

Prédiction du risque résiduel de rechute après un cancer du sein localisé

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Gustave Roussy

Plan

- Question posée
- Prédiction du risque de rechute dans les cancers du sein luminaux
- Prédiction du risque de rechute dans les cancers du sein triple négatifs

Question posée

Background

Breast Cancer: 1st cancer worldwide in women, 1.7 M cases/year
Early Breast Cancer (eBC): 95% of BC in US /Europe
85% of eBC patients will never relapse and are cured

Medical challenge

New drugs are being developed in populations of patients with >80% cure rate leading to failures of development or overtreatment

Goal of the project

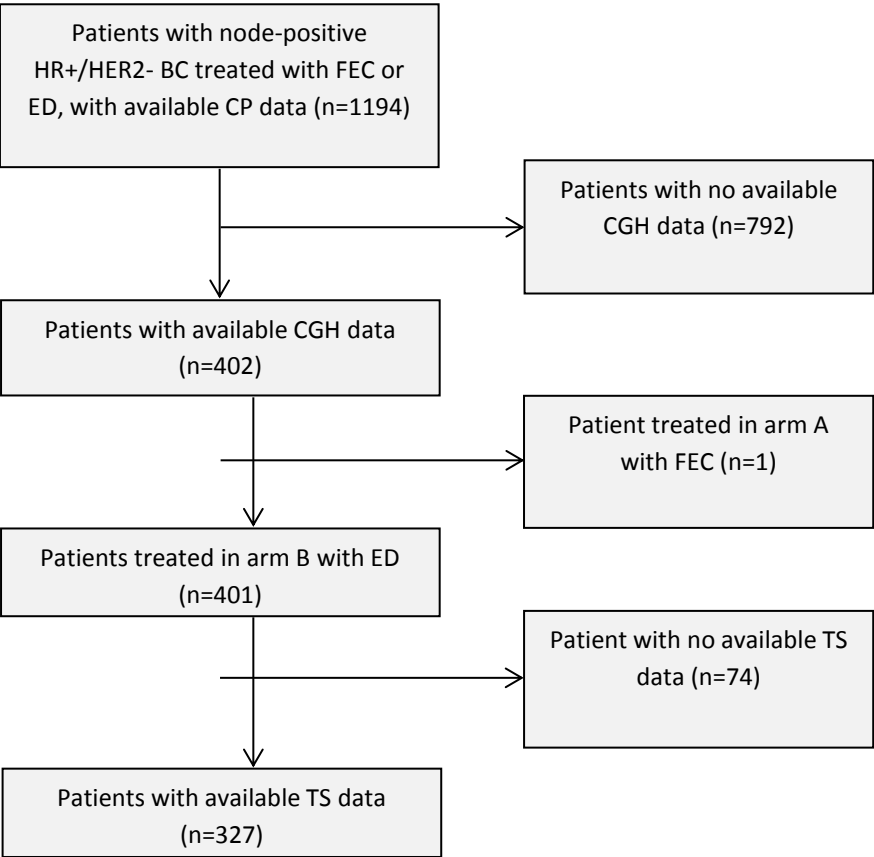
Develop molecular assays to identify which patients present a high risk of relapse after conventional therapies
in order to focus drug development, implementation and reimbursement in this population

Plan

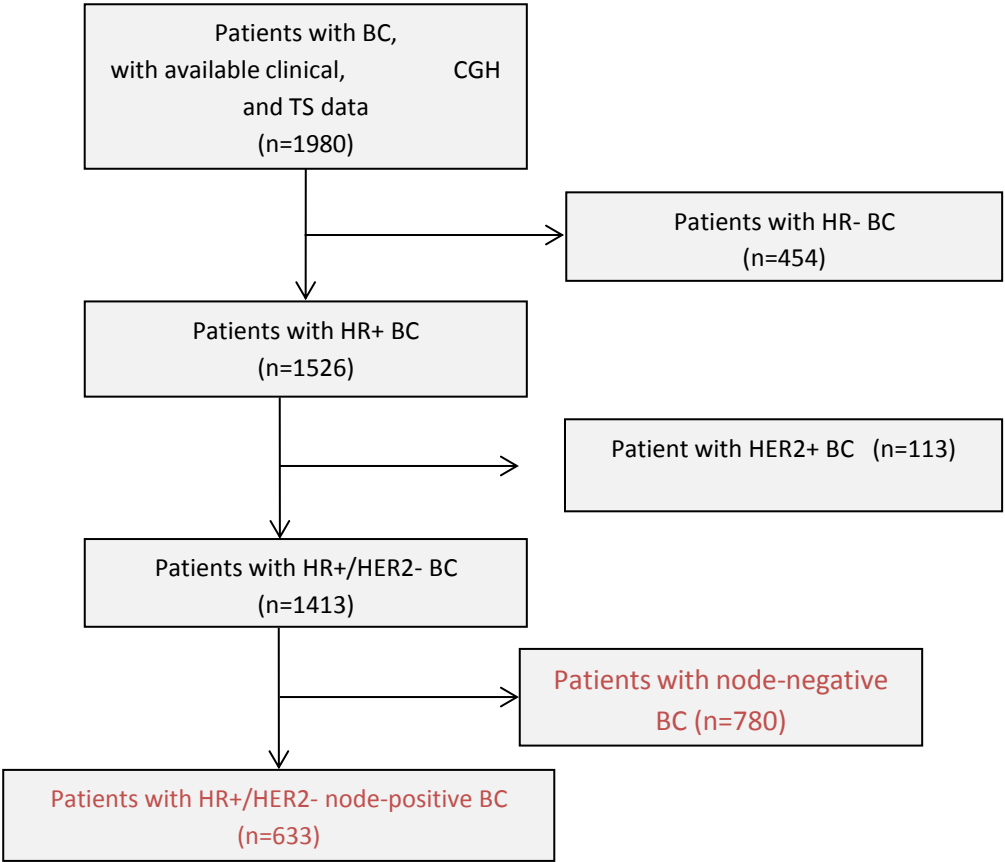
- Question posée
- Prédiction du risque de rechute dans les cancers du sein luminaux
- Prédiction du risque de rechute dans les cancers du sein triple négatifs

