Supplementary Material

Supplementary Tables

Supplementary Table S1. Number of patients who developed neutropenia on each administration date and the occurrence of delayed recovery

		Neutropenia Development	Delayed Recovery*
1st cycle	Day 8 (n=611)	131	26
	Day 15 (n=484)	136	0
2 nd cycle	Day 1 (n=341)	1	0
	Day 8 (n=312)	17	1
	Day 15 (n=293)	21	0
3 rd cycle	Day 1 (n=257)	1	0
	Day 8 (n=220)	8	0
	Day 15 (n=223)	12	0
4 th cycle	Day 1 (n=211)	_	_
	Day 8 (n=177)	14	0
	Day 15 (n=182)	8	0
5 th cycle	Day 1 (n=115)	_	_
	Day 8 (n=177)	5	2
	Day 15 (n=98)	4	0
6 th cycle	Day 1 (n=90)	_	_
	Day 8 (n=62)	2	0
	Day 15 (n=82)	4	_
Total		364	29

^{*}Delayed recovery was defined as a neutrophil count of $< 1,000 \,/\mu L$ on the scheduled initial dosing day after development in patients who experienced neutropenia.

Supplementary Table S2. Multivariate analysis exploring the risk factors for neutropenia using continuous variables

Variable	Odds ratio (95% CI)	p-value
Female	0.805 (0.428–1.515)	0.502
Age (years)	0.965 (0.939–0.992)	0.012
BSA	0.726 (0.114-4.620)	0.734
Dose reduction	1.329 (0.550–3.211)	0.528
Liver metastasis	1.315 (0.779–2.219)	0.305
Prior Tegafur Gimeracil Oteracil Potassium	0.680 (0.367–1.261)	0.221
Laboratory data on day 1		
of the first cycle		
RBC ($\times 10^3/\mu$ L)	0.974 (0.564–1.680)	0.924
PLT ($\times 10^3/\mu$ L)	0.997 (0.993–1.001)	0.206
Neutr ($\times 10^3/\mu$ L)	0.397 (0.301–0.524)	< 0.001
Lymph ($\times 10^3/\mu$ L)	0.804 (0.474–1.365)	0.419
ALP (U/L)	0.998 (0.997–1.000)	0.040
ALT (U/L)	0.998 (0.984–1.012)	0.753
UN (U/L)	0.987 (0.931–1.047)	0.671
CRP (mg/dL)	0.765 (0.503–1.164)	0.211

95% CI, 95% confidence interval; BSA, body surface area; RBC, red blood cell count; PLT, platelet count; Neutr, neutrophil count; Lymph, lymphocyte count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; UN, urea nitrogen; CRP, C-reactive protein

Supplementary Table S3. Chi-square test for exploring factors affecting delayed recovery: Pattern A

Variables	Delayed recovery (n=22)	Recovery (n=89)	p-value
$Age \ge 67$	14 (63.6%)	39(43.8%)	0.096
Laboratory data on day 1 of the first cycle			
RBC ($\times 10^3/\mu L$) < 3.98	20 (90.9%)	45 (50.6%)	< 0.001
PLT $(\times 10^3/\mu L)$ < 164	15 (68.2%)	17 (19.1%)	< 0.001
Neutr $(\times 10^3/\mu L) < 2.06$	16 (72.7%)	11 (12.4%)	< 0.001
Mono $(/\mu L)$ < 359.3	11 (57.9%) ^{†1}	38 (48.1%)†2	0.443
$ALP\left(U/L\right) \ge 196$	4 (18.2%)	23 (25.8%)	0.453
CRP $(mg/dL) \ge 0.08$	7 (31.8%)	56 (62.9%)	0.008
Laboratory data on day 8 of the first cycle			
RBC ($\times 10^3/\mu L$) < 3.87	21 (95.5%)	55 (61.8%)	0.002
PLT $(\times 10^3/\mu L)$ < 98	14 (63.6%)	13 (14.6%)	< 0.001
Neutr $(\times 10^3/\mu L) < 0.88$	21 (95.5%)	58 (65.2%)	0.005
Mono $(/\mu L)$ < 104.1	$14 (73.7\%)^{\dagger 1}$	$38 (48.1\%)^{\dagger 2}$	0.045
$ALP (U/L) \ge 295$	4 (18.2%)	33 (37.1%)	0.092
CRP $(mg/dL) \ge 0.96$	0 (0.0%)	17 (19.1%)	0.026
The range of decrease in number of neutrophils $(\times 10^3/\mu L) \ge 1.38$	7 (31.8%)	76 (85.4%)	< 0.001

