

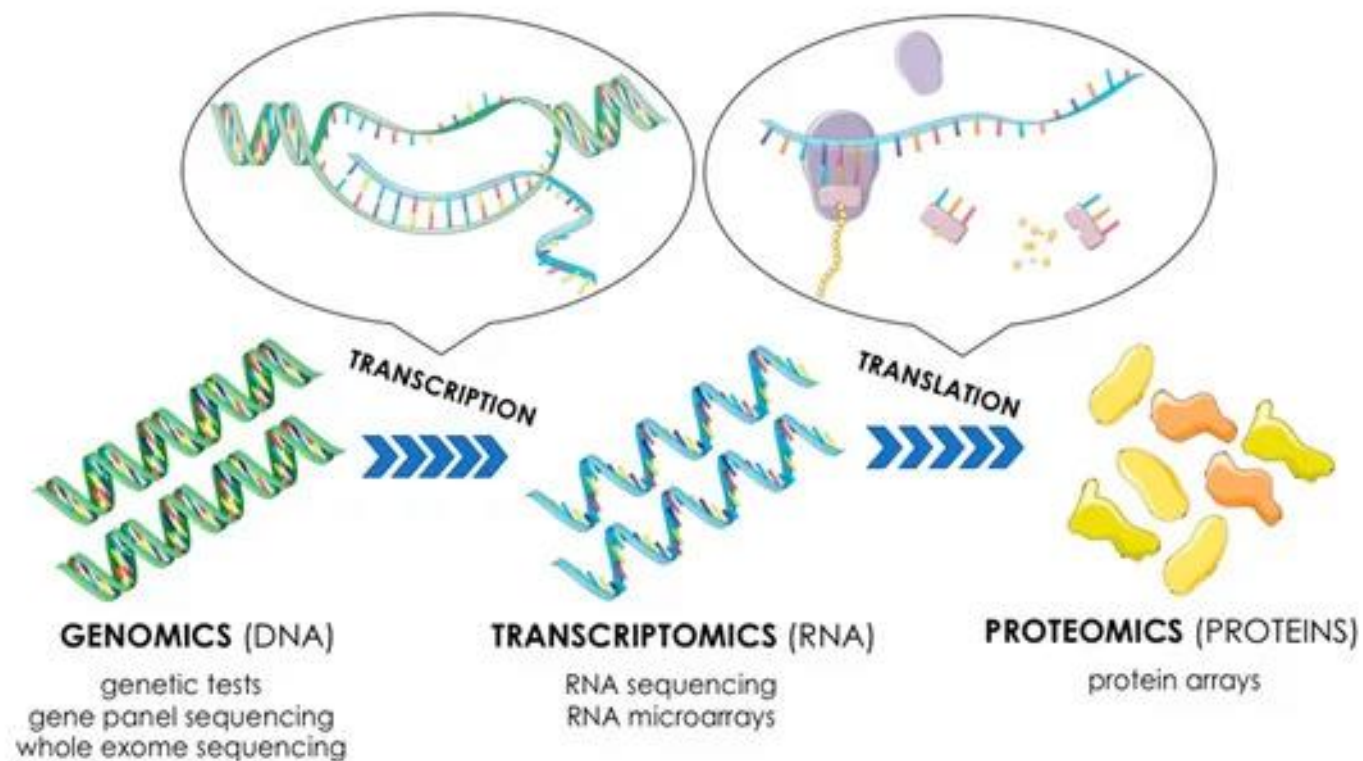
Implication clinique des classifications moléculaires du cancer du pancréas

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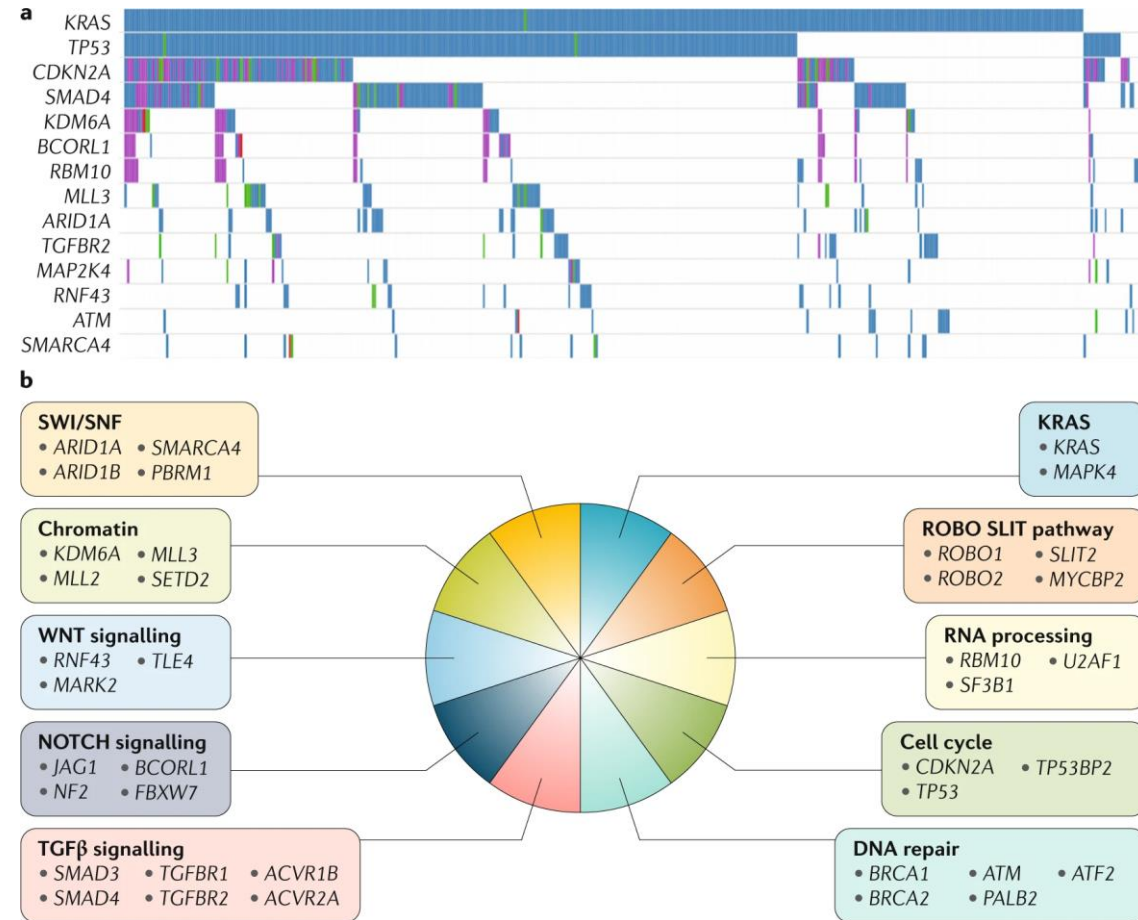
Center GF Leclerc, Dijon France