Study Flow

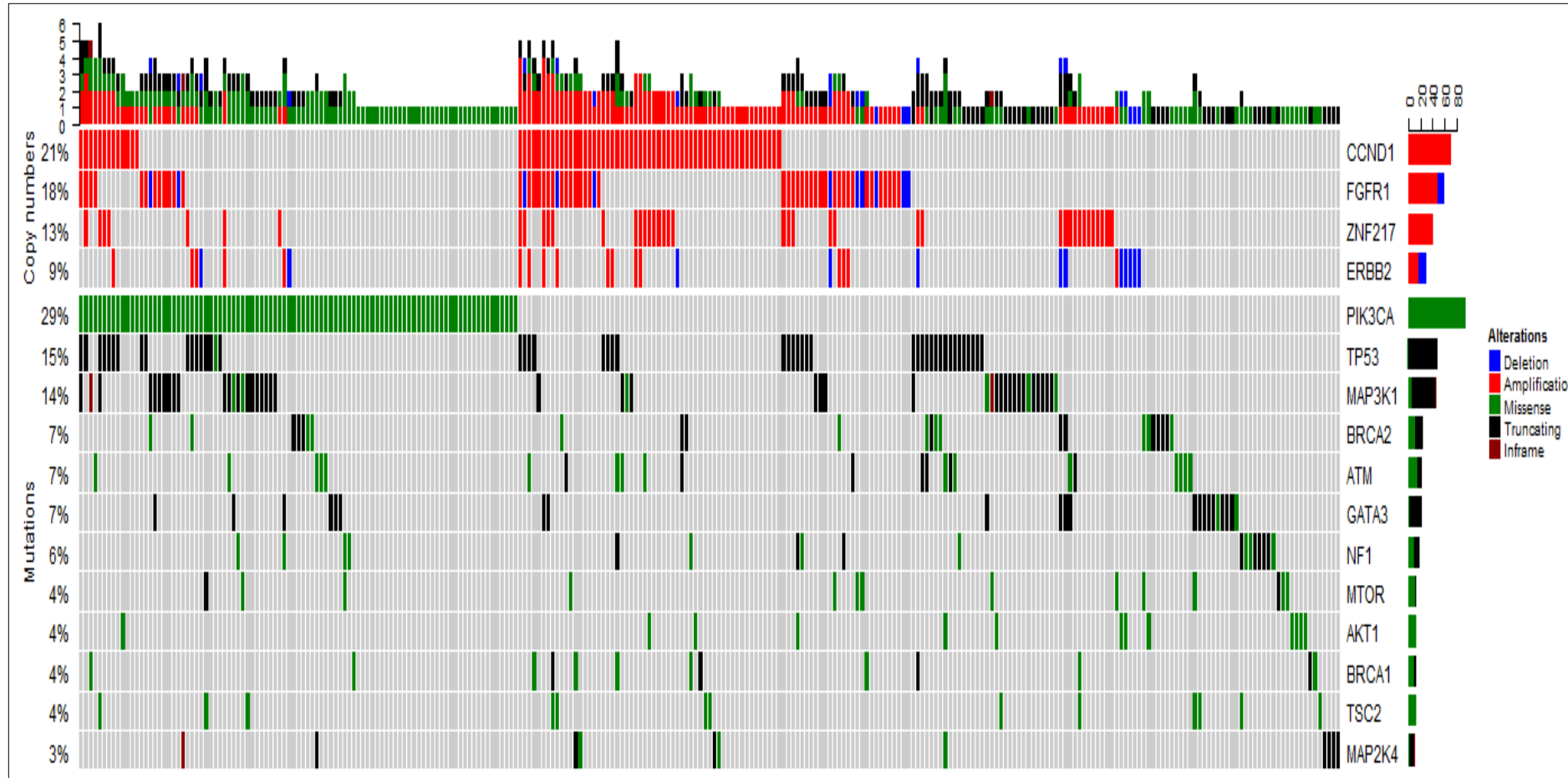
A. Training set: PACS04 Trial



B. External set: METABRIC Trial



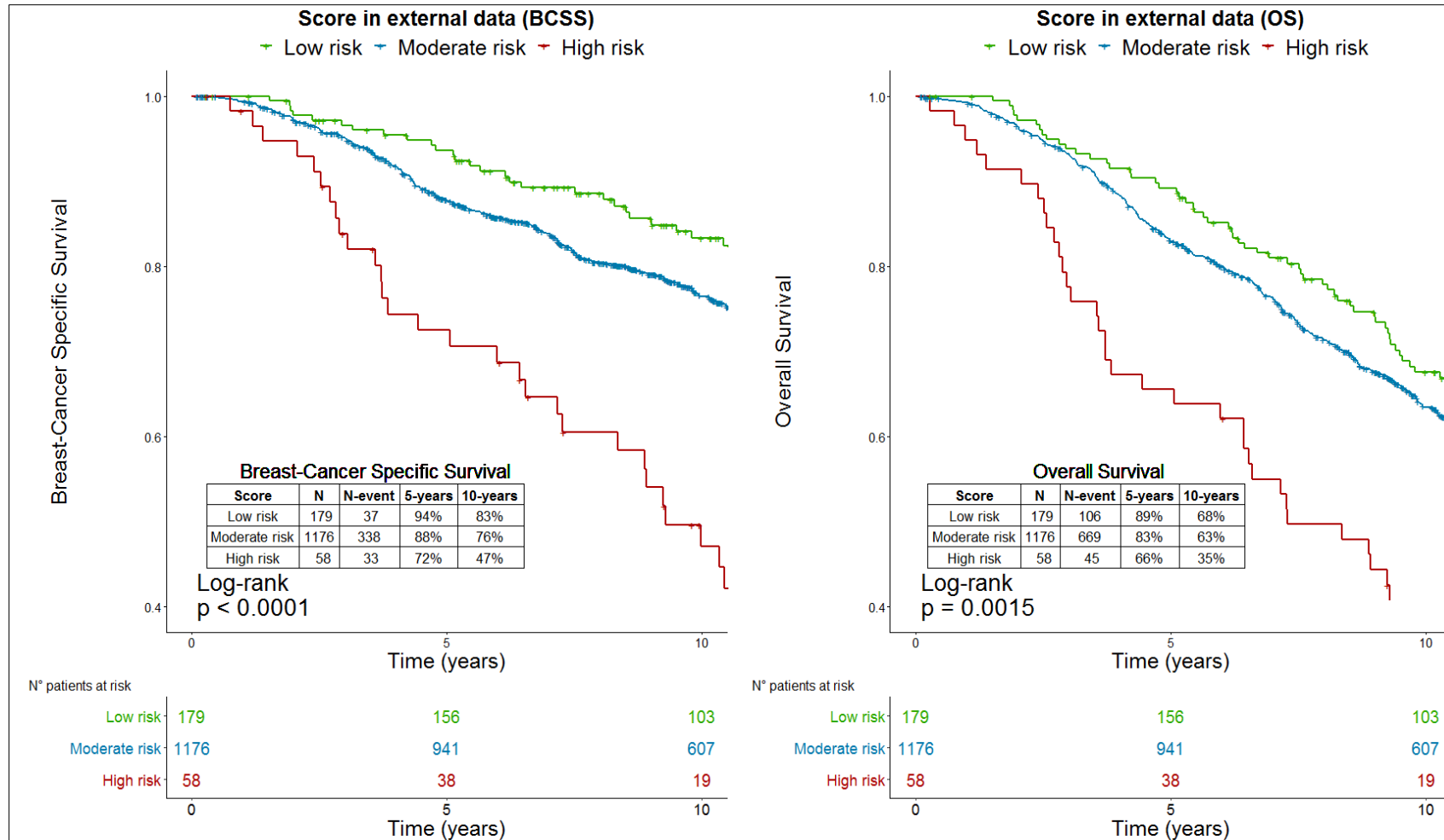
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Les mutations MAP3K1 et amplifications FGFR1 sont associés à un risque différentiel de rechute