Pattern A: The variables were converted to categorical variables using cut-off values by ROC curve analysis in the analyses of factors affecting delayed recovery. †1 N= 19, †2 N= 79. RBC, red blood cell; PLT, platelet count; Neutr, neutrophil count; Mono, monocyte count; ALP, alkaline phosphatase; CRP, C-reactive protein

Supplementary Table S4. Chi-square test for exploring factors affecting delayed recovery; Pattern B

Variable	Delayed recovery (n=22)	Recovery (n=89)	p-value
$Age \ge 63$	16 (72.7%)	53 (59.6%)	0.254
Laboratory data on day 1 of the first cycle			
RBC ($\times 10^3/\mu L$) < 3.92	17 (77.3%)	45 (50.6%)	0.024
PLT $(\times 10^3/\mu L) < 230$	19 (86.4%)	59 (66.3%)	0.065
Neutr $(\times 10^3/\mu L) < 3.60$	22 (100%)	71 (79.8%)	0.021
Mono $(/\mu L)$ < 418.5	$18 (94.7\%)^{\dagger 1}$	$50 (63.3\%)^{\dagger 2}$	0.076
$ALP (U/L) \ge 196$	15 (68.2%)	73 (82.0%)	0.152
CRP (mg/dL) \geq 0.25	2 (9.1%)	21 (23.6%)	0.133

Pattern B: Variables were converted to categorical variables using cutoff values by ROC curve analysis in the analyses of risk factors for neutropenia. $^{\dagger 1}$ N= 19, $^{\dagger 2}$ N= 79.

RBC, red blood cell count; PLT, platelet count; Neutr, neutrophil count; Mono, monocyte count; ALP, alkaline phosphatase; CRP, C-reactive protein

Supplementary Table S5. Chi-square test for exploring factors affecting delayed recovery; Pattern C

Variable	Delayed recovery (n=22)	Recovery (n=89)	p-value
Laboratory data on day 1 of the first cycle			
Neutr $(\times 10^3/\mu L) < 1.50$	3 (13.6%)	2 (2.2%)	0.021
Laboratory data on day 8 of the first cycle			
Neutr $(\times 10^3/\mu L) < 0.50$	8 (36.4%)	9 (10.1%)	0.002

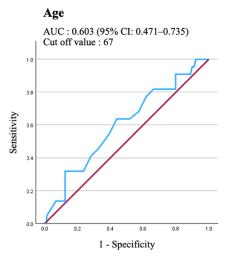
Pattern C: Neutrophil count less than 1,500/μL corresponds to grade 1 neutropenia in CTCAE v.5, and less than 500/μL corresponds to grade 4. Neutr, neutrophil count

Supplementary Figures

		1st cycle					2st cycle	
	day 1	8	15	22	1	8	15	
Gemcita	bine 🛧					•		
(1,000 mg	g/m2)							
(1,000 mg nab-pacli (125 mg	taxel /m2)	1	1		1	1		

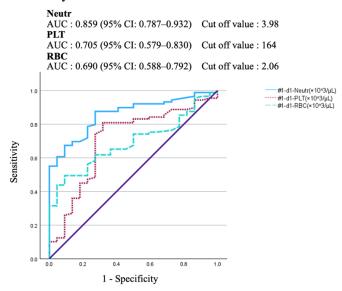
Supplementary Figure S1. Standard treatment schedule for gemcitabine plus nab-paclitaxel Laboratory data were obtained before drug administration

Supplementary Figures S2-11: Receiver operating characteristic curve for the analyses of factors affecting delayed recovery from neutropenia (Pattern A)



Supplementary Figure S2: A receiver operating characteristic curve of age AUC, area under the curve; CI, confidence interval; N= 111.