Les différentes classifications



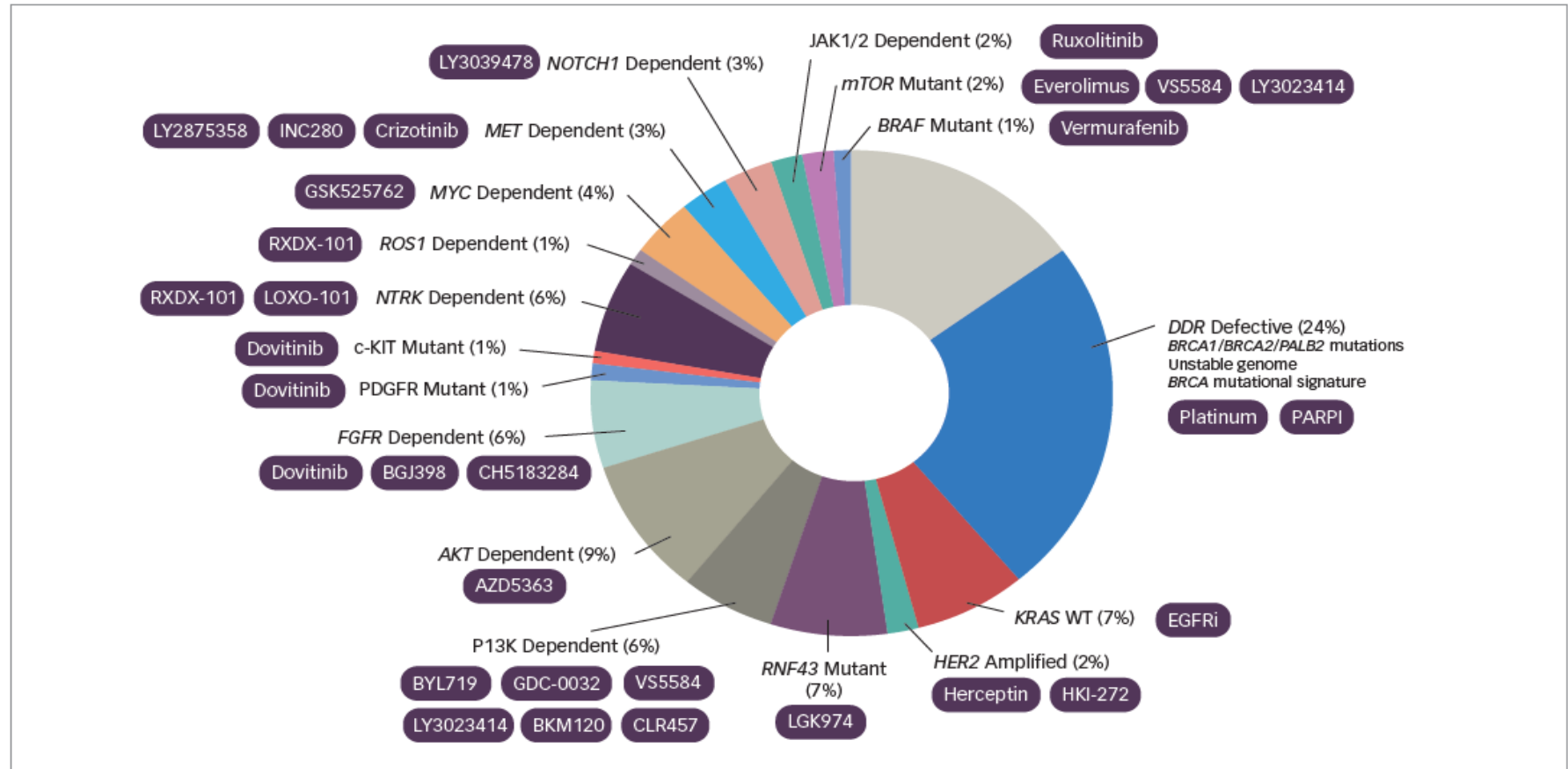
Classification génomique

KRAS, *TP53*, *SMAD4* and *CDKN2A*, >50% des patients



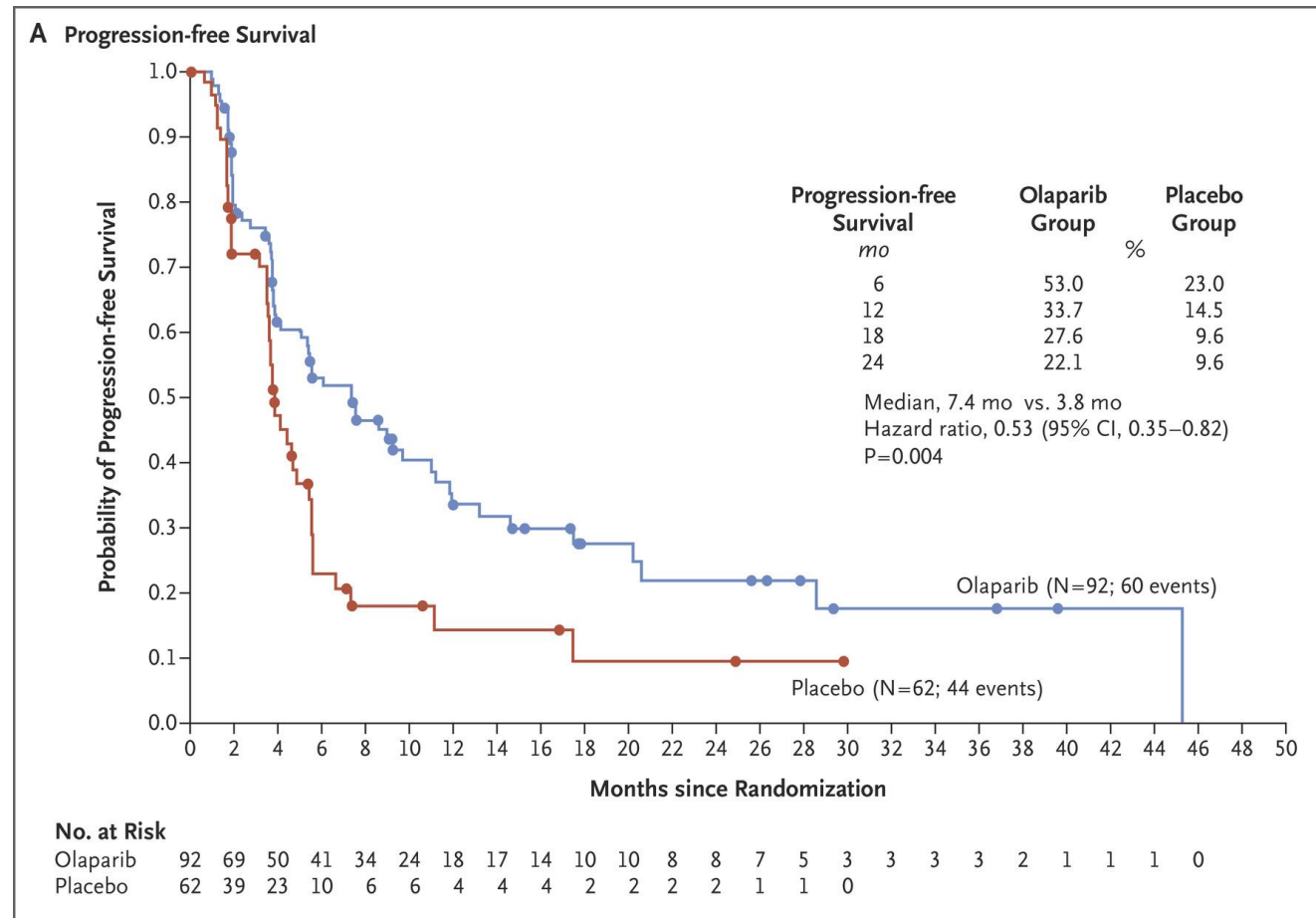
Classification génomique des marqueurs d'intérêts

Peu de mutations ciblables



AKT = ATP-dependent tyrosine kinase; c-KIT = tyrosine-protein kinase kit; DDR = DNA-damage response; EGFRi = epidermal growth factor receptor inhibitor; FGFR = fibroblast growth factor receptor; HER2 = human epidermal growth factor receptor 2; JAK = janus kinase; MET = tyrosin-protein kinase Met; mTOR = mammalian target of rapamycin; MYC = family of oncogenes carried by the avian virus myelocytomatosis and a human gene overexpressed in various cancers; NTRK = neurotrophic tyrosine receptor kinase; PARPi = poly ADP ribose polymerase inhibitor (e.g. olaparib); PDGFR = platelet-derived growth factor receptor; WT = wild type. Reused with permission from Dreyer et al., 2017.⁴⁴

Classification génomique des marqueurs d'intérêts: BRCA2



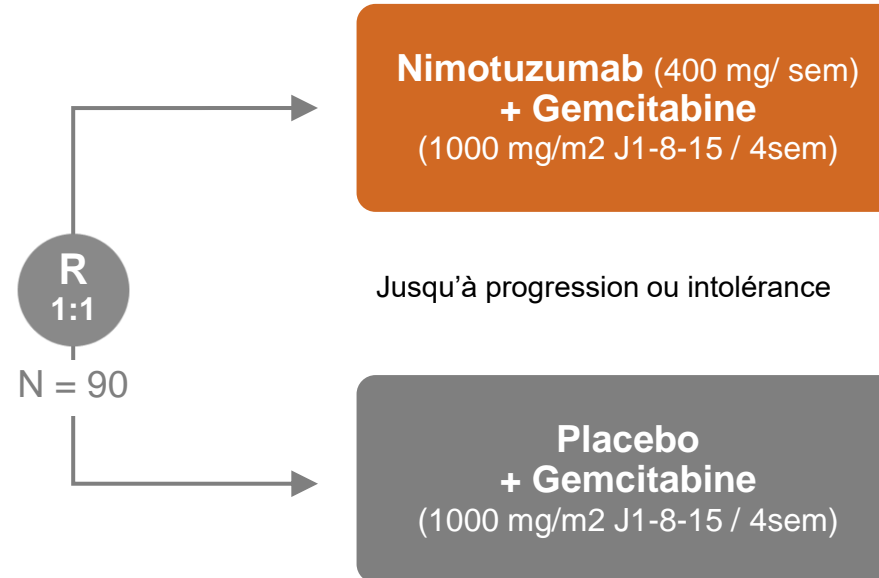
Classification génomique des marqueurs d'intérêts: KRAS WT

ADK pancréas

- Localement avancé ou M+
- Mesurable
- Karnofski ≥ 60
- **KRAS WT**
(évaluation centrale ou locale)

Stratification :

- tête / corps-queue,
- chir antérieure,
- traitement obstruction biliaire,
- chimio adjuvante



Objectif primaire :
Survie Globale

Objectifs secondaires :

- SSP
- TTP
- TCM
- RO
- Tolérance

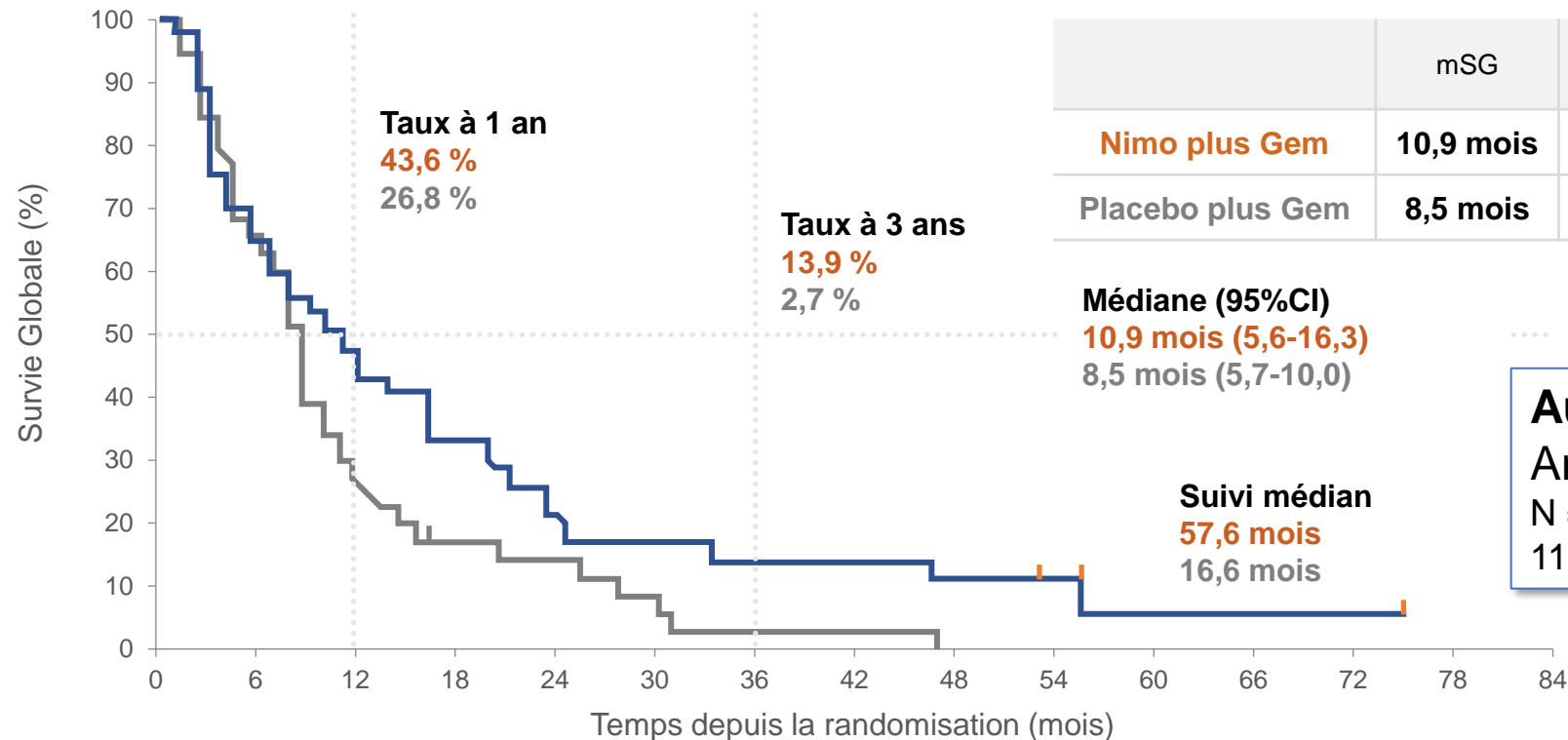
Plan statistique :

Détection de gain de 5,5 mois de SG / puissance 80% (Nimo : 11, 8 / Plo 5,65 mois),
→ n = 79, soit n = 92 avec perdus de vue

- S. Qin et al., ASCO[®] 2022, Abs #4011

Classification génomique des marqueurs d'intérêts: KRAS WT

480 screenés → **92 inclus** → **90 randomisés** → 30/45 traités bras Nimo + 33/45 traités bras Placebo
 Parmi les 90 : 7 KRAS mutés (après 2^{ème} analyse) et 1 ADK vésicule biliaire → **Full Set Analyse : N = 82**



	mSG	HR (95% CI)	valeur-p
Nimo plus Gem	10,9 mois	0,50	RMST-Log
Placebo plus Gem	8,5 mois	(0,06-0,94)	P = 0,024

