

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

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

Stepwise dose reduction for nab-paclitaxel/gemcitabine

Dose level	Nab-paclitaxel (mg/m ²)	Gemcitabine (mg/m ²)
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
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Complication	Nab-paclitaxel	Gemcitabine
Grade 3 or 4 peripheral neuropathy	Hold dose until recovery to at least \leq 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 ($10^9/L$)	Gemcitabine dose (%)
> 1.5	AND	> 75	100
≥ 1.0 - < 1.5	AND	> 50 - < 75	75
< 1.0	OR	< 50	Postponed