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# Unicancer PRODIGE 24/CCTG PA6 trial: Updated results of a multicenter international randomized phase 3 trial of adjuvant mFOLFIRINOX versus gemcitabine in patients with resected pancreatic ductal adenocarcinomas.

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# DECLARATION OF INTERESTS

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I have no conflict of interests with the integrity of ESMO and this work and no financial and non-financial interests with any relevant organisation

# Introduction

- PRODIGE 24/CCTG PA6 trial evaluated the safety and efficacy of adjuvant mFOLFIRINOX vs gemcitabine alone in patients with resected pancreatic cancer
- Disease-Free-Survival served as primary endpoint
- 490 patients were required to reach 342 events for final analysis
- In February 2018, the independent data and safety monitoring committee recommended early analysis and publication of the results
- Then analysis was performed with 314 events (91.8%) and a median follow-up of 33.6 months, and first results were published

Conroy T *et al.* N Engl J Med 2018;379:2395-406

- Here, we present updated 5-year OS and prognostic factors for OS in the ITT population

# PRODIGE 24/CCTG PA.6 trial: study design

**Patients:**
- R0 or R1 resected pancreatic cancer
- Mandatory postoperative CT-scan
- CA19-9 level < 180 U/mL
- Inclusion within 12 weeks after surgery

**Stratification:**
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

**RANDOMIZE**

1:1

## mFOLFIRINOX

Oxaliplatin 85 mg/m² at D1
Leucovorin 400 mg/m² at D1
Irinotecan 150-180 mg/m² at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
*Every 2 weeks; 12 cycles*

## Gemcitabine

1000 mg/m², qw 3/4 *weeks*
*6 cycles*

**Primary endpoint**: DFS

**Secondary endpoints:**
- overall survival
- metastasis-free survival
- cancer-specific survival
- safety.

for both arms:
- 6 months of adjuvant chemotherapy
- CT scans: every 3 months

# Patients baseline characteristics

| Characteristics | | mFOLFIRINOX Patients # =247 | Gemcitabine Patients # =246 | p-value |
|---|---|---|---|---|
| **Median age (yrs)** [range] | | **63** [30-79] | **64** [30-81] | **0.08** |
| **Gender male** | | **57.5%** | **54.9%** | **0.59** |
| **WHO PS** | **0** | **49.8%** | **52.2%** | **0.59** |
| | **1** | **50.2%** | **47.8%** | |
| **Diabetes** | | **25.3%** | **26.7%** | **0.45** |

# Pancreatic tumors baseline characteristics

| Characteristics (%) | mFOLFIRINOX # =247 | Gemcitabine # =246 | p-value |
|---|---|---|---|
| pT1-2/pT3-4 | 12.6/87.4 | 10.2/89.8 | 0.40 |
| pN0/pN1 | 22.3/77.7 | 24.8 /75.2 | 0.51 |
| Lymph node ratio | | | 0.53 |
| 0 | 23.1 | 24.9 | |
| 0-0.20 | 47.8 | 41.6 | |
| 0.20-0.40 | 21.5 | 23.3 | |
| >0.40 | 7.7 | 10.2 | |
| Stage: I/IIA/IIB/III-IV | 4.9/17.4 /74.1/3.6 | 5.7/19.1 /72.8/2.4 | 0.81 |
| Tumor differentiation: well/moderate/poor | 30.6/54.2/15.3 | 33.9/53.7/12.5 | 0.58 |
| R1 resection | 40.1 | 45.5 | 0.22 |
| Venous resection | 21.6 | 28.2 | 0.10 |
| Lymphovascular emboli | 73.7 | 63.1 | 0.02 |