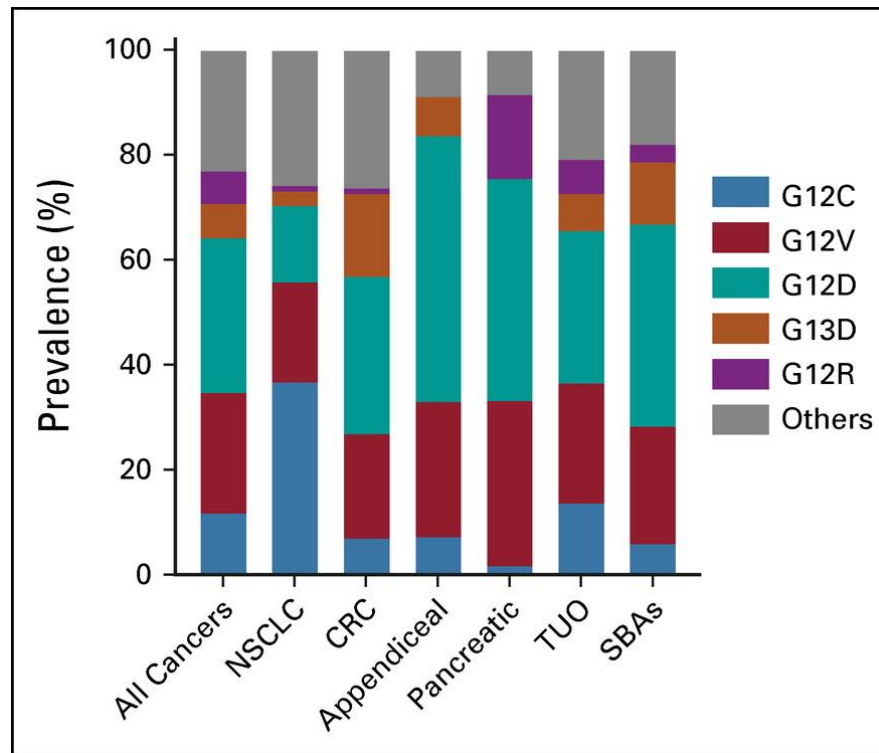
Autre résultat de SG
 Analyse *per protocol* :
 N = 28 (Nimo) / N = 21 bras (Placebo)
 11,5 vs 8,5 mois. p = 0,039

Nb à risque

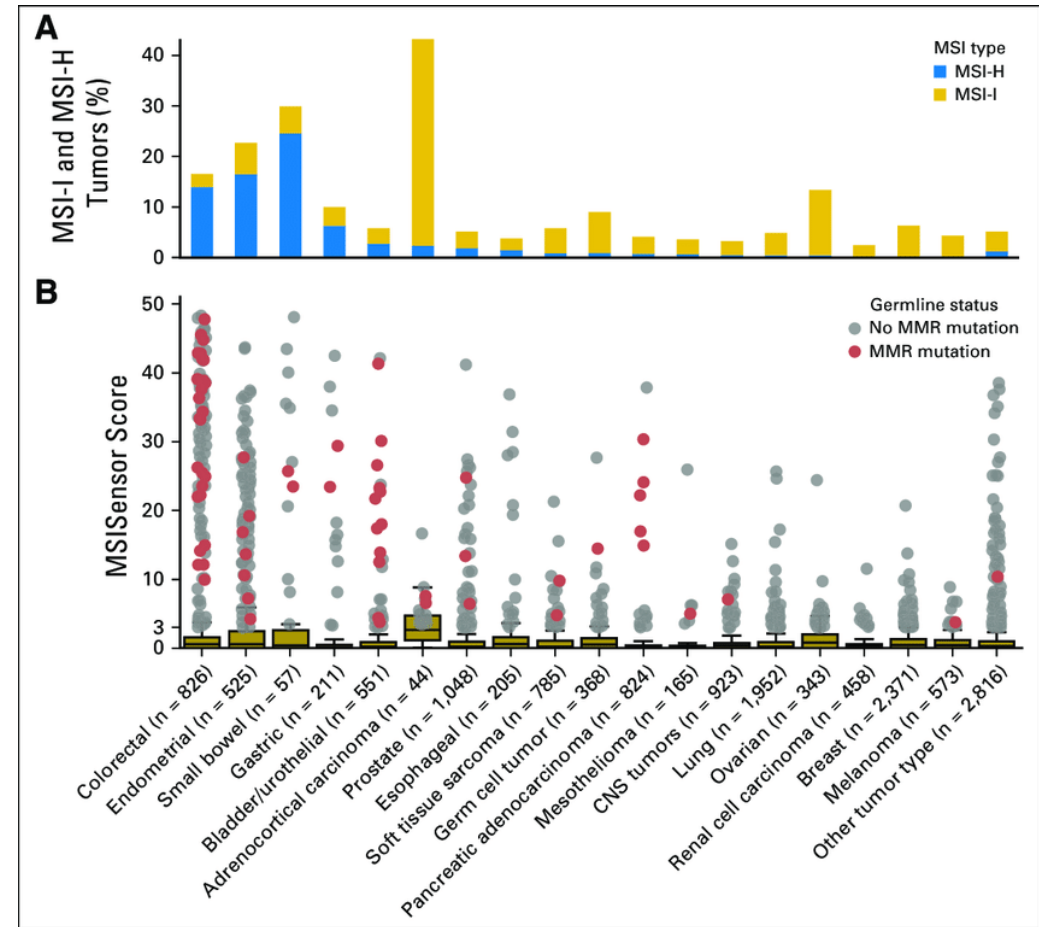
Nimotuzumab + Gem	41	27	17	13	7	6	5	5	4	3	1	1	1	0	41
Placebo + Gem	41	27	11	6	5	3	1	1	0						

Classification génomique des marqueurs d'intérêts

- MSI et KRAS: 2 cibles



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DOI: [10.1200/JCO.18.00283](#)

Classification génomique des marqueurs d'intérêts: MSI

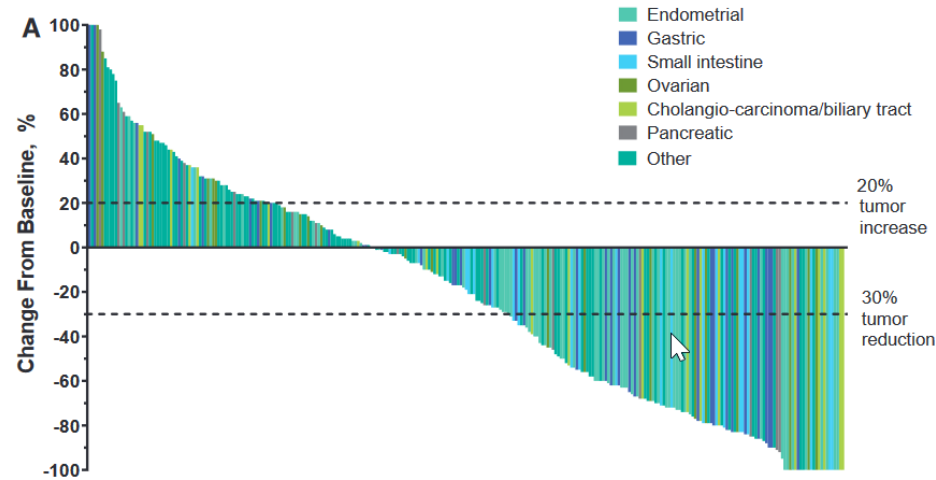


Table 3. Summary of efficacy outcomes by tumor types with the highest number of enrolled patients

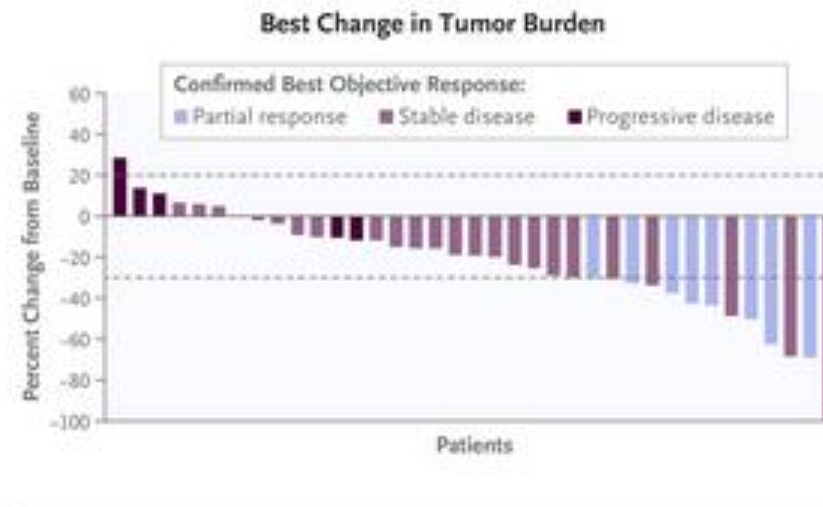
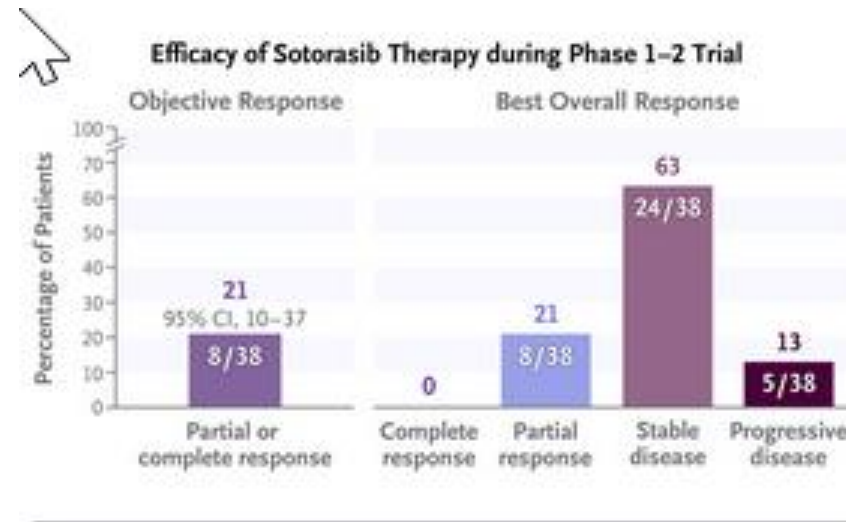
	Endometrial n = 68	Gastric n = 42	Small Intestine n = 25	Ovarian n = 24	Cholangiocarcinoma/ biliary tract n = 22	Pancreatic n = 22
ORR, % (95% CI)	48.5 (36.2-61.0)	31.0 (17.6-47.1)	48.0 (27.8-68.7)	33.3 (15.6-55.3)	40.9 (20.7-63.6)	18.2 (5.2-40.3)
Best objective response, n (%)						
CR	10 (14.7)	4 (9.5)	4 (16.0)	3 (12.5)	3 (13.6)	1 (4.5)
PR	23 (33.8)	9 (21.4)	8 (32.0)	5 (20.8)	6 (27.3)	3 (13.6)
SD	13 (19.1)	7 (16.7)	7 (28.0)	2 (8.3)	3 (13.6)	3 (13.6)
PD	19 (27.9)	15 (35.7)	5 (20.0)	12 (50.0)	8 (36.4)	8 (36.4)
Not evaluable	1 (1.5)	1 (2.4)	—	—	—	—
No assessment	2 (2.9)	6 (14.3)	1 (4.0)	2 (8.3)	2 (9.1)	7 (31.8)
DOR, median (range), months	NR (2.9 to 47.1+)	NR (6.3 to 51.1+)	NR (2.1— to 41.8+)	NR (4.2 to 43.5+)	30.6 (6.2 to 40.5+)	NR (8.1 to 24.3+)
Median PFS, months (95% CI)	13.1 (4.9-34.4)	3.2 (2.1-12.9)	23.4 (4.3-NR)	2.2 (2.0-6.2)	4.2 (2.1-24.9)	2.1 (1.9-3.4)
PFS rate ≥5 years ^a , %	33.9	28.5	49.1	29.2	12.7	NR
Median OS, months (95% CI)	NR (32.4-NR)	11.0 (5.8-31.5)	NR (16.2-NR)	33.6 (11.0-NR)	19.4 (6.5-NR)	3.7 (2.1-9.8)
OS rate ≥3 years ^a , %	62.1	34.5	38.7	42.6	30.3	22.7

^a— Indicates no progressive disease by the time of last disease assessment.

