Club Français du Pancréas

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Ramsay Générale de Santé

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FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer

The CONKO-001 Randomized Trial

	Gemcitabine	Observation
DFS (mois)	13.4	6.7
SG (médiane)	22.8	20.2
SG 5 ans (%)	20.7	10.4

JAMA. 2013;310(14):1473-1481. doi:10.1001/jama.2013.279201

Adjuvant 5-fluorouracil and folinic acid *vs* observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials

	5 Fluorouracile	Observation
SG (médiane)	23.2	16.8
SG 5 ans (%)	24	14

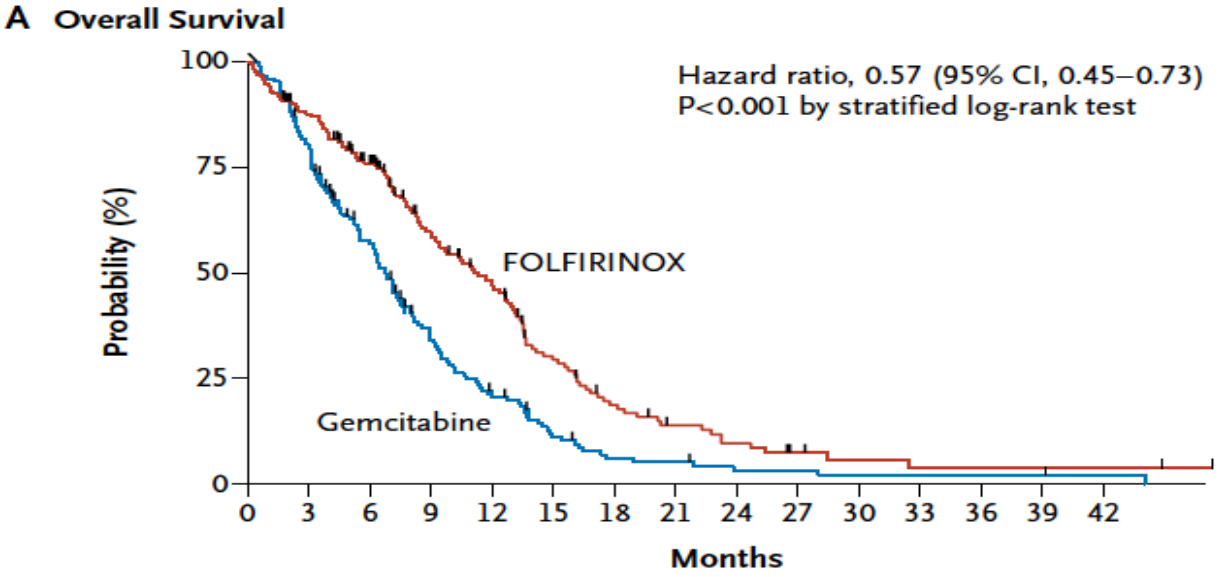
British Journal of Cancer (2009) 100, 246–250

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

Lancet 2017; 389: 1011–24

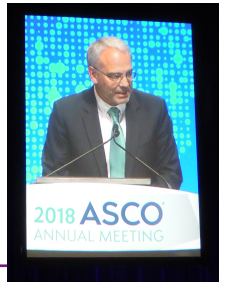
ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer



	FOLFIRINOX	Gemcitabine
SG (médiane, mois)	11.1	6.8
SG 12 mois (%)	48.4	20.6

PRODIGE 24 : TT adjuvant du cancer du pancréas réséqué : FOLFIRINOX *vs* gemcitabine



- Gemcitabine et/ou fluoropyrimidine (6 mois) : **standard en adjuvant**
  Oettle JAMA 2013, Neoptolemos JAMA 2010, Neoptolemos Lancet 2017
- FOLFIRINOX : **standard en 1ère ligne métastatique** Conroy NEJM 2011

– Résection R0 ou R1
– CA19-9 <180 U/mL dans les 12 semaines après la chirurgie
– Scanner post-opératoire requis.

