Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

SUPPLEMENTARY APPENDIX

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Supplementary Text 1

Dosage adjustment guidelines for toxicities

All dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 3.0).

I. Dosage adjustment guidelines for toxicities in the FOLFIRINOX arm

The dose of leucovorin is not modified for toxicity, but is omitted if fluorouracil is omitted. Once a dose is decreased, re-escalation is not permitted. Patients are off study if they develop the same grade 4 toxicity despite a first dose reduction.

1. Hematologic toxicity

Do not retreat until the granulocyte count is ≥ 1.5 x 10^9/L and the platelet count is ≥ 75 x 10^9/L.

1a. Doses according to the blood counts at the beginning of a cycle (Day 1)

Blood counts at Day 1	**DELAY OF CYCLE**	**DOSES REDUCTION**		
		Irinotecan	**Oxaliplatin**	Fluorouracil
Granulocytes < 1.5 x 10^9/L	Hold treatment until granulocytes ≥ 1.5 x 10^9/L (one or two weeks if necessary). In case of non recovery after 2 weeks delay, stop treatment*	1st occurrence: reduction of dose to 150 mg/m² 2nd occurrence: maintain the dose at 150 mg/m² 3rd occurrence: treatment discontinuation	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose to 60 mg/m2 3rd occurrence: treatment discontinuation	1st occurrence: delete bolus 5FU
Platelets < 75 x 10^9/L	Hold the treatment until recovery (platelets ≥75 x 10^9/L).	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose	1st occurrence: reduce the dose to 60 mg/m² 2nd occurrence: maintenance of	1st occurrence: reduce both the bolus and the continuous infusion to 75% of the original doses

	In case of non recovery after 2 weeks delay, stop treatment	to 150 mg/m² 3rd occurrence: treatment discontinuation	the reduced dose 3rd occurrence: treatment discontinuation	

1b. According to the low nadir blood counts or in case of infection

ADVERSE EVENTS	**REDUCTION OF DOSE FOR SUBSEQUENT CYCLES**
Febrile neutropenia **Grade 4 neutropenia during more than 7 days** **Infection with concomitant grade 3-4 neutropenia**	1st occurrence: reduce the dose of irinotecan to 150 mg/m² and delete the bolus 5FU dose 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m² 3rd occurrence: treatment discontinuation
Grade 3-4 thrombocytopenia	1st occurrence: reduce the oxaliplatin dose to 60 mg/m² and the continuous 5-FU dose to 75 % of the original dose

	2nd occurrence: reduce also the dose of irinotecan to 150 mg/m^2 and the dose of continuous 5FU of additional 25 % 3rd occurrence: treatment discontinuation

Consider the use of Filgrastim for recurrent grade 3/4 neutropenia despite a first-dose reduction or after febrile neutropenia.

2. Gastrointestinal toxicities

Patients must be instructed in the use of loperamide as treatment for diarrhea, and must have a supply of this drug upon starting FOLFIRINOX. Patients should not be retreated with irinotecan until recovery from diarrhea (without loperamide for at least 24 h) has occurred.

ADVERSE EVENTS	**REDUCTION OF DOSE FOR SUBSEQUENT CYCLES**
Diarrhea grade 3-4 **or** **Diarrhea + fever** **and/or** **neutropenia grade 3-4**	1st occurrence: reduce the irinotecan dose to 150 mg/m^2 and delete the bolus 5FU dose 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m² and reduce the dose of continuous 5FU to 75 % of the original dose

	3rd occurrence: treatment discontinuation
Diarrhea ≥ 48 h despite high doses loperamide	No systematic reduction of the irinotecan, oxaliplatin or 5FU doses after complete recovery, unless grade 3-4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3-4

3. Mucositis or "hand-foot" syndrome

In case of grade 3-4 toxicity, a reduction in dosages of 25% of both bolus 5FU and of continuous 5FU will be carried out for the subsequent cycles.

4. Cardiac toxicity

In case of angina pectoris or of myocardial infarction, 5FU has to be stopped.

5. Increase of bilirubin

In case of elevation of bilirubin, it is suggested to exclude an obstruction of the biliary stent or a progressive disease and to postpone chemotherapy. If bilirubin is >1.5xULN, irinotecan is not recommended. If chemotherapy is medically indicated, it is necessary to provide a dose adjustment of irinotecan.

6. Other toxicities

Any other toxicity ≥ grade 2, except anemia and alopecia, can justify a reduction of dose if medically indicated, for example reduction of irinotecan to 150 mg/m² and/or oxaliplatin to 60mg/m² and/or 5FU of 25% depending of the type of adverse event.

