# *Journal Meeting*

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# Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine (MPACT)

*The NEW ENGLAND JOURNAL of MEDICINE, Oct 3, 2013*

# Introduction

- 8th and 9th leading global cause of cancer-related death in men and women
- Peak incidence 7-8 decades
- Africans Americans : higher incidence
- >90% --ductal adenocarcinoma and its variants

## 100年十大主要癌症順位與死亡人數占率分別為:

(1)氣管、支氣管和肺癌20.1%。　(2)肝和肝內膽管癌18.8%。

(3)結腸、直腸和肛門癌11.6%。　(4)女性乳房癌4.4%。

(5)口腔癌5.8%。　(6)胃癌5.4%。

(7)前列腺(攝護腺)癌2.6%。　(8)胰臟癌3.8%。

(9)食道癌3.5%。　(10)子宮頸及部位未明示子宮癌1.6%。

# Introduction

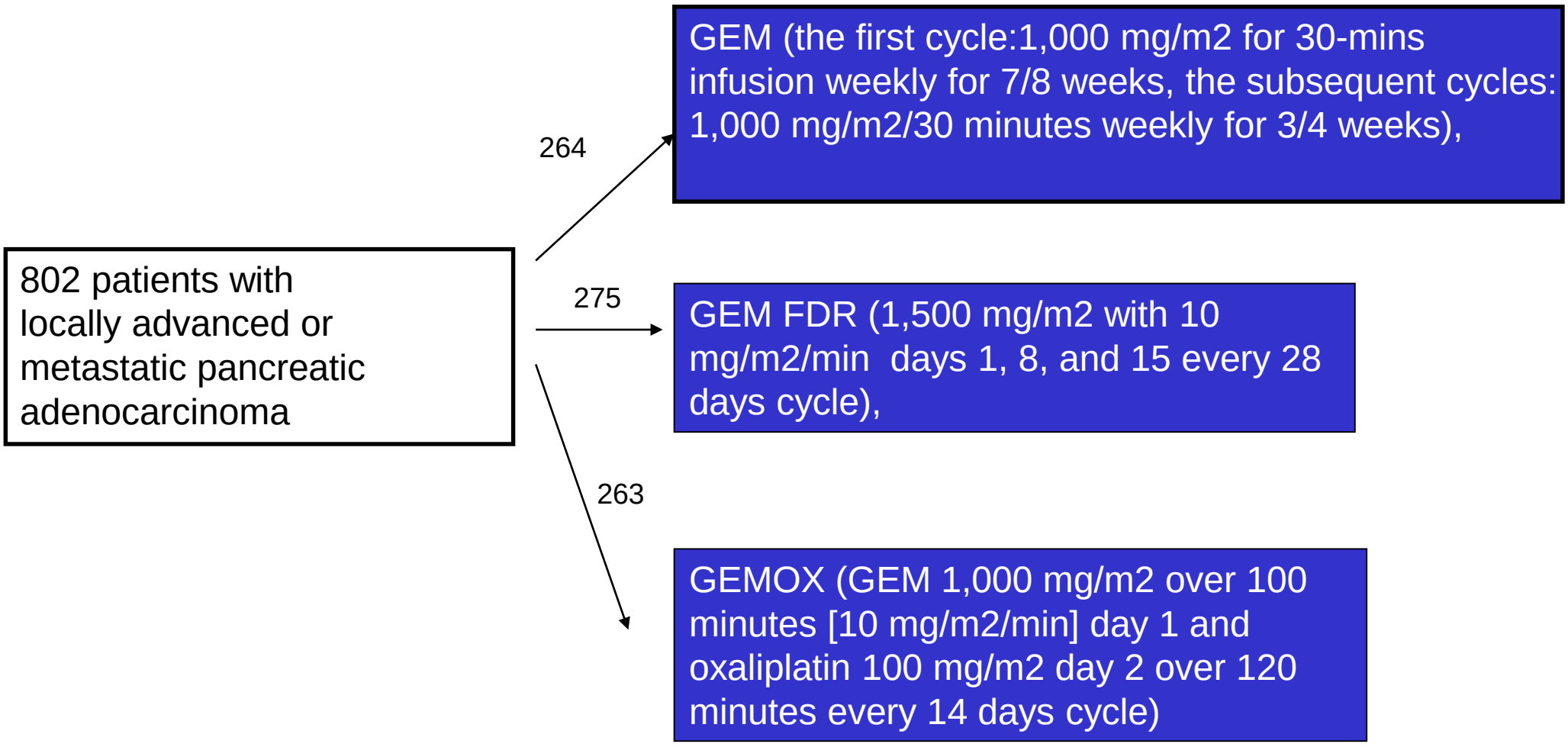
- Surgical resection remains the only curative therapeutic modality for early-stage pancreatic cancer
- Since 1997-- gemcitabine been the standard first-line treatment for unresectable locally advanced or metastatic pancreatic cancer—for metastatic setting, the 5-year survival rate is only 2%, 1-year survival rates:17 to 23%[1,2]