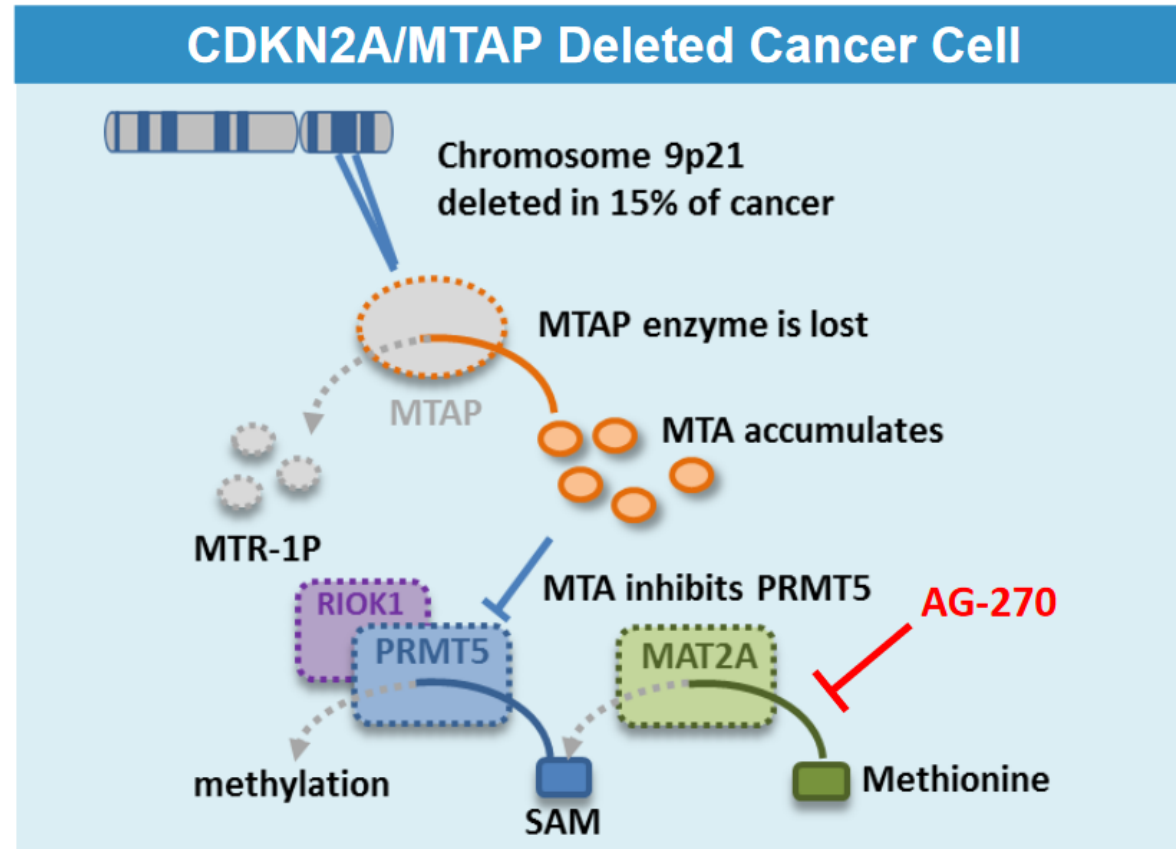
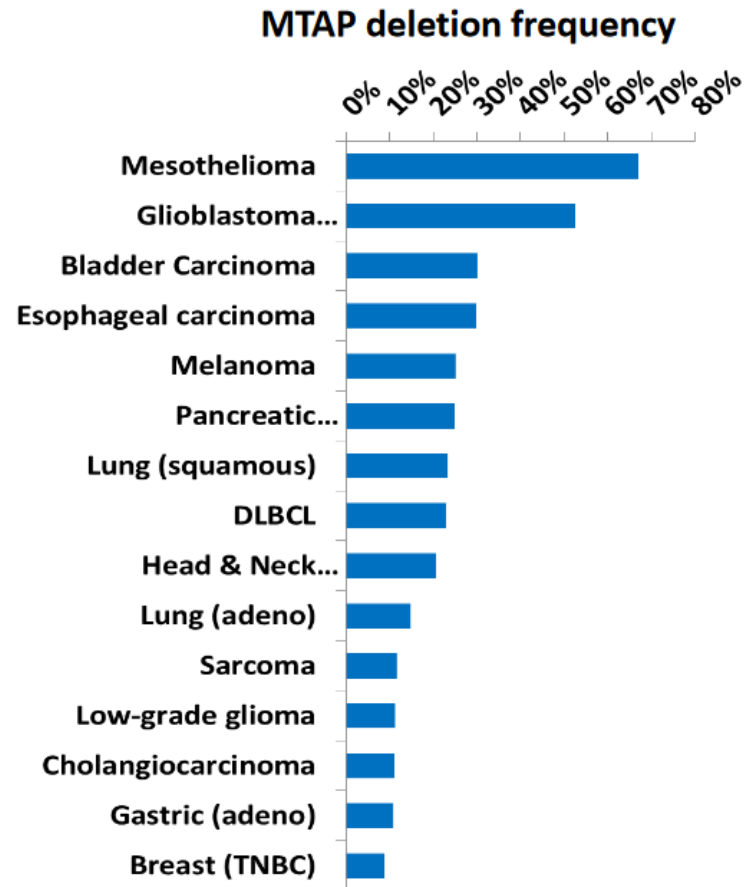
CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

^aAs per Kaplan-Meier method for censored data.

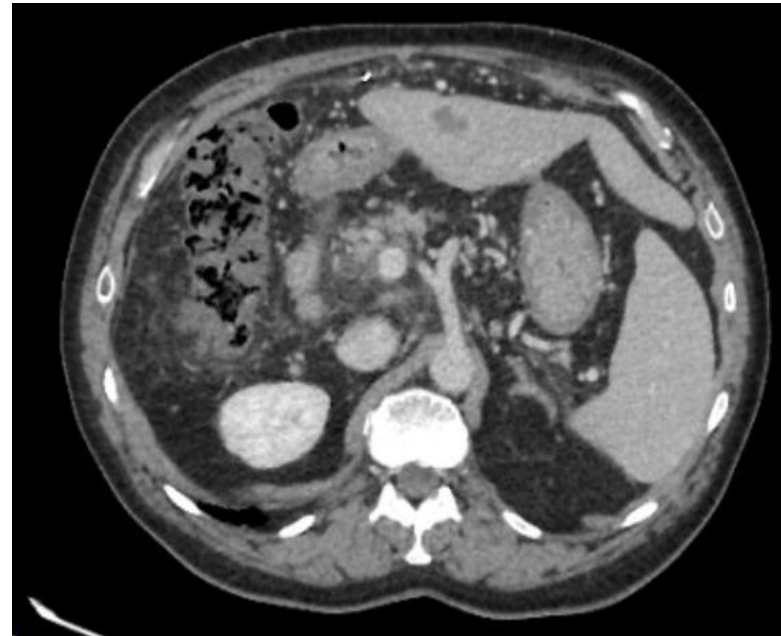
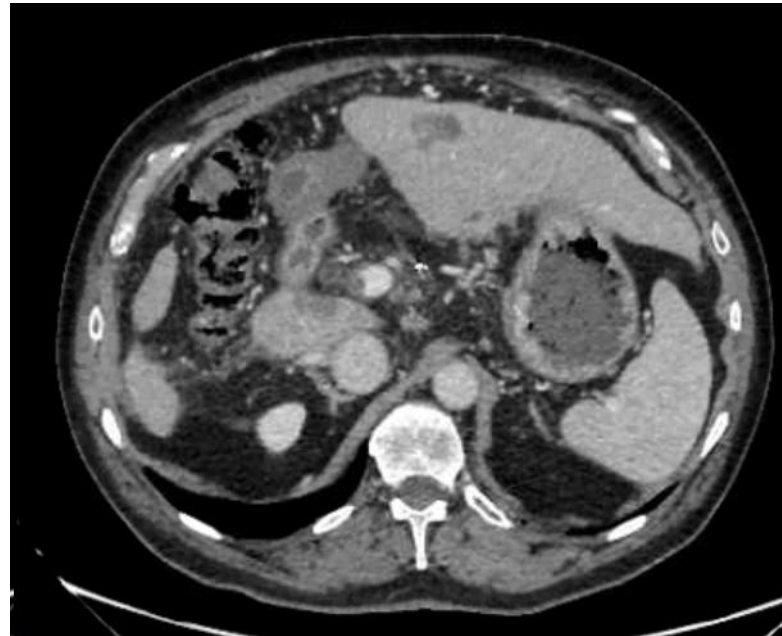
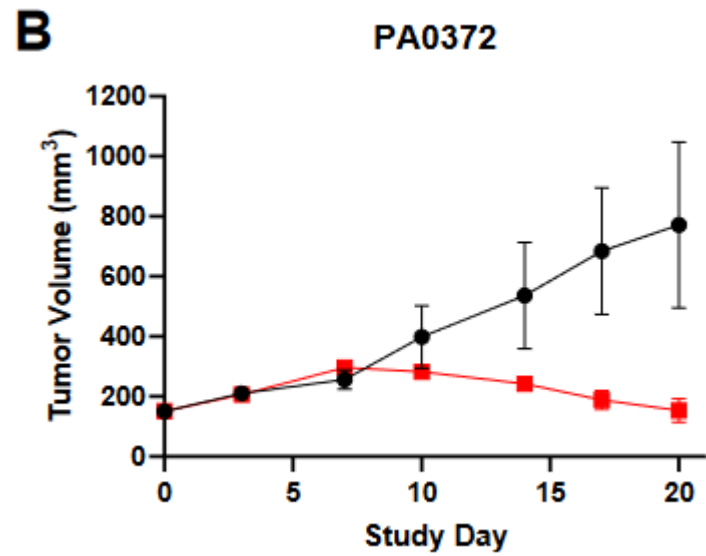
Classification génomique des marqueurs d'intérêts: KRAS G12C



