Supplementary information

Table S1. Baseline characteristics of the AUC subgroups and PK/PD and as-treated populations in RECOURSE

	FTD		TPI		Overall	
	High AUC (> median) (*n* = 69)	**Low AUC (≤ median) (*n* = 69)**	**High AUC (> median) (*n* = 69)**	**Low AUC (≤ median) (*n* = 69)**	**PK/PD population (*n* = 210)**	**Overall RECOURSE (*N* = 800)**
Male, *n* (%)	36 (52.2)	51 (73.9)	44 (63.8)	43 (62.3)	133 (63.3)	491 (61.4)
Age, years, mean (SD)	62.1 (10.8)	60.6 (9.9)	62.4 (10.7)	60.4 (10.0)	61.3 (10.4)	61.5 (10.3)
Age ≥65 years, *n* (%)	35 (50.7)	21 (30.4)	32 (46.4)	24 (34.8)	90 (42.9)	352 (44.0)
Race, *n* (%)						
Caucasian	41 (59.4)	41 (59.4)	41 (59.4)	41 (59.4)	121 (57.6)	461 (57.6)
Black/African American	1 (1.4)	1 (1.4)	0	2 (2.9)	6 (2.9)	9 (1.1)
Asian	22 (31.9)	17 (24.6)	22 (31.9)	17 (24.6)	64 (30.5)	278 (34.8)
Not collected	5 (7.2)	10 (14.5)	6 (8.7)	9 (13.0)	19 (9.0)	52 (6.5)
Body surface area, m^2, mean (SD)	1.768 (0.219)	1.856 (0.206)	1.797 (0.227)	1.827 (0.205)	1.804 (0.208)	1.784 (0.229)
ECOG PS, *n* (%)						
0	43 (62.3)	41 (59.4)	35 (50.7)	49 (71.0)	122 (58.1)	448 (56.0)

1	26 (37.7)	28 (40.6)	34 (49.3)	20 (29.0)	88 (41.9)	352 (44.0)
KRAS status[a], *n* (%)						
Wild type	30 (43.5)	39 (56.5)	31 (44.9)	38 (55.1)	100 (47.6)	393 (49.1)
Mutant	39 (56.5)	30 (43.5)	38 (55.1)	31 (44.9)	110 (52.4)	407 (50.9)
Time since diagnosis of first metastasis[a], *n* (%)						
<18 months	11 (15.9)	9 (13.0)	12 (17.4)	8 (11.6)	33 (15.7)	166 (20.8)
≥18 months	58 (84.1)	60 (87.0)	57 (82.6)	61 (88.4)	177 (84.3)	634 (79.3)
Baseline renal function[b], *n* (%)						
Normal (CrCL ≥90 mL/min)	30 (43.5)	54 (78.3)	30 (43.5)	54 (78.3)	121 (57.6)	452 (56.5)
Mild impairment (CrCL 60–89 mL/min)	27 (39.1)	11 (15.9)	26 (37.7)	12 (17.4)	68 (32.4)	269 (33.6)
Moderate impairment (CrCL 30–59 mL/min)	12 (17.4)	4 (5.8)	13 (18.8)	3 (4.3)	21 (10.0)	74 (9.3)[c]
Baseline eGFR[d], *n* (%)						
Normal (CrCL ≥90 mL/min/1.73 m^2)	33 (47.8)	53 (76.8)	33 (47.8)	53 (76.8)	128 (61.0)	495 (61.9)
Mild impairment (CrCL 60–89 mL/min/1.73 m^2)	28 (40.6)	14 (20.3)	28 (40.6)	14 (20.3)	66 (31.4)	235 (29.4)
Moderate impairment	6 (8.7)	1 (1.4)	7 (10.1)	0	12 (5.7)	49 (6.1)

(CrCL 30–59 mL/min/1.73 m^2)							
Missing	2 (2.9)	1 (1.4)	1 (1.4)	2 (2.9)	4 (1.9)	21 (2.6)	

[a]As randomized.

[b]CrCL based on Cockcroft-Gault using baseline creatinine.

[c]CrCL data for five patients from the RECOURSE population were missing.

[d]eGFR (mL/min/1.73 m^2) = 175 × (baseline creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

AUC, area under the curve; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; FTD, trifluridine; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; TPI, tipiracil.

Table S2. Analysis of efficacy in the PK/PD population of RECOURSE

	FTD			TPI			PK/PD population	
	High AUC (*n* = 69)	**Low AUC (*n* = 69)**	**Placebo (*n* = 72)**	**High AUC (*n* = 69)**	**Low AUC (*n* = 69)**	**Placebo (*n* = 72)**	**FTD/TPI (*n* = 138)**	**Placebo (*n* = 72)**
OS HR (95% CI)							0.58 (0.42–0.80)*	
High versus low AUC	0.72 (0.46–1.11)			1.09 (0.70–1.69)				
High AUC versus placebo			0.49 (0.32–0.76)*			0.64 (0.42–0.97)*		
Low AUC versus placebo			0.60 (0.39–0.92)*			0.49 (0.32–0.76)*		
PFS HR (95% CI)							0.34 (0.24–0.49)*	
High versus low AUC	0.82 (0.57–1.18)			0.97 (0.67–1.41)				
High AUC versus placebo			0.26 (0.17–0.40)*			0.38 (0.26–0.58)*		
Low AUC versus placebo			0.44 (0.29–0.66)*			0.30 (0.20–0.46)*		
Time to ECOG PS ≥2 HR (95% CI)								
High versus low AUC	0.64 (0.44–0.93)*			0.86 (0.58–1.26)				

*$P < 0.05$.

AUC, area under the curve; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; TPI, tipiracil.

Table S3. Incidence of any-grade adverse events and dose reductions by FTD and TPI AUC in the RECOURSE PK/PD population