1.J Clin Oncol 1997;15:2403-13 2. N Engl J Med 2011;364:1817-25

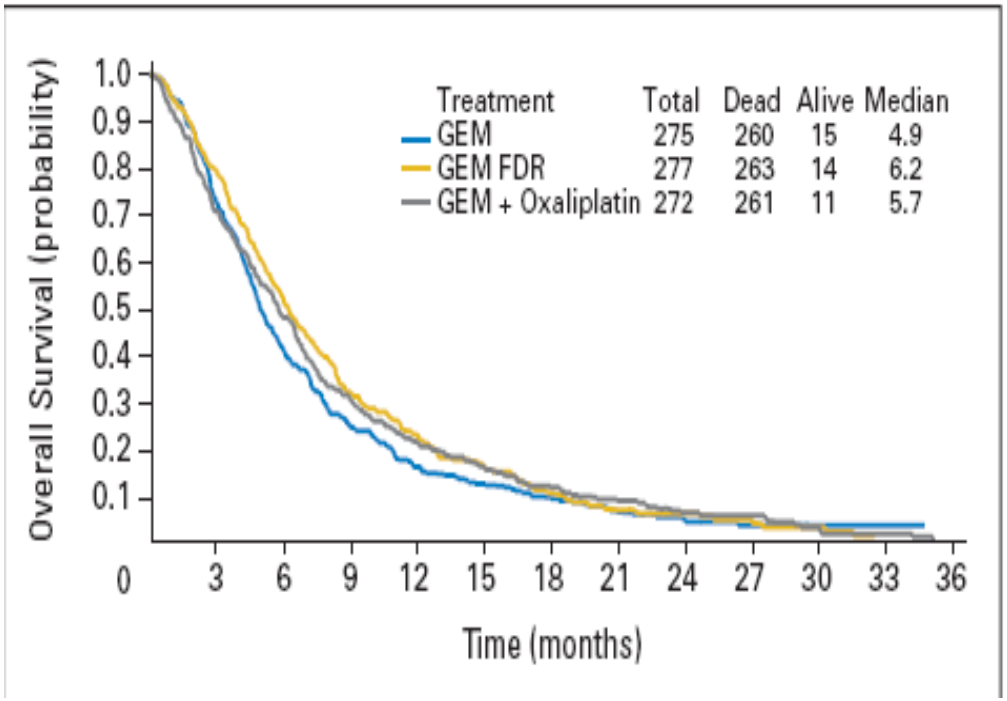
# Fixed-Dose-Rate Gemcitabine

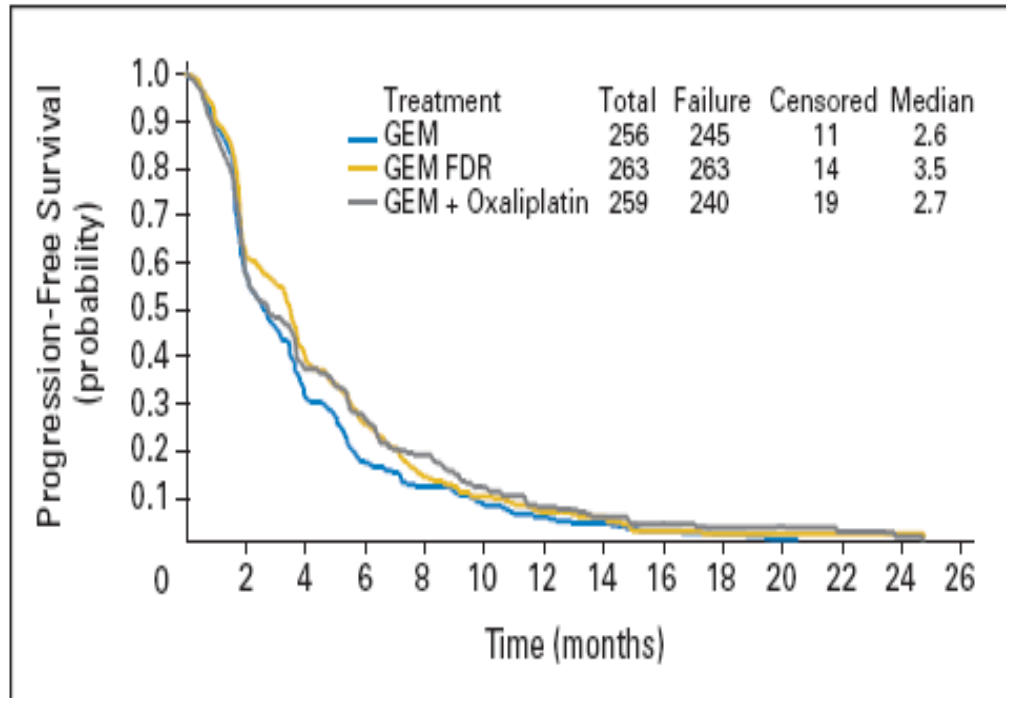
- Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity.
- Clinical studies shown that administering at a fixed-dose rate maximizes intracellular concentrations of the phosphorylated forms of gemcitabine

# Fixed-Dose-Rate Gemcitabine—ECOG-6201



# Fixed-Dose-Rate Gemcitabine—ECOG-6201




Median survival was 4.9 months for GEM (95% CI, 4.5 to 5.6),
6.2 months for GEM FDR (95% CI, 5.4 to 6.9 p=0.04), and 5.7 months for GEMOX (95% CI, 4.9 to 6.5 p=0.22) Median PFS : 2.6, 3.5, and 2.7 months,
Did not satisfy the protocol specified criteria for superiority—FDR Gem (category 2B)

# Doublet vs Single

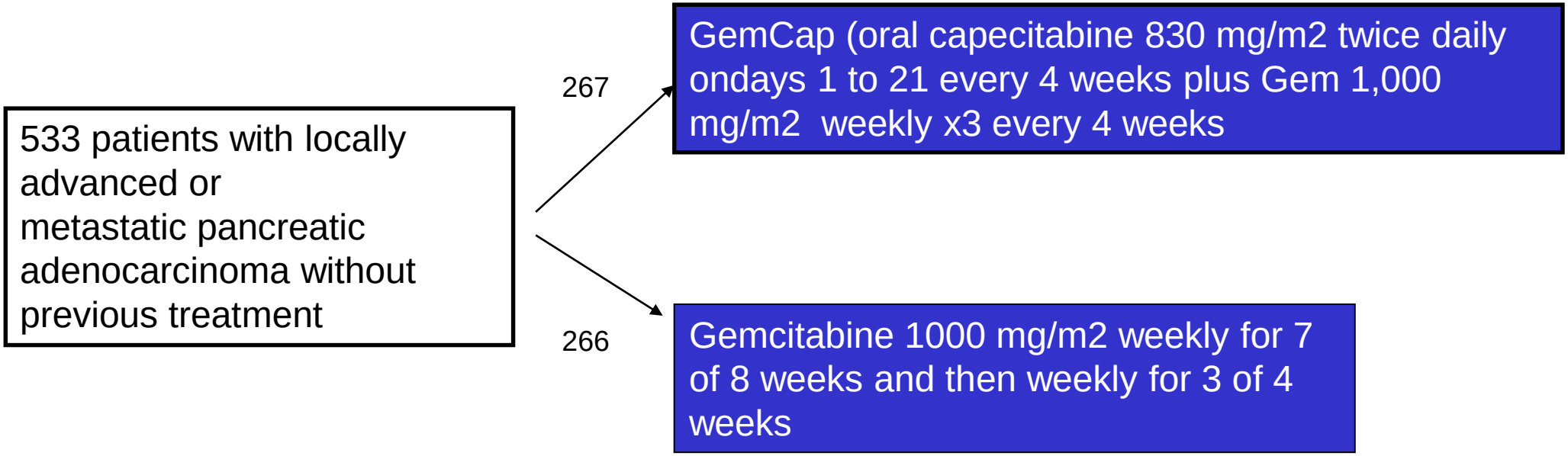
| Study | Patient | Regimen | Result |
|---|---|---|---|
| GIP-1 study | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Cis vs Gem | PFS:3.9 vs 3.8 m (p=0.8)<br>OS: 8.3 vs 7.2 m (p=0.38) |
| BAYPAN study | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Sorafenib v.s Gem | PFS: 5.7 vs 3.8 m (p=0.9)<br>OS: 9.2 vs 8 m (p=0.231) |
| CALGB 80303 | Advanced pancreatic adenocarcinoma | Gem + Bev v.s Gem | PFS: 3.8 vs 2.9 m (p=0.07)<br>OS: 5.8 vs 5.9 m (p=0.95) |
| ECOG-6201 trial | Locally advanced or metastatic pancreatic adenocarcinoma | Gem vs FDR gem vs Gemox | OS, PFS: 2>1 (但未達設計superior標準); 1 和 3比無統計意義 |

# Doublet vs Single

| Study | Patient | Regimen | Result |
|---|---|---|---|
| Stathopoulos GP et al | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Irinotecan vs Gem | TTP:2.8 vs 2.9 m<br>OS: 6.4 vs 6.5 m |
| Oettle H et al | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Pemetrexed v.s Gem | PFS: 3.9 vs 3.3 m (p=0.11)<br>OS: 6.2 vs 6.3 m (p=0.84) |
| Int S0205 | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Cetuximab v.s Gem | OS: 6.3 vs 5.9 m (p=0.23) |
| Abou-Alfa GK et al | Locally advanced or metastatic pancreatic adenocarcinoma | Gem + Exatecan v.s Gem | OS: 6.7 vs 6.2 m (p=0.52) |

# Exception

# Gem + Cap v.s Gem




J Clin Oncol 2009;27:5513-8.

