Additional file 2. Chemotherapy administration

FOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute intravenous infusion. This treatment will immediately be followed by fluorouracil at a dose of 400 mg/m2, administered by intravenous bolus, followed by a continuous infusion of 2400 mg/m2 over a 46-hour period every two weeks. In total, patients will receive 8 cycles of FOLFIRINOX after randomization.

The regimen of nab-paclitaxel/gemcitabine consists of a 30-to-40-minute intravenous infusion of nab-paclitaxel at a dose of 125 mg/m2, followed by a 30-minute infusion of gemcitabine at a dose of 1000 mg/m2, on days 1, 8 and 15 every four weeks. After randomization patients will receive four cycles.

The gemcitabine cycle consists of a 30-minute intravenous infusion of gemcitabine at a dose of 1000 mg/m2 on day 1, 8 and 15 followed by one week of rest. Patients will be treated with four cycles after randomization.

All patients receive prophylactic anti-emetics.

Modifications in the FOLFIRINOX regimen in case of deviations in neutrophils, platelets, renal and liver function

	Irinotecan	Oxaliplatin	5FU
Neutrophils			
1 st x low neutrophils,	Reduce to	Full dose	Omit bolus
febrile neutropenia	150 mg/m^2		
or < 0.5 more than 7			
days			
2nd x	Maintain	Reduce to 60 mg/m ²	Omit bolus

abovementioned	150 mg/m ²		
3 rd x		Stop treatment	
abovementioned			
Platelets			
1 st x platelets < 75	Full dose	Reduce to 60 mg/m ²	Reduce bolus and
*10 ⁹ /L			continuous infusion
			to 75%
2 nd x platelets < 75	Reduce to 150	Maintain	Reduce bolus and
*10 ⁹ /L	mg/m ²	60 mg/m^2	continuous infusion
			to 75%
3 rd x platelets < 75		Stop treatment	
*10 ⁹ /L			
Renal function			
Creat clearance	75%	100%	Reduce bolus and
>20 450 ml/min			continuous infusion
≥30 – <50 ml/min			to 75%
Creatinine clearance	50%	No oxaliplatin	50%
< 30 ml/min			
Liver function			
bilirubine 1.5 – 3 x	50%	100%	100%
ULN, transaminasen> 5			
x ULN			
Bilirubine> 3 x ULN	Non irinotecan	50%	50%

Stepwise dose reduction for nab-paclitaxel/gemcitabine

Dose level	Nab-paclitaxel (mg/m²)	Gemcitabine (mg/m²)
Full dose	125	1000
1 st step dose reduction	100	800
2 nd step dose reduction	75	600
When further dose reduction is necessary	Stop treatment	Stop treatment

Dose reductions for nab-paclitaxel/gemcitabine in case of neutropenia or thrombocytopenia.

Day of each cycle	Nab-paclitaxel	Gemcitabine

Day 1			
ANC < 1.5x10 ⁹ / L	Delay by 1 week intervals until recovery		
OR platelets < 100x10 ⁹ /L	,		
Day 8			
500 ≤ ANC < 1000 OR 50.000 ≤	Reduce dose with 1 step		
platelets < 75.000			
ANC < 500 OR platelets <	Hold dose		
50.000			
Day 15: If day 8: full dose was given			
500 ≤ ANC < 1000 OR 50.000 ≤	Add WBC growth factors to treatment OR decrease dose with		
platelets < 75.000	1 step		
•	·		
ANC < 500 OR platelets <	Hold dose Hold dose		
50,000			
Day 15: If day 8: dose reduction			
ANC ≥ 1000 AND platelets ≥	Return to dose given at day 1 + WBC growth factors OR same		
75,000			
73,000	dose as day 8		
500 ≤ ANC < 1000 OR 50.000 ≤	Same dose as day 8 + WBC growth factors OR reduce dose		
platelets < 75.000	with 1 step compared to day 8		
<u> </u>	<u> </u>		
ANC < 500 or platelets <	Hold dose		
50,000			
Day 15: if day 8: dose was hold			
ANC ≥ 1000 and platelets ≥	Return to dose given at day 1 + WBC growth factors OR		
75,000	reduce with 1 step compared to day 1		
500 ≤ ANC < 1000 OR 50.000 ≤	Reduce dose with 1 step + WBC growth factors OR Reduce		
platelets < 75.000	dose with two steps compared to day 1		
ANC . 500			
ANC < 500 or platelets <	Hold dose		
50,000			

Dose reductions for nab-paclitaxel/gemcitabine in case of other forms of toxicities

Complication	Nab-paclitaxel	Gemcitabine
Grade 3 or 4 peripheral neuropathy	Hold dose until recovery to at least ≤ grade 1; resume dose reduced with one step.	Treat with the same dose as before
Grade 2 or 3 cutaneous toxicity	Reduce dose with one step; stop treatment when toxicity persists	
Gastro-intestinal toxicity: grade 3 mucositis or diarrhea	Hold dose until recovery to \leq grade 1; resume dose reduced with one step.	

Dose modifications of gemcitabine

Absolute Neutrophil Count (10 ⁹ /L)		Platelets (10°/L)	Gemcitabine dose (%)
> 1.5	AND	> 75	100
≥ 1.0 - < 1.5	AND	> 50 - <75	75
< 1.0	OR	< 50	Postponed