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ORIGINAL ARTICLE

Efficacy and safety of irinotecan-based therapy in elderly patients with advanced gastric cancer receiving third-line or later chemotherapy: post-hoc age-subgroup analysis of the rindberg trial

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Abstract

Background In late-line treatment for advanced gastric cancer (AGC), evidence supporting the use of irinotecan in older patients remains limited. We conducted a post-hoc age-subgroup analysis of the phase III RINDBeRG study, which randomized AGC patients previously treated with ramucirumab-based chemotherapy to receive ramucirumab plus irinotecan (RAM + IRI) or irinotecan alone (IRI).

Methods Patients were classified as elderly (≥ 70 years; n = 83 [RAM + IRI], 80 [IRI]) or non-elderly (< 70 years; n = 117, 113). Efficacy outcomes—including overall survival (OS), progression-free survival (PFS), and overall response rate (ORR)—and safety were compared. Prognostic factors for OS were explored via multivariable Cox regression.

Results OS and PFS did not differ significantly between age groups. In the RAM + IRI group, median OS was 9.7 vs. 8.9 months (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.63–1.15), and PFS was 4.0 vs. 3.6 months (HR 0.84, CI 0.63–1.12). In the IRI group, OS was 8.5 months in both groups (HR 0.99, CI 0.7–1.34), and PFS was 3.1 vs. 2.2 months (HR 0.87, CI 0.65–1.17). ORRs were 20.5% vs. 14.5% (RAM + IRI) and 18.8% vs. 9.7% (IRI) in elderly vs. non-elderly patients. Grade ≥ 3 adverse events were comparable. Multivariable analysis identified ECOG PS 1, peritoneal metastasis, elevated LDH, modified Glasgow Prognostic Score ≥ 1, and low alkaline phosphatase as poor prognostic factors. Age was not prognostic.

Conclusions Irinotecan-based therapy offers comparable efficacy and tolerability in older and younger patients with refractory AGC.

Keywords Gastric cancer · Elderly patients · Irinotecan

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Introduction

Gastric cancer is the fourth leading cause of cancer-related death, with particularly high incidence in East Asia [1]. In Japan, the proportion of older patients with gastric cancer has increased markedly, with over 70% of deaths now occurring in those aged 70 years or older [2, 3]. As the population ages, clinicians are more frequently managing elderly patients with advanced gastric cancer (AGC), who often have comorbidities, polypharmacy, reduced organ function, and increased susceptibility to treatment-related toxicity [4]. These age-related factors complicate treatment decisions, yet elderly patients remain underrepresented in clinical trials. Consequently, prospective evidence to guide optimal chemotherapy strategies in this population—particularly in the later-line setting—is limited.

According to the Japanese Gastric Cancer Treatment Guidelines, irinotecan is recommended as one treatment option for patients with AGC who have progressed after second-line therapy [5]. However, most clinical studies of irinotecan have been conducted in the second-line setting, and few have evaluated its efficacy and safety specifically in elderly patients [6–9].

The RINDBeRG trial was a randomized phase III study comparing ramucirumab plus irinotecan with irinotecan monotherapy in patients previously treated with ramucirumab-based chemotherapy [10]. Although the addition of ramucirumab did not significantly improve overall survival (OS), it led to a statistically significant improvement in progression-free survival (PFS) and disease control rate. In this post-hoc subgroup analysis, we aimed to evaluate the efficacy and safety of irinotecan-based therapy in elderly patients (aged ≥ 70 years), who are increasingly encountered in clinical practice.

Methods

Patients

The RINDBeRG trial was a randomized, open-label, phase III study comparing the efficacy and safety of ramucirumab plus irinotecan versus irinotecan monotherapy in patients with AGC who had progressed during prior ramucirumab-based chemotherapy [8]. The trial was registered with the Japan Registry of Clinical Trials (jRCT2031200106). In total, 402 patients were randomized (1:1) to receive either ramucirumab plus irinotecan (n = 202) or irinotecan monotherapy (n = 200). Among them, nine patients were found to be ineligible after registration (2 in the ramucirumab plus irinotecan arm and 7 in the irinotecan monotherapy arm) and were excluded from the analysis, resulting in 393 eligible patients included in this subgroup evaluation.

Eligible patients were adults (age ≥ 20 years) with histologically confirmed gastric or gastroesophageal junction (GEJ) adenocarcinoma that was unresectable or recurrent and had progressed during prior ramucirumab-based chemotherapy. Patients had no previous history of irinotecan administration, and treatment with fluoropyrimidines, platinum, or taxane had failed. After an amendment in February 2022, patients who had received ramucirumab-based chemotherapy as second-line treatment following early recurrence during or within 180 days after perioperative adjuvant chemotherapy (counted as first-line) without platinum were eligible. Patients had at least one evaluable lesion on computed tomography (CT) or magnetic resonance imaging (MRI) according to RECIST version 1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, sufficient oral intake, and adequate organ function, including bone marrow, heart, lung, liver, and kidney.

In this subgroup analysis, patients aged ≥ 70 years were defined as elderly, and those aged < 70 years as non-elderly. Safety was assessed in the safety analysis set, which included patients who received at least one dose of irinotecan or ramucirumab. Efficacy was assessed in the full analysis set, which included patients who met the main inclusion criteria and had no major protocol violations.