# Gem + Cap v.s Gem

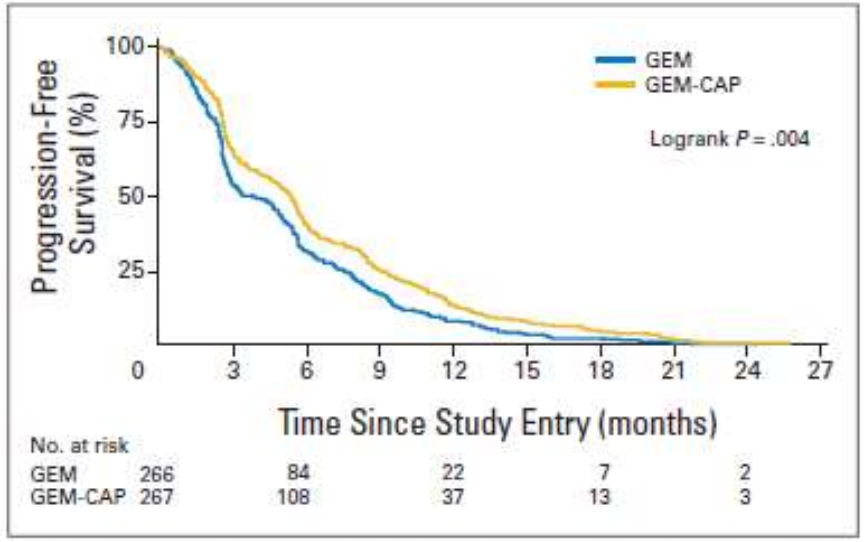



**Fig 2.** Progression-free survival by treatment arms. GEM-CAP, gemcitabine plus capecitabine; GEM, gemcitabine alone.

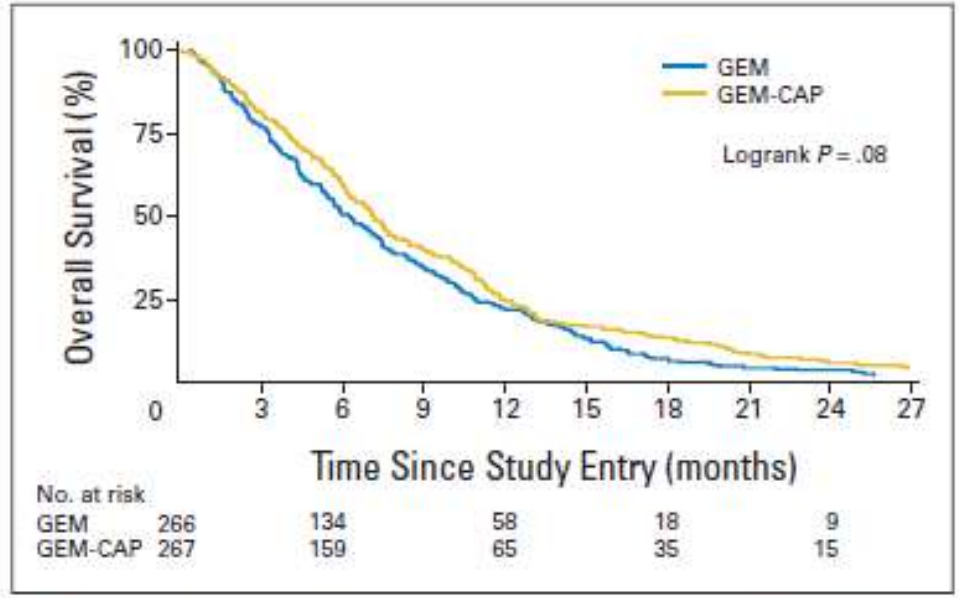
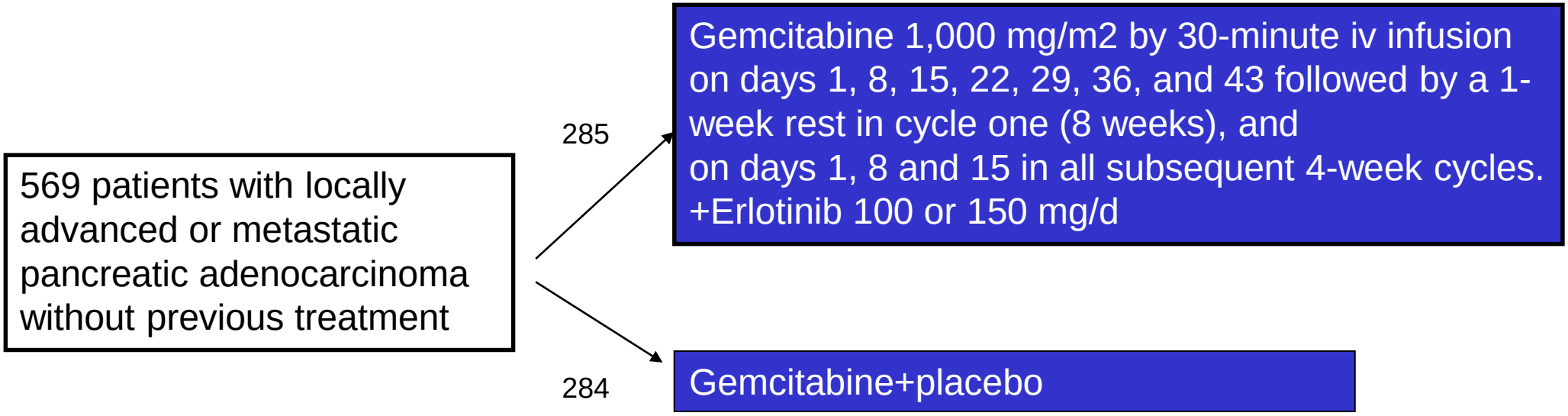



