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Stromal HSP47 and membranous ß-catenin as prognostic and predictive biomarkers in pancreatic ductal adenocarcinoma: **development and independent validation in the Phase III PRODIGE-24 trial**

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BACKGROUND & OBJECTIVES

- **Unmet need:** No routine biomarker to guide adjuvant chemotherapy (mFOLFIRINOX vs. gemcitabine) in resected PDAC.
- **Rationale:** Epithelial-stromal crosstalk drives chemoresistance and disease progression.
- **Objective:** Develop and independently validate an immunomorphological signature in the phase III PRODIGE-24 trial[1].

METHODS

Transcriptomic screening[2] (public datasets)

Candidate biomarkers selection
HSP47, ß-catenin, FAP, LRRC15, PTK7, α-SMA, CD3, CD8, CD20, red-sirius, saffron

Assessments on Tissue Microarrays (TMAs) by digital pathology and automated computational analysis (QuPath).

DEVELOPMENT COHORT
Resected PDAC (CHU Besançon 2000-2017)
N = 217

- Immune compartment (density, cells/mm²).
- Fibroblastic compartment (positively stained area %)
- Epithelial compartment (semi-quantitative scoring 0–3)

➔ Optimal cut-off determination (maxstat) on the mean values
➔ Multivariable Cox model
➔ Primary outcome: Recurrence-Free Survival (RFS)

Minimal biomarker signature ➔ ß-catenin, HSP47, CD8

Assesments on TMAs

VALIDATION COHORT
PRODIGE-24 phase III randomized trial
N = 316

- Pre-specified thresholds in the development cohort applied without re-optimization to the validation cohort.
- Treatment-biomarker interactions assessed using multivariable Cox models.

Table 1. Baseline Patient & Tumor Characteristics

Characteristic	Development (n=217)	PRODIGE-24 (n=316)	p-value
Median age, years [range]	67.0 [39–86]	63.0 [29–79]	0.100
Pancreatic head location	83.4% (181)	74.1% (234)	0.014
Median tumor size, mm [range]	35.0 [15–100]	30.0 [6–120]	0.500
Lymph node positive (pN+)	79.3% (172)	76.6% (242)	0.532
Complete resection (R0)	79.3% (172)	72.2% (228)	0.078
Poorly differentiated grade	18.0% (39)	12.0% (38)	0.147
Chemotherapy (Neoadj. / Adj.)	7.4% / 75.1%	0.0% / 100.0%	< 0.001

Bibliography: [1] Conroy T, *et al.* FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med*. 2018;379:2395-2406. [2] Vienot A, **Monnien F**, *et al.* SALL4-related gene signature defines a specific stromal subset of pancreatic ductal adenocarcinoma. *Mol Oncol.* 2023. [3] Rashid NU, *et al*. Purity Independent Subtyping of Tumors (PurIST), A Clinically Robust, Single-sample Classifier for Tumor Subtyping in Pancreatic Cancer. *Clin Cancer Res.* 2020;26(1):82-93.

Discovery & Multivariable Selection (development cohort, n=217)

Stepwise multivariable Cox modeling selected a 3-compartment biomarker signature

Recurrence Free Survival

- **CD8 infiltration** (Low): adjusted HR = 1.67 [1.17 - 2.40], p = 0.005
- **Tumoral β-catenin** (Low): adjusted HR = 1.42 [0.96 - 2.12], p = 0.081
- **Stromal HSP47** (High): adjusted HR = 1.33 [0.95 - 1.85], p = 0.091

Adjusted for adjuvant therapy, differentiation, and pN stage.

Overall Survival

- **CD8 infiltration** (Low): adjusted HR = 1.58 [1.10 - 2.28], p = 0.014
- **Tumoral β-catenin** (Low): adjusted HR = 1.55 [1.02 - 2.35], p = 0.038
- **Stromal HSP47** (High): adjusted HR = 1.47 [1.04 - 2.04], p = 0.027

Adjusted for age, adjuvant therapy, differentiation, and pN stage.

Independent Validation in Prodige-24 (validation cohort, n=316)

Membranous β-catenin loss: adverse RFS (adj. HR = 1.58 [1.21-2.07], p = 0.001)

High stromal HSP47: adverse RFS (adj. HR = 1.34 [1.02-1.76], p = 0.03)

CD8+ infiltration: not prognostic in PRODIGE-24.

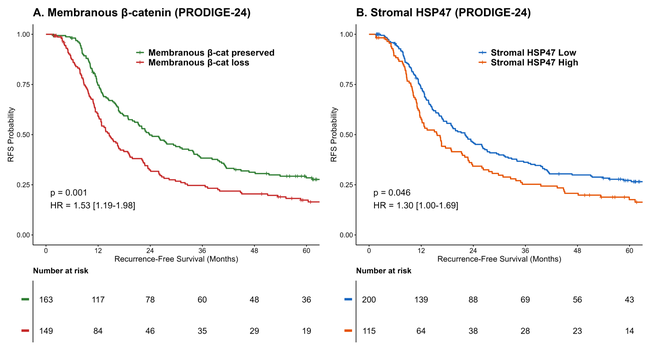
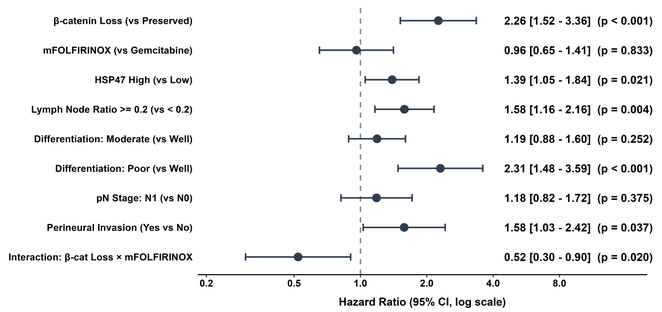


Figure 1. Recurrence-free survival according to (A) membranous β-catenin status and (B) stromal HSP47 expression in the PRODIGE-24 trial validation cohort (n = 316).