Treatment and assessment

Irinotecan was administered at a dose of 150 mg/m2 on day 1 and day 15 of a 28-day cycle. Ramucirumab was given at a dose of 8 mg/kg on the same schedule in the combination group. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. Tumors were assessed using CT or MRI at baseline and every 8 weeks by the investigator, using RECIST v1.1. Physical examination, safety evaluations, and laboratory tests were performed prior to administration of the agents. Adverse events (AEs) were evaluated for up to 30 days after the last dose of the study drug or until the initiation of a new anticancer therapy, whichever came first, according to the Common Terminology Criteria for Adverse Events version 4.00 [11].

Statistical analysis

The median OS and PFS were estimated using the Kaplan–Meier method. Differences between elderly and non-elderly groups were assessed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model.

Patient baseline characteristics and incidences of AEs (grade ≥ 3) in each age group were compared between the

ramucirumab plus irinotecan and irinotecan monotherapy arms using Fisher's exact test. Multivariate and backward stepwise analyses were performed to identify prognostic factors. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Baseline characteristics of elderly (n = 83 [ramucirumab plus irinotecan group], 80 [irinotecan monotherapy group]) and non-elderly (n = 117, 113) patients are shown in Table 1. The two age groups were generally well balanced, with no significant differences in metastatic patterns or prior treatment history. According to the eligibility criteria of the RINDBeRG trial, almost all patients had received prior fluoropyrimidine-, platinum-, taxane-, and ramucirumab-based chemotherapy, and none had been previously treated with irinotecan. Immune checkpoint inhibitors were administered in approximately 60% of patients across both treatment arms and age groups (ramucirumab + irinotecan: 63.9% vs 56.4%; irinotecan monotherapy: 66.2% vs 57.5%), with no significant differences between groups. Notably, baseline levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) were significantly higher in the elderly group compared to the non-elderly group.

Efficacy

OS and PFS were similar between elderly and non-elderly patients in both treatment arms (Figs. 1 and 2). In the ramucirumab plus irinotecan group, median OS was 9.7 vs. 8.9 months (HR = 0.85, 95%CI [0.63–1.15], log rank p = 0.297), and PFS was 4.0 vs. 3.6 months (HR = 0.84, 95%CI [0.63–1.12], log rank p = 0.250). In the irinotecan monotherapy group, median OS was 8.5 months in both elderly and non-elderly groups (HR = 0.99, 95%CI [0.73–1.34], log rank p = 0.957), and PFS was 3.1 vs. 2.2 months (HR = 0.87, 95%CI [0.65–1.17], log rank p = 0.384). Analysis by age cutoffs (60–80 years) showed no significant interaction between age and treatment effect (Supplemental Fig. 1).

In the ramucirumab plus irinotecan group, the ORR was 20.5% in elderly patients and 14.5% in non-elderly patients. In the irinotecan monotherapy group, the ORR was 18.8% in elderly patients and 9.7% in non-elderly patients. The DCR was 65.1% and 59.8% in the combination group, and 60.0% and 48.7% in the monotherapy group, respectively (Table 2).

Safety

Grade ≥ 3 AEs occurred at similar frequencies between elderly and non-elderly patients in both treatment arms (Table 3). Neutropenia was the most common grade ≥ 3 toxicity, observed in 44.2% and 48.8% of elderly and non-elderly patients, respectively, in the ramucirumab plus irinotecan group, and in 25.9% and 33.8% in the irinotecan monotherapy group. Other frequent grade ≥ 3 events in the combination group included febrile neutropenia (3.75% and 3.5%), diarrhea (11.2% and 8.0%), and anorexia (10.0% and 15.0%). Similar trends were observed in the monotherapy group. No consistent age-related differences were found in the overall incidence of grade ≥ 3 toxicities.

Dose modification

Early dose reduction of irinotecan (within the first 2 months of treatment) was more common in elderly patients, especially in the ramucirumab plus irinotecan group (46.8% and 28.3% in elderly and non-elderly patients, respectively). In the irinotecan monotherapy group, the corresponding rates were 31.1% and 26.7%. The most common reason for dose reduction was grade 4 neutropenia, observed in 15.1% and 8.8% of elderly and non-elderly patients, respectively, receiving combination therapy. Other causes included grade 4 diarrhea or stomatitis, and other non-hematologic toxicities. The detailed reasons for early dose reduction are shown in Table 4.

Post-discontinuation treatment

Post-discontinuation treatment was administered in 64–78% of patients across treatment arms and age groups, with no significant differences observed (Table 5). Among subsequent chemotherapies, immune checkpoint inhibitors were most frequently used (24–33%), followed by trifluridine/tipiracil (15–29%). The distribution of post-discontinuation treatments was similar between elderly and non-elderly patients in both treatment arms.

Prognostic factors

Multivariate analysis for OS was performed in all 393 patients who received irinotecan-based chemotherapy, including both the ramucirumab plus irinotecan and irinotecan monotherapy arms. This analysis identified ECOG PS 1, peritoneal metastasis, elevated lactate dehydrogenase (LDH) (≥ 200 U/L), and modified Glasgow Prognostic Score (mGPS) 1 or 2 as independent poor prognostic factors. Specifically, mGPS 2 was strongly associated with poor OS (HR = 2.41, 95% CI: 1.75–3.31, p < 0.001). In