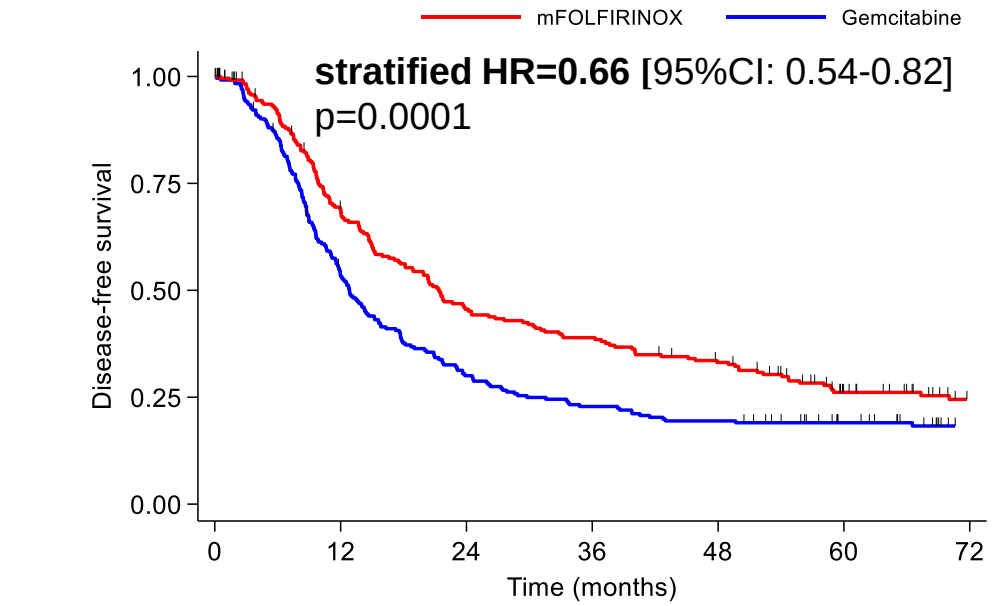
# Disease-Free Survival events

**Median follow-up: 69.7 months** [95%CI: 67.1-73.9]

**No late toxicity reported**

| | mFOLFIRINOX # =247 | Gemcitabine # =246 |
|---|---|---|
| **# events** | **173 (70%)** | **194 (78.9%)** |
| **First event :** | | |
| • Metastases | 94 (54.3%) | 91 (46.9%) |
| • Locoregional recurrence | 37 (21.4%) | 44 (22.7%) |
| • Locoregional + metastases | 29 (16.8%) | 47 (24.2%) |
| • Second cancer | 5 (2.9%) | 8 (4.1%) |
| • Death | 8 (4.6%) | 4 (2.1%) |

