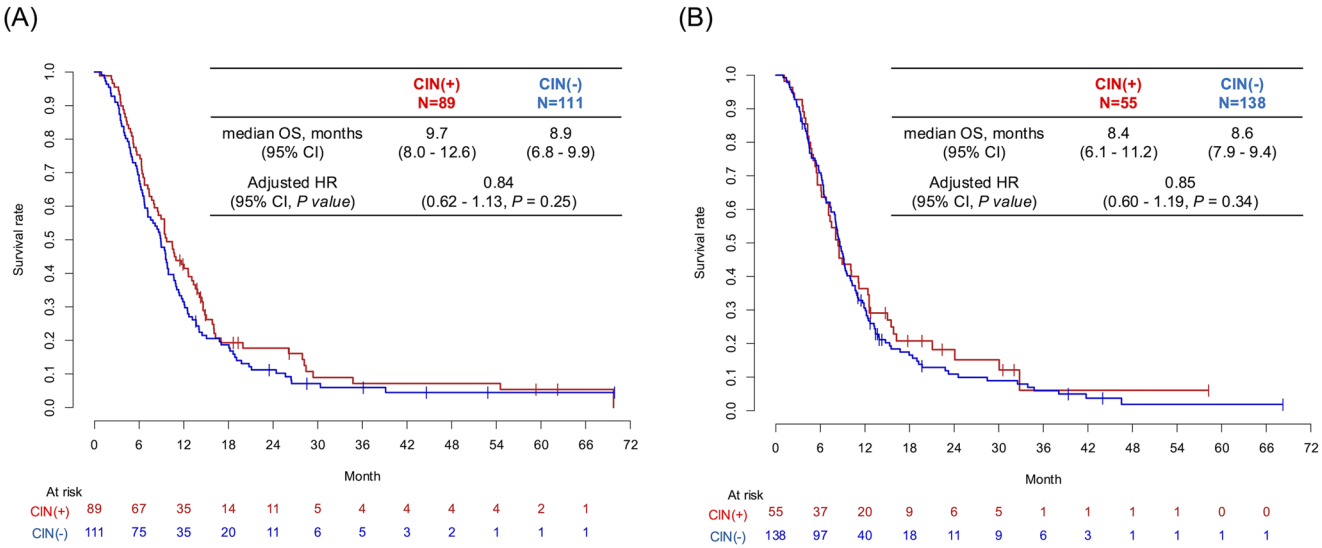



**Fig. 1** Kaplan–Meier curves for overall survival (OS) according to the occurrence of chemotherapy-induced neutropenia (CIN) during the entire treatment period. **a** Patients treated with irinotecan plus ramucirumab (IRI+RAM). **b** Patients treated with irinotecan monotherapy (IRI). CIN(+), patients who developed grade 3 or higher neutropenia at any time during treatment; CIN(−), patients who did not develop grade 3 or higher neutropenia at any time during treatment