Day 1 Blood cell count data



Supplementary Figure S3: A receiver operating characteristic curve of blood cell count on day 1 of the first cycle

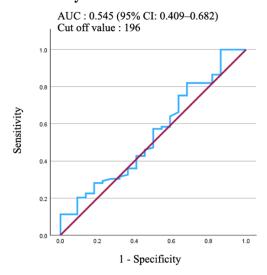
RBC, red blood cell count; PLT, platelet count; Neutr, neutrophil count; AUC, area under the curve; CI, confidence interval; N= 111.

Day 1 Mono AUC: 0.656 (95%CI: 0.522-0.789) Cut off value: 359.3

Supplementary Figure S4: A receiver operating characteristic curve of monocyte count on day 1 of the first cycle

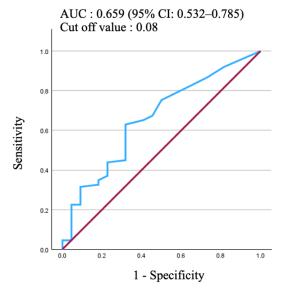
Mono, monocyte count; AUC, area under the curve; CI, confidence interval; N= 98.

Day 1 ALP



Supplementary Figure S5: A receiver operating characteristic curve of alkaline phosphatase on day 1 of the first cycle ALP, alkaline phosphatase; AUC, area under the curve; CI, confidence interval; N= 111.

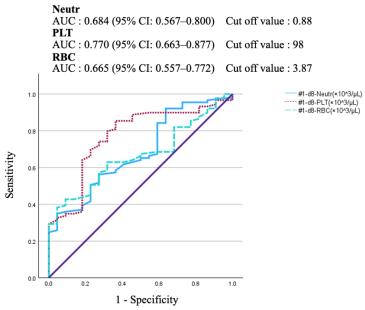
Day 1 CRP



Supplementary Figure S6: A receiver operating characteristic curve of C-reactive protein on day 1 of the first cycle

CRP, C-reactive protein; AUC, area under the curve; CI, confidence interval; N= 111.

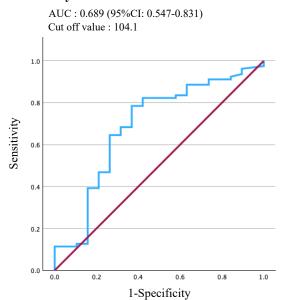
Day 8 Blood cell count data



Supplementary Figure S7: A receiver operating characteristic curve of blood cell count on day 8 of the first course

RBC, red blood cell count; PLT, platelet count; Neutr, neutrophil count; AUC, area under the curve; CI, confidence interval; N= 111.

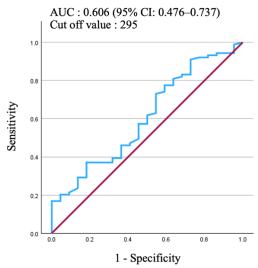
Day 8 Mono



Supplementary Figure S8: A receiver operating characteristic curve of monocyte count on day 8 of the first cycle

Mono, monocyte count; AUC, area under the curve; CI, confidence interval; N= 98.

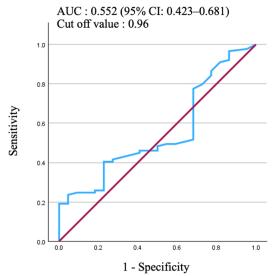
Day 8 ALP



Supplementary Figure S9: A receiver operating characteristic curve of alkaline phosphatase on day 8 of the first cycle

ALP, alkaline phosphatase; AUC, area under the curve; CI, confidence interval; N= 111.

Day 8 CRP

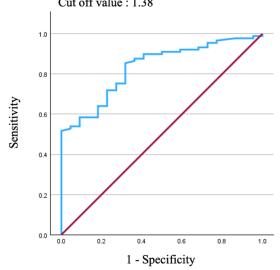


Supplementary Figure S10: A receiver operating characteristic curve of C-reactive protein on day 8 of the first cycle

CRP, C-reactive protein; AUC, area under the curve; CI, confidence interval; N= 111.

The range of decreased number of neutrophils

 $AUC: 0.832 \ (95\% \ CI: 0.750 – 0.915 \)$ Cut off value : 1.38



Supplementary Figure S11: A receiver operating characteristic curve of the range of decreased numbers of neutrophils

AUC, area under the curve; CI, confidence interval; N= 111.