Stratification :
– Centre
– Marge de résection (R0 vs R1)
– CA19-9 (≤90 U/mL vs 91-179 U/mL)
– pN0 (<12 vs ≥12 ganglions examinés) vs pN1

R **n = 493**
1:1

mFOLFIRINOX
- Oxaliplatine 85mg/m²
- LV 400mg/m²
- Irinotecan 180mg/m²,*
- 5 FU continu 2,4g/m² sur 46 heures
- Toutes les 2 semaines, 12 cycles

***Réduit à 150 mg/m² après le patient 162**

GEMCITABINE
1000mg/m²
3 semaines /4, 6 cycles

Pour les deux bras :
- **CT scans : tous les 3 mois**
- **6 mois de chimiothérapie**

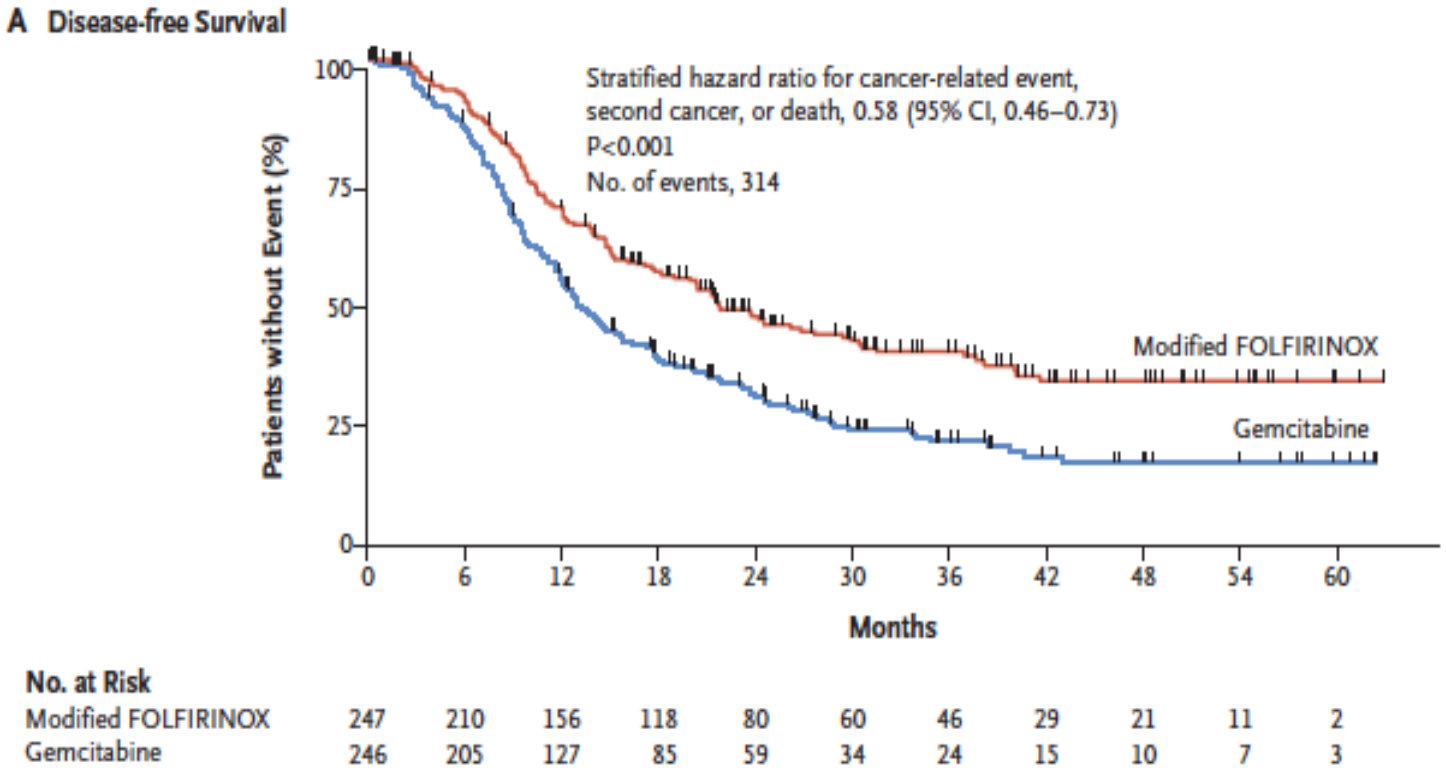
Objectif principal : **survie sans maladie à 3 ans**