Characteristics	N° patients (N° event) or Median [Q1-Q3]	CP HR (95%CI) p-value	CP+MAP3K1+FGFR1+ZNF217 HR (95%CI) p-value	CP+MAP3K1+FGFR1 HR (95%CI) p-value
Tumor size (mm)	20 [15-30]	1.02 (1.01 ; 1.03) p<0.001	1.02 (1.01 ; 1.03) p<0.001	1.02 (1.01 ; 1.03) p<0.001
Poorly differentiated	74 (21)	2.5 (0.9 ; 6.97) p=0.08	2.08 (0.72 ; 5.94) p=0.2	2.26 (0.80 ; 6.40) p=0.1
Lymph node status (ref: 1-3)	211 (28)			
4-9	72 (21)	2.19 (1.23 ; 3.9) p=0.007	2.59 (1.42 ; 4.73) p=0.002	2.56 (1.40 ; 4.68) p=0.002
≥	24 (9)	2.73 (1.24 ; 5.98) p=0.01	3.47 (1.55 ; 7.79) p=0.003	3.24 (1.46 ; 7.21) p=0.004
MAP3K1 (ref: Normal)	265 (57)			
Mutation	42 (1)		0.10 (0.01 ; 0.82) p=0.03	0.10 (0.01 ; 0.78) p=0.03
FGFR1 (ref: Normal)	251 (41)			
Amplification	47 (14)		2.37 (1.21 ; 4.64) p=0.01	2.44 (1.25 ; 4.76) p=0.009
ZNF217 (ref: Normal)	271 (48)			
Amplification	36 (10)		1.67 (0.79 ; 3.53) p=0.2	
Concordance		0.75	0.77	0.78
Likelihood ratio test		p<0.001	p<0.001	p<0.001

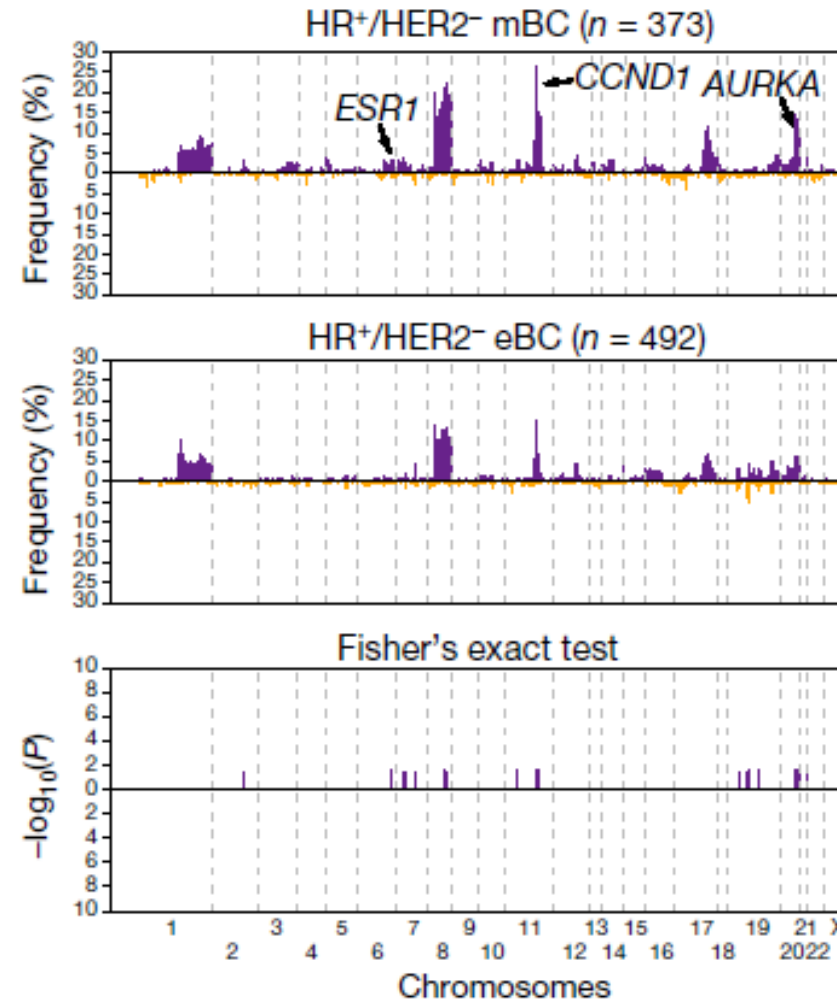
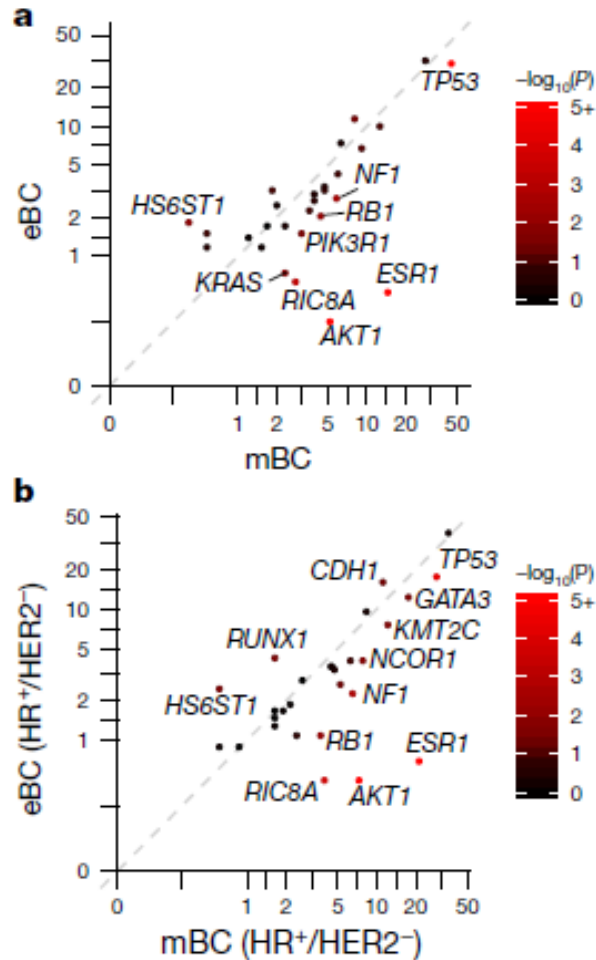
Set de validation



Autres données génomiques associées au pronostic

- Signature génomique basée sur les copy number alterations (brevet en cours)