	FTD		TPI		FTD/TPI	
	High AUC (> median) (*n* = 69)	**Low AUC (≤ median) (*n* = 69)**	**High AUC (> median) (*n* = 69)**	**Low AUC (≤ median) (*n* = 69)**	**PK/PD population (*n* = 138)**	**RECOURSE (*N* = 533)**
Any grade ≥3 AE, *n* (%)	49 (71.0)	49 (71.0)	49 (71.0)	49 (71.0)	98 (71.0)	370 (69.4)
RR versus low AUC (95% CI)	1.00 (0.81–1.24)		1.00 (0.81–1.24)			
Any grade ≥3 AE related to study medication, *n* (%)	39 (56.5)	31 (44.9)	36 (52.2)	34 (49.3)	70 (50.7)	261 (49.0)
RR versus low AUC (95% CI)	1.26 (0.90–1.76)		1.06 (0.76–1.47)			
Any-grade CIN, *n* (%)	58 (84.1)	41 (59.4)	50 (72.5)	49 (71.0)		
RR versus low AUC (95% CI)	1.41 (1.13–1.76)		1.02 (0.83–1.26)			
Grade ≥3 CIN, *n* (%)	33 (47.8)	21 (30.4)	29 (42.0)	25 (36.2)	54 (39.1)	200 (37.5)
RR versus low AUC (95% CI)	1.57 (1.02–2.42)		1.16 (0.76–1.76)			
Grade ≥3 thrombocytopenia, *n* (%)	3 (4.3)	2 (2.9)	3 (4.3)	2 (2.9)	5 (3.6)	27 (5.1)
RR versus low AUC (95% CI)	1.50 (0.26–8.70)		1.50 (0.26–8.70)			
Grade ≥3 anemia, *n* (%)	15 (21.7)	12 (17.4)	14 (20.3)	13 (18.8)	27 (19.6)	96 (18.0)
RR versus low AUC (95% CI)	1.25 (0.63–2.47)		1.08 (0.55–2.12)			
Grade ≥3 diarrhea, *n* (%)	3 (4.3)	4 (5.8)	2 (2.9)	5 (7.2)	7 (5.1)	16 (3.0)

RR versus low AUC (95% CI)	0.75 (0.17–3.23)		0.40 (0.08–1.99)			
Any dose reduction, *n* (%)	16 (23.2)	6 (8.7)	11 (15.9)	11 (15.9)	22 (15.9)	73 (13.7)
RR versus low AUC (95% CI)	2.67 (1.11–6.41)		1.00 (0.46–2.15)			

AE, adverse event; AUC, area under the curve; CI, confidence interval; FTD, trifluridine; PD, pharmacodynamics; PK, pharmacokinetics; RR, relative risk; TPI, tipiracil.

Table S4. Patients from the PK/PD population of RECOURSE experiencing grade ≥1 and grade ≥3 CIN during cycle 1 by FTD AUC

***n* (%)**		**Grade ≥1 CIN**		**Grade ≥3 CIN**	
		Experienced	**Not experienced**	**Experienced**	**Not experienced**
AUC	High FTD (*n* = 69)	43 (62.3)	26 (37.7)	12 (17.4)	57 (82.6)
	Low FTD (*n* = 69)	30 (43.5)	39 (56.5)	8 (11.6)	61 (88.4)

AUC, area under the curve; CIN, chemotherapy-induced neutropenia; FTD, trifluridine; PD, pharmacodynamics; PK, pharmacokinetics.

Table S5. Patients from the PK/PD population of RECOURSE experiencing grade ≥1 and grade ≥3 CIN during cycle 1 or 2 by FTD AUC

***n* (%)**		**Grade ≥1 CIN**		**Grade ≥3 CIN**	
		Experienced	**Not experienced**	**Experienced**	**Not experienced**
AUC	High FTD (*n* = 69)	53 (76.8)	16 (23.2)	23 (33.3)	46 (66.7)
	Low FTD (*n* = 69)	38 (55.1)	31 (44.9)	17 (24.6)	52 (75.4)

AUC, area under the curve; CIN, chemotherapy-induced neutropenia; FTD, trifluridine; PD, pharmacodynamics; PK, pharmacokinetics.

Table S6. Any-grade adverse events of interest according to maximum CIN grade in cycles 1 and 2 in RECOURSE

Any-grade adverse events	**CIN in cycles 1 and 2, *n* (%)**			
	Grade 0 (*n* = 204)	**Grade ≥1 (*n* = 329)**	**Grade 0–2 (*n* = 372)**	**Grade ≥3 (*n* = 161)**
Anemia	27 (13.2)	59 (17.9)	53 (14.2)	33 (20.5)
Anemia and/or decreased hemoglobin	27 (13.2)	93 (28.3)	60 (16.1)	60 (37.3)
Decreased appetite	9 (4.4)	10 (3.0)	14 (3.8)	5 (3.1)
Diarrhea	6 (2.9)	10 (3.0)	10 (2.7)	6 (3.7)
Fatigue	11 (5.4)	10 (3.0)	14 (3.8)	7 (4.3)
Febrile neutropenia	2 (1.0)	18 (5.5)	3 (0.8)	17 (10.6)
Nausea	3 (1.5)	7 (2.1)	7 (1.9)	3 (1.9)
Decreased platelet count	1 (0.5)	12 (3.6)	3 (0.8)	10 (6.2)
Thrombocytopenia	1 (0.5)	10 (3.0)	3 (0.8)	8 (5.0)
Thrombocytopenia and/or decreased platelet count	2 (1.0)	22 (6.7)	6 (1.6)	18 (11.2)
Vomiting	5 (2.5)	6 (1.8)	7 (1.9)	4 (2.5)
Decreased white blood cell count	1 (0.5)	54 (16.4)	12 (3.2)	43 (26.7)

CIN, chemotherapy-induced neutropenia.

Table S7. PK parameters of FTD for patients in the PK cohort who developed CIN during cycle 1, 2, or ≥3 and for those who did not develop CIN in RECOURSE

CIN earliest onset	**Patients, *n***	**Median AUC (h*µg/mL) [Q1; Q3][a]**	**Median C_{max} (µg/mL) [Q1; Q3][b]**
None	39	36 [28; 47]	4.6 [3.8; 5.7]
Cycle 1	73	46 [39; 53]	5.0 [4.1; 5.7]
Cycle 2	18	49 [38; 58]	5.1 [4.2; 5.5]
Cycle ≥3	8	45 [34; 49]	4.6 [4.4; 5.0]

[a]Median FTD AUC in the PK population was 44 h*µg/mL.

[b]Median FTD C_{max} in the PK population was 5.0 µg/mL.

AUC, area under the curve; CIN, chemotherapy-induced neutropenia; C_{max}, maximum serum concentration; FTD, trifluridine; PK, pharmacokinetics; Q1, quartile 1; Q3, quartile 3.

Table S8. First onset of chemotherapy-induced neutropenia in RECOURSE and J003

Grade, *n* (%)	**RECOURSE**				**J003**			
	Cycle 1 (*n* = 534)	**Cycle 2 (*n* = 285)**	**Cycle ≥3 (*n* = 153)**	**Any cycle (*n* = 534)**	**Cycle 1 (*n* = 112)**	**Cycle 2 (*n* = 43)**	**Cycle ≥3 (*n* = 15)**	**Any cycle (*n* = 112)**
0	285 (53.4)	153 (53.7)	71 (46.4)	175 (32.8)	43 (38.4)	15 (34.9)	4 (26.7)	33 (29.5)
1	58 (10.9)	18 (6.3)	4 (2.6)	36 (6.7)	6 (5.4)	0	0	2 (1.8)
2	110 (20.6)	42 (14.7)	12 (7.8)	117 (21.9)	32 (28.6)	5 (11.6)	1 (6.7)	19 (17.0)
3	56 (10.5)	19 (6.7)	7 (4.6)	140 (26.2)	24 (21.4)	3 (7.0)	1 (6.7)	37 (33.0)
4	19 (3.6)	7 (2.5)	1 (0.7)	60 (11.2)	7 (6.3)	0	0	21 (18.8)
N/A	6 (1.1)	46 (16.1)	58 (37.9)	6 (1.1)	0	20 (46.5)	9 (60.0)	0

N/A, not available.

