Supplementary Online Content

Kim Y-W, Bae J-M, Park Y-K, et al. Effect of intravenous ferric carboxymaltose on hemoglobin response among patients with acute isovolemic anemia following gastrectomy: the FAIRY randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.5703

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Percentage of Patients With Hb ≥10, 11, and 12 g/dL at Weeks 3 and 12

Parameter	Total No. (%)	Ferric Carboxymaltose	Placebo	Absolute Difference (95% CI), %	*P* Value	Odds Ratio (95% CI)
Week 3						
Hb ≥10 g/dL	365 (83.9)	210 (96.8)	155 (71.1)	25.7 (21.6-29.8)	.001*	12.19 (5.20-27.36)
Total (N/%)	435 (100)	217 (100)	218 (100)			
Hb ≥11 g/dL	255 (58.6)	165 (76.0)	90 (41.3)	34.7 (30.3-39.2)	.001*	4.51 (2.99-6.81)
Total (N/%)	435 (100)	217 (100)	218 (100)			
Hb ≥12 g/dL	104 (23.9)	77 (35.5)	27 (12.4)	23.1 (19.1-27.1)	.001*	3.89 (2.39-6.35)
Total (N/%)	435 (100)	217 (100)	218 (100)			
Week 12						
Hb ≥10 g/dL	365 (84.9)	211 (97.2)	154 (72.3)	24.9 (20.8-29.0)	.001*	13.47 (5.67-32.00)
Total (N/%)	430 (100)	217 (100)	213 (100)			
Hb ≥11 g/dL	291 (67.7)	191 (88.0)	100 (46.9)	41.1 (36.4-45.7)	.001*	8.30 (5.09-13.55)
Total (N/%)	430 (100)	217 (100)	213 (100)			
Hb ≥12 g/dL	187 (43.5)	138 (63.6)	49 (23.0)	40.6 (35.9-45.2)	.001*	5.85 (3.83-8.92)
Total (N/%)	430 (100)	217 (100)	213 (100)			

*Chi-square test

eTable 2. Use of Alternative Anemia Management Therapy (Oral Iron and/or Transfusion) in the Primary Analysis Population

Alternative Anemia Management Therapy	**Total No. (%)**	**Ferric Carboxymaltose**	**Placebo**	**Absolute Difference (95% CI), %**	***P* Value**	**Odds Ratio (95% CI)**
				5.5 (3.3-7.6)	.006*	5.2 (1.407- ∞)
No	419 (95.9)	215 (98.6)	204 (93.1)			
Yes	18 (4.1)	3 (1.4)	15 (6.8)			
Oral iron	9 (2.1)	0	9 (4.1)			
Transfusion	7 (1.6)	3 (1.4)	4 (1.8)			
Oral iron and transfusion	2 (0.5)	0	2 (0.9)			
Total (%)	437 (100)	218 (100)	219 (100)			