**Fig 3.** Overall survival by treatment arms. GEM-CAP, gemcitabine plus capecitabine; GEM, gemcitabine alone.

RR: 19.1% *v 12.4%, respectively; P .03,*
PFS: 5.3 vs 3.8 m *p=0.04,*
*OS:* 7.1 vs 6.2 m *p=0.08 (trend)*

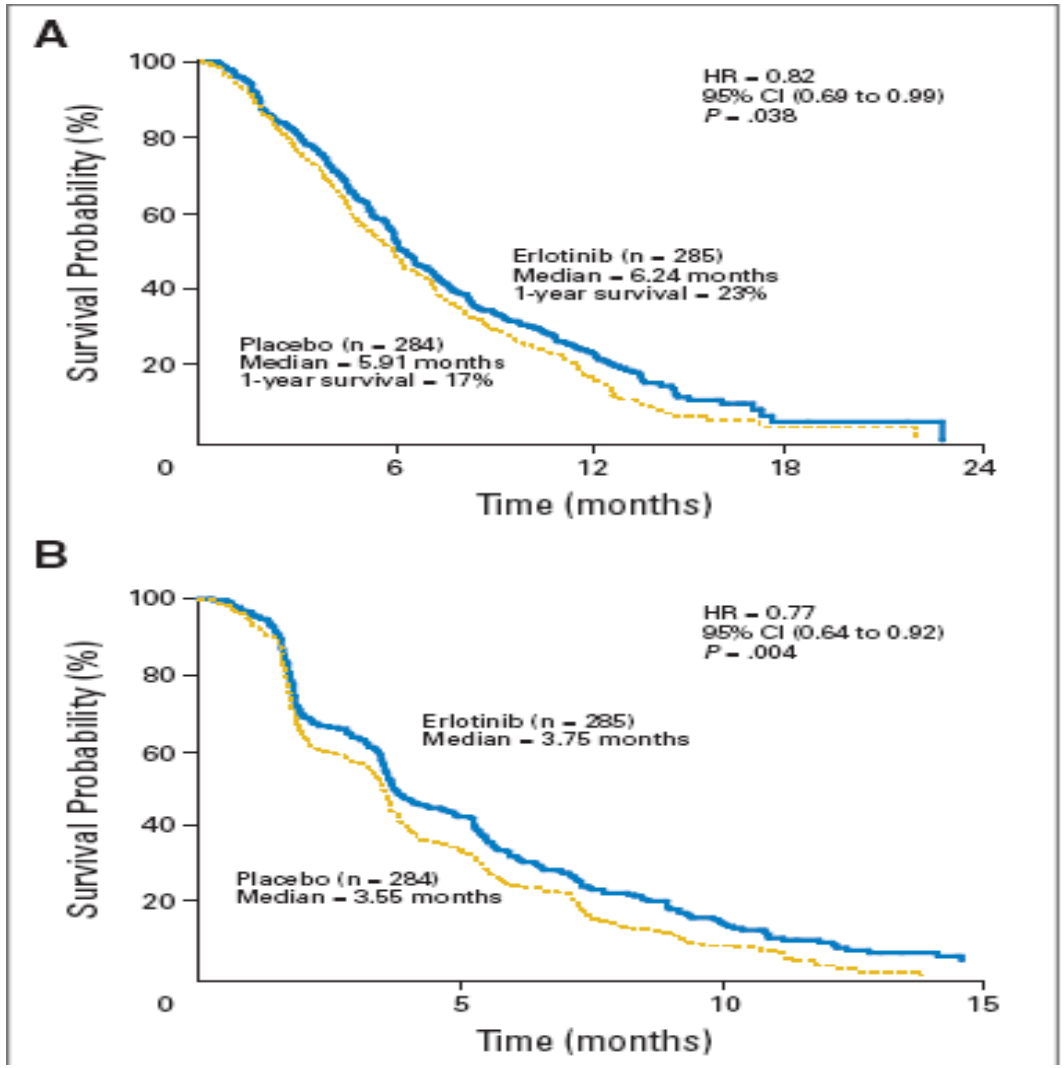
J Clin Oncol 2009;27:5513-8.

# NCIC CTG PA.3 trial




J Clin Oncol 2007;25:1960-6

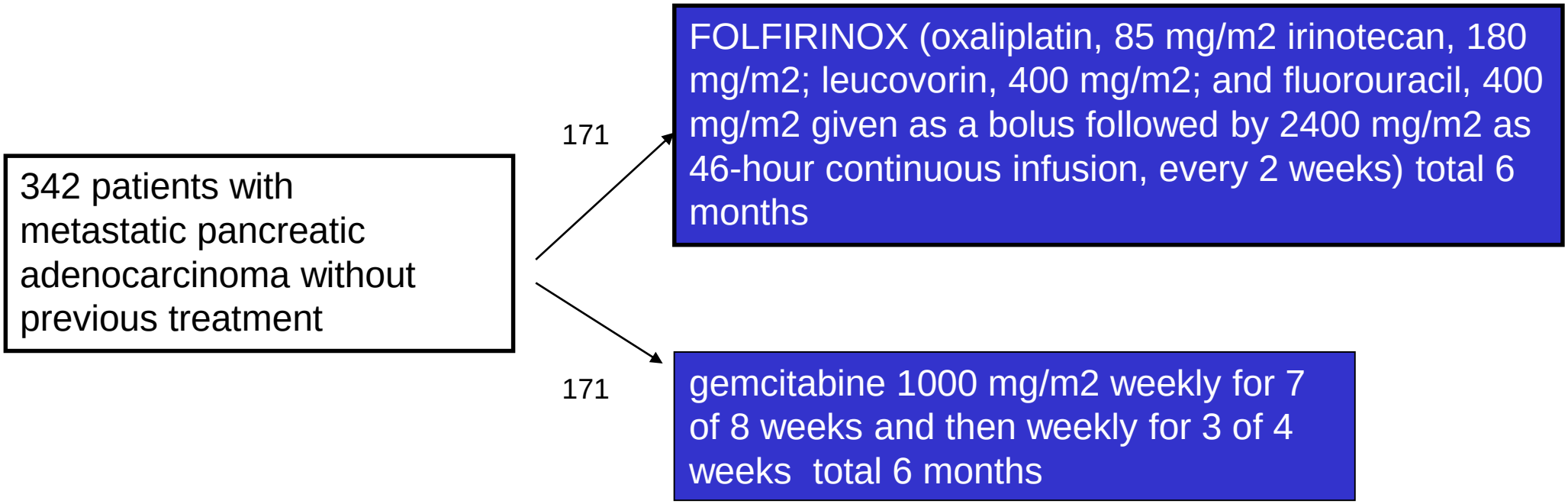
# NCIC CTG PA.3 trial




MOS 6.24 months *v* 5.91 months).
PFS 3.78 m vs 3.55 m HR of 0.77 (95% CI, 0.64 to 0.92; *P* .004).
Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization

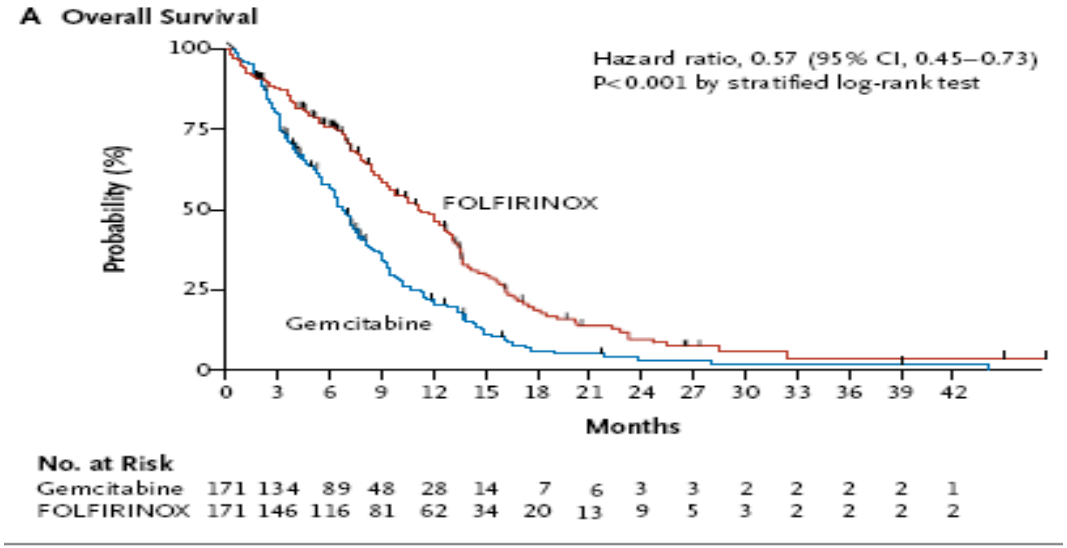
J Clin Oncol 2007;25:1960-6

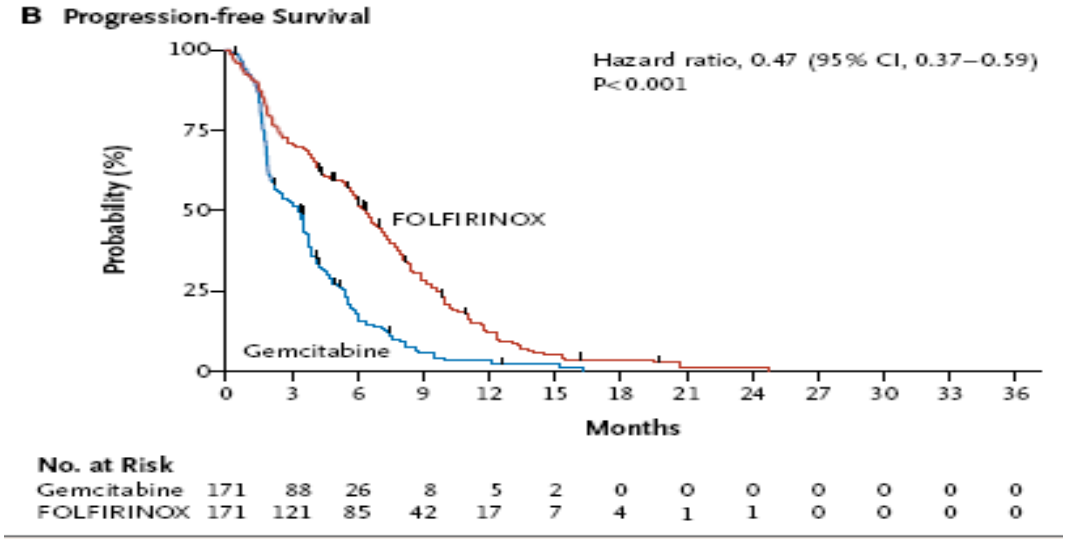
# PRODIGE trial




N Engl J Med 2011;364:1817-25

# PRODIGE trial




PFS (6.4 months vs. 3.3 months; P<0.001) and OS (11.1 months vs. 6.8 months; P<0.001)

N Engl J Med 2011;364:1817-25

# PRODIGE trial

**Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.***

| Event | FOLFIRINOX (N=171) | Gemcitabine (N=171) | P Value |
|---|---|---|---|
| | *no. of patients/total no. (%)* | | |
| Hematologic | | | |
| Neutropenia | 75/164 (45.7) | 35/167 (21.0) | <0.001 |
| Febrile neutropenia | 9/166 (5.4) | 2/169 (1.2) | 0.03 |
| Thrombocytopenia | 15/165 (9.1) | 6/168 (3.6) | 0.04 |
| Anemia | 13/166 (7.8) | 10/168 (6.0) | NS |
| Nonhematologic | | | |
| Fatigue | 39/165 (23.6) | 30/169 (17.8) | NS |
| Vomiting | 24/166 (14.5) | 14/169 (8.3) | NS |
| Diarrhea | 21/165 (12.7) | 3/169 (1.8) | <0.001 |
| Sensory neuropathy | 15/166 (9.0) | 0/169 | <0.001 |
| Elevated level of alanine aminotransferase | 12/165 (7.3) | 35/168 (20.8) | <0.001 |
| Thromboembolism | 11/166 (6.6) | 7/169 (4.1) | NS |

Fewer patients in the FOLFIRINOX group than in the gemcitabine group experienced a degradation in their quality of life at 6 months (31% versus 66%, P<0.01).