Table S9. Multivariate analyses performed for the RECOURSE and J003 trials

Treatment end points	Comparison	Multivariate comparison in RECOURSE[a] HR (95% CI)			Multivariate comparison in J003[b] HR (95% CI)		
		Grade ≥1	Grade 1–2	Grade 3–4	Grade ≥1	Grade 1–2	Grade 3–4
Median OS, months	Versus placebo	0.51 (0.42–0.61)	0.57 (0.46–0.70)	0.45 (0.36–0.57)	0.48 (0.33–0.69)	0.72 (0.44–1.17)	0.39 (0.25–0.59)
	Versus no CIN	0.43 (0.35–0.52)	0.48 (0.38–0.60)	0.40 (0.31–0.51)	0.32 (0.21–0.50)	0.57 (0.33–0.99)	0.22 (0.13–0.38)
Median PFS, months	Versus placebo	0.37 (0.31–0.44)	0.44 (0.35–0.55)	0.32 (0.25–0.40)	0.30 (0.20–0.46)	0.45 (0.26–0.80)	0.29 (0.18–0.46)
	Versus no CIN	0.56 (0.46–0.68)	0.62 (0.50–0.78)	0.51 (0.41–0.65)	0.34 (0.21–0.57)	0.48 (0.25–0.93)	0.29 (0.16–0.51)
Median time to ECOG PS ≥2, months	Versus placebo	0.45 (0.37–0.55)	0.47 (0.37–0.60)	0.44 (0.34–0.56)	0.55 (0.39–0.79)	0.76 (0.46–1.25)	0.47 (0.31–0.71)
	Versus no CIN	0.41 (0.33–0.50)	0.42 (0.32–0.54)	0.40 (0.31–0.53)	0.32 (0.21–0.51)	0.56 (0.32–0.97)	0.23 (0.14–0.39)

[a]Covariates adjusted in the multivariate model were included in the statistical analysis plan: *BRAF* status (wild type, mutant type, unknown), age (<65 versus ≥65 years), race (Caucasian, Asian, Black/African American, not collected), gender, primary tumor site (colon, rectal), ECOG PS (0, 1), number of prior regimens (2, 3, 4+), number of metastatic sites (1-2, 3+), and renal function (normal, mild, moderate).

[b]Covariates adjusted in the multivariate model were included in the statistical analysis plan of the RECOURSE study: age (<65 versus ≥65 years), gender, primary tumor site (colon, rectal), ECOG PS (0, 1–2), number of prior regimens, number of metastatic sites (1, 2+), and renal function (normal, mild,

moderate).

CI, confidence interval; CIN, chemotherapy-induced neutropenia; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table S10. Efficacy according to earliest onset of any-grade chemotherapy-induced neutropenia by treatment cycle in the RECOURSE as-treated population

	***n* (%)[a]**	**Median OS, months**	**Adjusted OS HR[b] (95% CI)**	**Median PFS, months**	**Adjusted PFS HR[b] (95% CI)**	**Median time to ECOG PS ≥2, months**	**Adjusted time to ECOG PS ≥2 HR (95% CI)**
FTD/TPI: cycle 1 onset (*n* = 533)	242 (45.4)	9.7	0.50 (0.41–0.61)*	3.5	0.36 (0.30–0.44)*	7.8	0.56 (0.46–0.68)*
Placebo: all patients (*n* = 265)	265 (100)	5.3		1.7		4.4	
FTD/TPI: cycle ≥2 onset (*n* = 533)	86 (16.1)	9.1	0.65 (0.49–0.85)*	3.5	0.42 (0.32–0.57)*	8.1	0.63 (0.48–0.84)*
Placebo: cycle ≥2 patients (*n* = 265)	215 (81.1)	6.3		1.8		5.5	
FTD/TPI: cycle ≥3 onset (*n* = 533)	25 (4.7)	10.4	0.83 (0.45–1.50)	6.9	0.42 (0.22–0.80)*	9.8	0.81 (0.42–1.58)
Placebo: cycle ≥3 patients (*n* = 265)	48 (18.1)	10.0		3.7		7.3	

[a]Percentage of as-treated patients in the specific treatment group.

[b]Adjusted HR versus placebo: comparison of FTD/TPI patients with onset of any-grade chemotherapy-induced neutropenia against placebo patients who started that cycle.

*Indicates significant ($P < 0.05$) improvement in survival for the FTD/TPI group versus the placebo group.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TPI, tipiracil.

Table S11. Efficacy according to earliest onset of grade ≥3 chemotherapy-induced neutropenia by treatment cycle in the RECOURSE as-treated population

	***n* (%)[a]**	**Median OS, months**	**Adjusted OS HR[b] (95% CI)**	**Median PFS, months**	**Adjusted PFS HR[b] (95% CI)**	**Median time to ECOG PS ≥2, months**	**Adjusted time to ECOG PS ≥2 HR (95% CI)**
FTD/TPI: cycle 1 onset (*n* = 533)	75 (14.1)	10.1	0.47 (0.35–0.64)*	3.7	0.35 (0.25–0.48)*	8.0	0.54 (0.40–0.73)*
Placebo: all patients (*n* = 265)	265 (100)	5.3		1.7		4.4	
FTD/TPI: cycle ≥2 onset (*n* = 533)	86 (16.1)	9.7	0.59 (0.44–0.78)*	3.7	0.34 (0.25–0.46)*	7.7	0.68 (0.51–0.90)*
Placebo: cycle ≥2 patients (*n* = 265)	215 (81.1)	6.3		1.8		5.5	
FTD/TPI: cycle ≥3 onset (*n* = 533)	39 (7.3)	14.5	0.57 (0.34–0.96)*	6.5	0.32 (0.18–0.56)*	13.4	0.43 (0.24–0.79)*
Placebo: cycle ≥3 patients (*n* = 265)	48 (18.1)	10.0		3.7		7.3	

[a]Percentage of as-treated population in the specific treatment group.

[b]Adjusted HR versus placebo: comparison of FTD/TPI patients with onset of any-grade chemotherapy-induced neutropenia against placebo patients who started that cycle.

FTD/TPI patients were classified according to the cycle of earliest onset of any-grade chemotherapy-induced neutropenia. Each FTD/TPI group was

compared with the total number of placebo patients who entered the corresponding cycle.