* Fisher's exact test

eTable 3. Results From QLQ-C30 and QLQ-STO22 Assessment

STAT C30/STO22	Cycle	Ferric Carboxymaltose, Mean (95% CI)	Placebo, Mean (95% CI)	*P* Value*
Global health status/QoL	Baseline	51.7 (48.6-54.8)	52.2 (49.3-55.1)	0.884
	3 weeks	61.6 (58.7-64.4)	60.5 (57.8-63.2)	0.486
	12 weeks	67.7 (64.9-70.5)	66.1 (63.5-68.7)	0.252
Physical functioning	Baseline	76.0 (73.3-78.8)	76.3 (73.7-78.9)	0.996
	3 weeks	77.9 (75.7-80.2)	76.2 (73.7-78.7)	0.337
	12 weeks	81.3 (79.1-83.4)	80.5 (78.4-82.7)	0.545
Role functioning	Baseline	82.2 (79.2-85.2)	84.2 (81.3-87.1)	0.343
	3 weeks	83.3 (80.2-86.4)	78.5 (75.0-82.1)	0.058
	12 weeks	84.9 (82.3-87.6)	84.9 (82.3-87.4)	0.715
Emotional functioning	Baseline	80.0 (77.1-82.8)	74.4 (71.2-77.6)	0.010
	3 weeks	85.8 (83.2-88.4)	83.1 (80.6-85.7)	0.053
	12 weeks	85.7 (83.4-88.0)	82.3 (79.7-84.9)	0.077
Cognitive functioning	Baseline	83.0 (80.2-85.7)	80.2 (77.4-83.1)	0.150
	3 weeks	88.2 (85.7-90.7)	88.0 (85.5-90.5)	0.963
	12 weeks	86.7 (84.3-89.1)	84.8 (82.0-87.6)	0.656
Social functioning	Baseline	76.4 (73.3-79.5)	75.8 (72.4-79.1)	0.964
	3 weeks	81.1 (78.5-83.8)	77.4 (74.3-80.5)	0.149
	12 weeks	82.7 (80.0-85.4)	82.2 (79.4-85.0)	0.865
Fatigue	Baseline	32.1 (28.7-35.5)	32.5 (29.1-35.8)	0.816
	3 weeks	30.0 (26.8-33.1)	34.6 (31.3-37.9)	0.041
	12 weeks	28.4 (25.4-31.5)	32.5 (29.3-35.7)	0.061
Nausea and vomiting	Baseline	9.8 (7.6-12.0)	10.3 (8.2-12.5)	0.517
	3 weeks	10.0 (7.9-12.2)	12.5 (9.9-15.1)	0.268
	12 weeks	15.1 (12.4-17.9)	14.1 (11.5-16.6)	0.824
Pain	Baseline	24.0 (20.3-27.6)	23.9 (20.5-27.3)	0.645
	3 weeks	18.8 (16.0-21.6)	19.4 (16.4-22.4)	0.978
	12 weeks	13.1 (10.6-15.7)	11.4 (9.1-13.8)	0.362
Dyspnea	Baseline	15.7 (12.7-18.7)	17.4 (14.3-20.6)	0.445
	3 weeks	11.7 (9.3-14.1)	15.4 (12.3-18.5)	0.182
	12 weeks	9.5 (7.2-11.8)	14.2 (11.3-17.1)	0.021
Insomnia	Baseline	23.3 (19.5-27.1)	25.4 (21.4-29.5)	0.554
	3 weeks	18.9 (15.4-22.4)	18.6 (14.9-22.3)	0.751

STAT C30/STO22	Cycle	Ferric Carboxymaltose, Mean (95% CI)	Placebo, Mean (95% CI)	*P* Value*
	12 weeks	16.1 (12.6-19.5)	20.1 (16.4-23.9)	0.084
Appetite loss	Baseline	24.3 (20.2-28.4)	24.0 (20.1-27.9)	0.896
	3 weeks	26.5 (22.2-30.8)	30.6 (26.1-35.0)	0.175
	12 weeks	21.9 (18.0-25.7)	21.9 (18.0-25.8)	0.958
Constipation	Baseline	19.6 (16.1-23.2)	20.0 (16.4-23.5)	0.928
	3 weeks	16.3 (12.9-19.7)	17.2 (13.6-20.9)	0.957
	12 weeks	10.7 (8.0-13.4)	10.8 (7.9-13.6)	0.875
Diarrhea	Baseline	13.5 (10.6-16.5)	15.9 (12.8-19.1)	0.277
	3 weeks	13.6 (10.8-16.4)	17.1 (14.0-20.1)	0.110
	12 weeks	23.2 (19.9-26.6)	24.4 (21.0-27.9)	0.564
Financial difficulties	Baseline	19.1 (15.4-22.8)	19.4 (15.9-22.8)	0.590
	3 weeks	13.9 (11.2-16.7)	19.9 (16.5-23.4)	0.022
	12 weeks	11.8 (9.2-14.4)	17.0 (13.8-20.2)	0.017
Body image	Baseline	75.8 (71.8-79.9)	76.6 (72.7-80.5)	0.899
	3 weeks	72.6 (68.6-76.6)	74.1 (70.1-78.2)	0.547
	12 weeks	74.5 (70.4-78.6)	74.6 (70.6-78.6)	0.796
Dysphagia	Baseline	14.5 (11.6-17.4)	15.4 (12.5-18.3)	0.530
	3 weeks	13.8 (11.4-16.2)	14.3 (11.8-16.7)	0.652
	12 weeks	9.5 (7.8-11.3)	10.1 (8.3-11.9)	0.809
Pain	Baseline	21.9 (18.8-25.0)	23.1 (20.1-26.0)	0.261
	3 weeks	17.5 (15.3-19.6)	19.8 (17.6-22.1)	0.152
	12 weeks	15.7 (13.5-17.9)	15.3 (13.1-17.4)	0.951
Reflux symptoms	Baseline	12.9 (10.4-15.4)	13.5 (10.9-16.0)	0.883
	3 weeks	9.9 (8.1-11.6)	12.9 (10.6-15.3)	0.138
	12 weeks	9.4 (7.7-11.1)	10.9 (9.0-12.8)	0.272
Eating restrictions	Baseline	14.0 (11.7-16.4)	13.0 (10.7-15.2)	0.724
	3 weeks	18.8 (16.4-21.2)	20.3 (17.9-22.8)	0.301
	12 weeks	17.0 (14.8-19.3)	15.8 (13.6-18.0)	0.496
Anxiety	Baseline	30.7 (27.3-34.0)	31.3 (28.1-34.6)	0.644
	3 weeks	33.1 (29.6-36.5)	33.3 (29.9-36.8)	0.863
	12 weeks	32.8 (29.2-36.4)	33.3 (29.8-36.8)	0.634
Dry mouth	Baseline	24.2 (20.1-28.2)	23.4 (19.5-27.3)	0.899
	3 weeks	27.4 (23.4-31.4)	25.9 (21.8-29.9)	0.547
	12 weeks	25.5 (21.4-29.6)	25.4 (21.4-29.4)	0.796
Taste	Baseline	10.9 (7.9-13.9)	11.0 (8.2-13.9)	0.709