Un nouveau biomarqueur la perte de MTAP



Un nouveau biomarqueur la perte de MTAP



Classification transcriptomiques

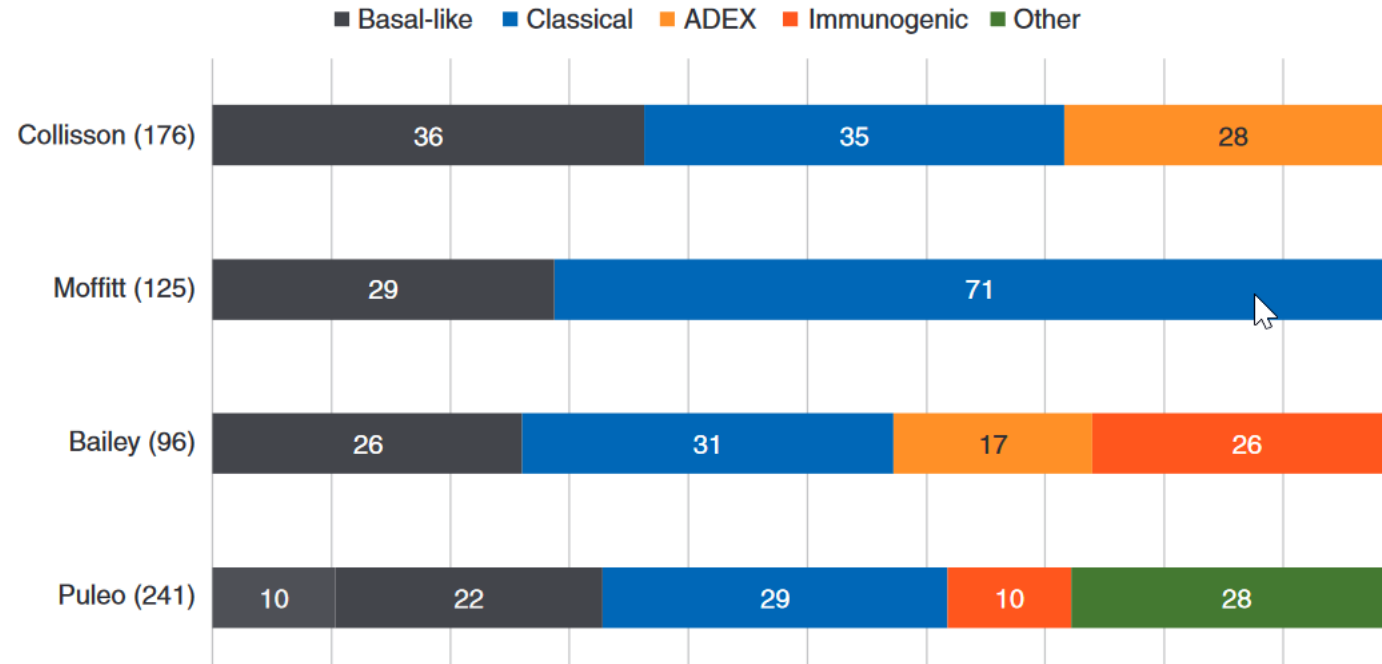
Table 1. Summary of studies that have subtyped pancreatic ductal adenocarcinoma (PDAC)

Study by	Defined subtypes (with potential overlap)			Other subtypes	
Bailey et al. [23]	Squamous	PP	ADEX	Immunogenic	
Collisson et al. [18]	QM-PDA	Classical	Exocrine-like		
Moffitt et al. [21]	Basal-like	Classical			Activated stroma, Normal stroma
Puleo et al. [26]	Pure basal-like	Pure classical		Immune classic	Desmoplastic, Stroma activated ^a
Maurer et al. [28]	Basal-like	Classical			ECM-rich stroma, Immune-rich stroma
Kim et al. [19]	Subtype 2	Subtype 1?	Subtype 3	Subtype 1?	
Mueller et al. [24]	Cluster 1	Cluster 2	Cluster 5?	Cluster 4	Cluster 3
Janky et al. [22]	k3.c13	k3.c11	k3.c12		
Noll et al. [30]	KRT81 ⁺ HNF1A ⁻	KRT81 ⁻ HNF1A ⁻	KRT81 ⁻ HNF1A ⁺		
Martinelli et al. [60]	GATA6 ^{low}		GATA6 ^{high}		
Sivakumar et al. [46]	Wnt ⁻ /HH ⁻		Notch	Cell cycle	
Daemen et al. [41]	Glycolytic	Lipogenic			Slow proliferating
Seino et al. [39]	WRi		W ⁻		W ⁺

Metabolique
Epigénétique

Martens et al Annals of Oncology 30: 1428–1436, 2019

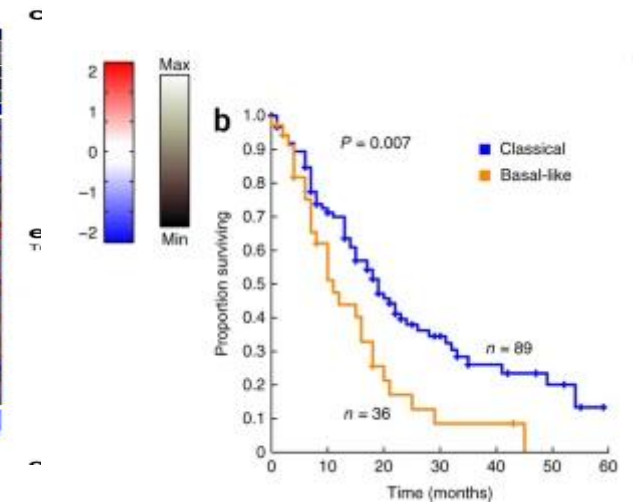
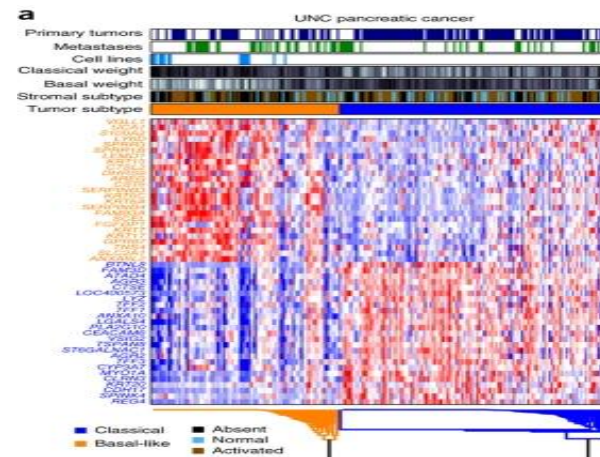
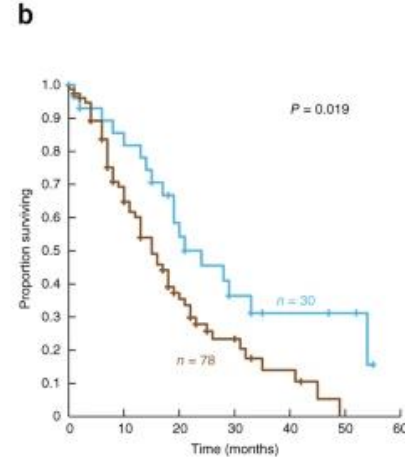
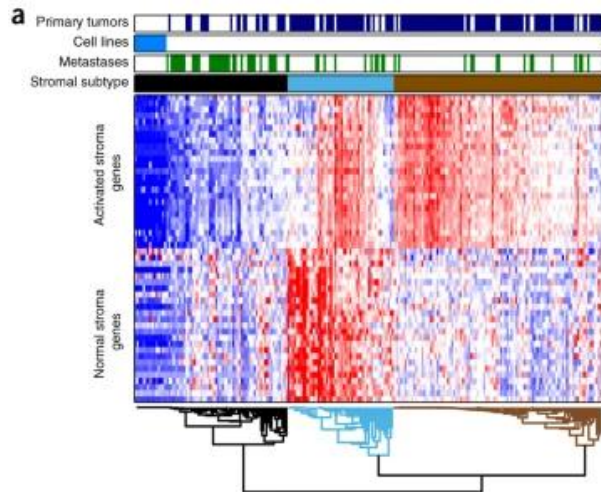
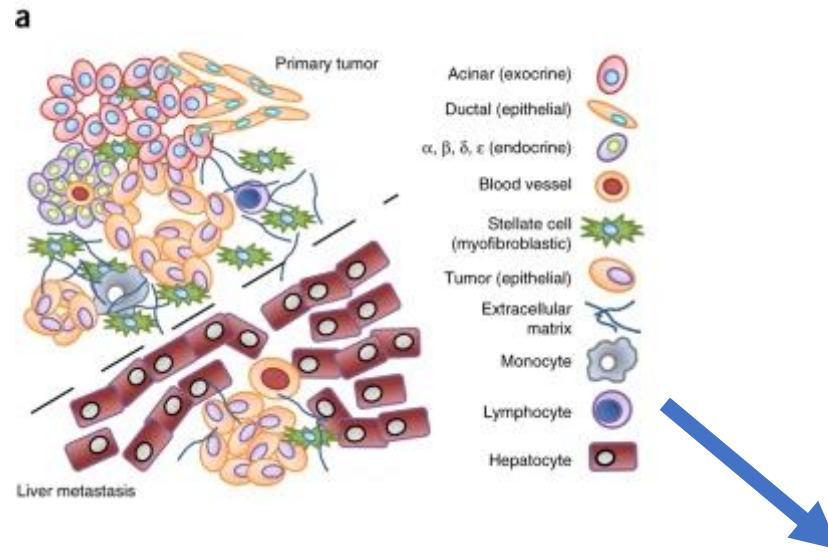
Classifications transcriptomiques