T. Conroy, *et al.*, ASCO® 2018, Abs #4001 ; NEJM 2018

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)
Age		
Median (range) — yr	63 (30–79)	64 (30–81)
≥70 yr — no. (%)	47 (19.0)	54 (22.0)
Male sex — no. (%)	142 (57.5)	135 (54.9)
WHO performance-status score — no./total no. (%)†		
0	122/245 (49.8)	127/242 (52.5)
1	123/245 (50.2)	115/242 (47.5)
Status of surgical margins — no. (%)‡		
R0	148 (59.9)	134 (54.5)
R1	99 (40.1)	112 (45.5)
Tumor histologic findings — no./total no. (%)		
Ductal adenocarcinoma	244/247 (98.8)	242/245 (98.8)
Nonductal carcinoma	3/247 (1.2)	3/245 (1.2)
Tumor stage — no. (%)§		
I	12 (4.9)	14 (5.7)
IIA	43 (17.4)	47 (19.1)
IIB	183 (74.1)	179 (72.8)
III	1 (0.4)	1 (0.4)
IV	8 (3.2)	5 (2.0)
Lymphovascular invasion — no./total no. (%)	154/209 (73.7)	135/214 (63.1)
Perineural invasion — no. (%)	205/221 (92.8)	207/231 (89.6)
Surgery		
Venous resection — no./total no. (%)	53/245 (21.6)	69/245 (28.2)
Portal-vein resection — no. (%)	32 (13.0)	42 (17.1)
Superior-mesenteric-vein resection — no. (%)	19 (7.7)	25 (10.2)
Arterial resection — no./total no. (%)	8/247 (3.2)	7/245 (2.9)

