APPENDIX

Supplemental Figure S1. Steps derived from the modified Hryniuk model (Lee et al.) for calculation of the cumulative relative dose intensity, for the combination (cmRDI) and for each FOLFIRINOX agent (csRDI).

Steps for calculating cmRDI

- Step 1. $sRDI = \frac{administered\ dose\ of\ single\ agent}{standard\ dose\ of\ single\ agent}$ x 100 (%)
- Step 2. mRDI = ($sRDI_{ox}$ + $sRDI_{ir}$ + $\frac{1 \times sRDIfb + 6 \times sRDIfc}{7}$) x $\frac{1}{3}$ (%)
- Step 3. Actual cumulative dose = ($\sum_{i=1}^{n-1} mRDI_i$) + $mRDI_n$ x $\frac{D_n}{14}$ (%)
- Step 4. Standard cumulative dose = $\frac{end\ date - start\ date}{14}$ x 100 (%)
- Step 5. cmRDI = $\frac{actual\ cumulative\ dose}{standard\ cumulative\ dose}$ x 100 (%)

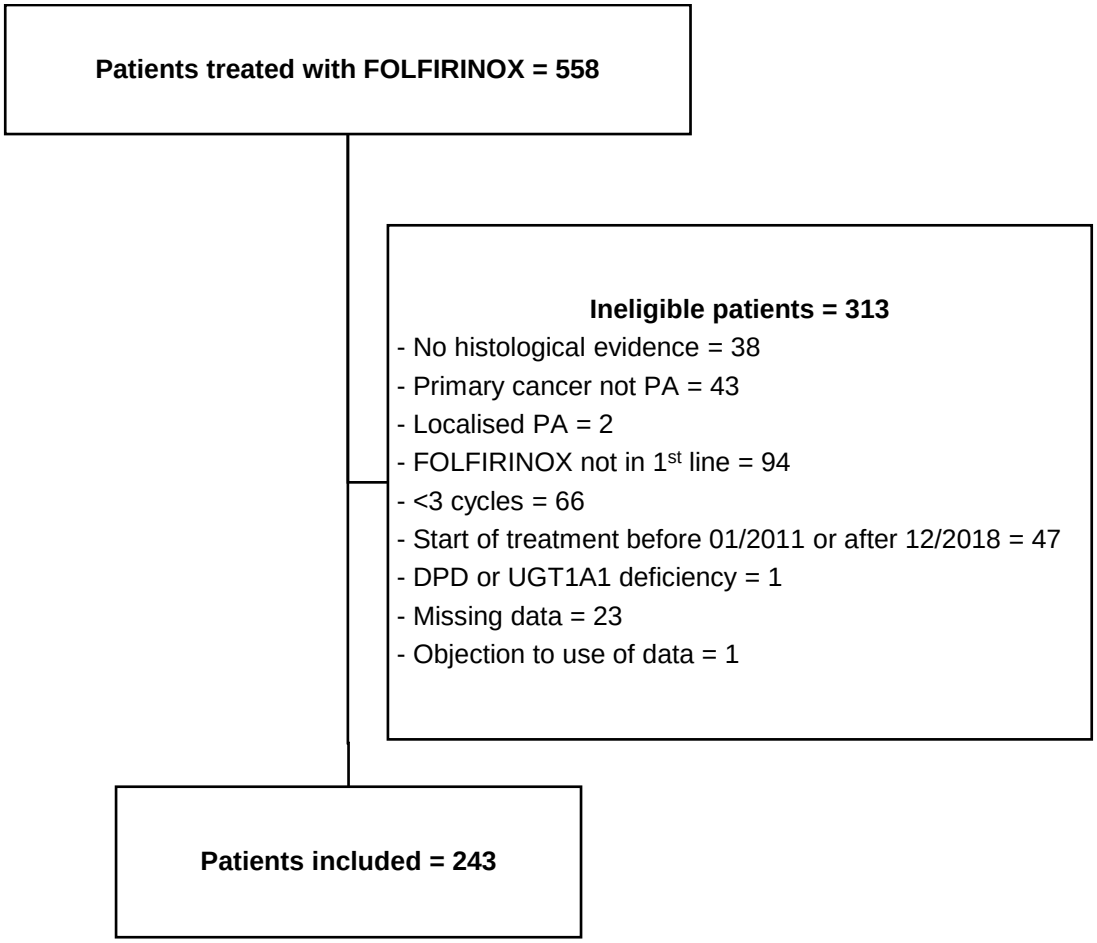
Steps for calculating csRDI

- Step 1. $sRDI = \frac{administered\ dose\ of\ single\ agent}{standard\ dose\ of\ single\ agent}$ x 100 (%)
- Step 2. Actual cumulative dose = ($\sum_{i=1}^{n-1} sRDI_i$) + $sRDI_n$ x $\frac{D_n}{14}$ (%)
- Step 3. Standard cumulative dose = $\frac{end\ date - start\ date}{14}$ x 100 (%)
- Step 4. csRDI = $\frac{actual\ cumulative\ dose}{standard\ cumulative\ dose}$ x 100 (%)

sRDI: single-agent relative dose intensity for a single cycle;
mRDI: multi-drug relative dose intensity for a single cycle;
ox: oxaliplatin; ir: irinotecan; fb: 5-FU bolus; fc: 5-FU continuous infusion;
csRDI: cumulative single-agent relative dose intensity;
cmRDI: cumulative multi-drug relative dose intensity.
n: number of the delivered cycles until the first tumor reassessment.
For the calculation of the actual cumulative dose, the RDI of the last cycle ($mRDI_n$ or $sRDI_n$) was weighted by the ratio of the time interval D_n divided by the standard 14-day cycle duration, where D_n is the time interval from the first day of the last cycle to the first tumor reassessment.
For the calculation of the "standard cumulative dose", we computed the time interval between the first day of the first cycle (C1J1) denoted "start date" and the date of the first day of the last cycle (CnJ1) plus 14 days (or the date of CT-scan if the tumor reassessment was performed before that date), denoted "end date".