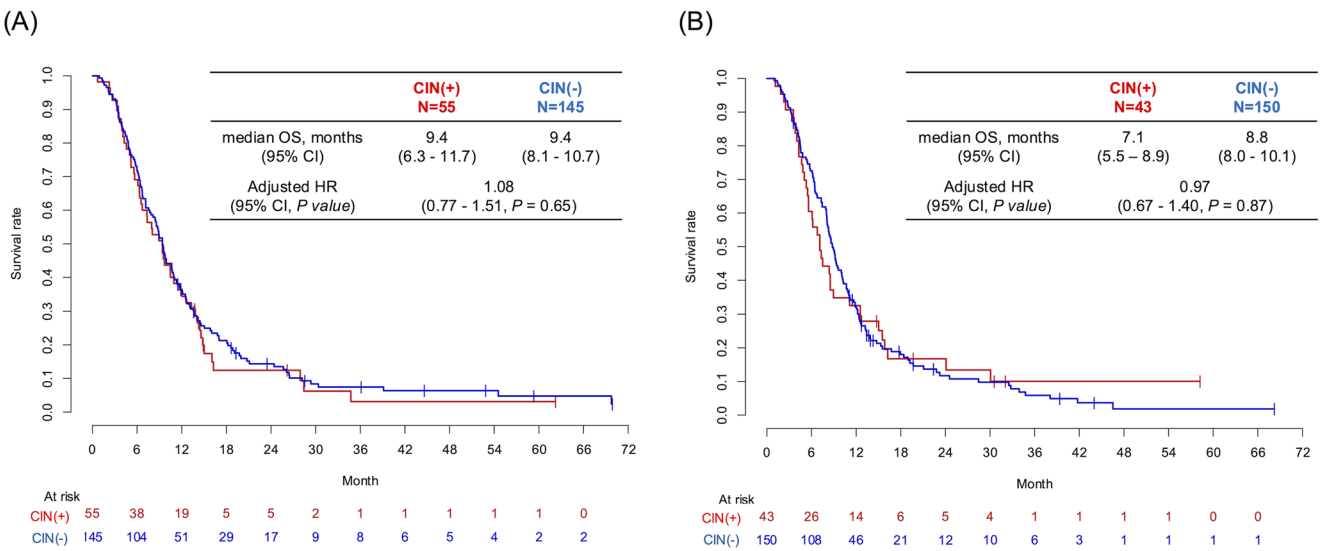



**Fig. 2** Kaplan–Meier curves for overall survival (OS) according to the occurrence of chemotherapy-induced neutropenia (CIN) during the first cycle. **a** Patients treated with irinotecan plus ramucirumab (IRI+RAM). **b** Patients treated with irinotecan monotherapy (IRI). CIN(+), patients who developed grade 3 or higher neutropenia during the first treatment cycle; CIN(−), patients who did not develop grade 3 or higher neutropenia during the first treatment cycle

## Discussion

This exploratory analysis of the RINDBeRG trial provides new insights into the long-standing neutropenia–survival paradigm in cytotoxic chemotherapy. In contrast to studies on several other cytotoxic regimens, the present study found that CIN conferred no prognostic value among patients with AGC receiving IRI with or without RAM. This lack of association was consistently observed even after evaluating CIN both during the entire treatment period and during the first treatment cycle, the latter analysis being conducted to minimize potential time-dependent bias. These findings contradict previous studies demonstrating a favorable prognostic impact of CIN across several cytotoxic regimens in gastric and colorectal cancer [3–6, 8, 9]. In these settings, CIN has been interpreted as a surrogate marker of adequate drug exposure and effective dose intensity. However, despite the high incidence of grade 3 or higher neutropenia observed in the RINDBeRG trial, particularly in the RAM plus IRI arm, the present study did not observe a corresponding survival

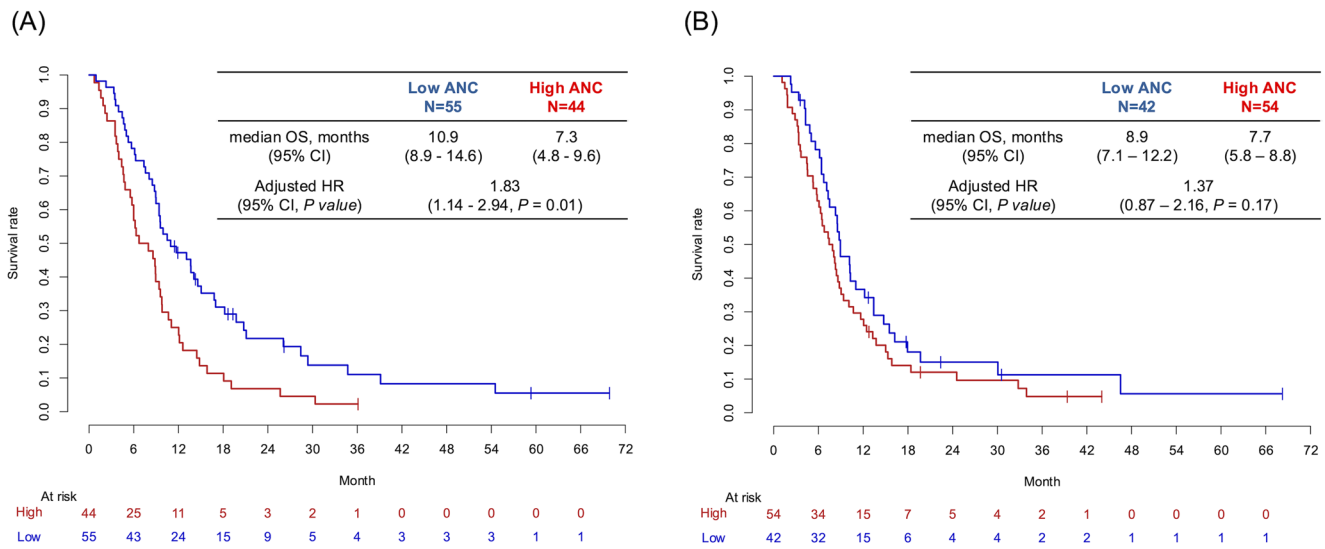



**Fig. 3** Kaplan–Meier curves for overall survival (OS) stratified according to baseline absolute neutrophil count (ANC). **a** Patients treated with irinotecan plus ramucirumab (IRI + RAM). **b** Patients treated with irinotecan monotherapy (IRI). Baseline ANC was categorized according to prespecified quartile-based cutoff values