STAT C30/STO22	Cycle	Ferric Carboxymaltose, Mean (95% CI)	Placebo, Mean (95% CI)	*P* Value*
	3 weeks	14.6 (11.3-17.9)	20.8 (16.5-25.0)	0.124
	12 weeks	16.1 (12.6-19.5)	14.7 (11.2-18.1)	0.477
Hair loss	Baseline	9.5 (6.6-12.4)	9.8 (6.7-12.9)	0.962
	3 weeks	5.5 (3.3-7.7)	7.4 (4.5-10.2)	0.574
	12 weeks	9.7 (7.2-12.3)	9.3 (6.7-11.9)	0.694

* Analyzed using ranksum test; FCM, ferric carboxymaltose

The 2 QoL assessments were scored from a range of 0 to 100; higher scores indicated healthier functioning for functional scales or worsening symptomatology for symptom scales Using the QLQ C30 assessment, significant differences were observed in favor of ferric carboxymaltose regarding two parameters: fatigue at week 3 and dyspnea at week 12. No significant difference was observed in the global health status/QoL scores at weeks 3 and 12. The predefined 10-point minimal difference was not met, and therefore no clinical significance was observed.

eTable 4. Most Commonly Reported Study Drug–Related Adverse Events

Adverse Events	Grade 1	Grade 2	Combined Grades 1 and 2	Total (%)	Grade 1	Grade 2	Combined Grades 1 and 2	Total (%)	*P* value
Urticaria	4	1	5	5 (2.25)	0	0	0	0	0.030
Injection site reaction	2	3	5	5 (2.25)	0	0	0	0	0.030
Constipation	1	0	1	1 (0.45)	0	0	0	0	0.499
Fever	1	0	1	1 (0.45)	0	0	0	0	0.499
Headache	1	0	1	1(0.45)	0	0	0	0	0.499
Insomnia	1	0	1	1 (0.45)	0	0	0	0	0.499
Palmar-plantar erythrodysesthesia syndrome	0	0	0	0	1	0	1	1 (0.45)	1.000
Phlebitis infective	1	0	1	1 (0.5)	0	0	0	0	0.499
Total	11	4	15	15 (6.76)	1	0	1	1 (0.45)	

According to the Common Terminology Criteria for Adverse Events Version 4.0, Grade 1 refers to mild, asymptomatic or mild symptoms, clinical or diagnostic observations only without indication of intervention; Grade 2 refers to moderate symptoms with minimal, local or noninvasive intervention indicated; Grade 3 refers to severe or medically significant but not immediately life-threatening consequence, hospitalization or prolongation of hospitalization indicated; Grade 4 refers to life-threatening consequences, urgent intervention indicated; and Grade 5 refers to death related to adverse event. There were no adverse events of Grade 3 or more for both the ferric carboxymaltose group and placebo group.