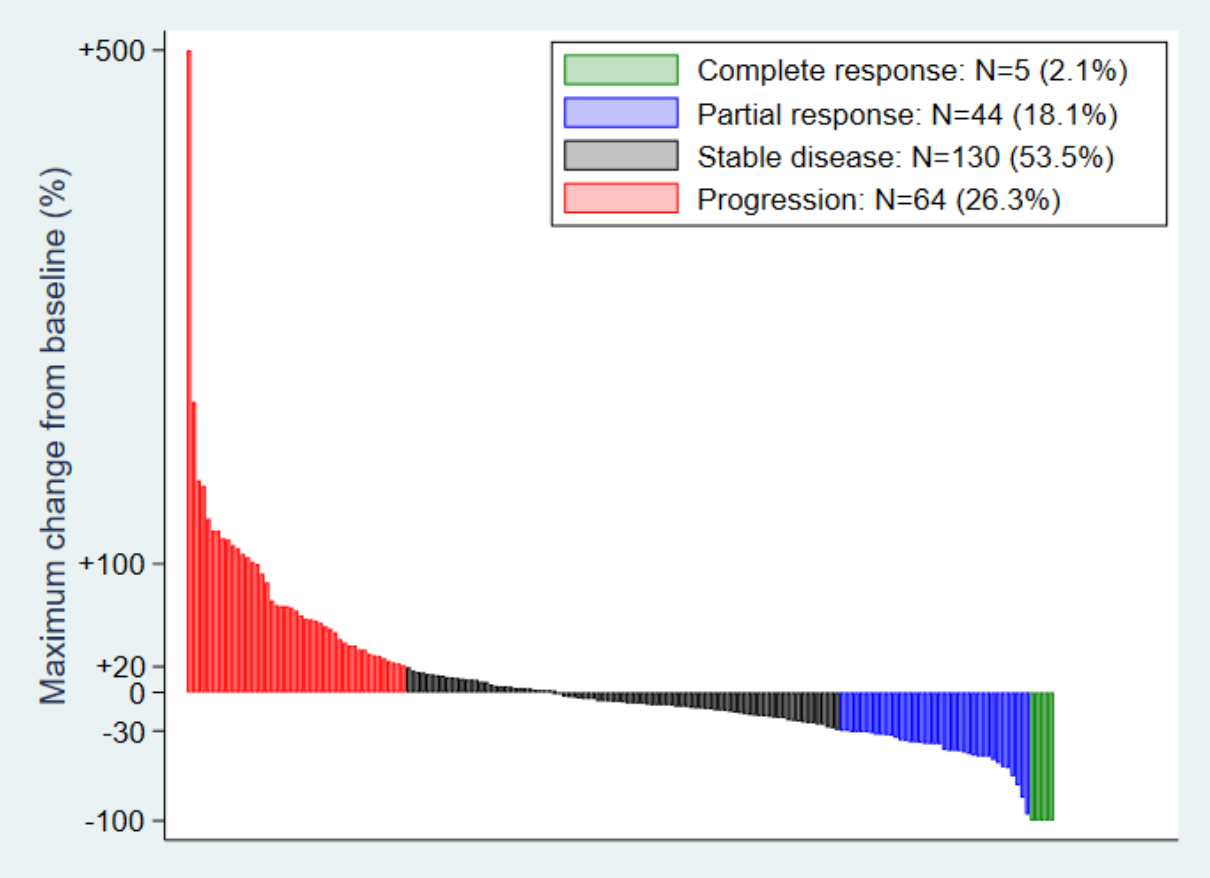
Results

Supplemental Figure S2. Patient selection flowchart.

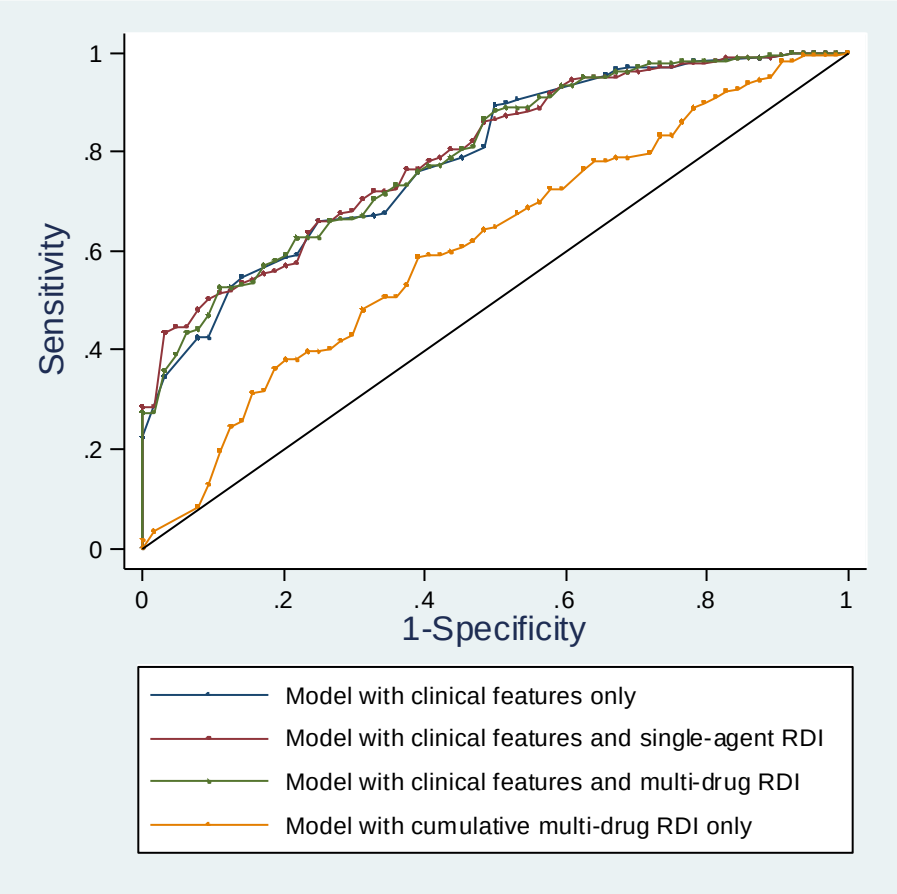


Abbreviations: PA, pancreatic adenocarcinoma; DPD, dihydropyrimidine dehydrogenase; UGT1A1, UDP-glycosyltransferase 1 polypeptide A1

Supplemental Figure S3. Waterfall plot of the depth of tumor response.