Résultats : DFS

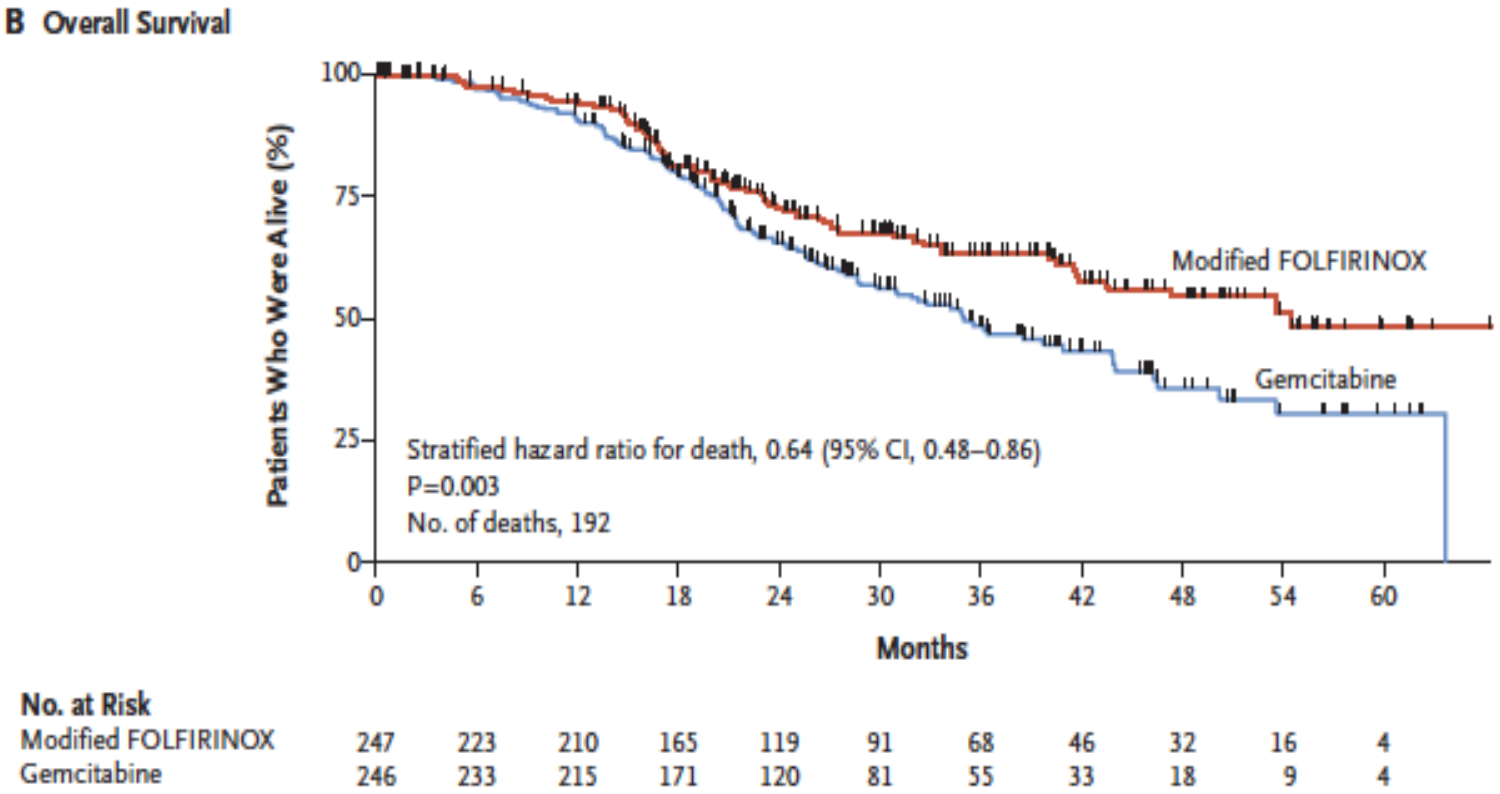


DFS (médiane, mois) : 21.6 vs 12.8

DFS 3 ans (%) : 40 vs 21*

** Objectif étude = > 10 %*

Résultats : SG



SG (médiane, mois) : 54.4 vs 35

SG 3 ans (%) : 63.4 vs 48.6

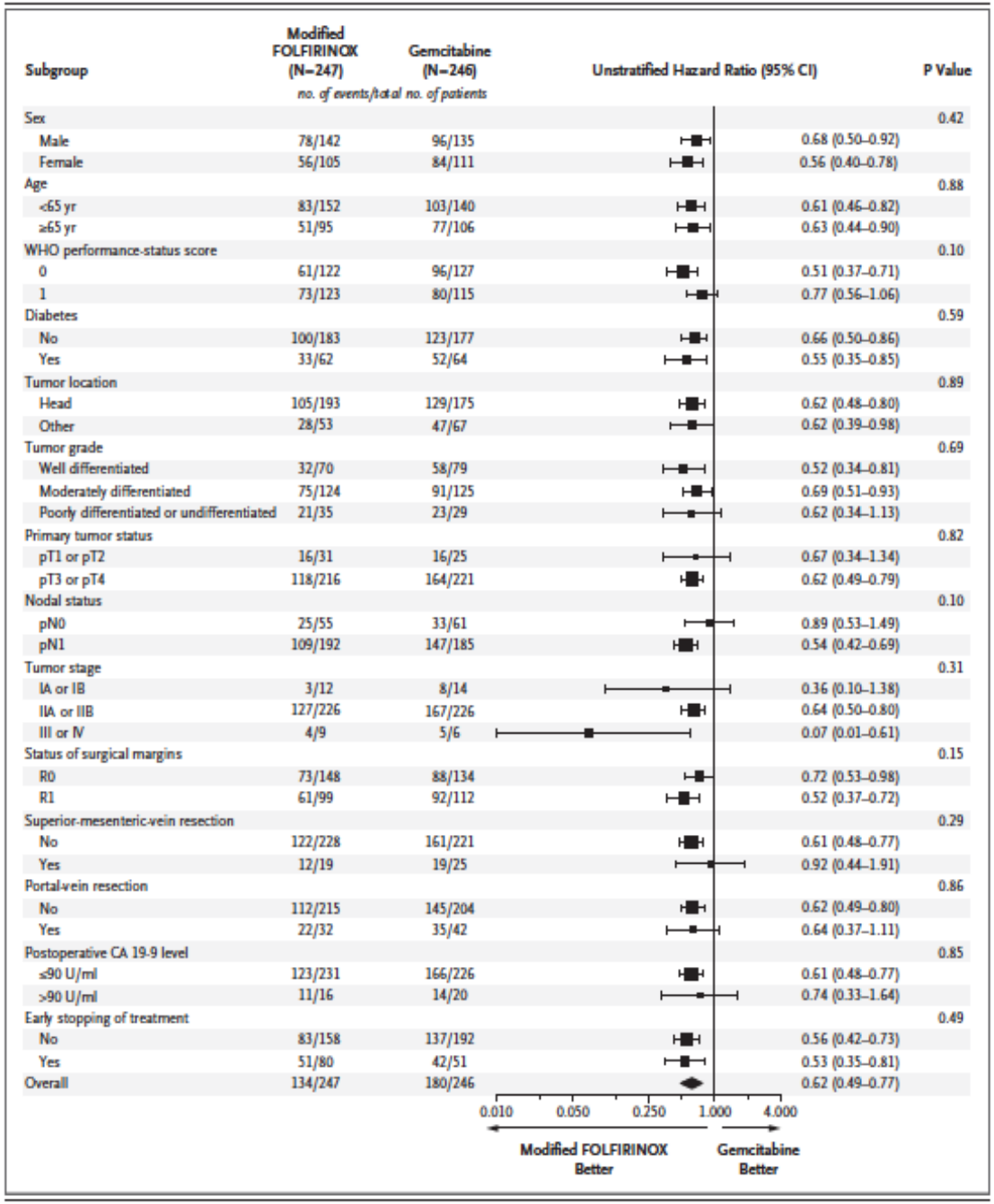

Subgroup
Modified FOLFIRINOX (N=247)
Gemcitabine (N=246)
no. of events/total no. of patients
Unstratified Hazard Ratio (95% CI)
P Value
Sex 0.42
Male 78/142 96/135 0.68 (0.50–0.92)
Female 56/105 84/111 0.56 (0.40–0.78)
Age 0.88
<65 yr 83/152 103/140 0.61 (0.46–0.82)
≥65 yr 51/95 77/106 0.63 (0.44–0.90)
WHO performance-status score 0.10
0 61/122 96/127 0.51 (0.37–0.71)
1 73/123 80/115 0.77 (0.56–1.06)
Diabetes 0.59
No 100/183 123/177 0.66 (0.50–0.86)
Yes 33/62 52/64 0.55 (0.35–0.85)
Tumor location 0.89
Head 105/193 129/175 0.62 (0.48–0.80)
Other 28/53 47/67 0.62 (0.39–0.98)
Tumor grade 0.69
Well differentiated 32/70 58/79 0.52 (0.34–0.81)
Moderately differentiated 75/124 91/125 0.69 (0.51–0.93)
Poorly differentiated or undifferentiated 21/35 23/29 0.62 (0.34–1.13)
Primary tumor status 0.82
pT1 or pT2 16/31 16/25 0.67 (0.34–1.34)
pT3 or pT4 118/216 164/221 0.62 (0.49–0.79)
Nodal status 0.10
pN0 25/55 33/61 0.89 (0.53–1.49)
pN1 109/192 147/185 0.54 (0.42–0.69)
Tumor stage 0.31
IA or IB 3/12 8/14 0.36 (0.10–1.38)
IIA or IIB 127/226 167/226 0.64 (0.50–0.80)
III or IV 4/9 5/6 0.07 (0.01–0.61)
Status of surgical margins 0.15
R0 73/148 88/134 0.72 (0.53–0.98)
R1 61/99 92/112 0.52 (0.37–0.72)
Superior-mesenteric-vein resection 0.29
No 122/228 161/221 0.61 (0.48–0.77)
Yes 12/19 19/25 0.92 (0.44–1.91)
Portal-vein resection 0.86
No 112/215 145/204 0.62 (0.49–0.80)
Yes 22/32 35/42 0.64 (0.37–1.11)
Postoperative CA 19-9 level 0.85