# Disease-Free Survival




**# DFS events: 367**

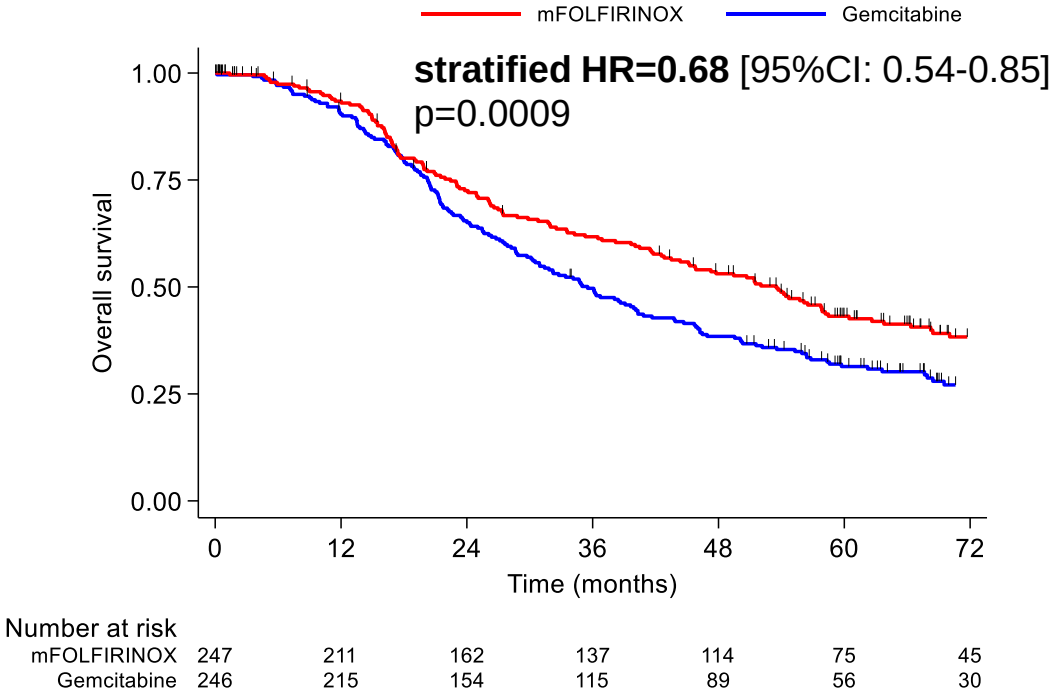
**5-year DFS:**

- **26.1%** [95%CI: 20.5-32.1] **with mFOLFIRINOX**
- **19.0%** [95%CI: 14.3-24.3] **with gemcitabine**

**Median DFS:**

- **21.4 months** [95%CI: 17.5-26.7] **with mFOLFIRINOX**
- **12.8 months** [95%CI: 11.6-15.2] **with gemcitabine**

# Overall Survival




**# OS events=304**

**5-year overall survival:**

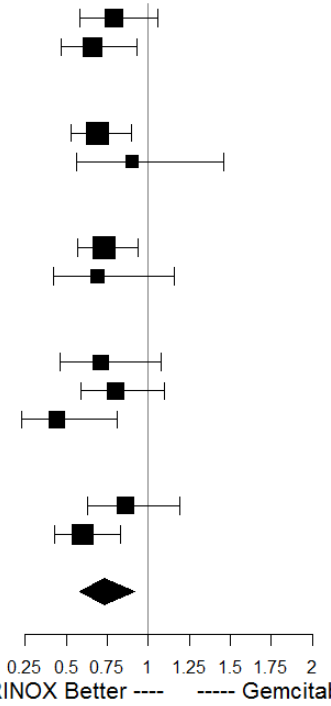
- **43.2%** [95%CI: 36.5-49.7] **with mFOLFIRINOX**
- **31.4%** [95%CI: 25.5-37.5] **with gemcitabine**

**Median overall survival:**

- **53.5 months** [95%CI: 43.5-58.4] **with mFOLFIRINOX**
- **35.5 months** [95%CI: 30.1-40.3] **with gemcitabine**

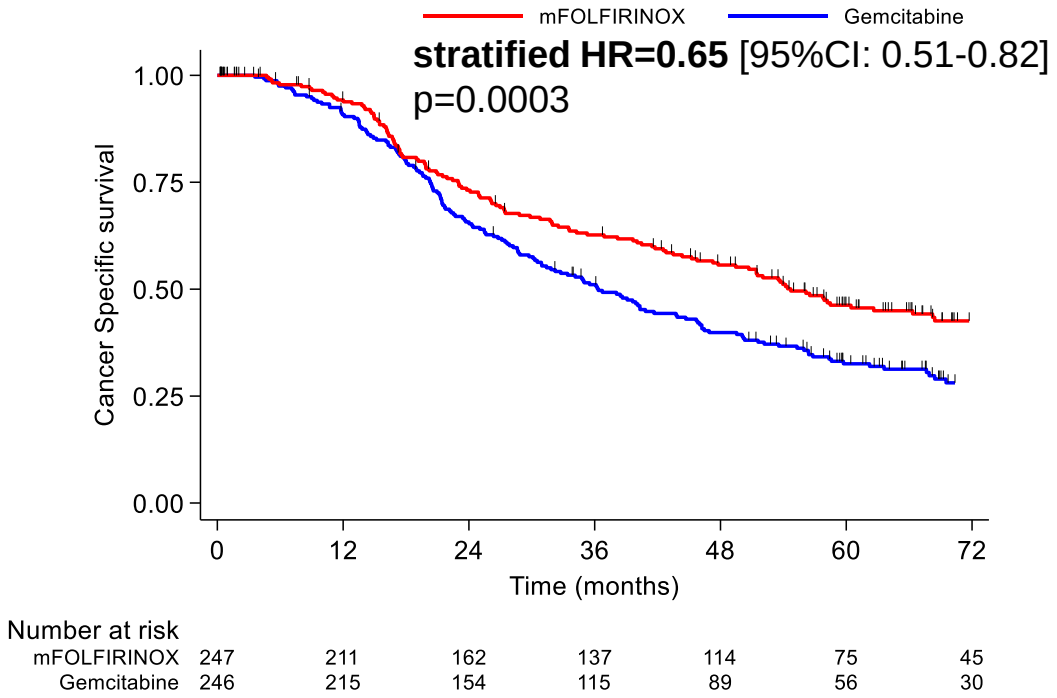
# Overall Survival in prespecified subgroups