benefit. These findings suggest that the prognostic implications of CIN may be regimen-specific rather than universal.

Our findings extend the observations from the post-hoc biomarker analysis of the RAISE trial [7]. Although the mentioned trial reported an association between treatment-emergent neutropenia during FOLFIRI administration with or without RAM and improved survival among patients with metastatic colorectal cancer, the study emphasized that baseline ANC, as a temporally earlier variable, was a stronger prognostic marker than was neutropenia itself. The observed relationship between neutropenia and survival can therefore be interpreted as reflecting the poorer prognosis of patients with high baseline ANC and their lower likelihood of experiencing a sufficient decline in neutrophil count to develop neutropenia rather than a direct beneficial effect of neutropenia itself. A similar pattern was observed in the present RINDBeRG analysis: the absence of an association between CIN and survival, together with the observed association between baseline ANC and OS, suggests that baseline inflammatory status may be more prognostically informative than treatment-emergent neutropenia during IRI-based therapy for AGC. It should be noted, however, that the present findings may not be directly comparable to those of the RAISE trial. Patients enrolled in RINDBeRG were more heavily pretreated than those in RAISE, and the two studies also differ in tumor type. These differences in patient population may affect the generalizability of the findings across treatment settings.

Several biological and clinical factors may explain the lack of a correlation between CIN and survival in this setting. IRI exhibits substantial interpatient variability in pharmacokinetics and metabolism due to hepatic function and UGT1A1 polymorphisms, which affect systemic exposure to its active metabolite SN-38 and the risk of hematologic toxicity [11–14]. In the present analysis, UGT1A1 status did not differ significantly between patients with and without CIN in either arm, and patients with marked hepatic dysfunction were excluded by the trial eligibility criteria (AST/ALT ≤ 100 IU/L, or ≤ 150 IU/L in the presence of liver metastasis; total bilirubin ≤ 1.5 mg/dL) [10]; these findings suggest that neither factor is likely to be a major confounder of the observed lack of association between CIN and OS, although the incomplete UGT1A1 testing rate (approximately 60% of patients) precludes a definitive conclusion. Moreover, IRI-based therapy frequently requires early dose modification or treatment interruption due to hematologic or gastrointestinal toxicities, potentially attenuating any relationship between early myelosuppression and sustained treatment efficacy. Furthermore, the heavily pretreated population enrolled in the RINDBeRG trial may have limited bone marrow reserve, which could reduce the discriminatory value of CIN as a prognostic marker in later-line treatment settings. Collectively, these factors may weaken the relationship between neutropenia and sustained antitumor efficacy, thereby limiting the prognostic utility of CIN in IRI-based therapy. These considerations further indicate that the neutropenia–survival relationship may depend on the specific pharmacologic and clinical context of the regimen.

In contrast to CIN, baseline ANC showed an association with OS, particularly among patients treated with IRI plus RAM, with shorter survival having been observed among those with higher baseline ANC. A similar but less pronounced trend was observed in the IRI monotherapy group. This association was also observed when baseline ANC was

analyzed as a continuous variable, and a sensitivity analysis varying the cutoff values around the prespecified quartiles yielded consistent results, suggesting that the association was not an artifact of the quartile-based dichotomization. These findings are consistent with prior studies suggesting that elevated neutrophil counts may reflect systemic inflammation or aggressive tumor biology, which can promote tumor progression and poorer survival outcomes, including in patients with gastric cancer [15–17]. Given that baseline ANC represents a pre-treatment characteristic rather than a treatment-emergent event, it may serve as a more stable prognostic indicator of host–tumor interactions. Of note, the treatment effect of RAM + IRI versus IRI monotherapy did not differ substantially between the low and high baseline ANC subgroups (adjusted HR, 0.84 and 1.01, respectively), suggesting that baseline ANC may function primarily as a prognostic rather than a predictive factor. However, considering that the current study analyzed baseline ANC as a supplementary component and that baseline ANC groups differed in several clinical characteristics, our findings should be interpreted cautiously and warrant further investigation.