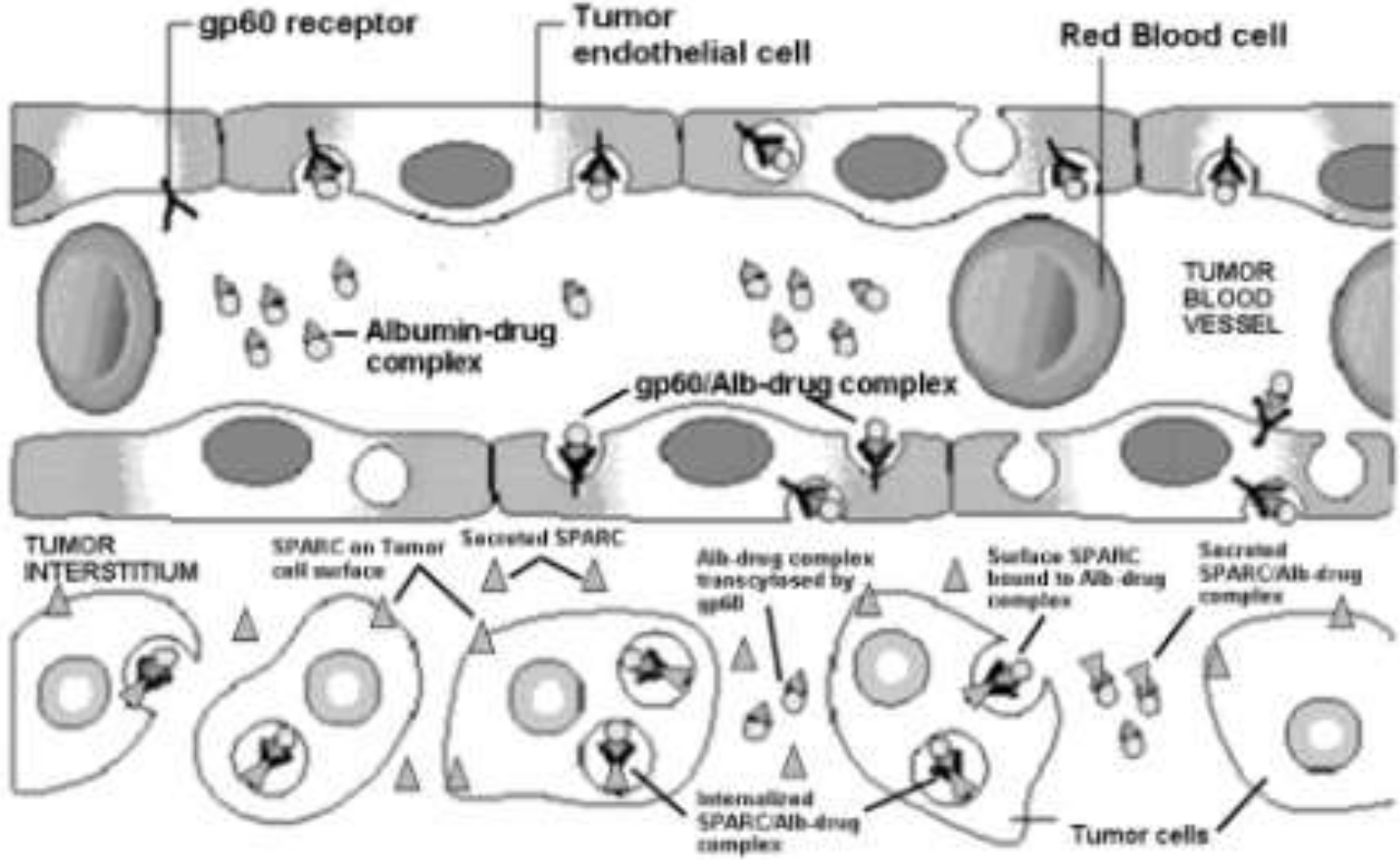
first-line treatment of good performance status patients with metastatic pancreatic cancer

N Engl J Med 2011;364:1817-25

# Rationale of this article

- The mechanism of nab-paclitaxel: active transport of albumin into the interstitial space via gp60-mediated transcytosis[1].
- In addition, secreted protein, acidic and rich in cysteine (SPARC), also known as osteonectin, is highly expressed and secreted by pancreatic adenocarcinoma peritumoral fibroblasts[2]


1. Am J Physiol Lung Cell Mol Physiol 2001;281:L1512–22
2. J Clin Oncol 2007;25:319–25


gp60 receptor
Tumor endothelial cell
Red Blood cell
TUMOR BLOOD VESSEL
Albumin-drug complex
gp60/Alb-drug complex
TUMOR INTERSTITIUM
SPARC on Tumor cell surface
Secreted SPARC
Alb-drug complex transcytosed by gp60
Surface SPARC bound to Alb-drug complex
Secreted SPARC/Alb-drug complex
Internalized SPARC/Alb-drug complex
Tumor cells

# Rationale of this article

- Preclinically, albumin-bound paclitaxel (nab-paclitaxel) showed antitumor activity in murine models--improved the intratumoral concentration of gemcitabine[1,2]
- In phase 1–2 clinical trial, nab-paclitaxel 125 mg/m$^2$ plus gem 1000 mg/m$^2$ on days 1, 8, and 15 every 4 weeks– median survival: 12.2 months and acceptable adverse events

1.J Clin Oncol 2011;29:4548-54
2.Cancer Discov 2012;2:260-9

# Patients

## Inclusion

- ≥18 years of age, KPS score ≥ 70
- Metastatic adenocarcinoma of the pancreas without previous chemotherapy
- Fluorouracil or gemcitabine as a radiation sensitizer in the adjuvant setting at least 6 months before randomization
- Adequate hematologic, hepatic, and renal function

# Patients

## Exclusion

- Cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting
- Islet-cell neoplasms
- Locally advanced disease

# STUDY DESIGN AND TREATMENT

- Total 861 patients: nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430)
- Nab-paclitaxel (125 mg/$m^2$) followed by gemcitabine (1000 mg /$m^2$) on days 1, 8, and 15 every 4 weeks v.s gemcitabine (1000 mg/$m^2$) weekly for 7 of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks until progression

Table 1. Characteristics of the Patients at Baseline.*

| Characteristic | nab-Paclitaxel plus Gemcitabine (N = 431) | Gemcitabine Alone (N = 430) | Total (N = 861) |
|---|---|---|---|
| Age | | | |
| No. of yr | | | |
| Median | 62 | 63 | 63 |
| Range | 27–86 | 32–88 | 27–88 |
| Distribution — no. (%) | | | |
| <65 yr | 254 (59) | 242 (56) | 496 (58) |
| ≥65 yr | 177 (41) | 188 (44) | 365 (42) |
| Sex — no. (%) | | | |
| Female | 186 (43) | 173 (40) | 359 (42) |
| Male | 245 (57) | 257 (60) | 502 (58) |
| Race or ethnic group — no. (%)† | | | |
| Asian | 8 (2) | 9 (2) | 17 (2) |
| Black | 16 (4) | 16 (4) | 32 (4) |
| White | 378 (88) | 375 (87) | 753 (87) |
| Hispanic | 25 (6) | 26 (6) | 51 (6) |
| Other | 4 (1) | 4 (1) | 8 (1) |
| Region — no. (%) | | | |
| Australia | 61 (14) | 59 (14) | 120 (14) |
| Eastern Europe | 64 (15) | 62 (14) | 126 (15) |
| North America | 268 (62) | 271 (63) | 539 (63) |
| Western Europe | 38 (9) | 38 (9) | 76 (9) |
| Karnofsky performance-status score — no./total no. (%)‡ | | | |
| 100 | 69/429 (16) | 69/429 (16) | 138/858 (16) |
| 90 | 179/429 (42) | 199/429 (46) | 378/858 (44) |
| 80 | 149/429 (35) | 128/429 (30) | 277/858 (32) |
| 70 | 30/429 (7) | 33/429 (8) | 63/858 (7) |
| 60 | 2/429 (<1) | 0/429 | 2/858 (<1) |

Table 1. (Continued.)