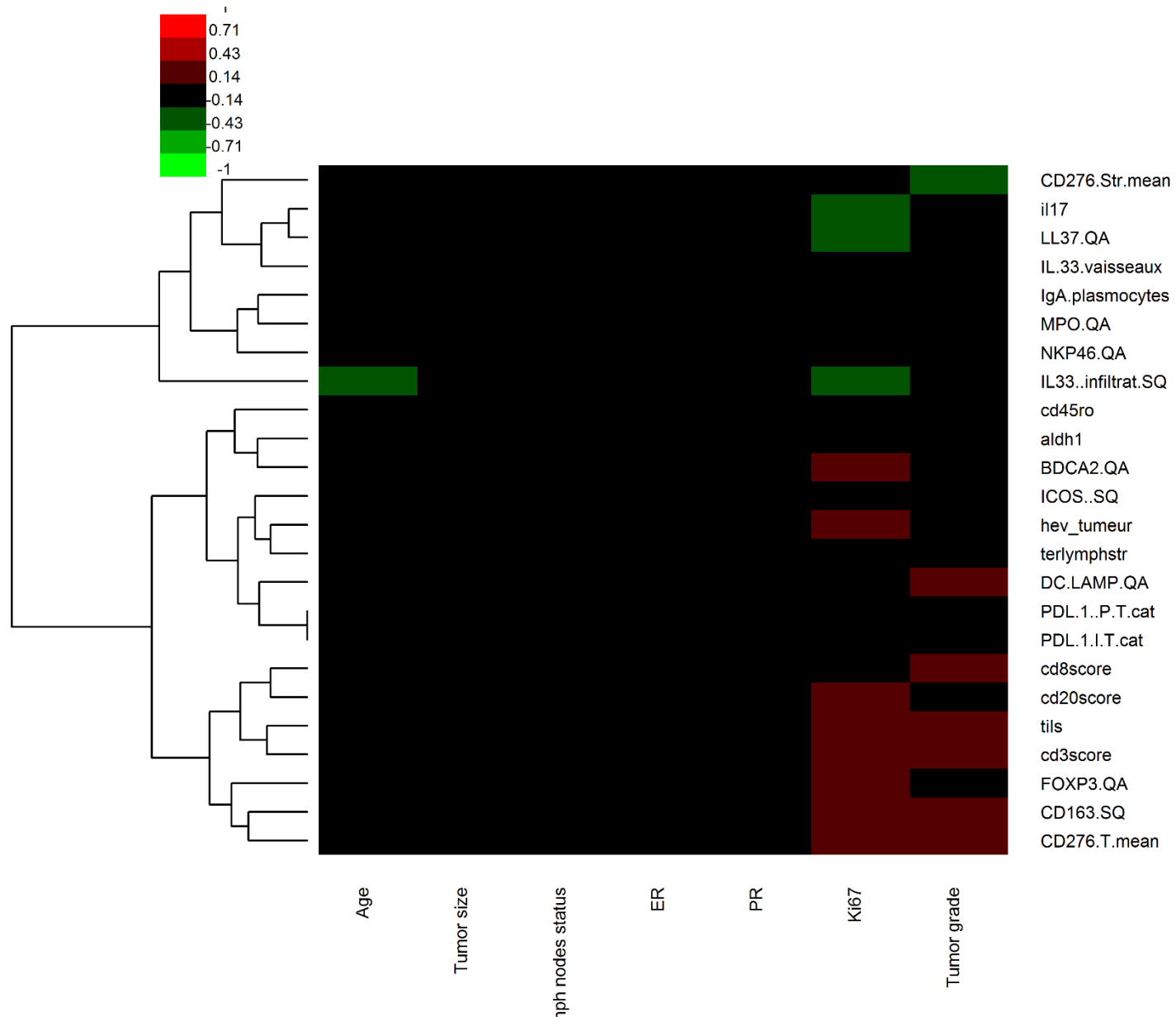
Marqueurs génomiques de résistance et de métastases



Genomic characterization of metastatic breast cancers

François Bertucci^{1,25}, Charlotte K. Y. Ng^{2,3,24,25}, Anne Patsouris^{4,5,25}, Nathalie Droin^{6,7,8}, Salvatore Piscuoglio^{2,3}, Nadine Carbuccia¹, Jean Charles Soria^{9,10}, Alicia Tran Dien¹¹, Yahia Adnani¹¹, Maud Kamal¹², Séverine Garnier¹, Guillaume Meurice¹¹, Marta Jimenez¹³, Semih Dogan¹⁴, Benjamin Verret¹⁴, Max Chaffanet¹, Thomas Bachelot¹⁵, Mario Camponé^{4,5}, Claudia Lefeuvre¹⁶, Herve Bonnefoi¹⁷, Florence Dalenc¹⁸, Alexandra Jacquet¹³, Maria R. De Filippo², Naveen Babbar¹⁹, Daniel Birnbaum¹, Thomas Filleron^{18,26}, Christophe Le Tourneau^{20,21,22,26} & Fabrice André^{9,14,23,26*}

Marqueurs immunologiques et risque de rechute dans les cancers du sein RH+/Her2-



	Prognostic value		Independent prognostic additional value		Added value to centrally measured Ki67	
	DDFS	OS	DDFS	OS	DDFS	OS
CD3 score	N= 1095	N= 1095	N= 1017	N= 1017	N= 488	N= 488
	d= 213	d= 130	d= 196	d= 118	d= 103	d= 64
Transformed data	p = 0.092	p = 0.467	p = 0.055	p = 0.437	p = 0.226	p = 0.424
CD8 score	N= 1094	N= 1094	N= 1016	N= 1016	N= 488	N= 487
	d= 213	d= 130	d= 196	d= 118	d= 103	d= 64
Transformed data	p = 0.010	p = 0.003	p = 0.014	p = 0.008	p = 0.466	p = 0.086
CD20 score	N= 1093	N= 1093	N= 1015	N= 1015	N= 487	N= 486
	d= 212	d= 129	d= 195	d= 117	d= 102	d= 63
	p = 0.089	p = 0.426	p = 0.020	p = 0.107	p = 0.022	p = 0.298
PD-L1-PT	NE	NE	NE	NE	NE	NE
PD-L1-IT	NE	NE	NE	NE	NE	NE
ICOS-SQ	NE	NE	NE	NE	NE	NE
CD45RO	N= 917	N= 917	N= 854	N= 854	N= 414	N= 414
	d= 179	d= 112	d= 164	d= 101	d= 88	d= 57
	p = 0.480	p = 0.895	p = 0.666	p = 0.871	p = 0.662	p = 0.617
FOXP3-QA	N= 793	N= 793	N= 746	N= 746	N= 366	N= 366
	d= 159	d= 98	d= 149	d= 91	d= 78	d= 49
raw data	p = 0.001	p = 0.020	p = 0.003	p = 0.042	p = 0.010	p = 0.267
Transformed data	p = 0.404	p = 0.224	p = 0.348	p = 0.154	p = 0.712	p = 0.513
ALDH1	N= 495	N= 495	N= 472	N= 472	N= 218	N= 218
	d= 111	d= 70	d= 105	d= 67	d= 47	d= 30
	p = 0.213	p = 0.112	p = 0.209	p = 0.092	p = 0.706	p = 0.423
CD276.Str.mean	N= 665	N= 665	N= 624	N= 624	N= 286	N= 286
	d= 123	d= 74	d= 113	d= 67	d= 64	d= 41
raw data	p = 0.135	p = 0.336	p = 0.961	p = 0.660	p = 0.361	p = 0.778
Transformed data	p = 0.086	p = 0.054	p = 0.150	p = 0.077	p = 0.030	p = 0.012
TILs (%)	N= 1120	N= 1120	N= 1043	N= 1043	N= 509	N= 509
	d= 222	d= 139	d= 206	d= 127	d= 112	d= 71
	p = 0.780	p = 0.700	p = 0.238	p = 0.648	p = 0.145	p = 0.342
Tertiary lymph. Str.	N= 1114	N= 1114	N= 1039	N= 1039	N= 509	N= 509
	d= 222	d= 139	d= 206	d= 127	d= 112	d= 71
	p = 0.988	p = 0.771	p = 0.485	p = 0.753	p = 0.178	p = 0.442