This study has several limitations worth noting. First, given that the analysis was post hoc and exploratory in nature and was not prespecified in the original RINDBeRG protocol, the results should be interpreted as hypothesis-generating. Second, although analyses based on first-cycle CIN were performed to mitigate time-dependent bias by requiring only survival to the end of cycle 1 rather than the full treatment period, it does not constitute a formal landmark analysis, since OS was still calculated from treatment initiation. Residual time-dependent bias related to survival long enough to be assessable for first-cycle neutropenia cannot be fully excluded. Third, the sample size was limited for subgroup analyses stratified according to treatment arm and CIN status. Fourth, pharmacokinetic data and detailed information on dose intensity were unavailable, precluding direct assessment of the relationships between drug exposure, neutropenia, and efficacy. Finally, the trial population was selected based on strict eligibility criteria, which may limit the generalizability of our findings to real-world clinical practice. Moreover, baseline ANC categories were defined using quartile-based cutoffs, which may not correspond to clinically meaningful thresholds. External validation in independent cohorts is therefore required before clinical application. Nevertheless, the use of data from a large randomized phase III trial provides a robust framework for hypothesis generation regarding prognostic biomarkers in later-line gastric cancer.

In conclusion, this exploratory analysis of the RINDBeRG trial demonstrated that CIN was not associated with survival outcomes among patients with AGC who received IRI with or without RAM. These findings challenge the generalizability of the neutropenia–survival paradigm and highlight the importance of baseline inflammatory status in IRI-based therapy. Further studies are warranted to clarify the clinical and biological determinants of prognosis among patients receiving IRI-based therapy.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10147-026-03221-w.

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**Authors' contributions** Tomoki Sakakida: Conceptualization, Methodology, Writing–Original Draft, Visualization. Yukiya Narita: Conceptualization, Methodology, Writing–Original Draft, Investigation, Project administration. Taro Mizuno, Yasunobu Ishizuka, Shigenori Kadowaki, Kei Muro, Shigeyuki Tamura, Hironori Yamaguchi: Investigation, Writing–Review & Editing. Toshio Shimokawa: Formal analysis, Writing–Review & Editing. Daisuke Sakai: Supervision, Project administration, Funding acquisition, Writing–Review & Editing. Taroh Satoh: Supervision, Project administration, Funding acquisition, Writing–Review & Editing.

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**Data availability** Data are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate** All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation, the Japanese Clinical Trials Act, and the 1964 Declaration of Helsinki and its later amendments. This study was a post-hoc analysis of the RINDBeRG trial (jRCT2031200106).
Informed consent for study participation, or an equivalent, was obtained from all patients

**Competing interests** Taro Mizuno reports receiving honoraria from Astellas and Merck BioPharma. Shigenori Kadowaki reports receiving grants from Ono Pharmaceutical, Taiho Pharmaceutical, MSD, Nobel Pharmaceutical, Janssen Pharmaceutical, Bayer, Eli Lilly, Chugai Pharmaceutical, Daiichi Sankyo, AbbVie, and AstraZeneca, and honoraria from Ono Pharmaceutical, Taiho Pharmaceutical, MSD, Daiichi Sankyo, Merck KGaA, Bristol-Myers Squibb, Eli Lilly, Chugai Pharmaceutical, Bayer, Eisai, and Novartis. Hironori Yamaguchi reports receiving grants from Nippon Kayaku Co., Ltd, Taiho Pharmaceutical Co., Ltd, and Chugai Pharmaceutical Co., Ltd, and honoraria from Nippon Kayaku Co., Ltd, Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., ONO Pharmaceutical Co., Ltd, Eisai Co., Ltd, and Bristol-Myers Squibb Company. Kei Muro reports receiving honoraria from Ono Pharmaceutical Co., Ltd, Astellas Pharma Inc., Bristol-Myers Squibb Co., Ltd, Daiichi-Sankyo Co., Ltd, MSD Co., Ltd, and Takata Co., Ltd, and consulting fees from Amgen Co., Ltd, AstraZeneca, Ono Pharmaceutical Co., Ltd, Astellas Pharma Inc., and Chugai Pharmaceutical Co., Ltd. Taroh Satoh reports receiving grants or contracts from Eli Lilly, Taiho Pharmaceutical, Daiichi

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