| Characteristic | nab-Paclitaxel plus Gemcitabine (N = 431) | Gemcitabine Alone (N = 430) | Total (N = 861) |
|---|---|---|---|
| Pancreatic tumor location — no. (%) | | | |
| Head | 191 (44) | 180 (42) | 371 (43) |
| Body | 132 (31) | 136 (32) | 268 (31) |
| Tail | 105 (24) | 110 (26) | 215 (25) |
| Unknown | 3 (1) | 4 (1) | 7 (1) |
| Site of metastatic disease — no. (%) | | | |
| Liver | 365 (85) | 360 (84) | 725 (84) |
| Lung | 153 (35) | 184 (43) | 337 (39) |
| Peritoneum | 19 (4) | 10 (2) | 29 (3) |
| No. of metastatic sites — no. (%) | | | |
| 1 | 33 (8) | 21 (5) | 54 (6) |
| 2 | 202 (47) | 206 (48) | 408 (47) |
| 3 | 136 (32) | 140 (33) | 276 (32) |
| >3 | 60 (14) | 63 (15) | 123 (14) |
| Level of carbohydrate antigen 19-9 — no./total no. (%) | | | |
| Normal§ | 60/379 (16) | 56/371 (15) | 116/750 (15) |
| ULN to <59× ULN | 122/379 (32) | 120/371 (32) | 242/750 (32) |
| ≥59× ULN | 197/379 (52) | 195/371 (53) | 392/750 (52) |
| Carbohydrate antigen 19-9 — U/ml¶ | | | |
| Median | 2293.7 | 2759.2 | 2469.7 |
| Range | 1.9–6,159,233.0 | 0.3–12,207,654.2 | 0.3–12,207,654.2 |
| Previous therapy — no. (%) | | | |
| Radiation therapy | 19 (4) | 11 (3) | 30 (3) |
| Chemotherapy | 23 (5) | 12 (3) | 35 (4) |
| Whipple procedure | 32 (7) | 30 (7) | 62 (7) |
| Biliary stent | 80 (19) | 68 (16) | 148 (17) |

# ASSESSMENTS

- Evaluated the response every 8 weeks by spiral CT or MRI.
- All scans were independently assessed by two readers and one adjudicator, all of whom were unaware of the treatment assignments
- The primary efficacy end point was overall survival
- The secondary end points were progression free survival and the response rate

# Results

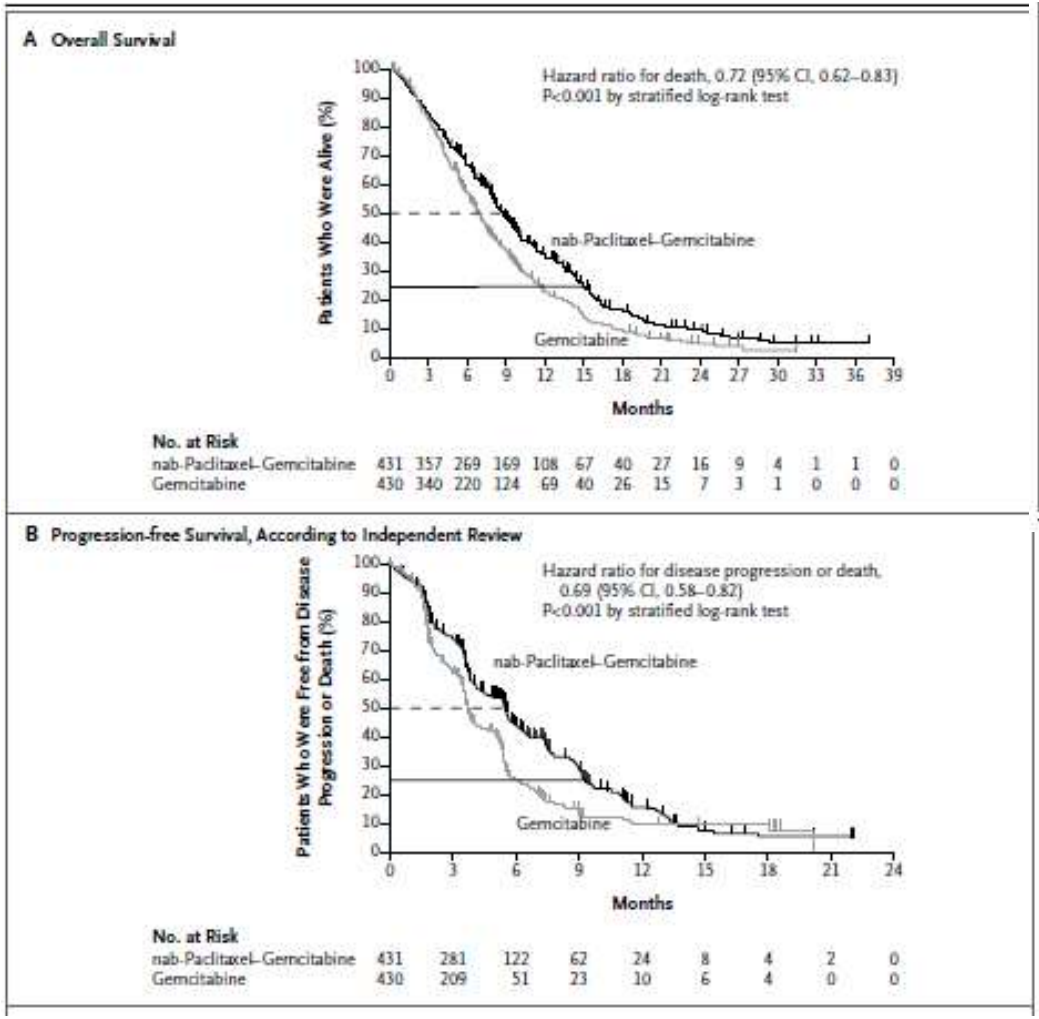
- 692 deaths (80% of patients), including 333 in the nab-paclitaxel–gemcitabine group (77%) and 359 in the gemcitabine group (83%)
- In the intention-to-treat population, the median survival was 8.5 months (95% confidence interval [CI], 7.89 to 9.53) v.s 6.7 months (95% CI, 6.01 to 7.23) hazard ratio for death, 0.72; 95% CI, 0.62 to 0.83; P<0.001)

# Results

- A Cox regression analysis: treatment, KPS score and the presence or absence of liver metastases were independent predictors of survival
- Subsequent anticancer therapy: 38% v.s 42% in the gemcitabine group.
- 27 patients (6%) in the gemcitabine group crossed over to receive a regimen that included nab-paclitaxel

# Results

- 542 patients (63%) had progression of disease or died – --- 64% vs.62%
- PFS: 5.5 months (95% CI, 4.5 to 5.9) versus 3.7 months (95% CI, 3.6 to 4.0) hazard ratio, 0.69; 95% CI, 0.58 to 0.82; P<0.001
- By investigator assessment: 5.3 months (95% CI, 4.4 to 5.5) versus 3.5 months (95% CI, 3.2 to 3.6) hazard ratio, 0.61; 95% CI, 0.52 to 0.71; P<0.001)