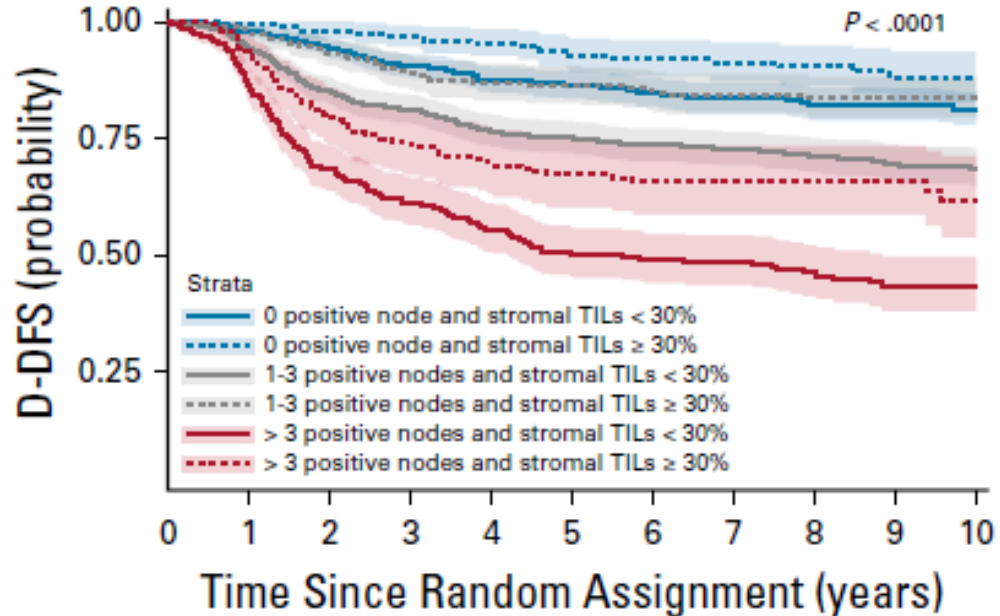
	N= 906	N= 906	N= 849	N= 849	N= 411	N= 411
CD163 SQ	d= 180	d= 110	d= 166	d= 101	d= 87	d= 56
Transformed data	p = 0.741	p = 0.898	p = 0.554	p = 0.940	p = 0.960	p = 0.753
DC-LAMP-QA	N= 870	N= 870	N= 805	N= 805	N= 389	N= 389
	d= 175	d= 106	d= 156	d= 96	d= 80	d= 51
Transformed data	p = 0.395	p = 0.406	p = 0.272	p = 0.484	p = 0.302	p = 0.268
MPO-QA	N= 870	N= 870	N= 813	N= 813	N= 399	N= 399
	d= 175	d= 106	d= 161	d= 96	d= 86	d= 55
Transformed data	p = 0.395	p = 0.406	p = 0.238	p = 0.360	p = 0.569	p = 0.824
LL37-QA	N= 881	N= 881	N= 827	N= 827	N= 409	N= 409
	d= 176	d= 107	d= 164	d= 99	d= 88	d= 56
Transformed data	p = 0.842	p = 0.409	p = 0.317	p = 0.091	p = 0.430	p = 0.297
BDCA2-QA	N= 882	N= 882	N= 830	N= 830	N= 411	N= 411
	d= 179	d= 108	d= 166	d= 99	d= 88	d= 55
Transformed data	p = 0.807	p = 0.665	p = 0.446	p = 0.585	p = 0.345	p = 0.545
IgA-plasmocytes-QA	N= 793	N= 793	N= 748	N= 748	N= 360	N= 360
	d= 158	d= 98	d= 149	d= 91	d= 79	d= 51
Transformed data	p = 0.470	p = 0.733	p = 0.803	p = 0.900	p = 0.497	p = 0.348
IL33-infiltrat-SQ	N= 375	N= 375	N= 343	N= 343	N= 169	N= 169
	d= 72	d= 42	d= 64	d= 37	d= 36	d= 23
	p = 0.584	p = 0.861	p = 0.946	p = 0.926	p = 0.267	p = 0.082
IL33-PCT	NE	NE	NE	NE	NE	NE
IL33-vaisseaux	N= 375	N= 375	N= 343	N= 343	N= 169	N= 169
	d= 72	d= 42	d= 64	d= 37	d= 36	d= 23
	p = 0.627	p = 0.939	p = 0.275	p = 0.602	p = 0.498	p = 0.364
NKP46-QA	N= 358	N= 358	N= 322	N= 322	N= 159	N= 159
	d= 73	d= 42	d= 63	d= 36	d= 34	d= 21
Transformed data	p = 0.730	p = 0.582	p = 0.816	p = 0.695	p = 0.715	p = 0.619
IL-17	N= 941	N= 941	N= 874	N= 874	N= 424	N= 424
	d= 185	d= 116	d= 169	d= 105	d= 90	d= 58
Transformed data	p = 0.762	p = 0.675	p = 0.760	p = 0.515	p = 0.907	p = 0.823

Plan

- Question posée
- Prédiction du risque de rechute dans les cancers du sein luminaux
- Prédiction du risque de rechute dans les cancers du sein triple négatifs

Valeur pronostique des TILs dans les cancers du sein triple négatifs traités par chimiothérapie adjuvante