Table 1 Patient characteristics

Age, years	Median (range)	Ramucirumab plus irinotecan		Irinotecan monotherapy	
		Age ≥ 70 years (n = 83)	Age < 70 years (n = 117)	Age ≥ 70 years (n = 80)	Age < 70 years (n = 113)
		73.00 [70.00, 87.00]	62.00 [40.00, 69.00]	73.00 [70.00, 82.00]	62.00 [31.00, 69.00]
Sex, n (%)					
	Male	65 (78.3%)	89 (76.1%)	65 (81.2%)	88 (77.9%)
	Female	18 (21.7%)	28 (23.9%)	15 (18.8%)	25 (22.1%)
ECOG PS, n (%)					
	0	34 (41.0%)	67 (57.3%)	32 (40.0%)	65 (57.5%)
	1	49 (59.0%)	50 (42.7%)	48 (60.0%)	48 (42.5%)
Site of Primary					
	Gastric	73 (88.0%)	94 (80.3%)	69 (86.2)	96 (85.0)
	GEJ	10 (12.0%)	23 (19.7%)	11 (13.8)	17 (15.0)
Pathological subtype					
	Diffuse	26 (31.3%)	59 (50.4%)	27 (33.8%)	58 (51.3%)
	Intestinal	50 (60.2%)	52 (44.4%)	50 (62.5%)	51 (45.1%)
	Undeterminated	1 (1.2%)	2 (1.7%)	2 (2.5%)	2 (1.8%)
	Mixed	6 (7.2%)	4 (3.4%)	1 (1.2%)	2 (1.8%)
HER2 status					
	Positive	17 (20.5%)	19 (16.2%)	22 (27.5%)	18 (16.1%)
	Negative	66 (79.5%)	98 (83.8%)	58 (72.5%)	94 (83.9%)
Primary tumor present					
	Yes	44 (53.0%)	53 (45.3%)	44 (55.0%)	51 (45.1%)
	No	39 (47.0%)	64 (54.7%)	36 (45.0%)	62 (54.9%)
Peritonealmetastasis					
	Yes	24 (28.9%)	53 (45.3%)	27 (33.8%)	44 (38.9%)
	No	59 (71.1%)	64 (54.7%)	53 (66.2%)	69 (61.1%)
Measurable lesion					
	Yes	68 (81.9%)	99 (84.6%)	70 (87.5%)	101 (89.4%)
	No	15 (18.1%)	18 (15.4%)	10 (12.5%)	12 (10.6%)
Previous treatment					
	Ramucirumab	83 (100.0%)	117 (100.0%)	80 (100.0%)	113 (100.0%)
	[a]Fluoropyrimidine	83 (100.0%)	117 (100.0%)	80 (100.0%)	113 (100.0%)
	[b]Platinum	82 (98.8%)	115 (98.3%)	77 (96.2%)	113 (100.0%)
	[c]Taxane	82 (98.8%)	117 (100.0%)	80 (100.0%)	113 (100.0%)
	[d]ICIs	53 (63.9%)	66 (56.4%)	53 (66.2%)	65 (57.5%)
	Trifluridine/tipiracil	6 (7.2%)	5 (4.3%)	7 (8.8%)	3 (2.7%)
	Trastuzumab	14 (16.9%)	21 (17.9%)	20 (25.0%)	18 (15.9%)
Number of previous chemotherapy, lines					
	2	1 (1.2%)	5 (4.3%)	2 (2.5%)	4 (3.5%)
	3	29 (34.9%)	52 (44.4%)	28 (35.0%)	52 (46.0%)
	4	42 (50.6%)	48 (41.0%)	36 (45.0%)	45 (39.8%)
	≥5	11 (12.2%)	12 (10.3%)	14 (17.5%)	12 (10.6%)
Body Mass Index	(kg/m^2)	20.2 [13.4, 30.8]	21.4 [14.0, 33.7]	20.2 [14.5, 27.1]	20.5 [14.8, 40.3]
T.Bil (mg/dl)		0.5 [0.3, 1.6]	0.5 [0.2, 1.5]	0.5 [0.2, 3.2]	0.5 [0.2, 1.5]
ALP (U/L)		127 [56, 524]	98 [0, 1457]	109 [43, 718]	104 [17, 828]
LDH (U/L)		213 [133, 1103]	194 [115, 714]	209 [126, 941]	201 [116, 1286]
Cre (mg/dl)		0.81 [0.35, 1.40]	0.78 [0.42, 1.59]	0.78 [0.41, 1.27]	0.75 [0.38, 1.49]
Alb (g/dl)		3.5 [2.5, 4.4]	3.6 [2.3, 4.7]	3.6 [2.3, 4.7]	3.6 [2.3, 4.4]
CRP (mg/dl)		0.23 [0.00, 15.94]	0.30 [0.00, 9.81]	0.22 [0.00, 10.57]	0.33 [0.01, 15.44]
CEA (ng/ml)		9.9 [0.0, 10429]	4.8 [0.0, 829]	11.2 [0.0, 3193]	5.6 [0.6, 525.7]
CA19-9 (ng/ml)		56.3 [0.4, 120000]	35.0 [0.0, 7304058]	35.7 [0.1, 12000]	30.5 [0.1, 96252]

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; ICIs, immune checkpoint inhibitors

[a]Fluoropyrimidine included fluorouracil, capecitabine, and S-1. [b]Platinum included oxaliplatin and cisplatin. [c]Taxane included paclitaxel, nab-paclitaxel, and docetaxel. [d]ICIs included nivolumab and pembrolizumab