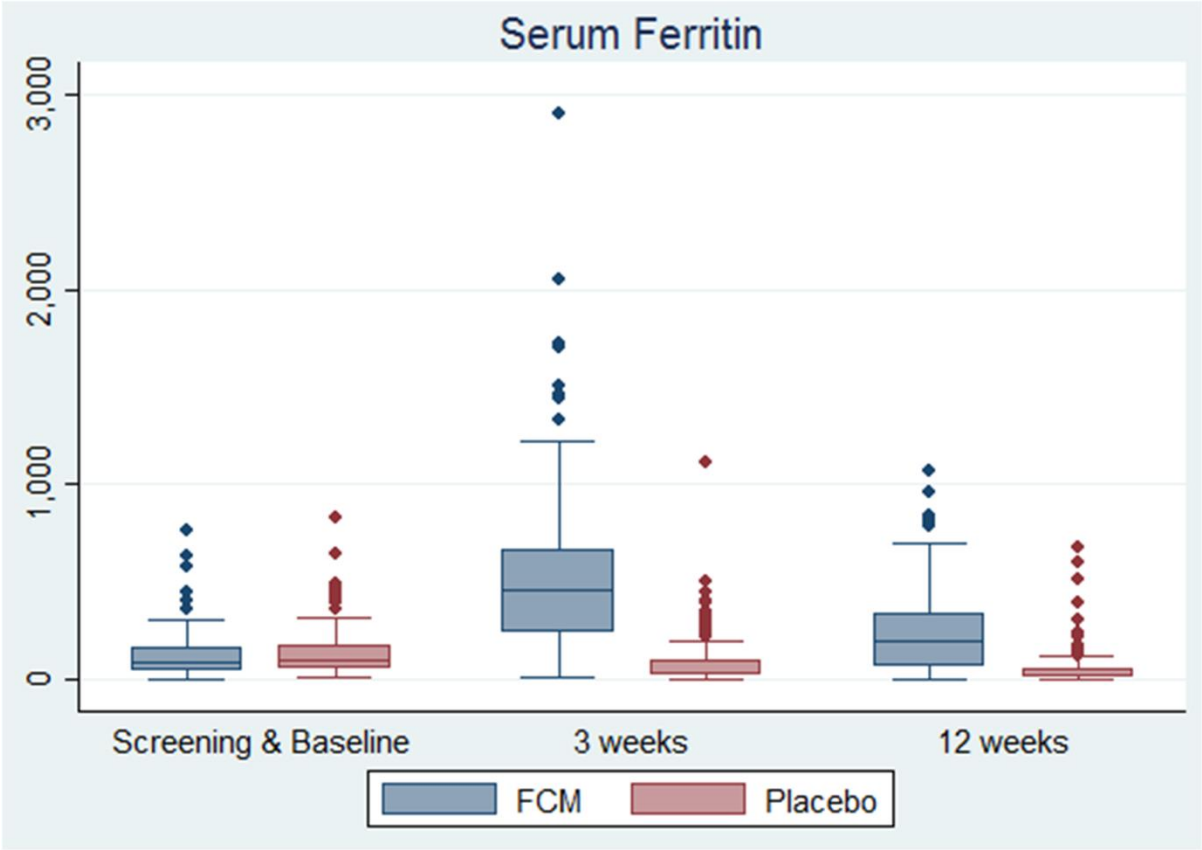
eTable 5. Multivariable Analysis. After adjusting for potentially significant differences in baseline factors, multivariable analysis showed that the ferric carboxymaltose group experienced significantly greater proportion of Hb responders compared with placebo (OR 12.08 [95% CI 6.70 to 21.78]; *P*>0.001

Multivariable Analysis		**No.(%)**	**Odds Ratio (95% CI)**	**SE**	***z* Score**	**P > *z* Score**
Group	Placebo	213 (49.5)	1 [Reference]			
	Ferric carboxymaltose	217 (50.5)	12.08 (6.70-21.78)	3.63	8.28	0.000
Age		430 (100)	0.98 (0.96-1.00)	0.01	-1.61	0.108
Sex	Male	192 (44.7)	1 [Reference]			
	Female	238 (55.3)	0.64 (0.38-1.08)	0.17	-1.66	0.096
Baseline hemoglobin		430 (100)	1.02 (0.69-1.51)	0.20	0.11	0.909
Comorbidities	No Diabetes	352 (81.9)	1 [Reference]			
	Diabetes	78 (18.1)	1.08 (0.55-2.10)	0.37	0.21	0.832
	No Hypertension	273 (63.5)	1 [Reference]			
	Hypertension	157 (36.5)	0.99 (0.57-1.74)	0.28	-0.02	0.982
	No Tuberculosis	403 (93.7)	1 [Reference]			
	Tuberculosis	27 (6.3)	1.19 (0.39-3.62)	0.67	0.30	0.765
	No Chronic liver disease	429 (99.8)	1 [Reference]			
	Chronic liver disease	1 (0.2)	1.00	-*	-*	-*
Type of operation	Total gastrectomy	163 (37.9)	1 [Reference]			
	Partial gastrectomy	267 (62.1)	1.34 (0.79-2.27)	0.36	1.09	0.278
Clinical stages	Stage I	212 (49.3)	1 [Reference]			
	Stage II/III/IV	218 (50.7)	0.83 (0.42-1.62)	0.28	-0.55	0.586
Chemotherapy	No	252 (58.6)	1 [Reference]			
	Yes	178 (41.4)	0.93 (0.48-1.81)	0.32	-0.20	0.842