Multivariable Cox model for RFS

Independent Prognostic & Predictive Values



Distinct Roles: In this multivariable model, membranous β-catenin confirms its status as an independent predictive biomarker, whereas stromal HSP47 acts as an independent prognostic factor.

Robustness: The predictive value of β-catenin loss for mFOLFIRINOX benefit remains statistically significant (interaction p = 0.020) after full adjustment for major clinical confounders.

Predictive Value for Adjuvant Chemotherapy Benefit

β-catenin loss identifies mFOLFIRINOX responders

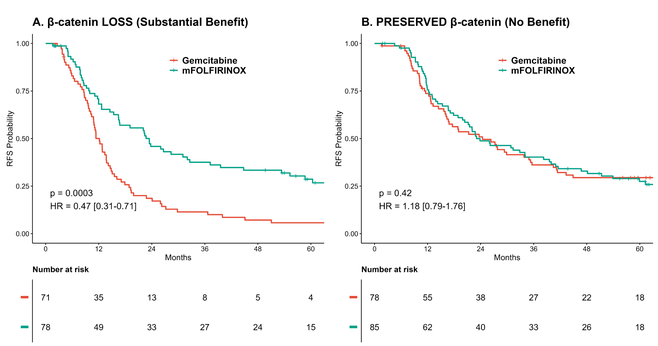


Figure 2. Recurrence-free survival according to adjuvant chemotherapy regimen (mFOLFIRINOX vs Gemcitabine) in patients with (A) β-catenin loss and (B) preserved β-catenin in the PRODIGE-24 trial.

Benefit by Biomarkers Subgroups (PRODIGE-24

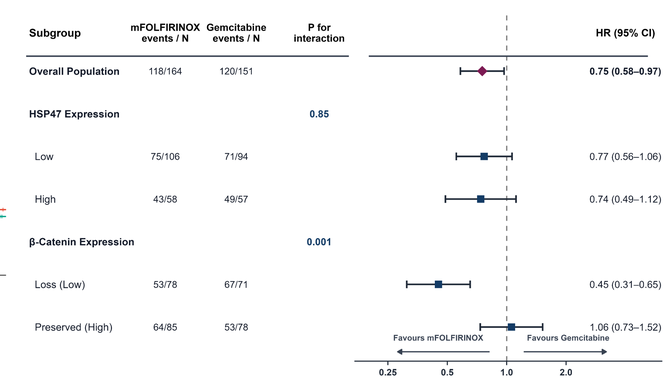


Figure 3. Subgroup analysis. mFOLFIRINOX benefit is restricted to patients with β-catenin loss (HR 0.45 vs 1.06; interaction p = 0.001). HSP47 is not predictive.

Transcriptomic Integration (PurIST[3])

Basal-like: Poor outcomes, no benefit from mFOLFIRINOX regardless of β-catenin status.

Classical: mFOLFIRINOX benefit is strictly restricted to tumors with β-catenin loss (p < 0.0001).

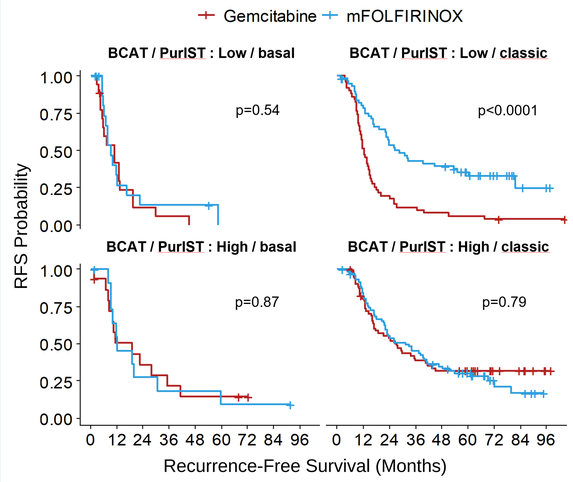
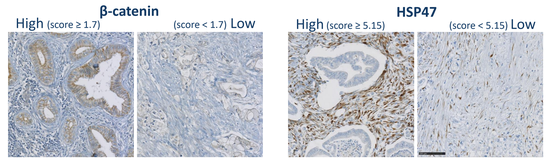


Figure 4. Recurrence-free survival according to adjuvant chemotherapy regimen stratified by PurIST subtype and membranous *β*-catenin status in PRODIGE-24.



CONCLUSION & CLINICAL IMPLICATIONS

1. **Robust prognostic IHC signature:** Membranous β-catenin loss and high stromal HSP47 are independent adverse prognostic factors in resected PDAC, validated in PRODIGE-24.
2. **Predictive value for mFOLFIRINOX:** β-catenin loss identifies patients deriving substantial clinical benefit from adjuvant mFOLFIRINOX over gemcitabine (p = 0.0013).
3. **Refining transcriptomics:** Simple IHC acts as an accessible filter within the "Classical" subtype to pinpoint true mFOLFIRINOX responders.
4. **Routine practice:** A cost-effective, digital pathology tool ready to guide personalized adjuvant chemotherapy and post-operative risk stratification.

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