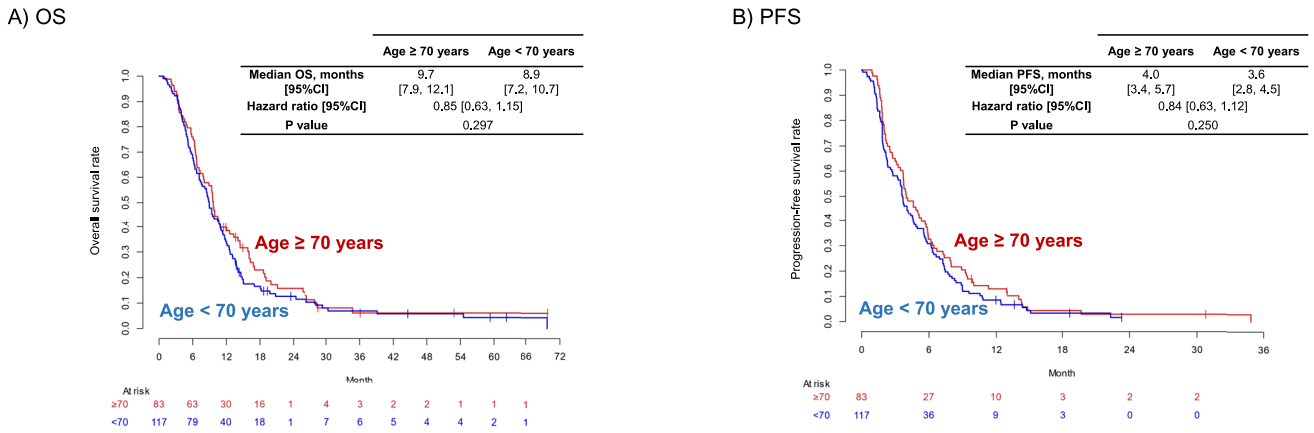

Fig. 1 Overall survival (OS) and progression-free survival (PFS) in the ramucirumab plus irinotecan group by age subgroup

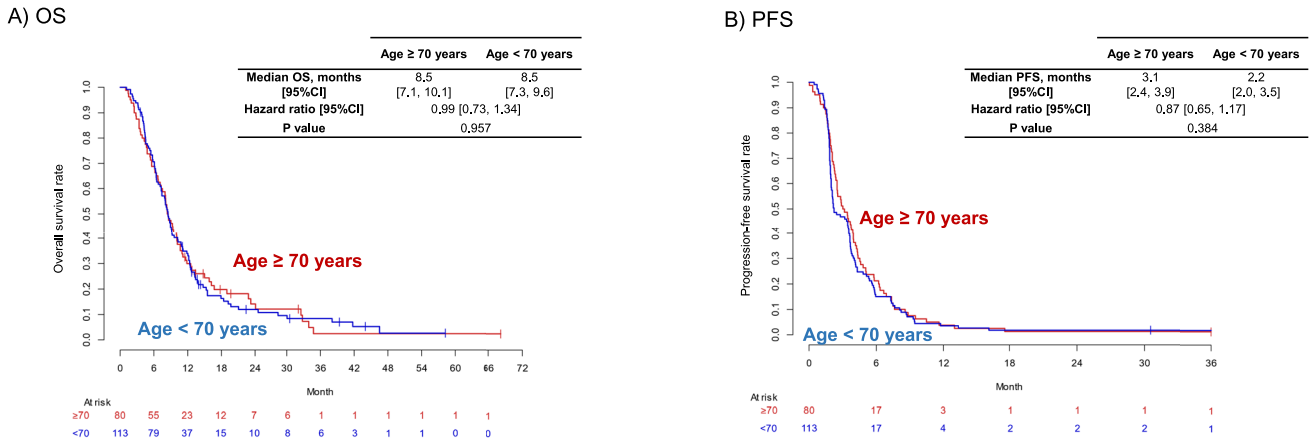

Fig. 2 Overall survival (OS) and progression-free survival (PFS) in the irinotecan monotherapy group by age subgroup

Table 2 Efficacy according to age groups

	Ramucirumab plus irinotecan			Irinotecan monotherapy		
	Age≥70 years (n=83)	Age<70 years (n=117)	p value	Age≥70 years (n=80)	Age<70 years (n=113)	p value
Complete response	0 (0.0%)	1 (0.9%)		0 (0.0%)	0 (0.0%)	
Partial response	17 (20.5%)	16 (13.7%)		15 (18.8%)	11 (9.7%)	
Stable disease	37 (44.6%)	53 (45.3%)		33 (41.2%)	44 (38.9%)	
Progressive disease	20 (24.1%)	41 (35.0%)		25 (31.2%)	55 (48.7%)	
Not evaluable	9 (10.8%)	6 (5.1%)		7 (8.8%)	3 (2.7%)	
Overall response rate	20.5% [12.4%, 30.8%]	14.5% [8.7%, 22.2%]	0.340	18.8% [10.9%, 29.0%]	9.7% [5.0%, 16.8%]	0.088
Disease control rate	65.1% [53.8%, 75.2%]	59.8% [50.4%, 68.8%]	0.464	60.0% [48.4%, 70.8%]	48.7% [39.2%, 58.3%]	0.144