| Subgroup | mFOLFIRINOX (Event/N) | Gemcitabine (Event/N) | Unstratified HR [95%CI] | P Value |
|---|---|---|---|---|
| **Sex** | | | | **0.46** |
| Male | 80/142 | 91/135 | 0.79 (0.58-1.06) | |
| Female | 56/105 | 77/111 | 0.66 (0.47-0.93) | |
| **Age** | | | | **0.32** |
| < 70 yr | 104/200 | 132/192 | 0.69 (0.53-0.90) | |
| >= 70 yr | 32/47 | 36/54 | 0.90 (0.56-1.46) | |
| **Tumor location** | | | | **0.89** |
| Head | 112/197 | 130/183 | 0.73 (0.57-0.94) | |
| Other | 24/50 | 38/63 | 0.69 (0.42-1.16) | |
| **Tumor grading** | | | | **0.14** |
| Well differentiated | 35/70 | 53/79 | 0.71 (0.46-1.08) | |
| Moderately differentiated | 75/124 | 87/125 | 0.80 (0.59-1.10) | |
| Poorly differentiated or undifferentiated | 19/35 | 23/29 | 0.44 (0.23-0.81) | |
| **Status of surgical margins** | | | | **0.14** |
| R0 | 72/148 | 78/134 | 0.86 (0.63-1.19) | |
| R1 | 64/99 | 90/112 | 0.60 (0.43-0.83) | |
| **Overall** | **136/247** | **168/246** | **0.73 (0.58-0.92)** | |



# Specific Survival, death from cancer

Specific survival is defined as the interval between randomization and occurrence of death due to any cancer or related treatment toxicity.




**# SS events=286**

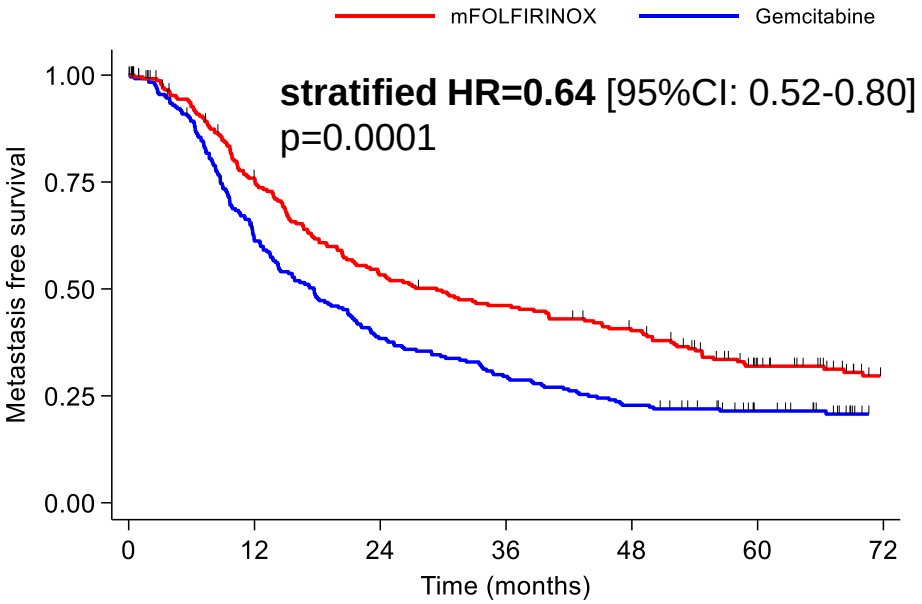
**5-year specific survival:**

- **46.3%** [95%CI: 39.4-52.8] **with mFOLFIRINOX**
- **32.6%** [95%CI: 26.5-38.8] **with gemcitabine**