II. Gemcitabine dosage adjustment guidelines for toxicities

1. Doses according to the blood counts prior to each dose

Blood counts on the day of therapy	DELAY OF CYCLE	DOSES REDUCTION
Granulocytes > 1.0 x 10^9/L **and** platelets > 100 x 10^9/L	No delay	No dose reduction
0.5 < Granulocytes ≤ 1.0 x 10^9/L **or** 50.0 x 10^9/L < platelets ≤ 100 x 10^9/L	No delay	Reduce the dose to 75% of the original dose
Granulocytes ≤ 0.5 x 10^9/L **or** platelets ≤ 50.0 x 10^9/L	Hold treatment until granulocytes ≥ 0.5 x 10^9/L **and** platelets > 50.0 x 10^9/L	No dose reduction

2. Other toxicities

Any other toxicity ≥ grade 2, except anemia and alopecia, can justify a reduction of dose of 25% if medically indicated.

Supplementary Text 2.

Summary of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

1. ELIGIBILITY

Measurable disease: lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable disease: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan),i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, abdominal masses that are not confirmed and not followed by imaging techniques and cystic lesions.

2. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Computed tomography (CT)/MRI - CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

3. BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

Target lesions: All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 10 lesions should be selected on the basis of their size (longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. If there are > 10 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

4. EVALUATION OF BEST OVERALL RESPONSE

In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria as outline below:

Complete response (CR): disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*).

Partial response (PR): at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

Progressive disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment

started or the appearance of one or more new lesions. Appearance of new lesions will also constitute PD.

Stable disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category also requires**
CR	CR	No	CR	≥4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once > 6 weeks from baseline
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	No prior SD, PR or CR
Any	Any	Yes	PD	

Every effort should be made to document the objective progression even after discontinuation of treatment

Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented.

Stable disease duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Supplementary Text 3.

Sample size determination – Statistical methods

Phase 2

The sample size was calculated using a multi-stage Fleming design (3 stages) [Fleming 1982] to reject a 10% response rate in favor of a target response rate of 24% for the FOLFIRINOX group, with a significance level of 0.05 and a power of 92%. In the initial stage, a total of 20 evaluable patients were to be included and evaluated for response. If there were less than 3 responses, accrual was to be terminated. If more than 2 responses were observed in the first stage, then 10 additional patients were to be included in the second stage to achieve a target sample size of 30 evaluable patients in the FOLFIRINOX group. Further accrual of 10 patients was planned if more than 4 responses were observed in the first 30 patients in the FOLFIRINOX group. A sample size of 80 patients (40 patients per study group) was needed. Assuming 5% of the patients would not be evaluable, 44 patients were planned to be randomly assigned to each treatment group. The trial was planned to continue as a phase 3 study to demonstrate an improvement in overall survival if more than 11 responses were observed in the first 40 evaluable patients randomized in the FOLFIRINOX group.

Phase 3

The study was initially designed to have 80% power to detect an increase in survival rate at 6 months from 50% to 65%, respectively, for the gemcitabine and the FOLFIRINOX groups, respectively. To meet this hypothesis the sample size would have to include 260 patients (α risk 5%, β risk 20%). In 2008, based on unexpected rapid patient accrual (9 patients/month) and previous negative studies, the Independent Data Monitoring Committee (IDMC) suggested (before any analysis) to postpone the interim analysis and to increase the sample size to 360 patients to reach 250 events required to demonstrate an increase in median overall survival from 7 to 10 months (HR=0.70) based on the use of the log-rank test with a two-sided significance level of 5 % and a power of 80%. Interim analysis was planned after the observation of 2/3 of required events (167 events).

With the interim analysis results among the first 250 monitored patients, the IDMC (on 30 September 2009) recommended that patient accrual stop as the primary objective had been met (P <0.001).

References

Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38:143-51.