Table 3 Adverse events according to age groups

Adverse Event	Ramucirumab plus irinotecan				Irinotecan monotherapy			
	Age ≥ 70 years		Age < 70 years		Age ≥ 70 years		Age < 70 years	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Leukopenia	73 (64.6)	24 (21.2)	58 (72.5)	23 (28.7)	46 (41.1)	19 (17.0)	44 (57.1)	21 (27.3)
Neutropenia	81 (71.7)	50 (44.2)	66 (82.5)	39 (48.8)	61 (54.5)	29 (25.9)	52 (67.5)	26 (33.8)
Thrombocytopenia	36 (31.9)	1 (0.9)	26 (32.5)	2 (2.5)	23 (20.5)	1 (0.9)	18 (23.4)	3 (3.9)
Hypoalbuminemia	52 (46.0)	6 (5.3)	45 (56.2)	4 (5.0)	34 (30.4)	4 (3.6)	27 (35.1)	6 (7.8)
Total bilirubin increased	6 (5.3)	1 (0.8)	3 (3.7)	0 (0.0)	8 (7.1)	1 (0.8)	12 (15.5)	2 (2.5)
AST increased	43 (38.0)	3 (2.6)	33 (41.2)	3 (3.7)	27 (24.1)	5 (4.4)	29 (37.6)	4 (5.1)
ALT increased	35 (31.0)	1 (0.9)	25 (31.2)	2 (2.5)	32 (28.6)	2 (1.8)	24 (31.2)	4 (5.2)
Creatinine increased	13 (11.5)	1 (0.8)	14 (17.5)	1 (1.2)	15 (13.3)	1 (0.8)	14 (18.1)	2 (2.5)
Diarrhea	47 (58.8)	9 (11.2)	66 (58.4)	9 (8.0)	37 (48.1)	3 (3.9)	49 (43.8)	8 (7.1)
Oral mucositis	17 (21.2)	1 (1.2)	26 (23.0)	1 (0.8)	10 (12.9)	0 (0.0)	6 (5.3)	0 (0.0)
Nausea	39 (48.8)	0 (0.0)	59 (52.2)	6 (5.3)	40 (51.9)	3 (3.9)	57 (50.9)	2 (1.8)
Vomiting	15 (13.2)	0 (0.0)	34 (30.0)	3 (2.6)	22 (28.5)	1 (1.2)	18 (16.0)	3 (2.6)
Anorexia	57 (71.2)	8 (10.0)	77 (68.1)	17 (15.0)	52 (67.5)	12 (15.6)	62 (55.4)	8 (7.1)
Fatigue	54 (67.5)	8 (10.0)	75 (66.4)	11 (9.7)	47 (61.0)	6 (7.8)	54 (48.2)	6 (5.4)
Febrile neutropenia	3 (3.75)	3 (3.75)	4 (3.5)	4 (3.5)	6 (7.7)	6 (7.7)	6 (5.3)	6 (5.3)
Hypertension	12 (15.0)	6 (7.5)	11 (9.7)	4 (3.5)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase

Numbers represent n (% of patients within each subgroup)

Table 4 Reasons for early dose reductions of irinotecan, defined as dose modifications occurring within the first 2 months of treatment

The reasons for early dose reduction of irinotecan	Ramucirumab plus irinotecan		Irinotecan monotherapy	
	Age ≥ 70 years	Age < 70 years	Age ≥ 70 years	Age < 70 years
Total	**37 (46.8%)**	**32 (28.3%)**	**24 (31.1%)**	**30 (26.7%)**
Grade 4 neutropenia	12 (15.1%)	10 (8.8%)	8 (10.3%)	6 (5.3%)
Grade 4 thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 4 diarrhea or stomatitis	8 (10.1%)	7 (6.1%)	2 (2.5%)	3 (10.0%)
Other grade 4 non-hematologic toxicities	10 (12.6%)	11 (9.7%)	5 (6.4%)	5 (2.6%)
Physician's judgment (not linked to grade 4 toxicity)	20 (25.3%)	21 (18.5%)	12 (15.5%)	20 (17.8%)

Table 5 Post-discontinuation treatment

	Ramucirumab plus irinotecan		Irinotecan monotherapy	
	Age ≥ 70 years (n = 83)	Age < 70 years (n = 117)	Age ≥ 70 years (n = 80)	Age < 70 years (n = 113)
Post-discontinuation treatment, n (%)	**59 (71.1%)**	**80 (68.4%)**	**51 (63.8%)**	**88 (77.9%)**
Surgery	2 (2.4%)	2 (1.7%)	0 (0.0%)	1 (0.9%)
Radiotherapy	5 (6.0%)	5 (4.3%)	4 (5.0%)	15 (13.3%)
Chemotherapy	57 (68.7%)	77 (65.8%)	51 (63.8%)	84 (74.3%)
[a]ICIs	27 (32.5%)	29 (24.8%)	22 (27.5%)	31 (27.4%)
Trifluridine/tipiracil	24 (28.9%)	17 (14.5%)	19 (23.8%)	22 (19.5%)
[b]Fluoropyrimidine	10 (12.0%)	11 (9.4%)	15 (18.8%)	14 (12.4%)
[c]Platinum	7 (8.4%)	11 (9.4%)	10 (12.5%)	7 (6.2%)
Irinotecan	9 (10.8%)	7 (6.0%)	4 (5.0%)	7 (6.2%)
Ramucirumab	6 (7.2%)	4 (3.4%)	5 (6.3%)	7 (6.2%)
[d]Taxane	4 (4.8%)	3 (2.6%)	4 (5.0%)	4 (3.5%)
Trastuzumab deruxtecan	5 (6.0%)	1 (0.9%)	0 (0.0%)	5 (4.4%)
Others	4 (4.8%)	6 (5.1%)	7 (8.8%)	10 (8.8%)