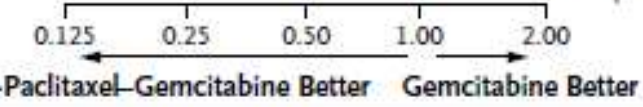

A. OS: 8.5 months v.s 6.7 months (P<0.001)

B. PFS by independent review: 5.5 months v.s 3.7 months (P<0.001)

C. PFS by investigator assessment: 5.3 months v.s 3.5 months (P<0.001)

**A Overall Survival**

| Subgroup | nab-Paclitaxel–Gemcitabine | Gemcitabine | Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | *no. of events/no. of patients* | | |
| All patients | 333/431 | 359/430 | 0.72 (0.62–0.83) |
| Age | | | |
| <65 yr | 188/254 | 209/242 | 0.65 (0.53–0.79) |
| ≥65 yr | 145/177 | 150/188 | 0.81 (0.63–1.03) |
| Sex | | | |
| Female | 138/186 | 141/173 | 0.72 (0.57–0.93) |
| Male | 195/245 | 218/257 | 0.72 (0.59–0.88) |
| Karnofsky performance-status score | | | |
| 70–80 | 142/179 | 146/161 | 0.61 (0.48–0.78) |
| 90–100 | 187/248 | 212/268 | 0.75 (0.62–0.92) |
| Primary tumor location | | | |
| Head | 142/191 | 155/180 | 0.59 (0.46–0.75) |
| Other | 188/237 | 201/246 | 0.80 (0.65–0.98) |
| Liver metastases | | | |
| Yes | 290/365 | 309/360 | 0.69 (0.59–0.81) |
| No | 43/66 | 50/70 | 0.86 (0.56–1.33) |
| No. of metastatic sites | | | |
| 1 | 21/33 | 16/21 | 0.41 (0.19–0.88) |
| 2 | 159/202 | 163/206 | 0.75 (0.60–0.95) |
| 3 | 104/136 | 121/140 | 0.79 (0.61–1.04) |
| >3 | 49/60 | 59/63 | 0.50 (0.33–0.76) |
| Level of CA19-9 | | | |
| Normal | 47/60 | 43/56 | 1.07 (0.69–1.66) |
| <59× ULN | 96/122 | 95/120 | 0.83 (0.61–1.12) |
| ≥59× ULN | 151/197 | 171/195 | 0.61 (0.48–0.77) |
| Region | | | |
| Australia | 50/61 | 53/59 | 0.67 (0.44–1.01) |
| Eastern Europe | 62/64 | 59/62 | 0.84 (0.58–1.23) |
| Western Europe | 14/38 | 17/38 | 0.72 (0.35–1.47) |
| North America | 207/268 | 230/271 | 0.68 (0.56–0.82) |



# Results

- Time to treatment failure: 5.1 months (95% CI, 4.1 to 5.5) v.s 3.6 months (95% CI, 3.5 to 3.9) hazard ratio, 0.70; 95% CI, 0.60 to 0.80; P<0.001)
- Response rate :23% (95% CI, 19 to 27) vs. 7% (95% CI, 5 to 10); P<0.001
- The rate of disease control (confirmed response or stable disease for ≥16 weeks): 48% (95% CI, 43 to 53) v.s 33% (95% CI, 28 to 37)  P<0.001

# Results

- The median duration of treatment: 3.9 months
  v.s 2.8 months
- 71% of all nab-paclitaxel doses administered during the study v.s 67% of gemcitabine group

# Results

**Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.***

| Event | nab-Paclitaxel plus Gemcitabine (N=421) | Gemcitabine Alone (N=402) |
|---|---|---|
| Adverse event leading to death — no. (%) | 18 (4) | 18 (4) |
| Grade ≥3 hematologic adverse event — no./total no. (%)† | | |
| Neutropenia | 153/405 (38) | 103/388 (27) |
| Leukopenia | 124/405 (31) | 63/388 (16) |
| Thrombocytopenia | 52/405 (13) | 36/388 (9) |
| Anemia | 53/405 (13) | 48/388 (12) |
| Receipt of growth factors — no./total no. (%) | 110/431 (26) | 63/431 (15) |
| Febrile neutropenia — no. (%)‡ | 14 (3) | 6 (1) |
| Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡ | | |
| Fatigue | 70 (17) | 27 (7) |
| Peripheral neuropathy§ | 70 (17) | 3 (1) |
| Diarrhea | 24 (6) | 3 (1) |
| Grade ≥3 peripheral neuropathy | | |
| Median time to onset — days | 140 | 113 |
| Median time to improvement by one grade — days | 21 | 29 |
| Median time to improvement to grade ≤1 — days | 29 | NR |
| Use of nab-paclitaxel resumed — no./total no. (%) | 31/70 (44) | NA |

# Discussion

- Nab-paclitaxel plus gemcitabine led to a significant improvement in survival at all time points
- The survival curves separated early
- A sensitivity analysis of survival: the difference could not be attributed to the use of second-line therapy

# Discussion

- 31%  reduction in the risk of progression or death with nab- paclitaxel plus  gemcitabine, as compared with gemcitabine.
- The response rate was tripled with nab-paclitaxel plus gemcitabine
- A higher percentage of patients in the nab-paclitaxel–gemcitabine group had a reduction of at least 90% in the CA19-9 level--associated with an improvement in survival

# Discussion

- The rate of serious life-threatening adverse events was not increased with nab-paclitaxel plus gemcitabine
- Adverse events were generally grade 3 or lower and resolved without specific treatment.
- The most notable difference was peripheral neuropathy
  --- cumulative and rapidly reversible with temporary discontinuation of nabpaclitaxel and a subsequent reduction in the dose

# Discussion

- A limitation of the study was quality of life not measured and rare Asian people included
- The FOLFIRINOX study differed from this one
  --- pooled data from the phase 2 and 3 portions
  --- excluded patients older than 75 years of age (10% in this study)
  --- excluded patients with ECOG performance status of 2 (8% in this study)

# Conclusion

- Nab-paclitaxel combined with gemcitabine is superior to gemcitabine alone but causes more myelosuppression and peripheral neuropathy; these side effects appear to be reversible.

# Take Home Message

- Since 1997, gemcitabine was the standard first-line treatment for unresectable locally advanced or metastatic pancreatic adenocarcinoma
- Many agents that have shown promising results in phase 2 trials of pancreatic cancer fail to improve survival in phase 3 trials
- Compared to gemcitabline plus erlotinib, Nab-paclitaxel plus gemcitabine seemed to be more effective
- Compared to FOLFIRINOX, Nab-paclitaxel plus gemcitabine seemed to be safer
- Nab-paclitaxel combined with gemcitabine are effective and have promising adverse event

***Thanks for your attention***