*Indicates significant ($P < 0.05$) improvement in survival for the FTD/TPI group versus the placebo group.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TPI, tipiracil.

Table S12. Clinical end points in FTD/TPI-treated patients according to CIN grade during cycles 1 and 2 in J003

Treatment end points[a]	CIN grade				Comparison	Univariate comparison, HR (95% CI)[b]		
	No CIN (*n* = 35)	Grade ≥1 (*n* = 77)	Grade 1–2 (*n* = 27)	Grade ≥3 (*n* = 50)		Grade ≥1	Grade 1–2	Grade ≥3
Median OS, months	5.3	11.5	7.5	13.6	Versus placebo	0.49 (0.35–0.70) *P* < 0.0001	0.80 (0.51–1.28) *P* = 0.44	0.40 (0.26–0.59) *P* < 0.0001
					Versus no CIN	0.36 (0.23–0.55) *P* < 0.0001	0.63 (0.38–1.05) *P* = 0.12	0.27 (0.17–0.44) *P* < 0.0001
Median PFS, months	1.1	2.8	2.7	2.9	Versus placebo	0.32 (0.21–0.48) *P* < 0.0001	0.41 (0.24–0.71) *P* = 0.0014	0.30 (0.19–0.48) *P* < 0.0001
					Versus no CIN	0.39 (0.25–0.63) *P* < 0.0001	0.50 (0.28–0.91) *P* = 0.033	0.37 (0.22–0.62) *P* < 0.0001
Median time to ECOG PS ≥2, months	4.3	10.4	7.4	13.0	Versus placebo	0.57 (0.40–0.81) *P* = 0.0018	0.86 (0.54–1.36) *P* = 0.67	0.47 (0.32–0.71) *P* = 0.0001
					Versus no CIN	0.37 (0.24–0.56) *P* < 0.0001	0.61 (0.36–1.02) *P* = 0.10	0.29 (0.18–0.47) *P* < 0.0001

[a]Kaplan-Meier estimates.

[b]Stratified log-rank test (stratification factors: ECOG PS).

CI, confidence interval; CIN, chemotherapy-induced neutropenia; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TPI, tipiracil.

Figure S1. Kaplan-Meier estimates of overall survival (OS) according to chemotherapy-induced neutropenia (CIN) grade or placebo in cycle 1 in RECOURSE

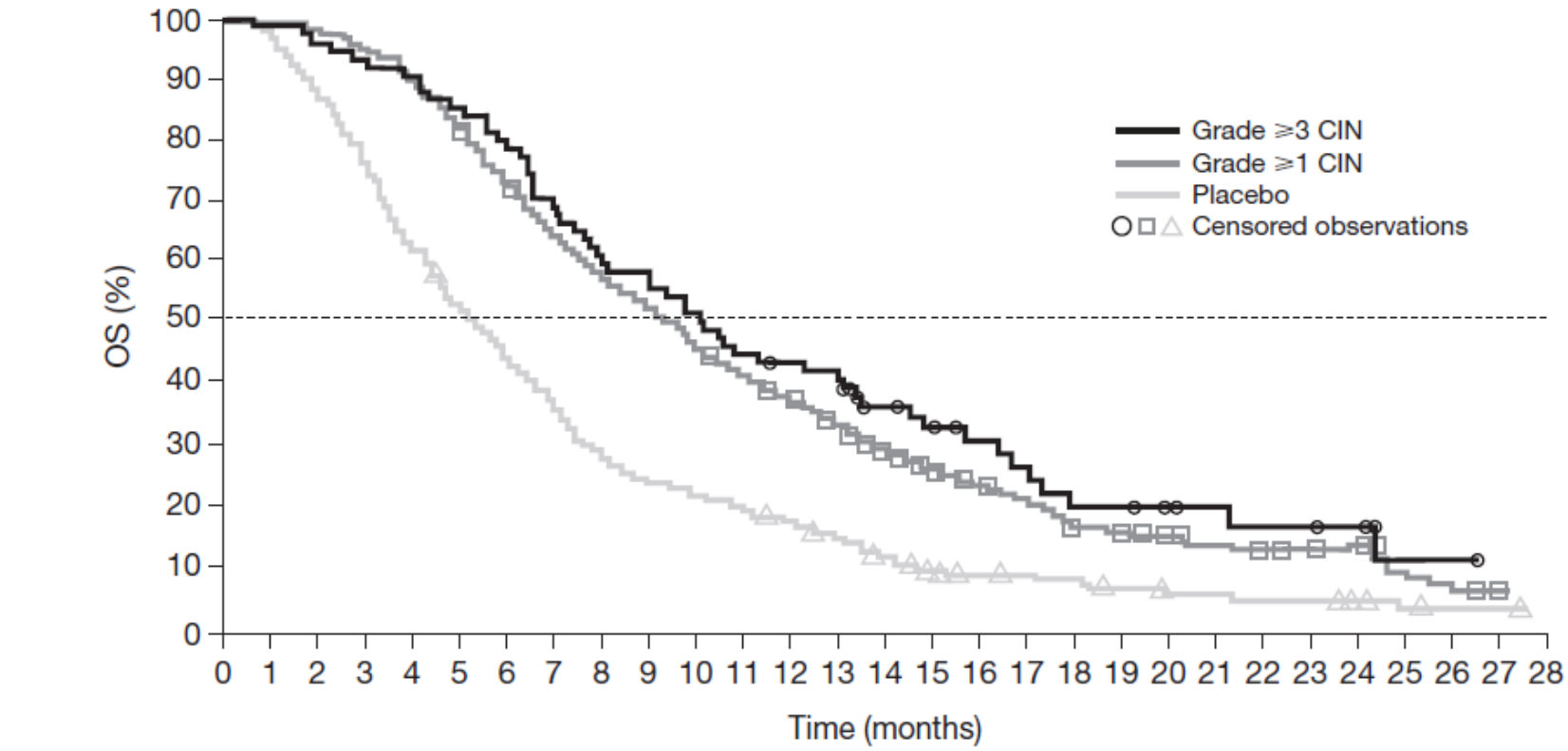


Figure S2. Kaplan-Meier estimates of overall survival (OS) according to chemotherapy-induced neutropenia (CIN) grade or placebo in cycle 2 in RECOURSE