B



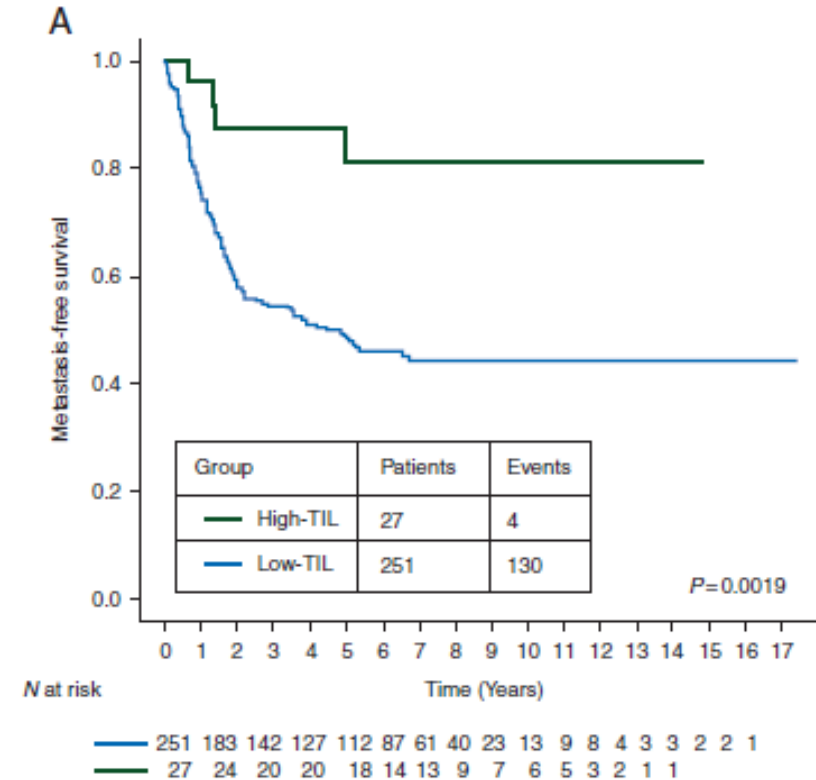
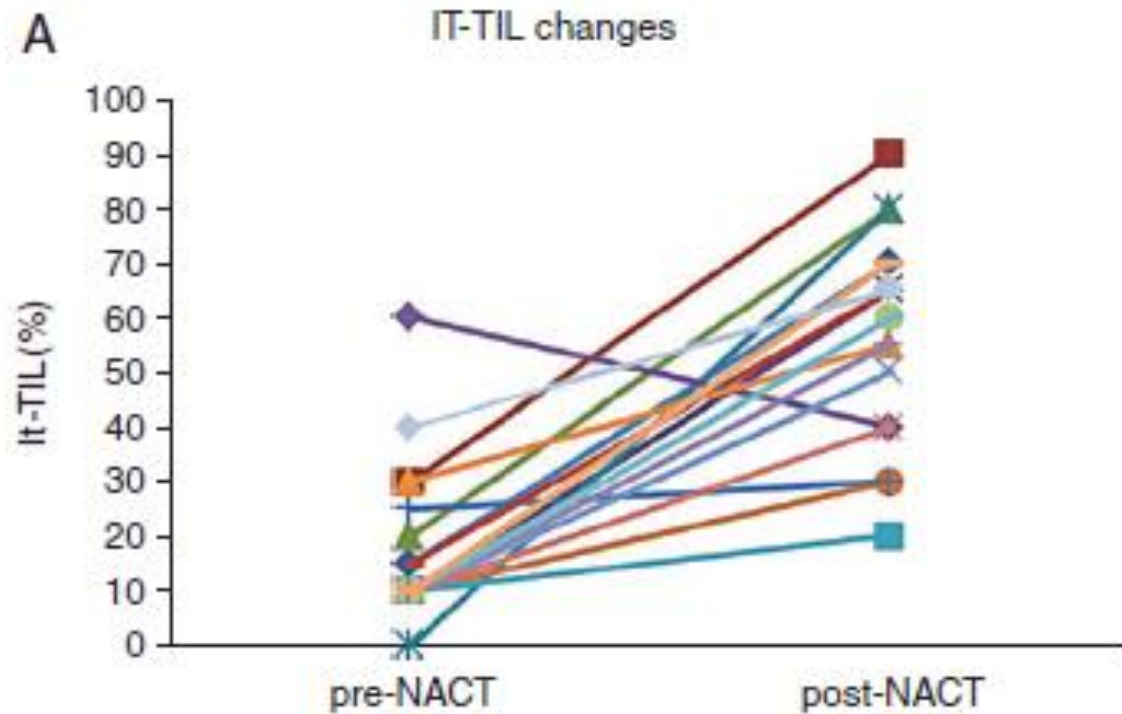
No. at risk (by time weighted by inverse sampling probability):

Strata	0	1	2	3	4	5	6	7	8	9	10
0 positive node and stromal TILs < 30%	542	528	501	468	435	397	359	312	259	223	174
0 positive node and stromal TILs ≥ 30%	213	210	204	193	181	158	139	118	87	68	52
1-3 positive nodes and stromal TILs < 30%	630	593	525	490	451	412	377	331	256	183	132
1-3 positive nodes and stromal TILs ≥ 30%	294	284	270	251	242	222	194	166	135	97	63
> 3 positive nodes and stromal TILs < 30%	365	311	242	209	183	154	138	122	77	51	36
> 3 positive nodes and stromal TILs ≥ 30%	166	155	130	115	105	97	87	77	57	40	25

Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers

Sherene Loi, MD¹; Damien Drubay, PhD^{2,3}; Sylvia Adams, MD⁴; Giancarlo Pruneri, MD⁵; Prudence A. Francis, MD¹; Magali Lacroix-Triki, MD²; Heikki Joensuu, MD⁷; Maria Vittoria Dieci, MD^{8,9}; Sunil Badve, MD¹⁰; Sandra Demaria, MD¹¹; Robert Gray, PhD¹²; Elisabetta Munzone, MD¹³; Jerome Lemonnier, PhD¹⁴; Christos Sotiriou, MD¹⁴; Martine J. Piccart, MD¹⁴; Pirko-Liisa Kellokumpu-Lehtinen, MD¹⁵; Andrea Vingiani, MD¹⁶; Kathryn Gray, PhD¹²; Fabrice Andre, MD^{2,3}; Carsten Denkert, MD¹⁷; Roberto Salgado, MD^{1,18}; and Stefan Michiels, PhD^{2,3}

Valeur pronostique des TILs post-chimiothérapie néoadjuvante dans les cancers du sein triple négatifs



Prognostic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: a retrospective multicenter study

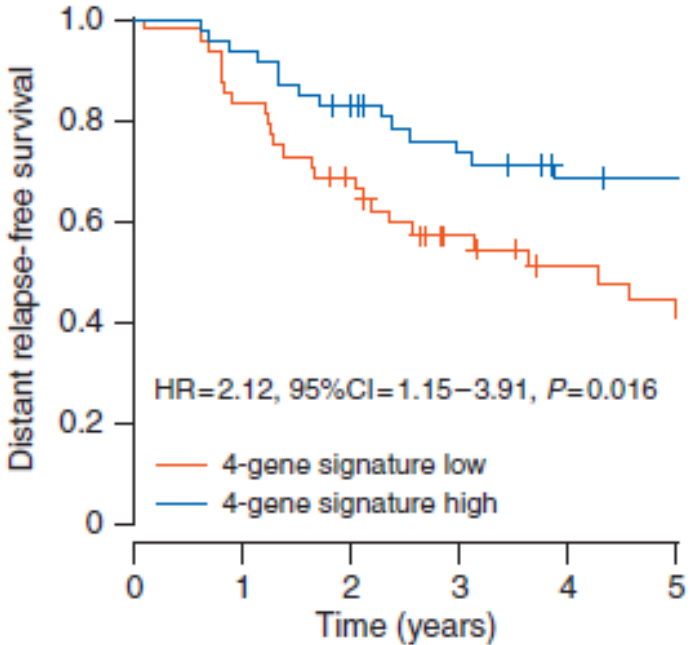
M. V. Dieci^{1,2,3,†}, C. Criscitiello^{4,†}, A. Goubar¹, G. Viale^{5,6}, P. Conte^{2,3}, V. Guarneri^{2,3}, G. Ficarra⁷, M. C. Mathieu⁸, S. Delaloge^{1,9}, G. Curigliano^{2,3,‡} & F. Andre^{1,9,10,‡*}

Signature génomique préchimio pour prédire les TILs... post chimio

Table 2. A four-gene signature to predict post-chemotherapy tumor-infiltrating lymphocytes

PROBEID	Gene	Description	Coefficient
202269_x_at	GBP1	Guanylate binding protein 1, interferon-inducible	0.288
204753_s_at	HLF	Hepatic leukemia factor	-1.027
205242_at	CXCL13	Chemokine (C-X-C motif) ligand 13	0.392
219934_s_at	SULT1E1	Sulfotransferase family 1E, estrogen-preferring, member 1	-1.726