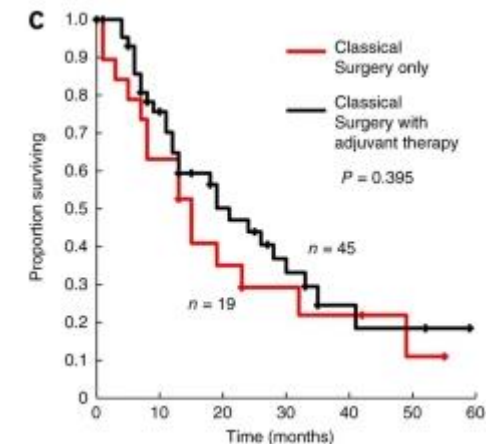
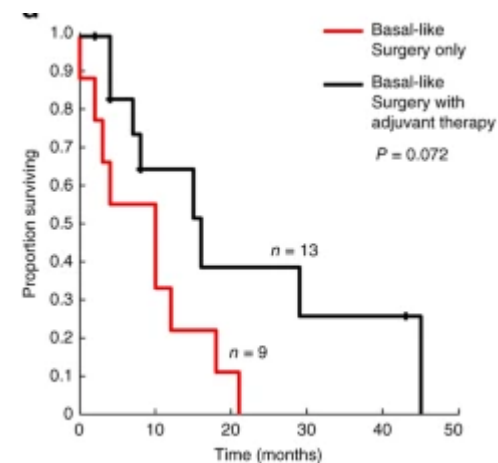
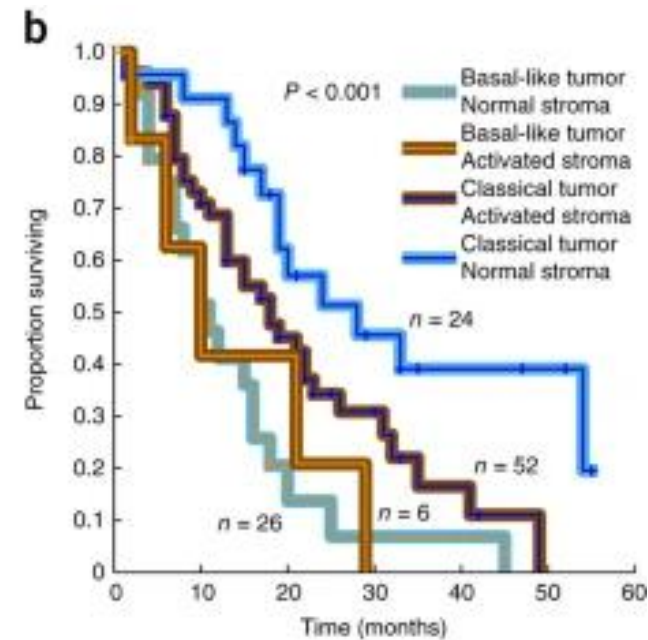
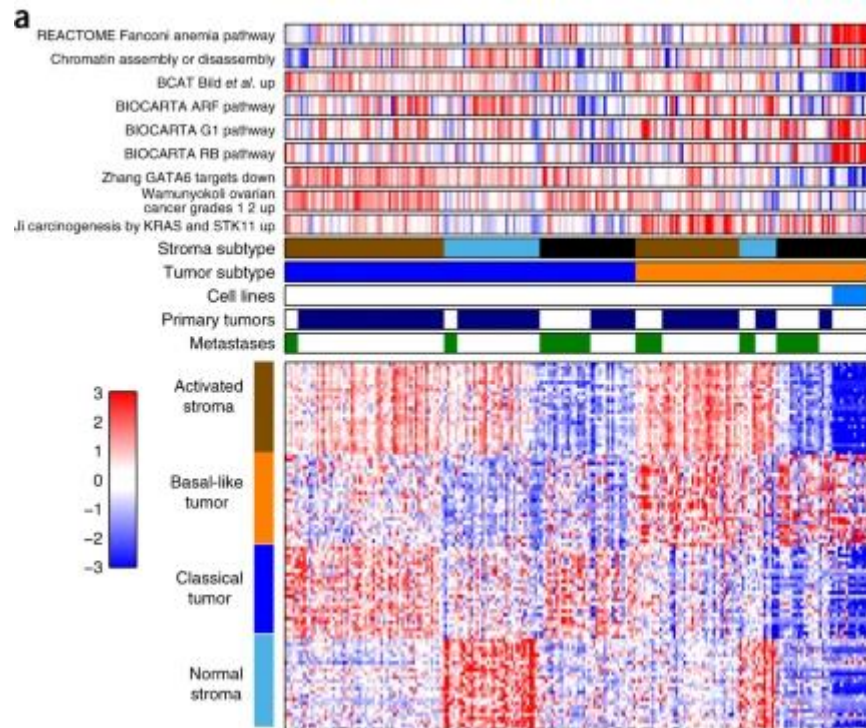
Moffitt et al. considère les ADEX comme des clusters de genes du pancreas exocrine normal
Puleo et Bailey decouvre une variété immunitaire

Martens et al Annals of Oncology 30: 1428–1436, 2019

Particularité de la classification de Moffitt



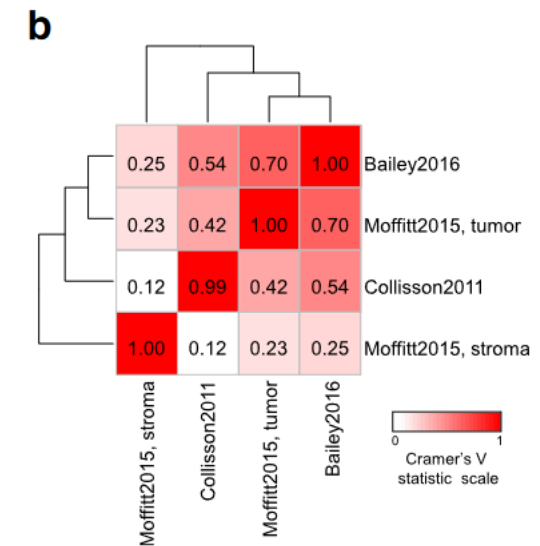
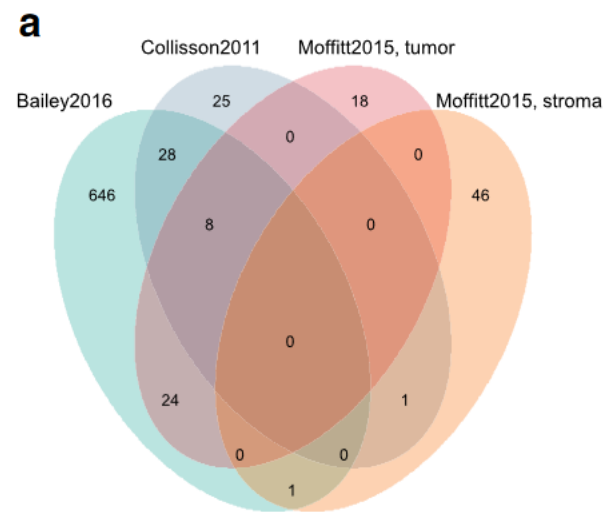
Particularité de la classification de Moffitt



Validation and comparison of the molecular classifications of pancreatic carcinomas

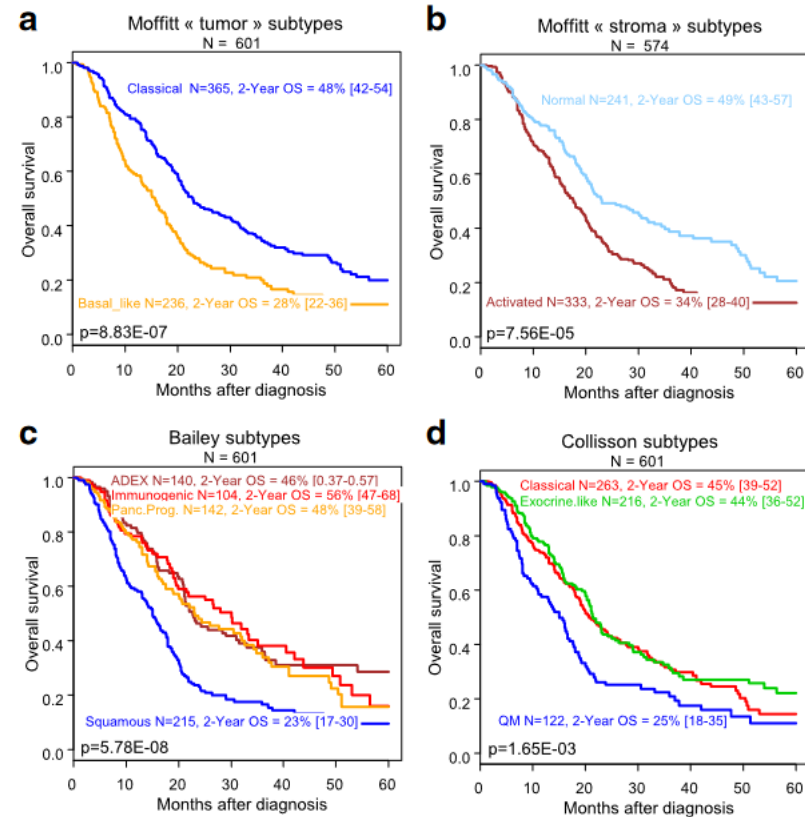
David J. Birnbaum^{1,2,3}, Pascal Finetti¹, Daniel Birnbaum¹, Emilie Mamessier^{1†} and François Bertucci^{1,3,4*†}

- 15 Dataset
- 846 patients
- Concordance partielle entre les classifications

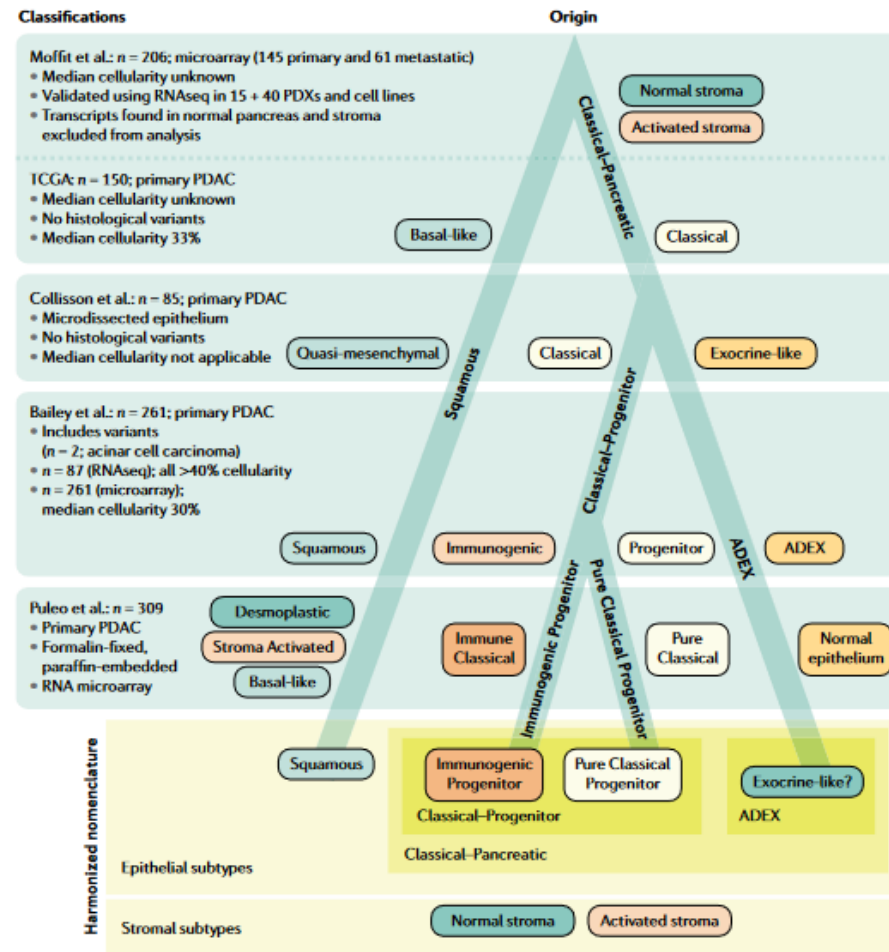


Validation and comparison of the molecular classifications of pancreatic carcinomas