Supplementary Text 4

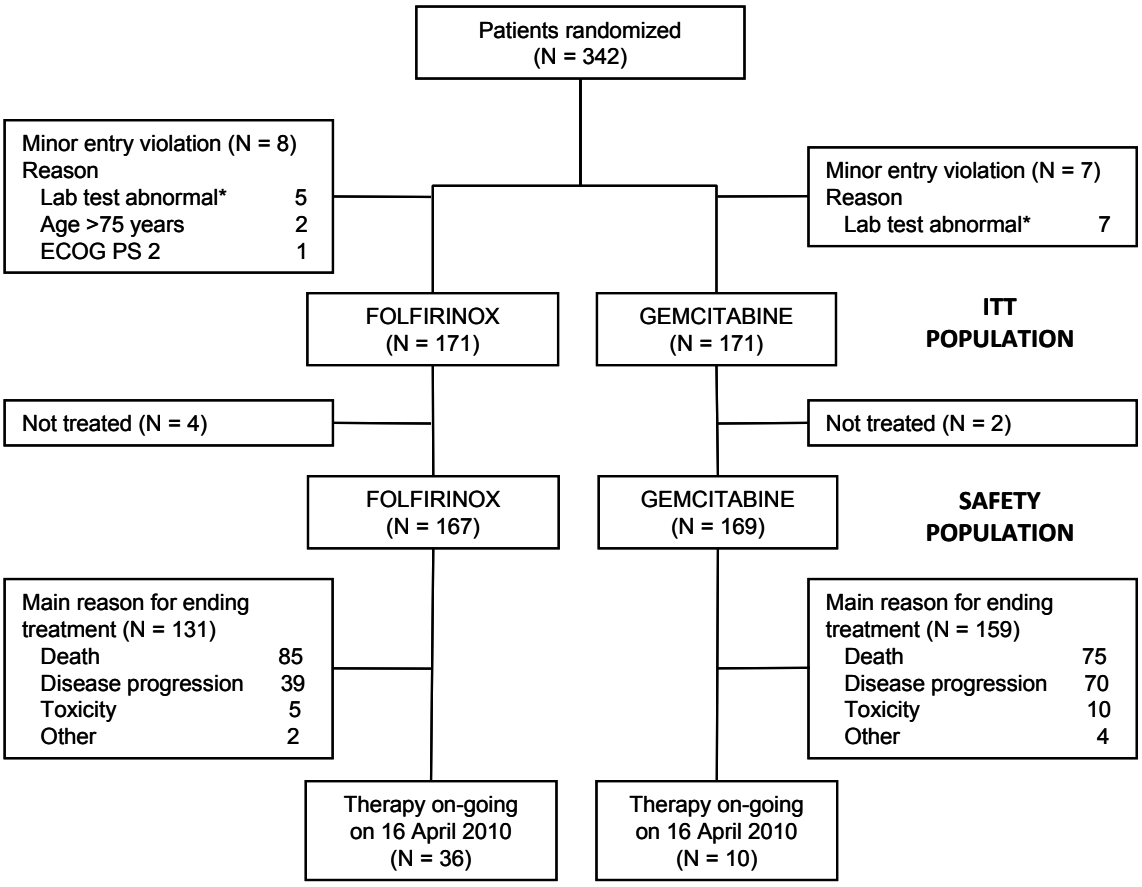
Univariate and multivariate analyses

Univariate analysis were performed to identify potential prognostic factors using stratified log-rank test among the following baseline characteristics: ECOG performance status, age, sex, primary tumor location, number of metastatic sites, timing of metastases (synchronous vs. metachronous), hepatic and pulmonary metastases, baseline albumin level, CEA and CA 19-9 levels.

ECOG performance status 1, male gender, body or tail primary tumor, synchronous metastases, presence of hepatic metastases, low baseline albumin (<3.5g/dL) level and abnormal CEA level were identified as adverse independent prognostic factors.

Synchronous metastases (hazard ratio 2.47; 95% CI, 1.30 to 4.69; P<0.003), hepatic metastases (hazard ratio 1.58; 95% CI, 0.99 to 2.49; P=0.051), low baseline albumin level (<3.5g/dL) (hazard ratio 1.85; 95% CI, 1.38 to 2.48; P<0.001), and age >65 years (hazard ratio 1.47; 95% CI, 1.07 to 2.02, p = 0.019) were identified as independent prognostic factors for overall survival, using the Cox regression model stratified on ECOG performance status and location of primary tumor and adjusted on pulmonary metastases. The hazard ratio for FOLFIRINOX treatment adjusted for these variables remains statistically significant (adjusted hazard ratio 0.54, 95% CI, 0.40 to 0.71, P<0.001).

Supplementary Figure I. Patient Flow Chart



*High bilirubin, high creatinine, or low platelets.

Supplementary Figure II. Kaplan–Meier estimates for the time until definitive deterioration of Global Health Status/Quality of Life (minimal clinically important difference of 10 points): At 3 and 6 months, 31% and 66% of the patients in the gemcitabine group had a definitive degradation of the Global Health Status/Quality of Life versus 17% and 31% in the FOLFIRINOX group respectively. The median time until definitive deterioration was not reached in the FOLFIRINOX group and was 5.7 months in the gemcitabine group (hazard ratio for risk reduction of 0.47; 95% CI, 0.30 to 0.74; P <0.001).