A

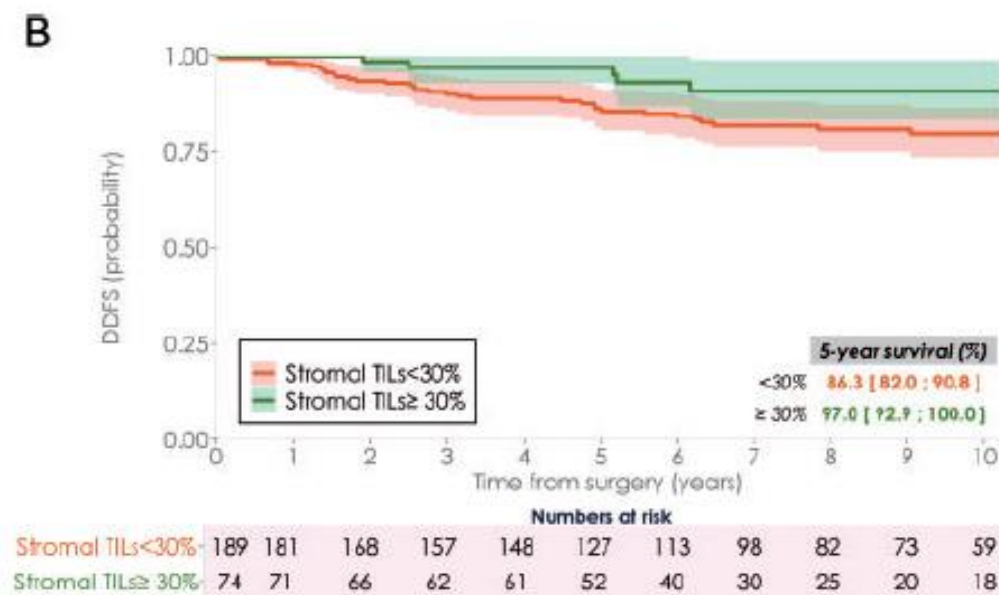
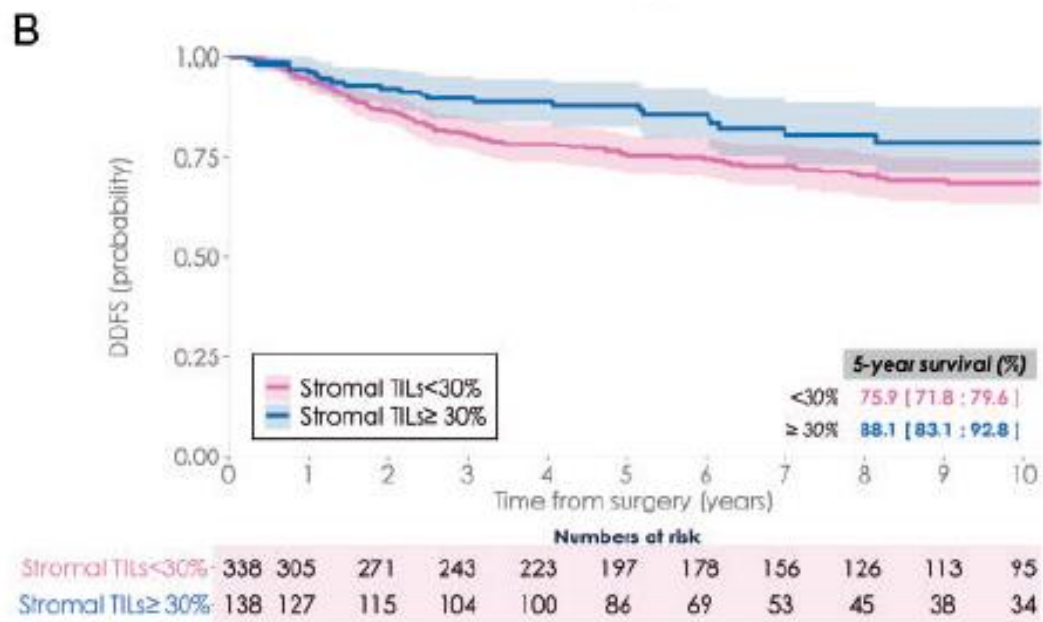


	No. at risk	0	1	2	3	4	5
4-gene signature low	48	40	31	20	15	12	
4-gene signature high	47	44	37	31	25	24	

A gene signature to predict high tumor-infiltrating lymphocytes after neoadjuvant chemotherapy and outcome in patients with triple-negative breast cancer

C. Criscitiello^{1†}, M. A. Bayar^{2,3†}, G. Curigliano¹, F. W. Symmans⁴, C. Desmedt⁵, H. Bonnefoi⁶, B. Sinn⁴, G. Pruner⁷, C. Vicier^{8,9}, J. Y. Pierga¹⁰, C. Denkert¹¹, S. Loibl¹¹, C. Sotiriou⁵, S. Michiels^{2,3†} & F. André^{8,9*†}

Valeur pronostique des TILs dans les cancers du sein triple négatifs en l'absence de chimiothérapie adjuvante