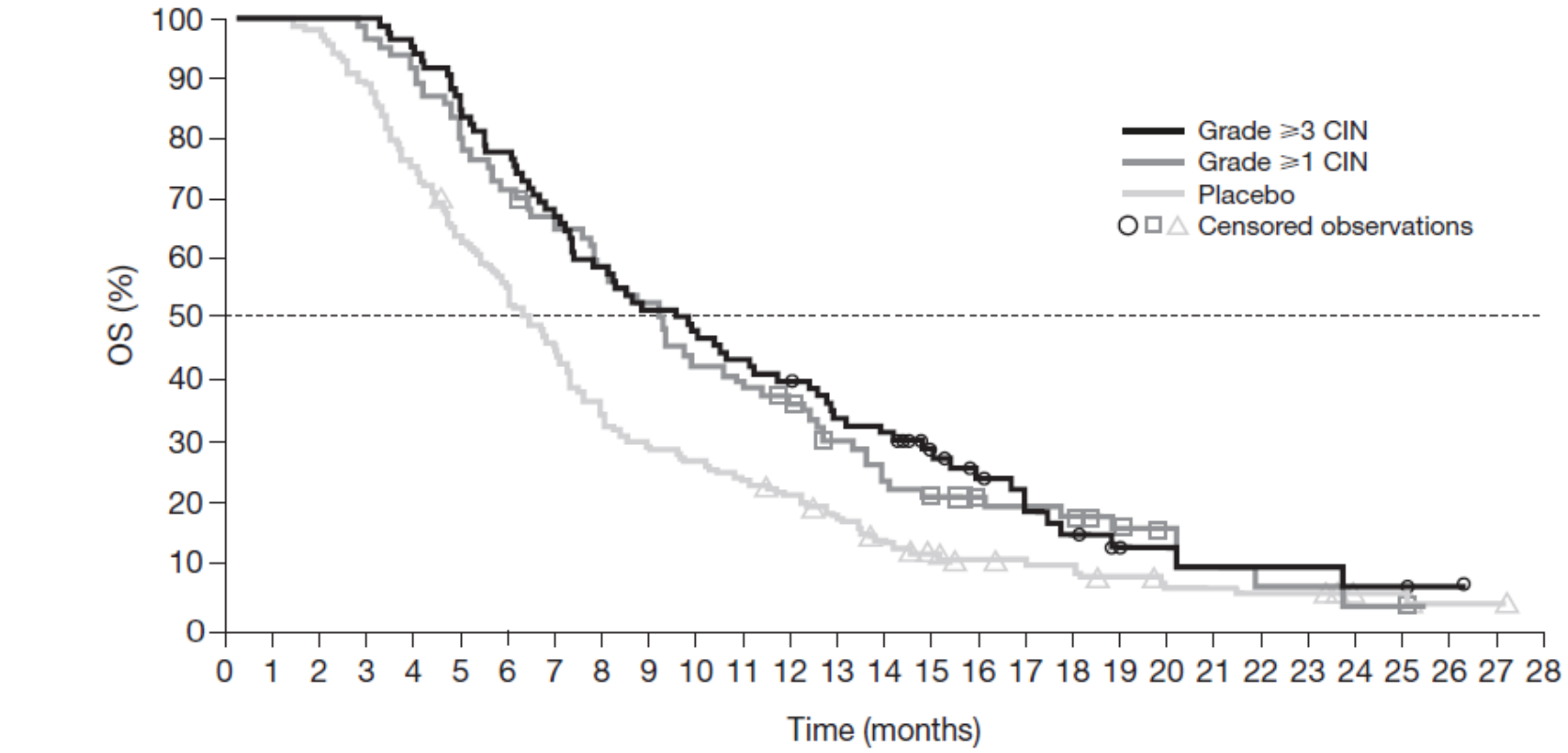


Figure S3. Kaplan-Meier estimates of overall survival (OS) according to chemotherapy-induced neutropenia (CIN) grade or no CIN in cycle 1 in RECOURSE

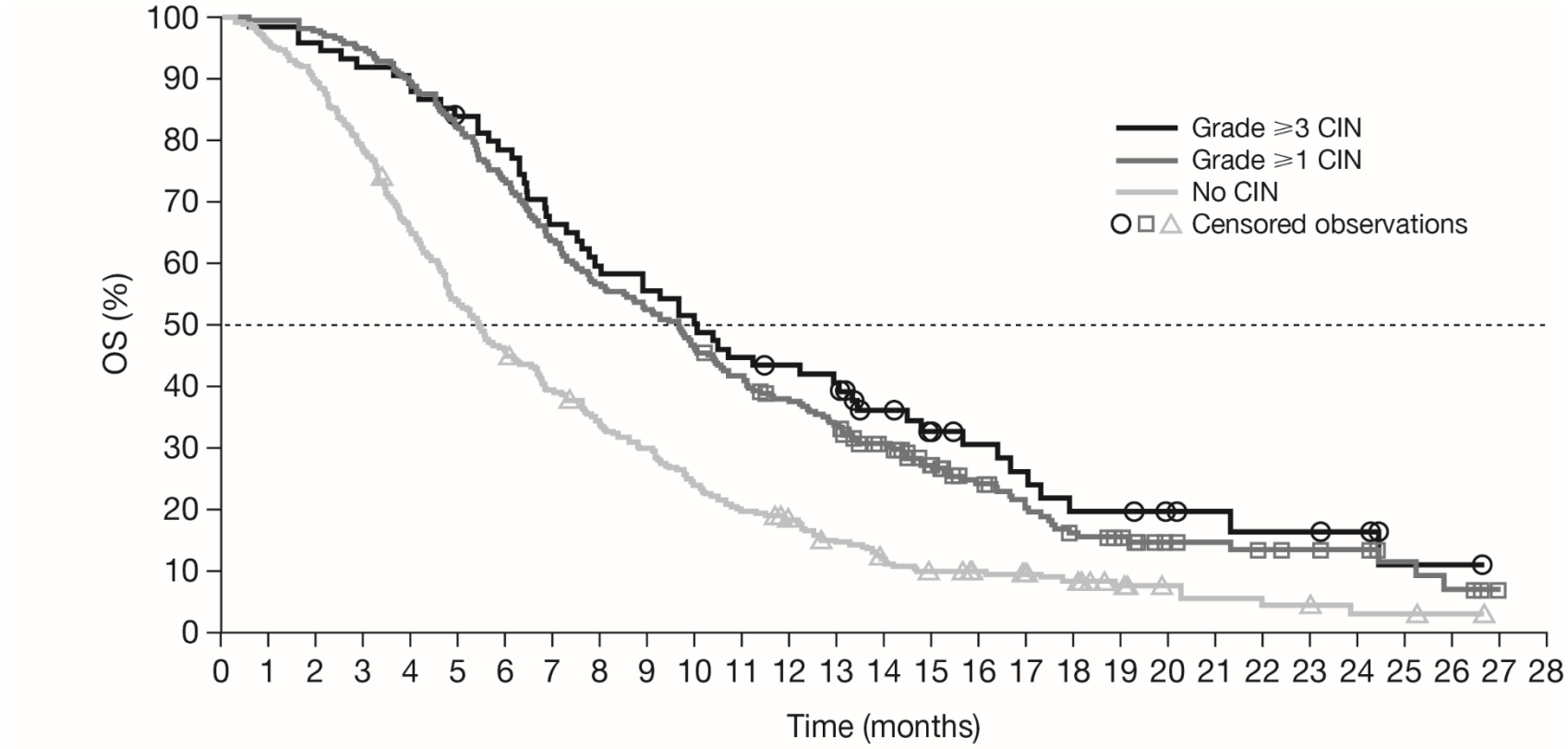


Figure S4. Kaplan-Meier estimates of overall survival (OS) according to chemotherapy-induced neutropenia (CIN) grade or no CIN in cycle 2 in RECOURSE