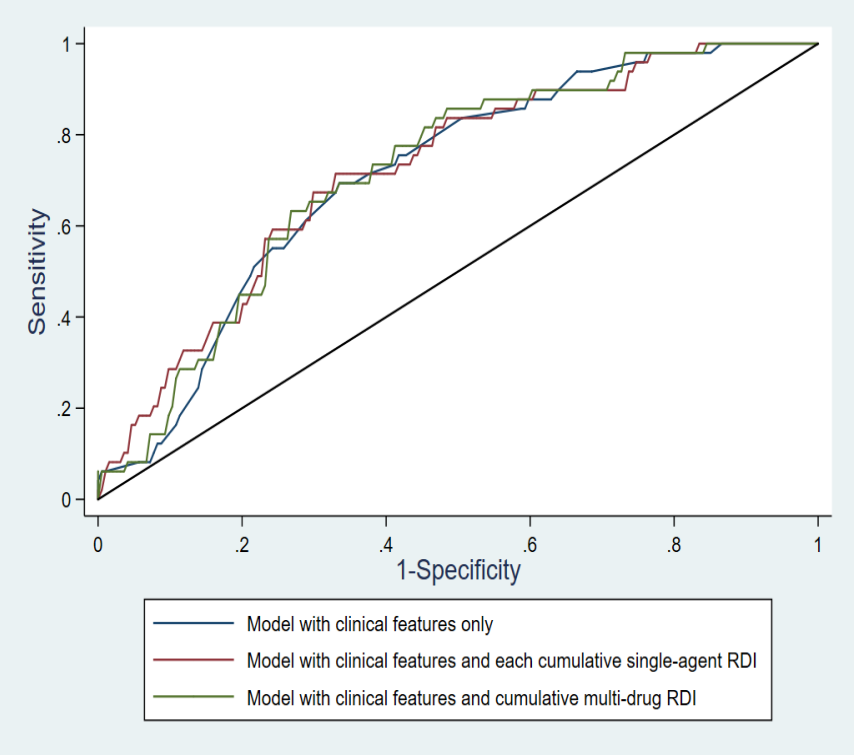
Supplemental Figure S4. ROC curve of disease control models. Models included 1) only the clinical characteristics of patients; 2) clinical characteristics and four csRDIs; 3) clinical characteristics and cmRDI; and 4) cmRDI only (univariate analysis). The multivariable models included ECOG performance status, liver metastasis, number of cycles before first assessment, and center,



- alone in model 1
- plus the csRDI of the four component agents (oxaliplatin, irinotecan, 5FU bolus, and 5FU continuous infusion) in model 2
- plus the cmRDI in model 3

ROC, receiver operating characteristic; csRDI, cumulative single-agent relative dose intensity; cmRDI, cumulative multi-drug relative dose intensity.

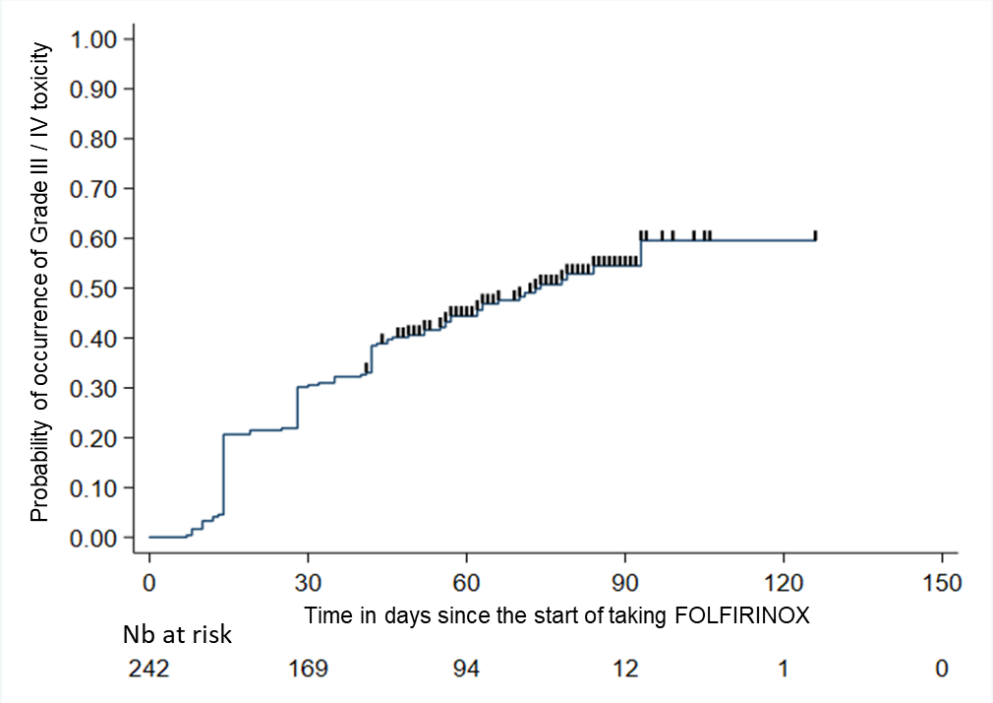
Supplemental Figure S5. ROC curve of objective response. Models including 1) only clinical characteristics of patients, 2) clinical characteristics and four csRDIs, 3)clinical characteristics and cmRDI. The multivariable models include ECOG, liver metastasis, number of cycles before first reassessment and center