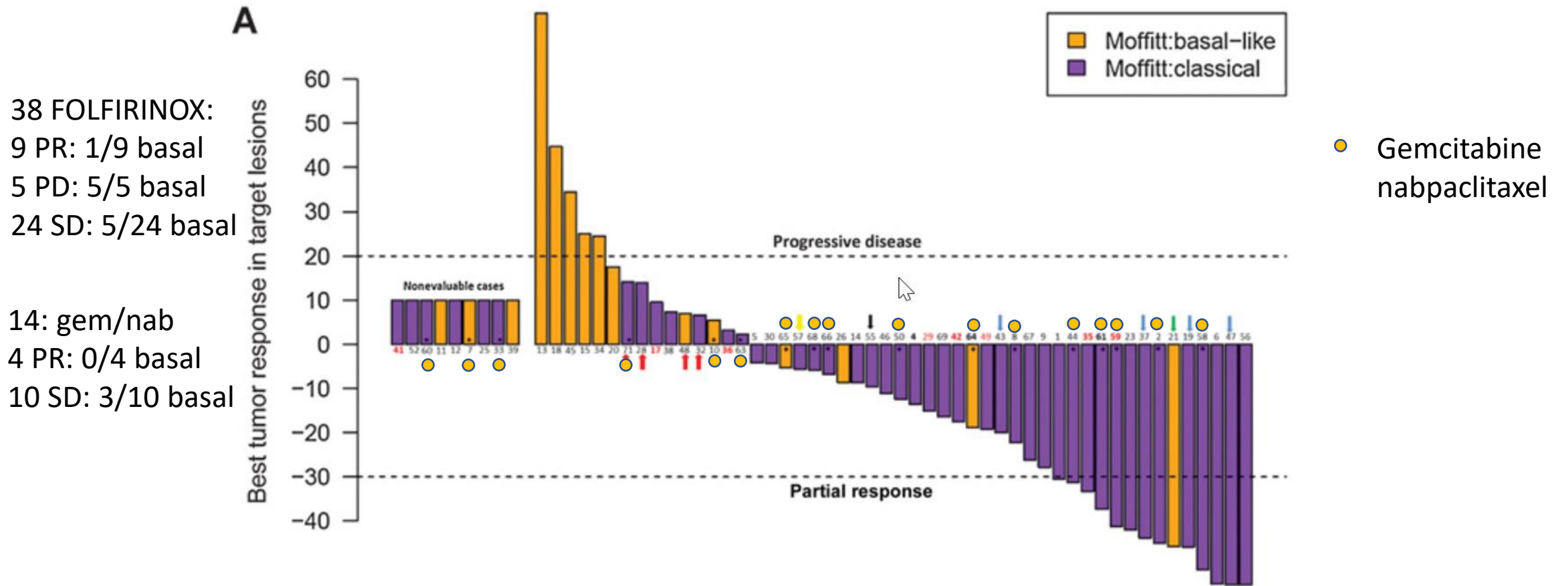
David J. Birnbaum^{1,2,3}, Pascal Finetti¹, Daniel Birnbaum¹, Emilie Mamessier^{1†} and François Bertucci^{1,3,4*†}



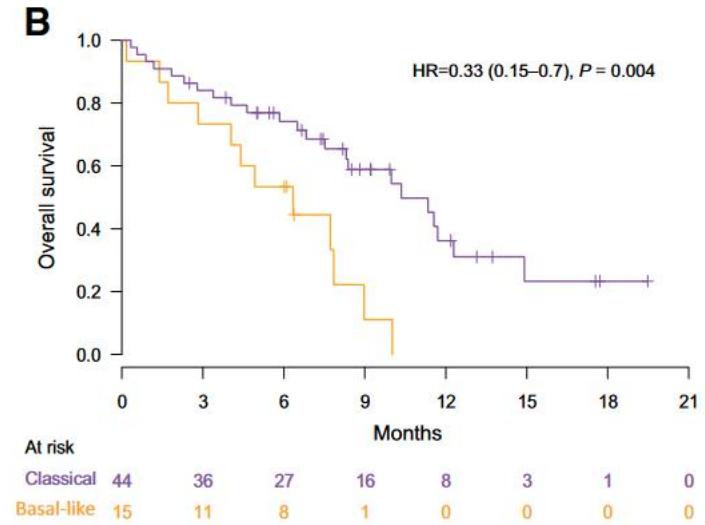
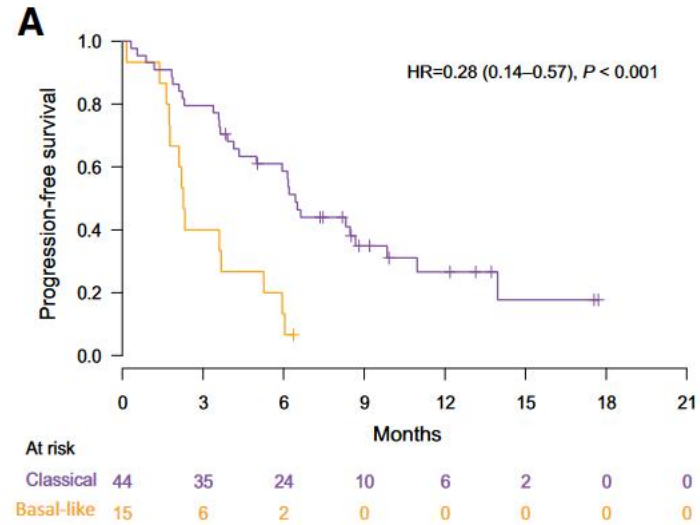
Vers un consensus



Role prédictif: COMPASS study

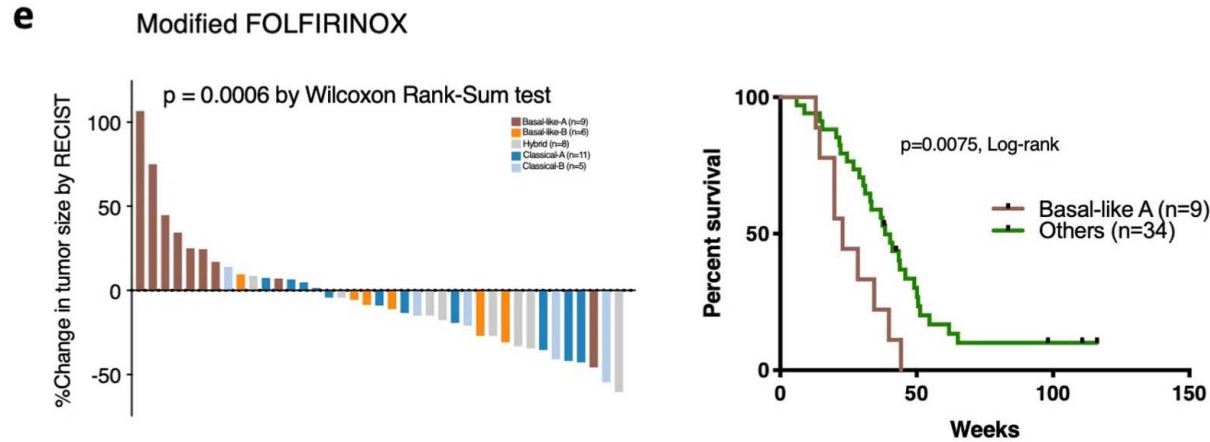


Role prédictif: COMPASS study

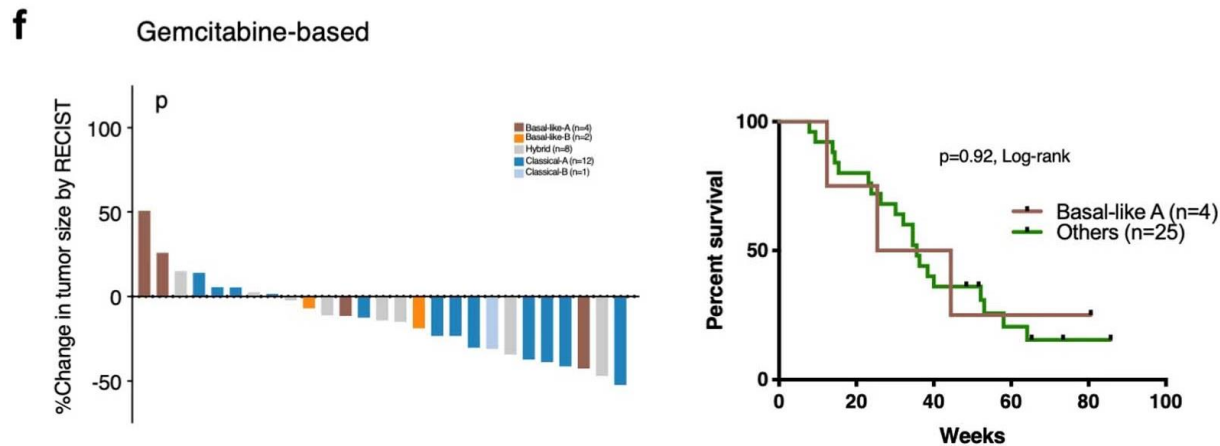


Rôle prédictif: analyse rétrospective des phases III

Conroy

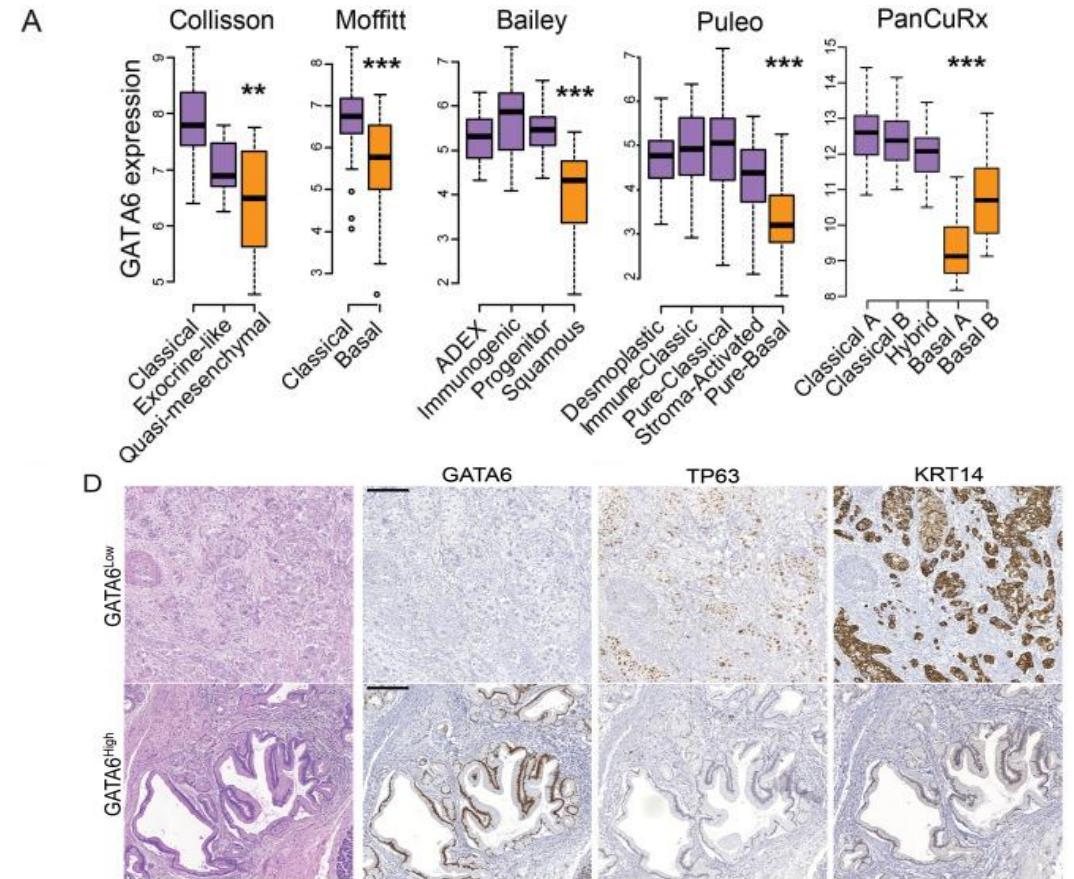
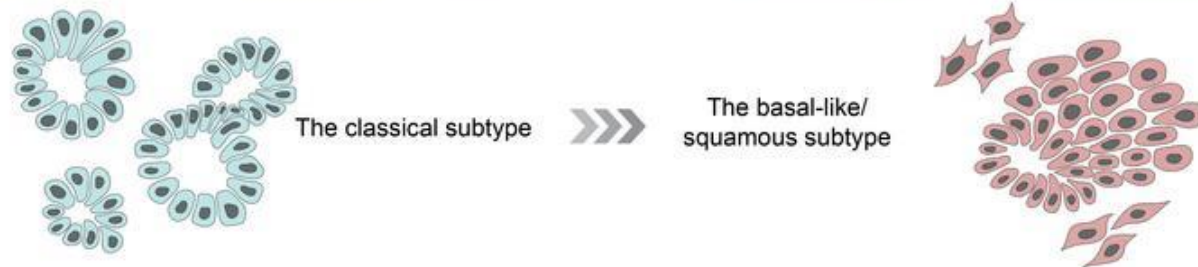
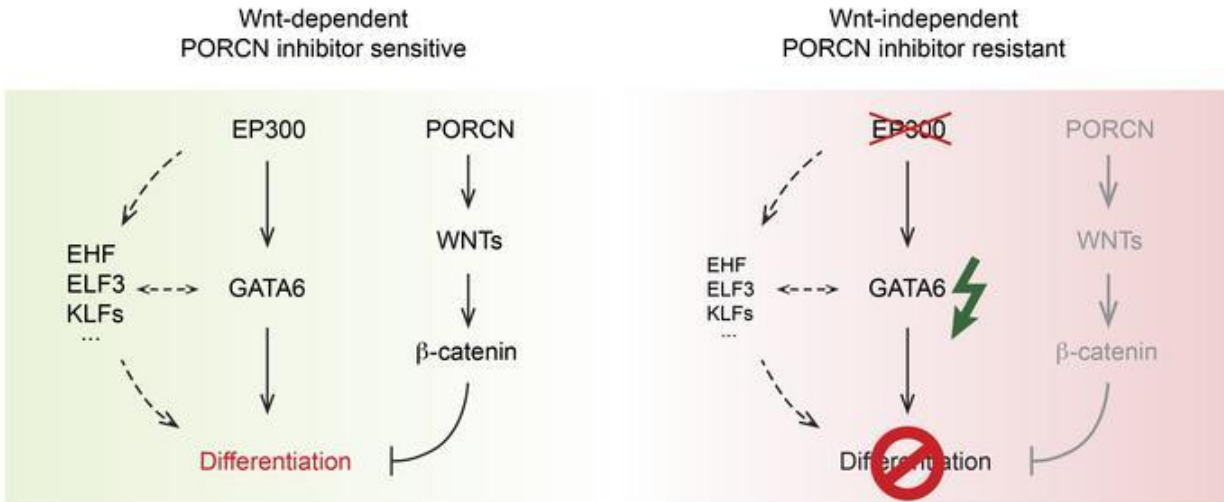