*No values because odds ratio of experimental group was same as the reference group.

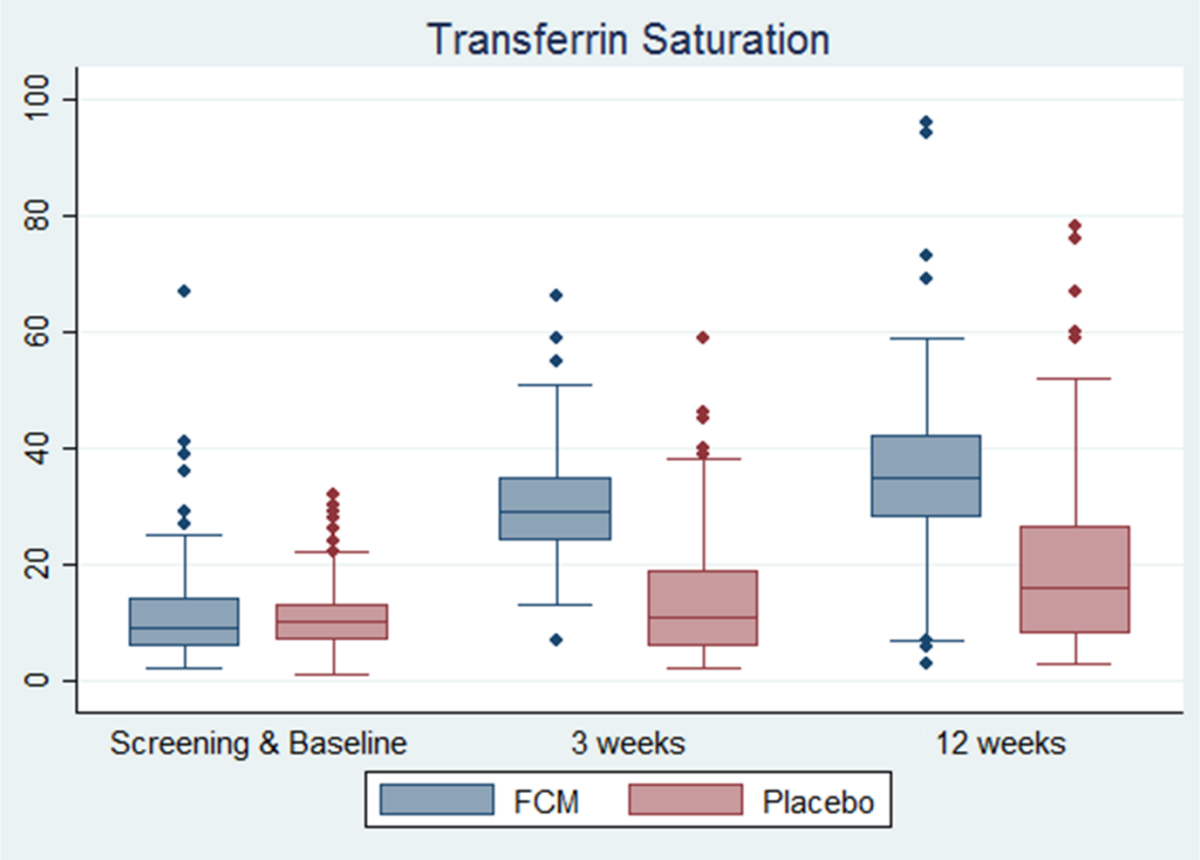
eFigure 1. Box-and-Whisker Plot Depicting the Evolution of Hematologic Factors for Ferritin and Transferrin Saturation Levels

(A) Ferritin levels (ng/mL)