**Median survival without death from cancer:**

- **54.7 months** [95%CI: 45.8-68.4] **with mFOLFIRINOX**
- **36.3 months** [95%CI: 30.5-43.9] **with gemcitabine**

# Metastasis-Free Survival




**# MFS events=350**

**5-year survival without metastases:**

- **31.9%** [95%CI: 25.8-38.2] **with mFOLFIRINOX**
- **21.5%** [95%CI: 16.5-26.9] **with gemcitabine**

**Median survival without metastases:**

- **29.4 months** [95%CI: 21.4-40.1] **with mFOLFIRINOX**
- **17.7 months** [95%CI: 14.0-21.2] **with gemcitabine**

# Prognostic factors for OS, univariate analysis

| Favorable factor | 5-year OS | HR [95% CI] | p-value |
|---|---|---|---|
| **mFOLFIRINOX group** | **43.2%** (vs gemcitabine: 31.4%) | **0.68** [0.54-0.85] | **< 0.001** |
| **Body/tail tumor location** | **44.9%** (vs head location: 34.7%) | **0.72** [0.54-0.95] | **0.017** |
| **No venous resection (PV or SMV)** | **39.1%** (vs venous resection: 30.7%) | **0.73** [0.57-0.94] | **0.019** |
| **R0 resection** | **43.4%** (vs R1: 28.8%) | **0.59** [0.47-0.74] | **< 0.001** |
| **Well differentiated grade** | **41.6%** (vs moderate/poor diff: 32.9%) | **0.76** [0.59-0.98] | **0.03** |
| **pT1-pT2** | **50.4%** (vs pT3-pT4: 35.3%) | **0.64** [0.44-0.95] | **< 0.02** |
| **pN0** | **51.5%** (vs pN1: 32.6%) | **0.59** [0.44-0.79] | **< 0.001** |
| **Tumor staging (I ; IIA ; IIB vs III/IV)** | **71.3%** (45.3%; 33.2% vs 0%) | **0.14 ; 0.32 ; 0.46** | **<0.001** |
| **Lymph node ratio (0 ; 0-0.20 ; 0.20-0.40 vs >0.40)** | **51.9%** (40.9%; 21.0% vs 19.3%) | **0.37 ; 0.48 ; 0.82** | **<0.001** |

Age, WHO PS, sex, diabetes, CA-A 19.9 level after surgery, delay between surgery and chemotherapy were not significant prognostic factors for OS. High-volume center (inclusion ≥ 10 pts) is associated with a better survival, p value of 0.051

# Prognostic factors for OS, multivariate analysis

| #=462* # Events=292 | HR** [95%CI] | p-value*** |
|---|---|---|
| **mFOLFIRINOX group** | **0.65** [0.51-0.82] | **< 0.001** |
| **Center including ≥10 patients** | **0.77** [0.61-0.98] | **0.032** |
| **Age <70 years** | **0.70** [0.52-0.93] | **0.02** |
| **Well differentiated tumor** | **0.69** [0.53-0.90] | **0.005** |
| **Tumor stage:** | | **0.002** |
| **Stage IA/IB** | **0.1** [0.03-0.33] | |
| **Stage IIA** | **0.24** [0.09-0.60] | |
| **Stage IIB** | **0.35** [0.17- 0.72] | |
| **Stage III/IV** | **1** | |

* Missing data on tumor grading on 31 patients

** Stratified on lymph node status, resection margins, and postoperative CA19-9

*** Likelihood-ratio test

In a post-hoc exploratory analysis, the center effect is linked to a significantly longer OS in high-volume centers after metastatic or locoregional recurrence, median: 16 months vs 13 months (HR 0.76 [95%CI 0.60-0.97], p=0.02)