Von Hoff

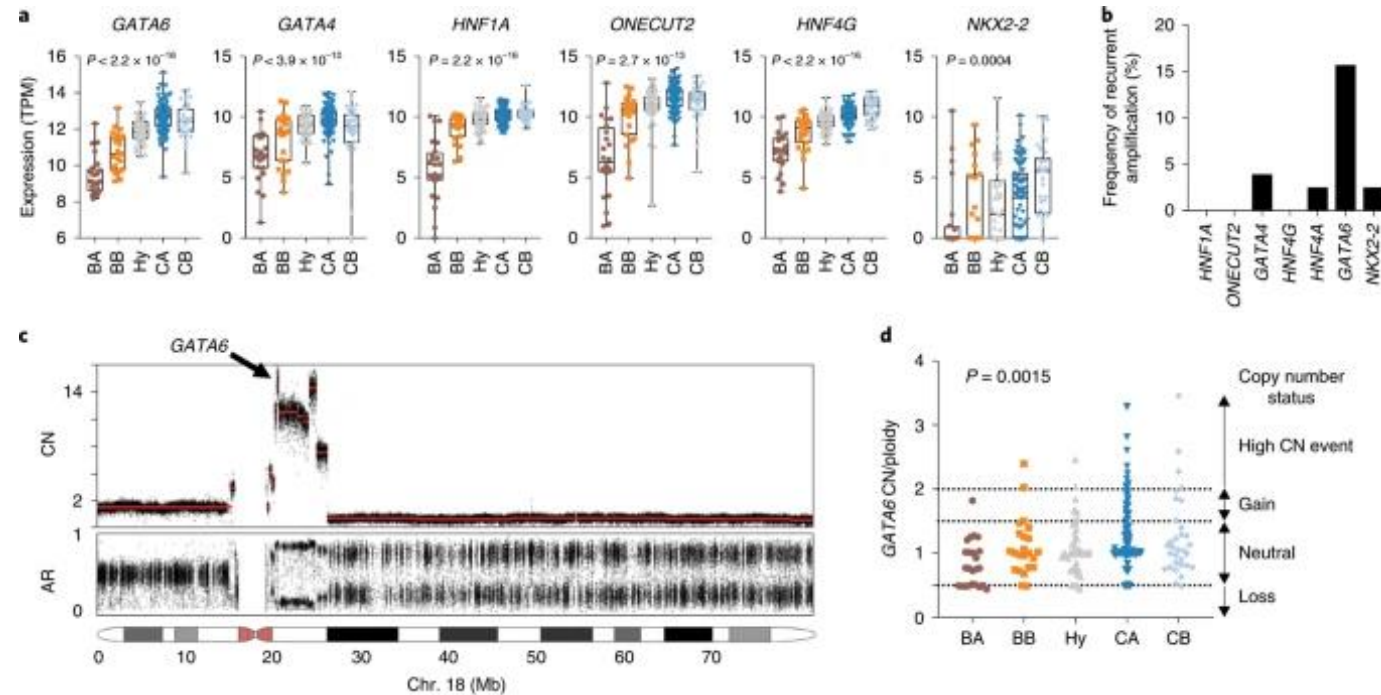


Approximation histologique des classifications

Gata6 est régulé positivement dans les tumeurs classiques

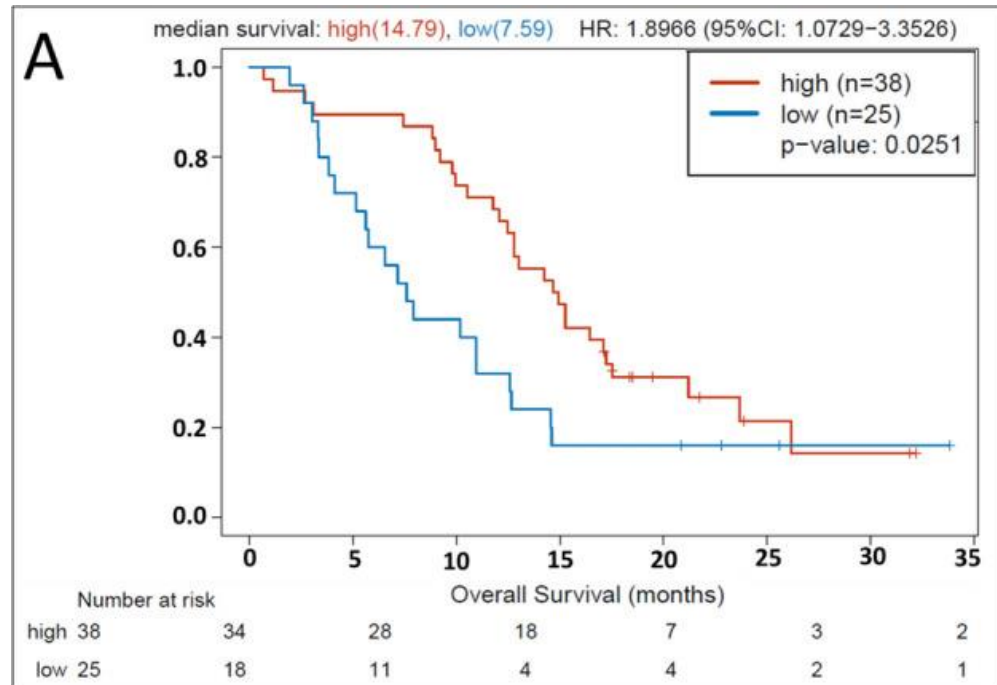


Approximation histologique des classifications Gata6 est amplifié dans les tumeurs classiques

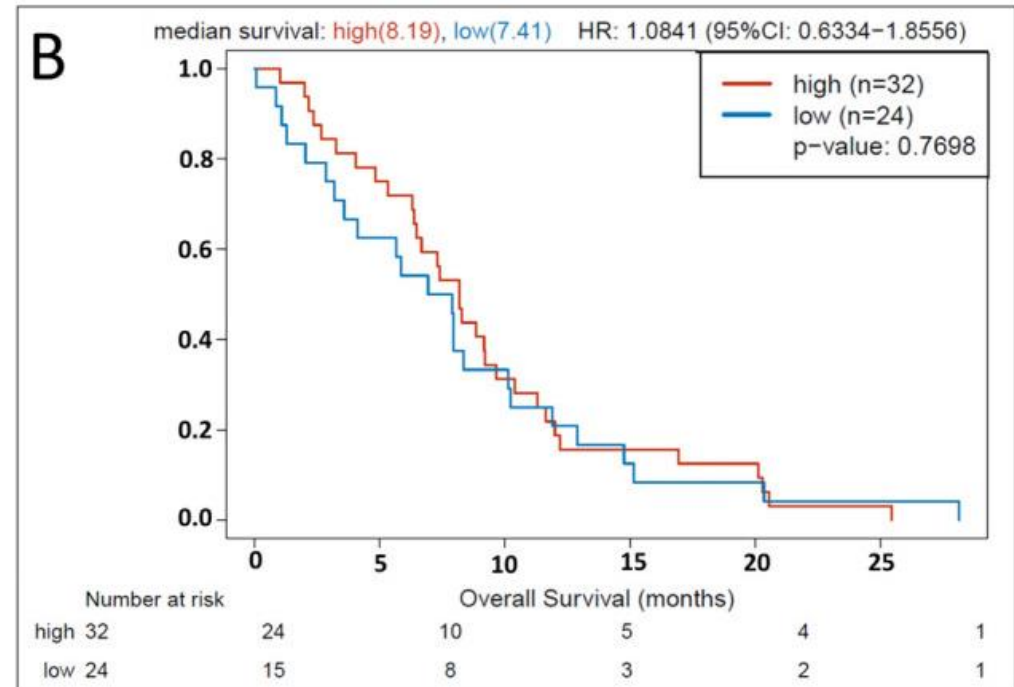


Approximation histologique des classifications

FOLFIRINOX



Gemcitabine nabpaclitaxel



Conclusion

- Les marqueurs génétiques ont un intérêt théranostic majeur
- BRCA, KRAS, MSI, NTRK peuvent aboutir a des options thérapeutiques
- Les signatures transcriptomiques peuvent aider à stratifier le pronostic (tumeur basale de mauvais pronostic)
- Les tumeurs classiques semblent sensibles au FOLFIRINOX
- GATA6 est un marqueur des tumeurs classiques