Analyzed using ranksum test; Baseline, *P*=0.094; 3 weeks, *P*=0.001; 12 weeks, *P*=0.001

(B) Transferrin saturation levels (%)

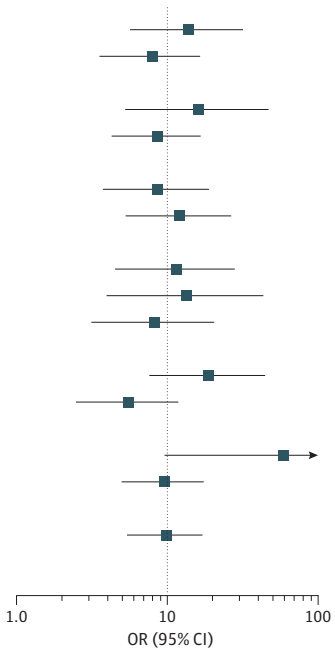


Analyzed using ranksum test, Baseline, *P*=0.662; 3 weeks, *P*=0.001; 12 weeks, *P*=0.001

(A) Number of participants at baseline (ferric carboxymaltose: 227 patients, placebo: 225 patients), 3 weeks (ferric carboxymaltose: 217 patients, placebo: 226 patients), and 12 weeks (ferric carboxymaltose: 215, placebo: 213). (B) Number of participants at baseline (ferric carboxymaltose: 227 patients, placebo: 225 patients), 3 weeks (ferric carboxymaltose: 217 patients, placebo: 217 patients), and 12 weeks (ferric carboxymaltose: 215, placebo: 212). The middle line of each box represents the median. The top and bottom lines of each box represents the 75th and 25th percentiles, respectively. The top and bottom whiskers represent the upper and lower adjacent values, respectively. The dots represent the outlier values. *P < 0.05 using the Wilcoxon rank sum test.

eFigure 2. Subgroup Analysis for Hemoglobin Responders* Included in the Primary Analysis

	Ferric Carboxymaltose	Placebo		
	No. of Responders/ Total No. of Patients	No. of Responders/ Total No. of Patients	OR (95% CI)	Absolute Difference (95% CI)
Age, y				
<65	112/119	59/108	13.29 (5.67-31.16)	39.5 (33.1-45.8)
≥65	88/98	56/105	7.7 (3.61-16.43)	36.5 (29.8-43.1)
Sex				
Male	92/96	57/96	15.74 (5.34-46.38)	36.5 (29.7-43.3)
Female	108/121	58/117	8.45 (4.28-16.68)	39.7 (33.5-45.9)
Chemotherapy				
No	118/126	70/126	11.8 (5.32-26.20)	38.1 (32.1-44.1)
Yes	82/91	45/87	8.50 (3.80-19.05)	38.4 (31.2-45.5)
Gastric cancer TNM stage				
I	103/109	66/109	11.18 (4.51-27.79)	33.9 (27.7-40.2)
II	35/39	18/45	13.13 (3.98-43.32)	49.7 (39.1-60.4)
III or IV	62/69	31/59	8.00 (3.15-20.35)	37.3 (28.9-45.7)
Gastrectomy				
Subtotal	123/129	71/135	18.48 (7.62-44.83)	42.8 (36.8-48.7)
Total	77/88	44/78	5.41 (2.49-11.73)	31.1 (24.0-38.1)
Serum ferritin, ng/mL				
<30	27/31	2/19	57.38 (9.46-348.00)	76.6 (64.8-88.3)
≥30	172/185	113/193	9.37 (4.98-17.63)	34.4 (29.6-39.2)
Transferrin saturation level, %				
<20	182/199	105/198	9.49 (5.36-16.77)	38.4 (33.6-43.2)
≥20 **	17/17	10/14	1.00	28.6 (12.7-44.5)



OR, odds ratio; TNM indicates tumor-node-metastasis. To convert ferritin to pmol/Lng/mL, multiply by 2.247. P value was .001 for every subgroup with χ^2 test, except transferrin saturation level of 20% or more (P = .03; Fisher exact test).

* Hemoglobin responder was defined as a hemoglobin increase of 2 g/dL or more from baseline, a hemoglobin level of 11 g/dL or more, or both at week 12.

** OR cannot be calculated in transferrin saturation level of 20% or more because all of these patients in ferric carboxymaltose group achieved a hemoglobin level increase of 2 g/dL or more compared with baseline hemoglobin value or a hemoglobin level of 11 g/dL or more.