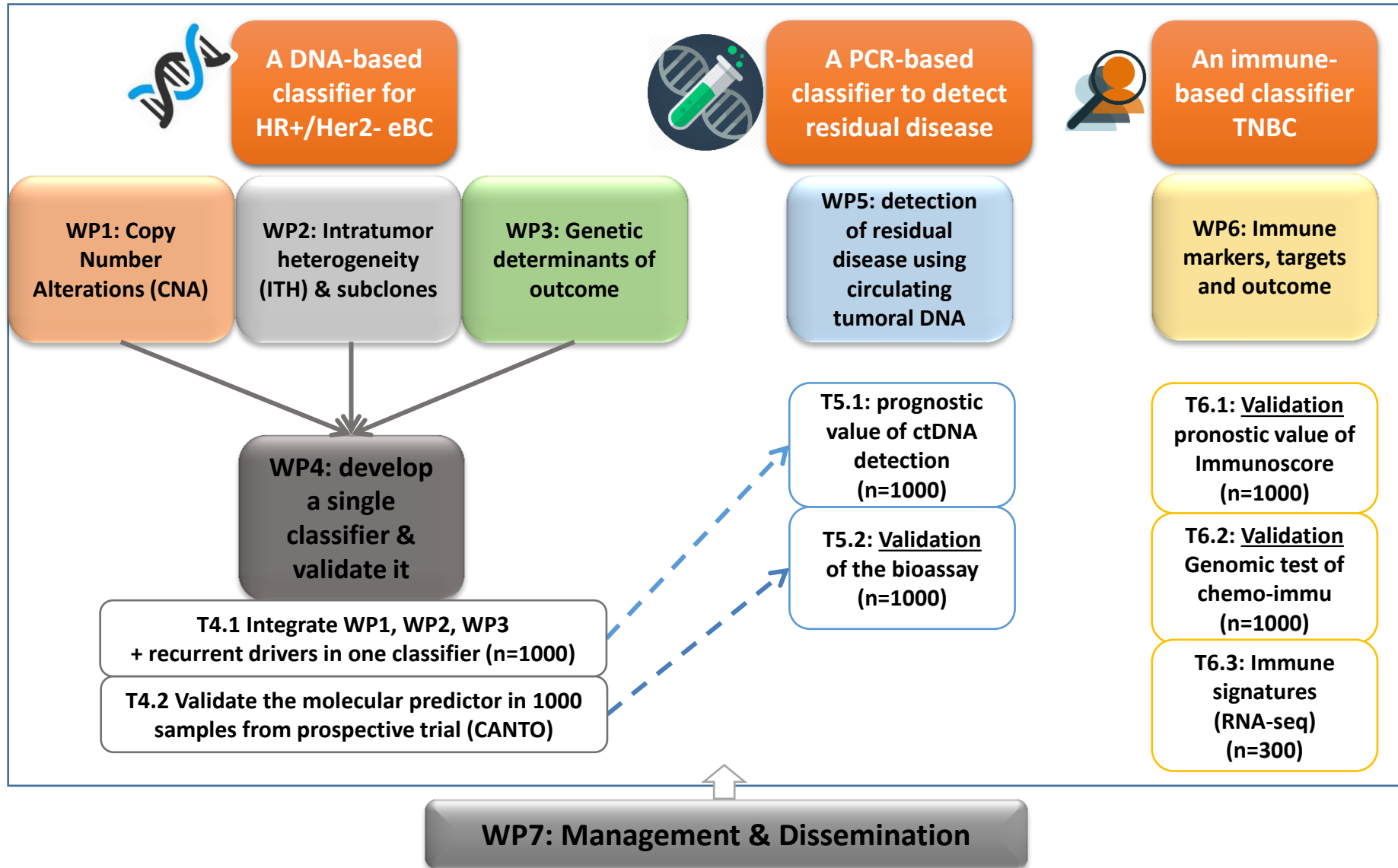


Prognostic value of tumor-infiltrating lymphocytes in patients with early-stage triple-negative breast cancers (TNBC) who did not receive adjuvant chemotherapy

Prochaines étapes

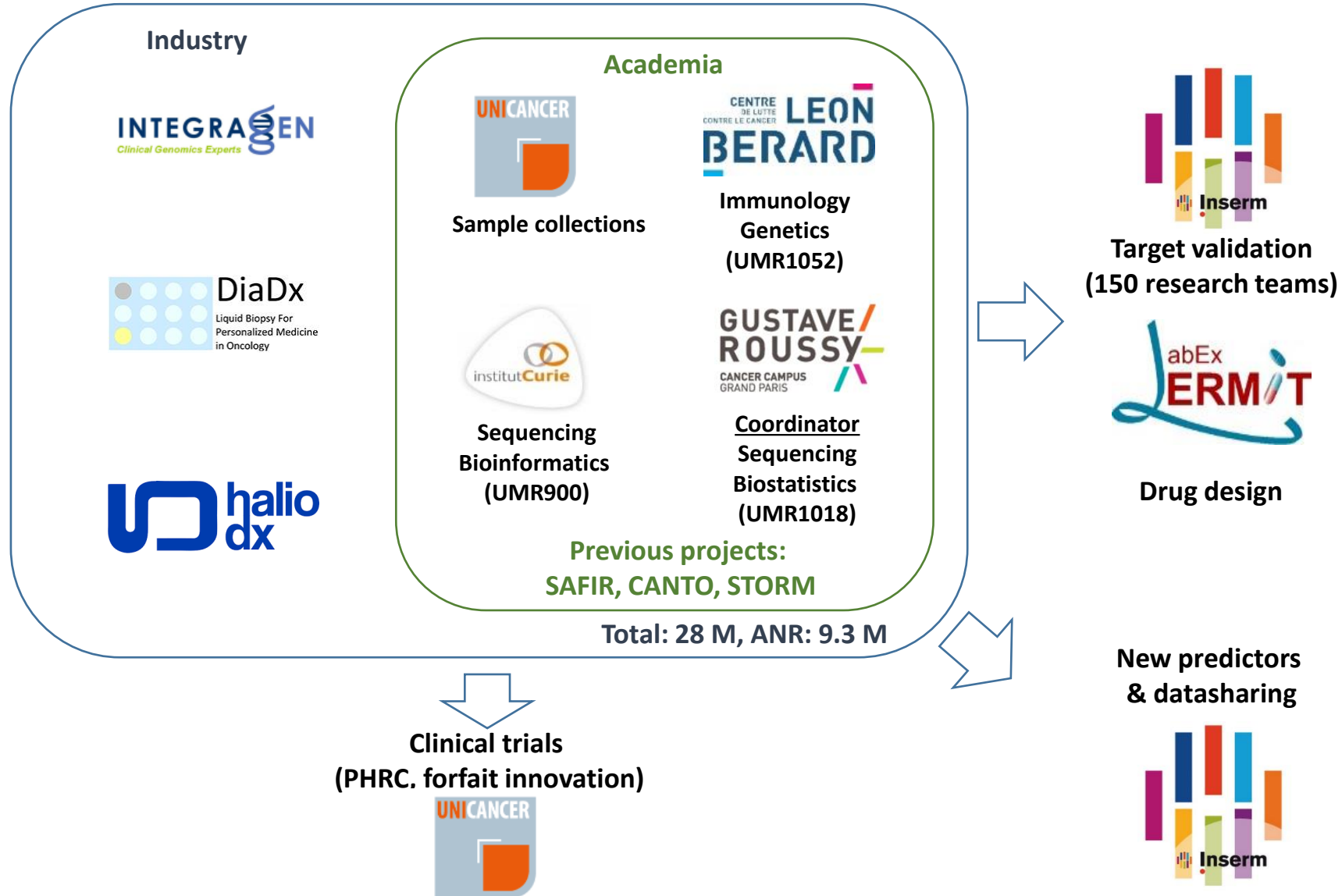
- Création d'un score intégrant infiltrat immunitaire et instabilité chromosomique pour prédire le risque résiduel dans les cancers du sein (RHU MyProbe)

PROJECT DESCRIPTION



CONSORTIUM

MyPROBE partners



	Characteristics	N° patients (N° event)	HR (95%CI) p-value
Copy number	CCND1 (ref: Normal)	257 (47)	
	Amplification	70 (18)	1.44 (0.84 ; 2.48) p=0.2
	FGFR1 (ref: Normal)	267 (45)	
	Amplification	49 (15)	2.18 (1.21 ; 3.91) p<0.01
	Deletion	11 (5)	3.22 (1.28 ; 8.12) p=0.01
	ZNF217 (ref: Normal)	286 (52)	
	Amplification	41 (13)	1.99 (1.08 ; 3.65) p=0.03
	ERBB2 (ref: Normal)	298 (57)	
	Amplification	17 (4)	1.24 (0.45 ; 3.44) p=0.7
	Deletion	12 (4)	1.85 (0.67 ; 5.09) p=0.2
	PIK3CA (ref: Normal)	232 (43)	
	Mutation	95 (22)	1.17 (0.7 ; 1.96) p=0.5
	TP53 (ref: Normal)	279 (52)	
	Mutation	48 (13)	1.55 (0.84 ; 2.86) p=0.2
	MAP3K1 (ref: Normal)	281 (64)	
	Mutation	46 (1)	0.09 (0.01 ; 0.63) p=0.02