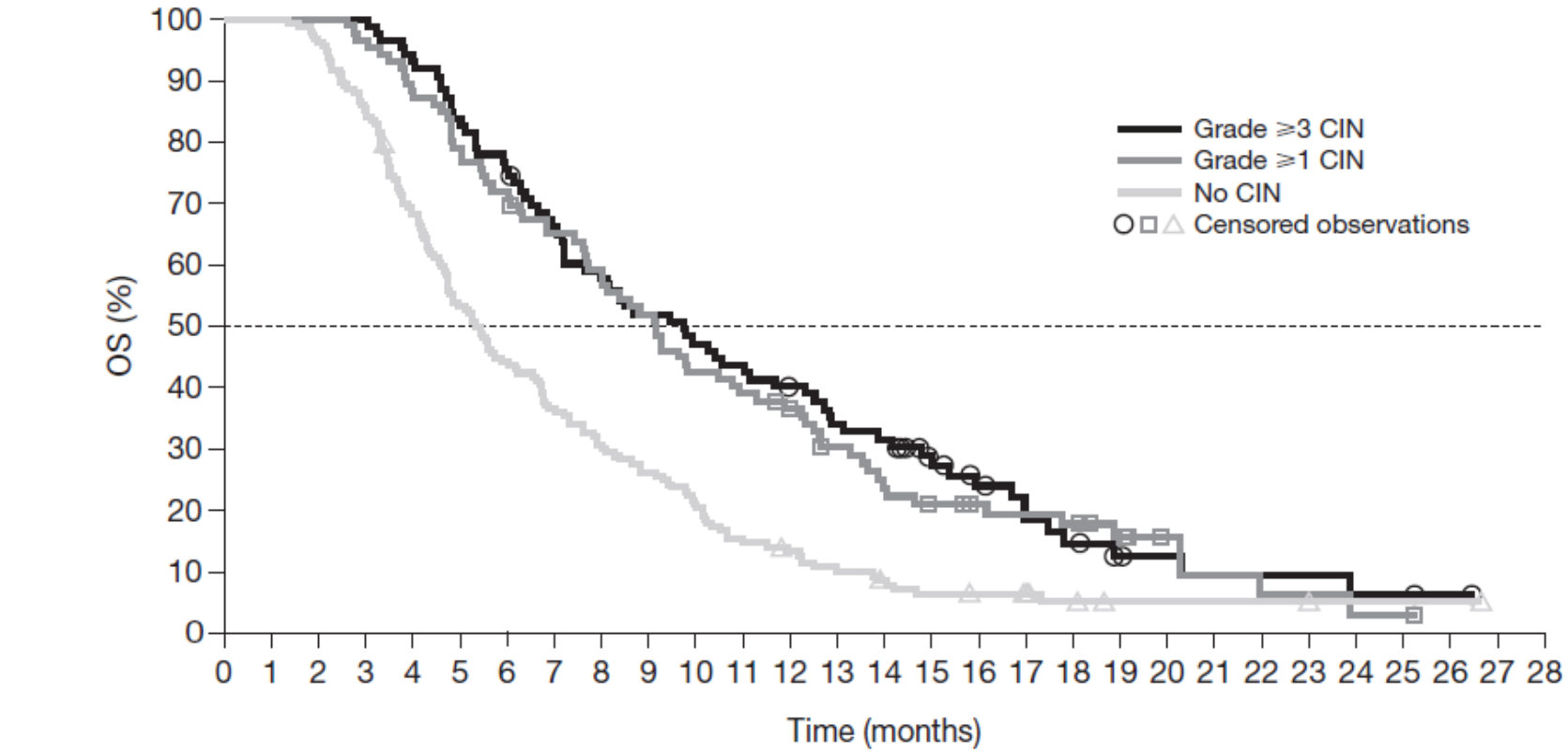


Figure S5. Kaplan-Meier estimates of overall survival (OS) in the trifluridine/tipiracil (FTD/TPI) and placebo groups at final data collection (January 19, 2015) in J003