≤90 U/ml 123/231 166/226 0.61 (0.48–0.77)
>90 U/ml 11/16 14/20 0.74 (0.33–1.64)
Early stopping of treatment 0.49
No 83/158 137/192 0.56 (0.42–0.73)
Yes 51/80 42/51 0.53 (0.35–0.81)
Overall 134/247 180/246 0.62 (0.49–0.77)
0.010
0.050
0.250
1.000
4.000
Modified FOLFIRINOX Better
Gemcitabine Better

Table 2. Adverse Events during Treatment (Safety Population).*

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—
Biochemical event¶							
Increased alanine aminotransferase level	151 (64.0)	10 (4.2)	0	178 (73.6)	12 (5.0)	0	0.71
Increased aspartate aminotransferase level	158 (66.9)	9 (3.8)	1 (0.4)	167 (69.0)	8 (3.3)	0	0.76
Increased alkaline phosphatase level	173 (73.6)	5 (2.1)	0	111 (45.9)	5 (2.1)	0	1.00
Increased γ-glutamyltransferase level	150 (65.2)	42 (18.3)	6 (2.6)	110 (46.0)	20 (8.4)	3 (1.3)	0.002
Hyperglycemia	59 (24.9)	7 (3.0)	0	59 (24.4)	5 (2.1)	0	0.53

Toxicité grade 3 / 4 (%) : 75.9 vs 52.9

- % patients ayant reçu totalité TT : 66.4 vs 79 ; p=0.002
- Dose intensité relative > 70 % : 48.7 vs 91.4 ; p<0.001

TT adjuvant :

- 2 standards :
  - Patient en bon état général : FOLFIRINOX
  - Alternative : Gemcitabine (+ capecitabine ???)

- L'avenir :
  - Gemcitabine – Abraxane : non

    Essai APACT négatif

  - Chimiothérapie péri-opératoire : séquence de CT neo-adjuvante
    - France : Essai Panache 01 – Prodige 48
    - Autre : FOFLIRINOX / Gem-Abraxane

TT adjuvant : synthèse

	SSP GEM	SG GEM	SSG GEM-CAP	SG GEM-CAP	SSP FFOX	SG FFOX	SSP GEM NPAC	SG GEM NPAC
CONKO 001	**13.4**	**22.8**						
ESPAC 3	**14.3**	**23.6**						
ESPAC 4	**13.1**	**25.5**	**13.9**	**28**				
PRODIGE 24	**12.8**	**35**			**21.6**	**54**		
APACT	**18.8/13.7**	**36**					**19.4/16.6**	**40**