[a]ICIs included nivolumab and pembrolizumab. [b]Fluoropyrimidine included fluorouracil, capecitabine, and S-1. [c]Platinum included oxaliplatin and cisplatin. [d]Taxane included paclitaxel, nab-paclitaxel, and docetaxel

Table 6 Multivariate and backward stepwise analysis of overall survival in all patients receiving irinotecan-based chemotherapy, including both ramucirumab plus irinotecan and irinotecan monotherapy arms, in the third-line or later setting

		Multivariate analysis		Backward Stepwise (Akaike's Information Criteria)	
		HR [95%CIs]	*p* value	HR [95%CIs]	*p* value
Age	≧70 /<70	0.910 [0.720, 1.150]	0.430	–	
ECOG PS	1 / 0	1.498 [1.182, 1.899]	<0.001	1.468 [1.168, 1.844]	<0.001
Pathological subtype	Intestinal / Diffuse	0.862 [0.682, 1.090]	0.215	–	
Peritoneal metastasis	Yes / No	1.610 [1.256, 2.064]	<0.001	1.616 [1.279, 2.041]	<0.001
Liver metastasis	Yes / No	1.112 [0.861, 1.437]	0.416	–	
Creatinine	≥0.79 /<0.79	0.802 [0.640, 1.005]	0.054	0.810 [0.647, 1.013]	0.064
Previous gastrectomy	Yes / No	0.894 [0.707, 1.129]	0.346	–	
Baseline ALP level	≥109 /<109	0.754 [0.591, 0.964]	0.023	0.759 [0.597, 0.965]	0.024
Baseline LDH level	≥200 /<200	1.518 [1.191, 1.936]	<0.001	1.549 [1.220, 1.967]	<0.001
Modified Glasgow prognostic score	1	1.404 [1.062, 1.855]	<0.001	1.496 [1.143, 1.957]	<0.001
	2	2.410 [1.753, 3.313]		2.604 [1.917, 3.538]	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status

contrast, elevated alkaline phosphatase (ALP) (≥109 U/L) was associated with better OS (HR = 0.75, 95% CI: 0.59–0.96, p = 0.024). Age itself was not prognostic (HR = 0.91, 95%CI: 0.720–1.150, p = 0.430). These findings were consistent in backward stepwise analysis (Table 6). As a sensitivity analysis, a multivariate model for progression-free survival (PFS) was also performed, which demonstrated consistent trends in the associations of key prognostic factors (Supplemental Table S1).

Discussion

Although clinical studies have supported the utility of irinotecan in second-line or later settings [6–9], few have provided evidence specifically focused on elderly patients. In this context, the current post-hoc subgroup analysis aims to address this gap by evaluating the efficacy and safety of irinotecan-based therapy in patients aged 70 years and older using data from a randomized phase III trial. The results demonstrated that overall survival (OS), progression-free survival (PFS), safety profiles, and the proportion of patients who received post-discontinuation treatment were comparable between elderly and non-elderly patients. These findings suggest that irinotecan-based therapy is a viable treatment option in third-line or later settings for appropriately selected elderly patients, provided that performance status and organ function are preserved. While the RINDBeRG trial enrolled patients meeting clinical trial eligibility criteria and thus may not fully represent a real-world population, the present results provide supportive evidence for implementing irinotecan-based therapy in older patients with advanced gastric cancer in routine clinical practice.

When considering treatment options for elderly patients with AGC in the third-line or later setting, nivolumab, irinotecan, and trifluridine/tipiracil (FTD/TPI) are listed as therapeutic options in the Japanese gastric cancer treatment guidelines [5]. Importantly, the guidelines note that the optimal sequencing or relative efficacy among these agents remains unclear. In the TAGS trial, patients aged≥65 years in the FTD/TPI group demonstrated a median OS of 5.7 months and a median PFS of approximately 2.0 months, whereas the Japanese subgroup analysis of the ATTRACTION-2 trial reported a median OS of 5.4 months among patients in the nivolumab group (median age 65 years) [12, 13]. Although cross-trial comparisons must be interpreted with caution due to differences in study populations and treatment histories, our results from the RINDBeRG trial, in which elderly patients treated with irinotecan-based therapy achieved a median OS of 9.4 months and a disease control rate of 65.1%, suggest that this treatment approach might offer favorable tumor control in selected elderly patients.

Early dose reductions of irinotecan, defined as those occurring within the first two months of treatment, were more frequently observed in elderly patients, particularly in the ramucirumab plus irinotecan group (46.8% in elderly patients and 28.3% in non-elderly patients). The most frequent reason for early modification was grade 4 neutropenia, suggesting that elderly patients might have increased susceptibility to early hematologic toxicity. Timely dose adjustments and close toxicity monitoring might help preserve treatment feasibility and maximize clinical benefit in this population. Importantly, despite the higher frequency of early dose reductions in elderly patients, both OS and PFS remained comparable to those of younger patients. This finding suggests that early dose modification—when clinically indicated—may be a reasonable and acceptable

strategy to improve tolerability without compromising therapeutic efficacy in selected older adults. Prospective studies are needed to further evaluate optimal dose management in this population.

