Indiquer la même chimiothérapie pour toutes les formes moléculaires ?

Olivier Trédan

Centre Léon Bérard
LYON ET RHÔNE-ALPES

Liens d’intérêt

- Participation à des boards Roche, Novartis

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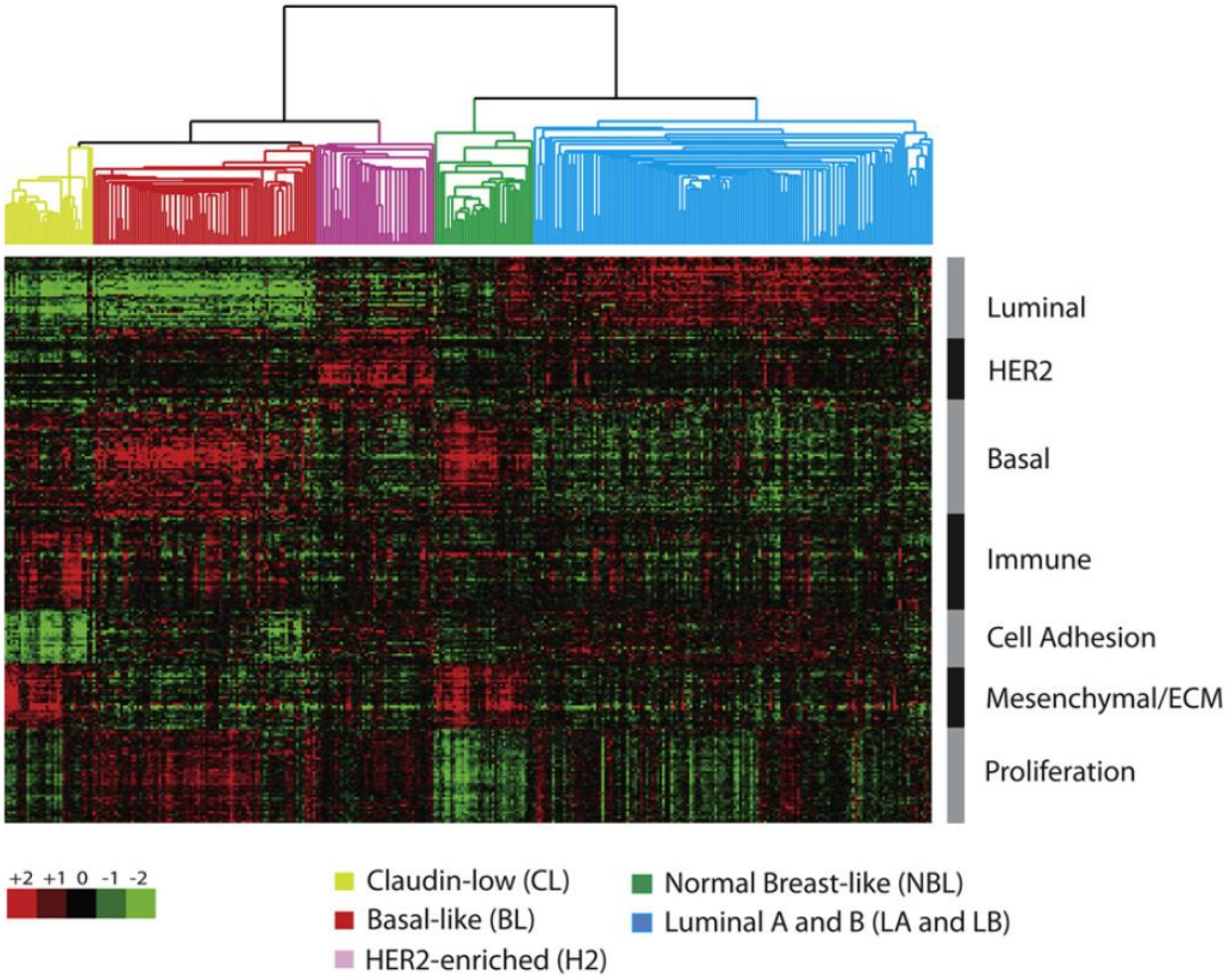
Les différentes formes moléculaires



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Prat & Perou 2011

Les différentes formes moléculaires

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'Luminal A-like' and 'Luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b]	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'Luminal A-like' and 'Luminal B-like (HER2 negative)'.
	'Luminal B-like (HER2 positive)' ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