- alone in model 1,
- plus the csRDI of the four components agents (oxaliplatin, irinotecan, 5FU bolus and 5FU continuous infusion) in model 2
- plus the cmRDI in model 3

ROC, receiver operating characteristic; csRDI, cumulative single-agent relative dose intensity; cmRDI, cumulative multi-drug relative dose intensity.

Supplemental Figure S6. Cumulative probability of occurrence of Grade III/IV toxicity from the date of initiation of treatment with FOLFIRINOX estimated by means of a 1 - Kaplan-Meier curve as a function of time (in days).



Patients who did not develop toxicity were censored on the date of reassessment. N = 242, because 1 patient in the study did not undergo an imaging reassessment due to clinical progression.

Supplemental Table S1. Cumulative relative dose intensity per agent and overall (N = 243).

Cumulative relative dose intensity	csRDI Oxaliplatin	csRDI Irinotecan	csRDI 5FU bolus	csRDI 5FU continuous infusion	cmRDI FOLFIRINOX
≤10%	0 (0.0%)	1 (0.4%)	15 (6.2%)	0 (0.0%)	0 (0.0%)
10–20%	0 (0.0%)	4 (1.2%)	13 (5.3%)	0 (0.0%)	0 (0.0%)
20–30%	1 (0.4%)	2 (0.8%)	9 (3.7%)	1 (0.4%)	1 (0.4%)
30–40%	3 (1.2%)	3 (1.2%)	6 (2.5%)	0 (0.0%)	0 (0.0%)
40–50%	8 (3.3%)	14 (5.8%)	13 (5.3%)	9 (3.7%)	12 (4.9%)
50–60%	20 (8.2%)	16 (6.6%)	17 (7.0%)	13 (5.3%)	17 (7.0%)
60–70%	27 (11.1%)	35 (14.4%)	28 (11.5%)	28 (11.5%)	37 (15.2%)
70–80%	60 (24.7%)	51 (21.0%)	37 (15.2%)	55 (22.6%)	52 (21.4%)
80–90%	44 (18.1%)	45 (18.5%)	34 (14.0%)	43 (17.7%)	50 (20.6%)
>90%	80 (32.9%)	72 (29.6%)	71 (29.2%)	94 (38.7%)	74 (30.5%)

Abbreviations: csRDI, cumulative single-agent relative dose intensity; cmRDI, cumulative multi-drug relative dose intensity.

Supplemental Table S2. Clinical factors associated with disease control rate in the entire population.

	Complete model (N=203)			Final model (N=243)		
Characteristics	**Adjusted OR**	**95% CI adjusted OR**	**Adjusted p-value**	**Adjusted OR**	**95% CI adjusted OR**	**Adjusted p-value**
ECOG PS			0.008			0.002
1	0.30	(0.12–0.73)		0.29	(0.13–0.63)	
0	1 (ref)			1 (ref)		
Hepatic metastasis			0.11			0.004
Yes	0.52	(0.25–1.15)		0.35	(0.17–0.72)	
No	1 (ref)			1 (ref)		
CA19-9 (MD = 40) before FOLFIRINOX*			0.23	-		
OR / ln	0.85	(0.65–1.11)				
Number of cycles before first reassessment			<0.0001			<0.0001
OR / 1 cycle	2.36	(1.52–3.66)		2.31	(1.55–3.47)	
Center			0.01			0.02
Center 1	1 (ref)			1 (ref)		
Center 2	0.65	(0.21–1.97)		0.49	(0.17–1.39)	
Center 3	0.32	(0.07–1.50)		0.40	(0.09–1.67)	
Center 4	0.16	(0.04–0.64)		0.17	(0.05–0.59)	
Center 5	1.84	(0.50–6.84)		1.31	(0.43–4.03)	
Center 6	4.96	(0.99–24.6)		2.31	(0.68–7.86)	

Abbreviations: OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CA19-9, carbohydrate antigen 19-9; MD, Missing data.