In this study, multivariate analysis identified several clinical variables associated with poor prognosis in the third-line or later treatment setting, including ECOG PS of 1, elevated mGPS, peritoneal metastasis, and high levels of LDH. These findings are consistent with previous reports demonstrating that impaired performance status, elevated systemic inflammatory markers such as mGPS and LDH, and metastatic burden, including peritoneal dissemination, are important prognostic factors in advanced gastric cancer [14–19]. Consistent trends were also observed in the sensitivity analysis using PFS, further supporting the robustness of these findings. Although elevated ALP has generally been reported as a poor prognostic factor [14–16, 18], recent evidence suggests that abnormally low ALP may also indicate aggressive tumor biology in certain cancers such as breast and colorectal cancer, where low ALP has been linked to poor differentiation, enhanced invasiveness, and unfavorable survival outcomes [20]. In our cohort, derived from a post-hoc analysis, low baseline ALP was associated with worse overall survival, which may reflect impaired hepatic synthetic function or reduced systemic metabolism related to frailty, malnutrition, or sarcopenia, rather than indicating favorable tumor biology. This finding should therefore be interpreted cautiously, as it may partly represent a chance observation rather than a true biological effect. Both high and low ALP levels may reflect distinct adverse biological conditions associated with poor prognosis. Taken together, these findings highlight the complex, bidirectional role of ALP in tumor progression and systemic homeostasis, warranting further validation in independent cohorts. Of note, age was not identified as a prognostic factor, suggesting that chronological age may be less informative than functional or biological status when selecting appropriate treatments for older adults.

In this study, elderly patients were defined as those aged ≥ 70 years. This cutoff was selected based on its frequent use in clinical trials of gastric cancer and on demographic data showing that over 75% of gastric cancer–related deaths in Japan occur in patients aged 70 years or older [21–23]. The age threshold is also consistent with subgroup classifications in the Japanese gastric cancer treatment guidelines. Although age ≥ 75 years is sometimes used to define "older elderly," sensitivity analyses by 5-year intervals (from 60 to 80 years) did not reveal any clear interaction between age and treatment effect (Supplemental Fig. 1), supporting the robustness of our findings.

This study has several limitations. First, although the RINDBeRG trial was a prospective, randomized phase III study, the present subgroup analysis by age was conducted retrospectively and was not pre-specified in the protocol. As such, the study was not powered to detect statistically significant differences between elderly and non-elderly patients, and the findings should be interpreted with caution. Second, while baseline characteristics were generally balanced between age groups, unmeasured confounding factors—such as differences in disease biology or treatment history—may have influenced outcomes. Notably, approximately 60% of the patients had received prior immune checkpoint inhibitor (ICI) therapy, and its potential impact on the efficacy of subsequent irinotecan-based treatment remains unclear. Third, as this analysis defined elderly patients solely by chronological age (≥ 70 years) and did not incorporate geriatric-specific endpoints such as frailty, comorbidities, or functional status, its applicability to more vulnerable older adults may be limited. In particular, the absence of a comprehensive geriatric assessment (CGA) hinders our ability to stratify which elderly patients might derive the greatest benefit from irinotecan-based therapy. Incorporating CGA into future prospective trials, as recommended by the International Society of Geriatric Oncology and the American Society of Clinical Oncology, could improve patient selection and support individualized treatment strategies for this population [4, 24, 25]. Finally, the absence of biomarker data and quality of life assessments hinders a more comprehensive evaluation of treatment efficacy and tolerability.

Nonetheless, this analysis contributes valuable evidence from a prospective phase III trial to inform later-line treatment decisions in elderly patients with AGC—a population often underrepresented in clinical studies.

Conclusion

This subgroup analysis demonstrated that irinotecan-based therapy is effective and well-tolerated in elderly patients with advanced gastric cancer, with survival and safety outcomes comparable to those in younger patients. These findings support the inclusion of appropriately selected older adults in late-line treatment strategies for AGC.

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Author contributions RKawabata, DS, TSatoh contributed to the conception and design of the study. RKawabata, DS, RKizawa and TI were responsible for data collection and curation. TShimokawa conducted the statistical analysis and interpretation. RKawabata drafted the manuscript. All authors reviewed and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Declarations

Conflict of interest The authors declare the following financial interests/personal relationships, which may be considered potential competing interests: DS reports receiving speaker's fees from Chugai Pharmaceutical Co., Ltd., and Daiichi Sankyo Co., Ltd./UCB Japan Co., Ltd.; and institutional research funding from Chugai Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Ono Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Astellas Pharma Inc., Incyte Biosciences Japan G.K., Taiho Pharmaceutical Co., Ltd., and Eisai Co., Ltd. TSatoh reports receiving honoraria from Chugai Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Bristol-Myers Squibb Co., Takeda Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., Ono Pharmaceutical Co., Ltd., Merck & Co., Inc., Astellas Pharma Inc., Taiho Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., and Daiichi Sankyo Co., Ltd.; and serving in a consulting or advisory role for Bayer Yakuhin, Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co., Ltd., Takara Bio Inc., Merck Serono Co., Ltd., and Nippon Kayaku Co., Ltd. All other authors (Ryohei Kawabata, Toshio Shimokawa, Rika Kizawa, Toru Ishiguro, Hiroki Yukami, Shogen Boku, Toshifumi Yamaguchi, Shunji Endo, Toshimasa Tsujinaka) declare no conflicts of interest.