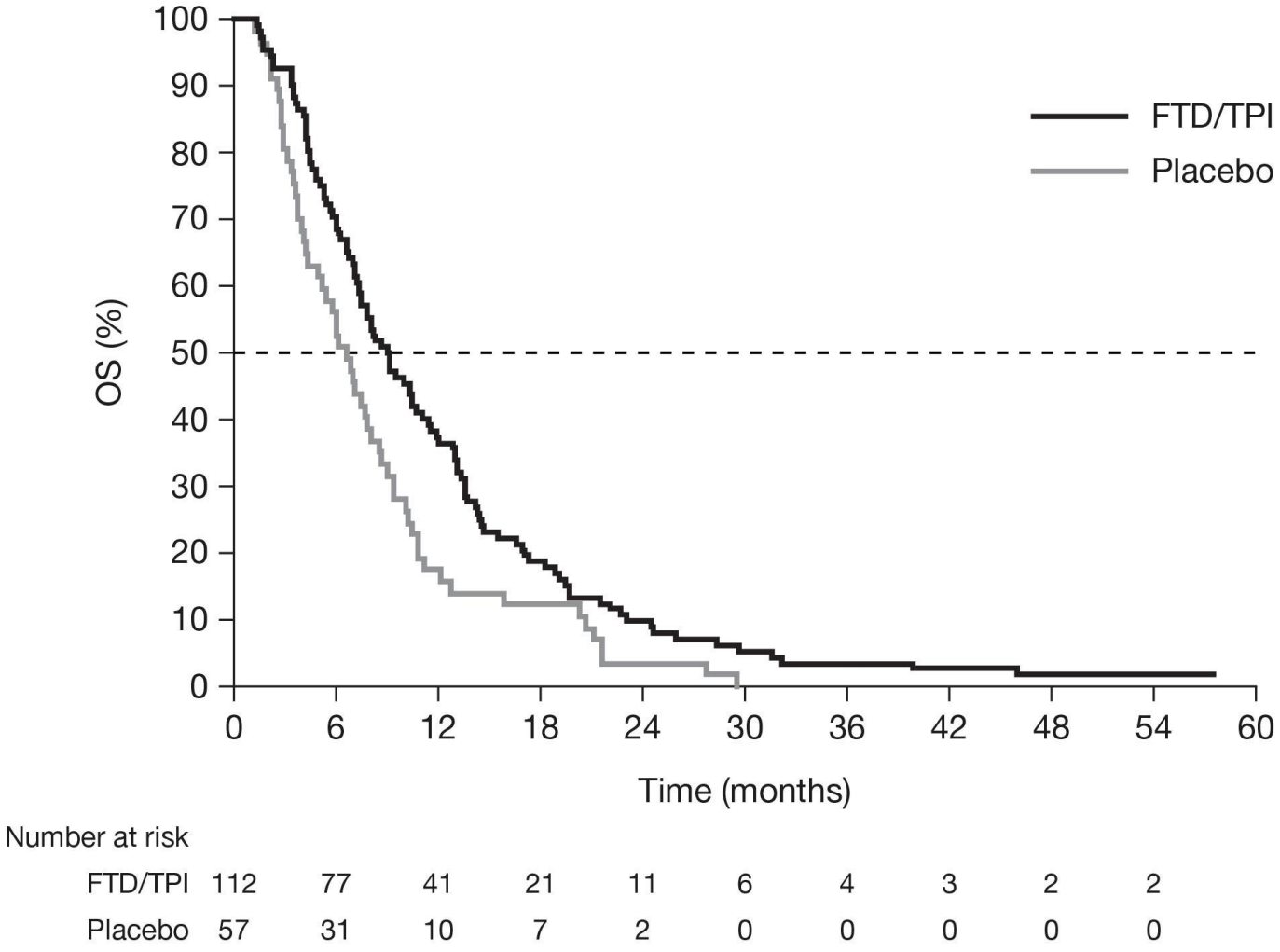
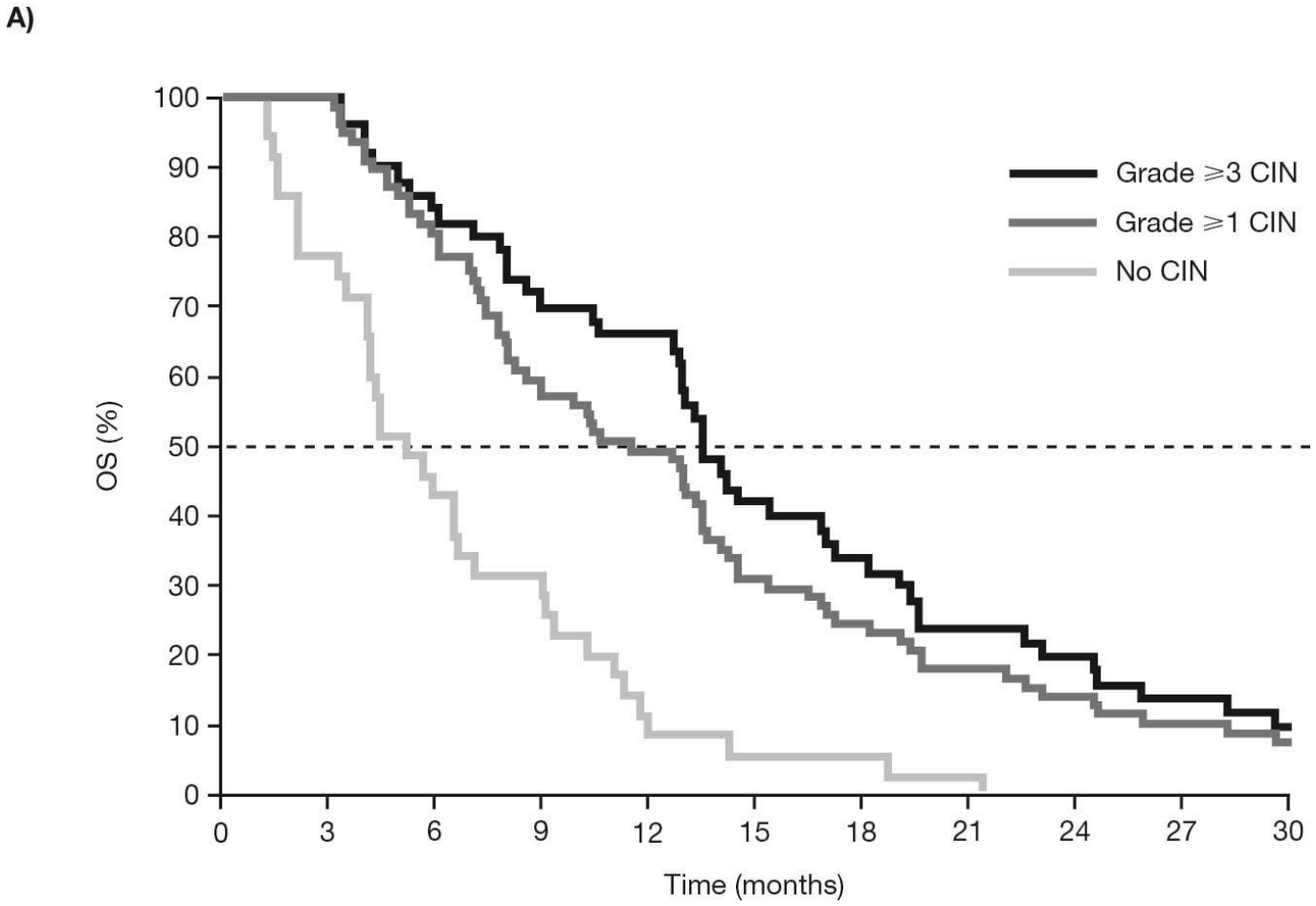
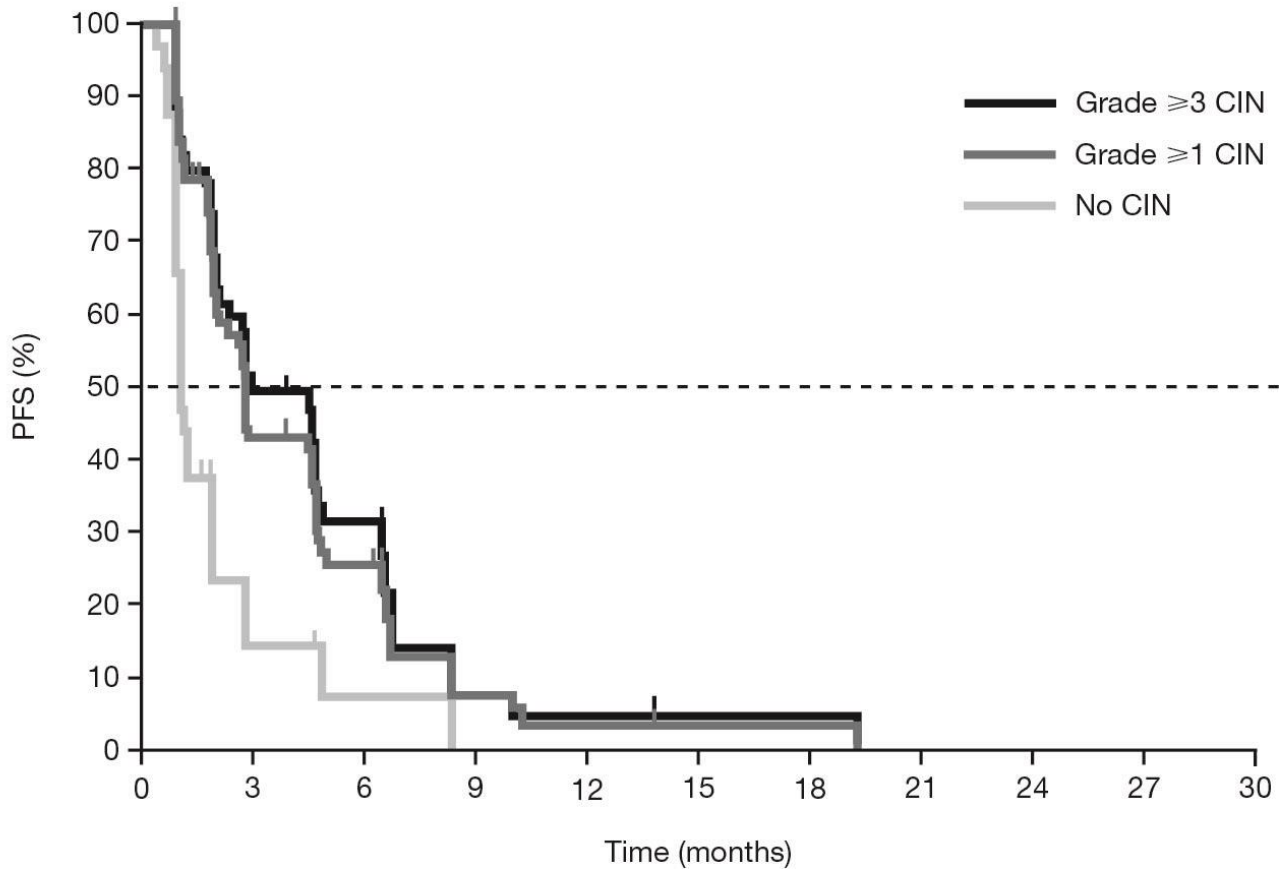