*We performed a logarithmic transformation of this variable before studying its relationship with disease control rate due to the very high values obtained in some patients.

Supplemental Table S3. Factors associated with the depth of tumor response in the entire population.

	Depth of tumor response		
Characteristics	**Regression coefficient**	**95% CI**	**p-value**
cmRDI of FOLFIRINOX (/10%)	-2.88	(-9.2–3.40)	0.367
ECOG PS			0.245
1	12.0	(-8.3–32.4)	
0	0 (ref)		
Hepatic metastasis			0.360
Yes	9.2	(-10.6–28.9)	
No	0 (ref)		
Number of cycles before first reassessment			0.10
/ 1 cycle	-10.1	(-22.1–1.84)	
Center			0.13
Center 1	0 (ref)		
Center 2	4.57	(-26.6–35.7)	
Center 3	42.2	(0.02–84.8)	
Center 4	31.7	(-7.50–70.9)	
Center 5	-4.50	(-37.3–28.3)	
Center 6	-14.5	(-49.5–20.6)	

Abbreviations: CI, confidence interval; cmRDI, cumulative multi-drug relative dose intensity; ECOG, Eastern Cooperative Oncology Group; PS performance status.

The regression coefficients, confidence intervals and p-values were estimated from in the model including cmRDI, ECOG performance status, presence of liver metastasis, number of cycles before first reassessment and center.

Supplemental Table S4. Association between the cumulative relative dose intensity of FOLFIRINOX and progression-free survival in the entire population.

	All patients (N=243)		
Relative dose intensity	**Adjusted HR***	**95% CI adjusted HR***	**Adjusted p-value***
HR / 10%			
csRDI oxaliplatin	1.06	(0.85–1.31)	0.58
csRDI irinotecan	0.98	(0.86–1.13)	0.83
csRDI 5FU bolus	1.04	(0.97–1.11)	0.19
csRDI 5FU continuous infusion	0.93	(0.72–1.20)	0.56
cmRDI of FOLFIRINOX	1.02	(0.93–1.13)	0.67

Abbreviations: HR, Hazard ratio; CI, confidence interval; csRDI, cumulative single-agent relative dose intensity; cmRDI, cumulative multi-drug relative dose intensity.

*The hazard-ratios, confidence intervals and p-values were estimated in models adjusted for ECOG performance status, presence of liver metastases, number of cycles before first reassessment and center.

Supplemental Table S5. Association between the cumulative relative dose intensity of FOLFIRINOX and overall survival in the entire population.

	All patients (N=243)		
Relative dose intensity	**Adjusted HR***	**95% CI adjusted HR***	**Adjusted p-value***
HR / 10%			
csRDI oxaliplatin	1.02	(0.83–1.25)	0.83
csRDI irinotecan	0.96	(0.84–1.08)	0.49
csRDI 5FU bolus	1.03	(0.97–1.10)	0.34
csRDI 5FU continuous infusion	0.99	(0.77–1.27)	0.95
cmRDI of FOLFIRINOX	0.99	(0.90–1.11)	0.99

Abbreviations: HR, Hazard ratio; CI, confidence interval; csRDI, cumulative single-agent relative dose intensity; cmRDI, cumulative multi-drug relative dose intensity.

*The hazard-ratios, confidence intervals and p-values were estimated in models adjusted for ECOG performance status, presence of liver metastases, number of cycles before first reassessment and center.

Supplemental Table S6. Grade III or IV toxicities occurring with FOLFIRINOX in the entire population (N = 243).

Characteristics	N	%
Grade III or IV toxicity		
No	125	51.4%
Yes	118	48.6%
Nature of toxicity		
Deterioration in overall health/fatigue	45	18.5%
Neutropenia (febrile or not)	61	25.1%
Febrile neutropenia	15	6.2%
Thrombocytopenia	5	2.1%
Anaemia	5	2.1%
Gastrointestinal disorders	40	16.5%
Mucositis	3	1.2%
Peripheral neuropathy	4	1.6%
Thrombosis	9	3.7%