Ethical approval All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), the Japanese Clinical Trials Act, and the Helsinki Declaration of 1964 and later versions. Informed consent for the study, or an equivalent, was obtained from all patients.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63. https://doi.org/10.3322/caac.21834.
2. Shitara K, Muro K, Matsuo K, Ura T, Takahari D, Yokota T, et al. Chemotherapy for patients with advanced gastric cancer with performance status 2. Gastrointest Cancer Res. 2009;3:220–4.
3. Kakeji Y, Takahashi A, Hasegawa H, Ueno H, Eguchi S, Endo I, et al. <article-title update="added">Surgical outcomes in gastroenterological surgery in Japan: report of the National Clinical Database 2011-2018. Ann Gastroenterol Surg. 2020;4:250–74. https://doi.org/10.1002/ags3.12324.
4. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36:2326–47. https://doi.org/10.1200/JCO.2018.78.8687.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2021 (6th edition). Gastric Cancer. 2023;26:1–25. https://doi.org/10.1007/s10120-022-01331-8.
6. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. <article-title update="added">Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47:2306–14. https://doi.org/10.1016/j.ejca.2011.06.002.
7. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013;31:4438–44. https://doi.org/10.1200/JCO.2012.48.5805.
8. Nishikawa K, Fujitani K, Inagaki H, Akamaru Y, Tokunaga S, Takagi M, et al. Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial. Eur J Cancer. 2015;51:808–16. https://doi.org/10.1016/j.ejca.2015.02.009.
9. Tanabe K, Fujii M, Nishikawa K, Kunisaki C, Tsuji A, Matsuhashi N, et al. Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). Ann Oncol. 2015;26:1916–22. https://doi.org/10.1093/annonc/mdv265.
10. Sakai D, Kadowaki S, Kawabata R, Hara H, Satake H, Takahashi M, et al. Randomized phase III trial of ramucirumab beyond progression plus irinotecan in patients with ramucirumab-refractory advanced gastric cancer: RINDBeRG trial. J Clin Oncol. 2025;43:2196–207. https://doi.org/10.1200/JCO.24.01119.
11. Common Terminology Criteria for Adverse Events (CTCAE) v4.00. National Cancer Institute. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50(accessed April 12, 2025).
12. Shitara K, Doi T, Hosaka H, Thuss-Patience P, Santoro A, Longo F, et al. Efficacy and safety of trifluridine/tipiracil in older and younger patients with metastatic gastric or gastroesophageal junction cancer: subgroup analysis of a randomized phase 3 study (TAGS). Gastric Cancer. 2022;25:586–97. https://doi.org/10.1007/s10120-021-01271-9.

13. Kato K, Satoh T, Muro K, Yoshikawa T, Tamura T, Hamamoto Y, et al. A subanalysis of Japanese patients in a randomized, double-blind, placebo-controlled, phase 3 trial of nivolumab for patients with advanced gastric or gastro-esophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2). Gastric Cancer. 2019;22:344–54. https://doi.org/10.1007/s10120-018-0899-6.
14. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer—pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol. 2004;22:2395–403. https://doi.org/10.1200/JCO.2004.08.132.
15. Takahari D, Boku N, Mizusawa J, Takashima A, Yamada Y, Yoshino T, et al. Determination of prognostic factors in Japanese patients with advanced gastric cancer using the data from a randomized controlled trial (JCOG9912). Oncologist. 2014;19:358–66. https://doi.org/10.1634/theoncologist.2013-0381.
16. Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol. 2007;18:886–91. https://doi.org/10.1093/annonc/mdl501.
17. Fanotto V, Cordio S, Pasquini G, Fontanella C, Rimassa L, Leone F, et al. Prognostic factors in 868 advanced gastric cancer patients treated with second-line chemotherapy in the real world. Gastric Cancer. 2017;20:825–33. https://doi.org/10.1007/s10120-016-0681-6.
18. Fuchs CS, Muro K, Tomasek J, Van Cutsem E, Cho JY, Oh SC, et al. Prognostic factor analysis of overall survival in gastric cancer from two phase III studies of second-line ramucirumab (REGARD and RAINBOW) using pooled patient data. J Gastric Cancer. 2017;17:132–44. https://doi.org/10.5230/jgc.2017.17.e16.
19. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer. 2006;94:637–41. https://doi.org/10.1038/sj.bjc.6602965.
20. Jiang T, Zeng Q, He J. Do alkaline phosphatases have great potential in the diagnosis, prognosis, and treatment of tumors? Transl Cancer Res. 2023;12:2932–45. https://doi.org/10.21037/tcr-23-1190.
21. Bando H, Yamada Y, Tanabe S, Nishikawa K, Gotoh M, Sugimoto N, et al. Efficacy and safety of S-1 and oxaliplatin combination therapy in elderly patients with advanced gastric cancer. Gastric Cancer. 2016;19:919–26. https://doi.org/10.1007/s10120-015-0549-1.
22. Kawabata R, Chin K, Takahari D, Hosaka H, Muto O, Shindo Y, et al. Multicenter phase II study of capecitabine plus oxaliplatin in older patients with advanced gastric cancer: the Tokyo Cooperative Oncology Group TCOG GI-1601 study. Gastric Cancer. 2023;26:1020–9. https://doi.org/10.1007/s10120-023-01423-z.
23. Asaka M, Kobayashi M, Kudo T, Akino K, Asaka Y, Fujimori K, et al. Gastric cancer deaths by age group in Japan: outlook on preventive measures for elderly adults. Cancer Sci. 2020;111:3845–53. https://doi.org/10.1111/cas.14586.
24. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595–603. https://doi.org/10.1200/JCO.2013.54.8347.
25. Dale W, Klepin HD, Williams GR, Alibhai SMH, Bergerot CD, Brintzenhofeszoc K, et al. Practical assessment and management of vulnerabilities in older patients receiving systemic cancer therapy: ASCO guideline update. J Clin Oncol. 2023;41:4293–312. https://doi.org/10.1200/JCO.23.00933.