Goldhirsch, Ann Oncol 2011

Plan

- Quelles sont les données pour les cancers ‘luminaux’
- Quelles sont les données pour les cancers ‘HER2-positif’
- Quelles sont les données pour les cancers ‘triple-négatifs’

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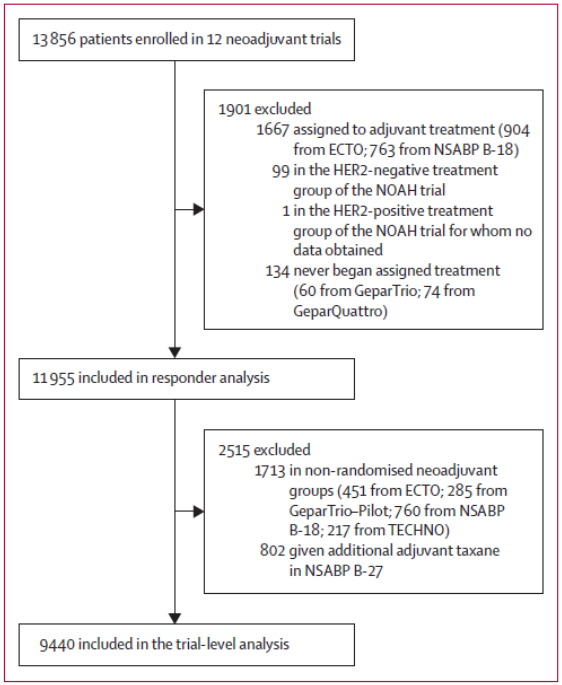
Quelle chimio pour les ‘luminaux’ ?

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz



Cortazar, Lancet 2014

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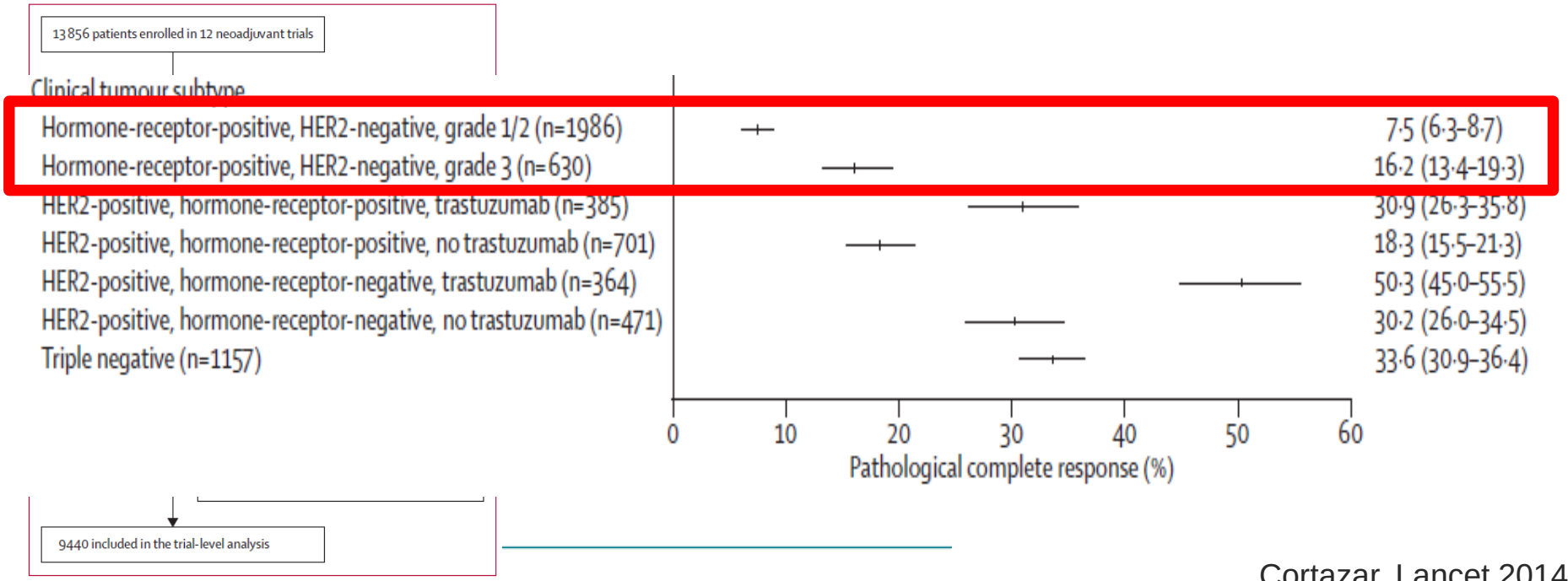

Cortazar, Lancet 2014

Quelle chimio pour les 'luminaux' ?