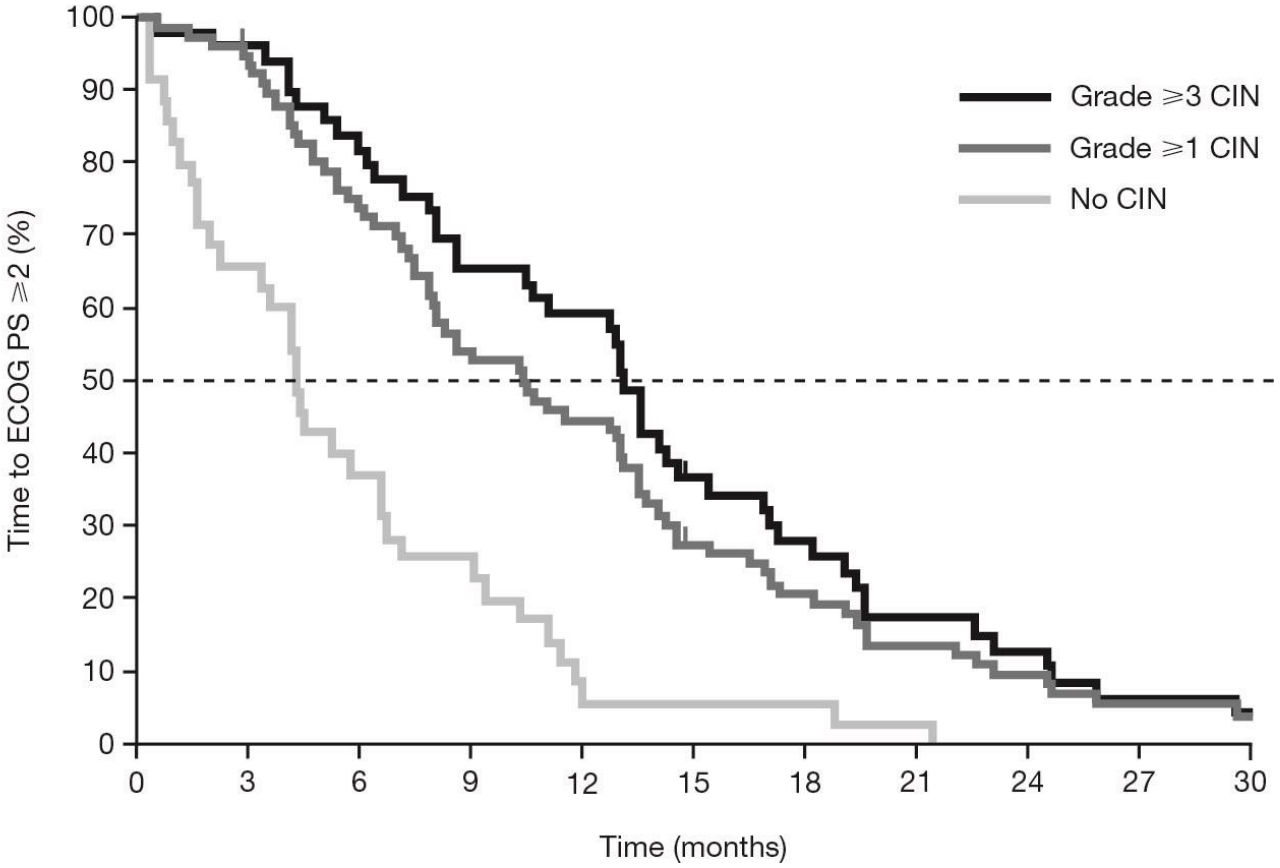
Figure S6. Kaplan-Meier estimates of (A) overall survival (OS), (B) progression-free survival (PFS), and (C) time to Eastern Cooperative Oncology Group performance status (ECOG PS) worsening to ≥2, in cycles 1 and 2 according to chemotherapy-induced neutropenia (CIN) grade, in J003



B)


100
90
80
70
60
50
40
30
20
10
0
PFS (%)
0
3
6
9
12
15
18
21
24
27
30
Time (months)
Grade ⩾3 CIN
Grade ⩾1 CIN
No CIN

C)


Grade ⩾3 CIN
Grade ⩾1 CIN
No CIN
Time to ECOG PS ⩾2 (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
30
Time (months)