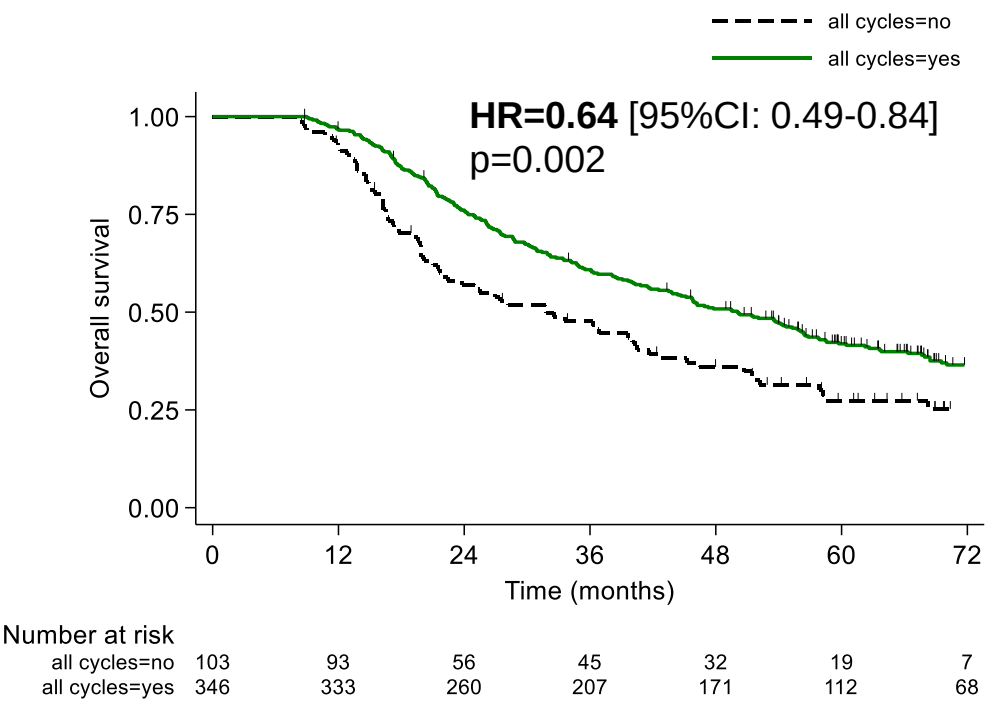
# Prognostic factors for OS collected at the end of treatment, univariate analysis, post-hoc analysis

| #: 449* # events: 285<br>Factor | | 5-year OS | HR [95% CI] | p-value |
|---|---|---|---|---|
| Dose intensity ≥ 80% for all drugs | No | 39.2% | 1 | 0.93 |
| | Yes | 38.2% | 1.01 [0.80-1.28] | |
| Duration of treatment | < 6 months | 38.0% | 1 | 0.44 |
| | ≥ 6 months | 46.1% | 0.85 [0.57-1.29] | |
| All cycles received** | No | 27.4% | 1 | 0.002 |
| | Yes | 41.9% | 0.64 [0.49-0.84] | |

*Post-hoc analysis of patients in both arms, excluding 44 patients lost to follow-up or who died within 8 months of randomization (landmark method, Valle JW, *et al.* J Clin Oncol 2014 ;32: 504-12)

**In the Folfirinox arm, all 12 cycles have included at least 5-Fluorouracil and leucovorin

# Overall Survival according to completion of treatment (all cycles received yes/no)




**# OS events=285**

**5-year survival:**

**— All cycles received: 41.9%**

**- - - Incomplete treatment: 27.4%**

**Data are also significant in each arm:**

**p= 0.02 in the gemcitabine arm**

**p=0.007 in the mFOLFIRINOX arm**

# Conclusions

- Published data of the primary analysis are fully confirmed: adjuvant chemotherapy with mFOLFIRINOX with >5 years follow-up is superior to gemcitabine with significantly improved outcomes, Disease-free survival, Metastasis-free survival, Specific survival and Overall Survival

- Completion of all cycles appeared as an important prognostic factor

- The mature data of this study confirms that mFOLFIRINOX remains the most efficient regimen in adjuvant setting for fit patients

# Acknowledgments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