Breast Cancer Res Treat (2012) 132:1049–1062
DOI 10.1007/s10549-011-1895-2

CLINICAL TRIAL

Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657)

Laura J. Esserman · Donald A. Berry · Maggie C. U. Cheang · Christina Yau ·

	Overall distribution available for analysis, % (*n*)	pCR, % (*n*)
Entire population	*n* = 215	27% (58/215)
IHC/FISH	*n* = 210	27% (56/210)
HR+/HER2−	44% (*n* = 93)	9% (8/93)
Intrinsic subtype	*n* = 120	*n* = 116
Luminal A	30% (*n* = 36)	3% (1/36)
Luminal B	22% (*n* = 26)	16% (4/25)
Her2-enriched	9% (*n* = 11)	50% (5/10)
Basal	36% (*n* = 43)	33% (14/42)

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Esserman, Breast Cancer Res Treat 2012

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	Pathological complete response (pCR)		Recurrence-free survival	
	Rate of pCR (*n*)	Odds ratio (*P* value)	Hazard ratio (95% CI)	Hazard ratio, pCR vs. no PCR (95% CI within subgroup)
All patients with surgery	27% (215)	–	–	0.41* (0.18–0.82)
Luminal PAM50 (luminal vs. other)	Luminal: 8% (5/61) Other: 36% (20/55)	0.16 (<0.001)	0.47* (0.23–0.93)	Luminal: 0.00 (–) Other: 0.26* (0.06–0.79)

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Esserman, Breast Cancer Res Treat 2012

Quelle chimio pour les 'luminaux' ?

Breast Cancer Res Treat (2013) 140:63–71
DOI 10.1007/s10549-013-2620-0

PRECLINICAL STUDY

Breast cancer subtyping by immunohistochemistry and histological grade outperforms breast cancer intrinsic subtypes in predicting neoadjuvant chemotherapy response

E. H. Lips · L. Mulder · J. J. de Ronde ·

	Definition	Comments	Count	%
Immunohistochemical				
TN	ER−, PR−, HER2−		152	27.1
HER2+/ER−	HER2+, ER−, PR−		56	10.0
HER2+/ER+	HER2+, ER+, PR±		65	11.6
ER+/HER2−	ER+ HER2−, PR±		287	51.3
PAM50[a]				
Basal	Based on expressionof 50 genes		48	19.4
HER2-enriched			43	17.4
Luminal A			81	32.8
Luminal B			49	19.8
Normal			26	10.5

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Lips, Breast Cancer Res Treat 2013

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Table 3 Response according to different subtype classifications

	%	Ratio	*p* value[a]
Immunohistochemical ($n = 560$)			
TN	36.2	55/152	
HER2+/ER−	55.4	31/56	
HER2+/ER+	30.8	20/65	
ER+/HER2−	4.9	14/287	
PAM50 ($n = 247$)			
Basal	41.7	20/48	
HER2-enriched	48.8	21/43	
Luminal A	4.9	4/81	
Luminal B	8.2	4/49	0.47
Normal	19.2	5/26	

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Lips, Breast Cancer Res Treat 2013

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Table 4 Multivariate analysis of pCR in ER+/HER2− tumors

	OR	95 % CI	*p* value	LR-χ^2
Model based on PAM50				
Age (≥50 vs. <50 years)	0.62	0.06–6.32	0.68	
T-stage (T3/4 vs. <T1/2)	0.83	0.08–8.93	0.88	
N-stage (N+ vs. N−)	0.67	0.07–6.75	0.73	
PAM50 (Luminal B vs. Luminal A)	1.74	0.22–13.64	0.60	0.28
Model based on grade				
Age (≥50 vs. <50 years)	0.12	0.01–0.95	**0.04**	
T-stage (T3/4 vs. <T1/2)	0.75	0.3–1.85	0.53	
N-stage (N+ vs. N−)	0.94	0.53–1.66	0.82	
Grade (3 vs. 1/2)	6.36	1.82–22.3	**0.004**	**9.08**

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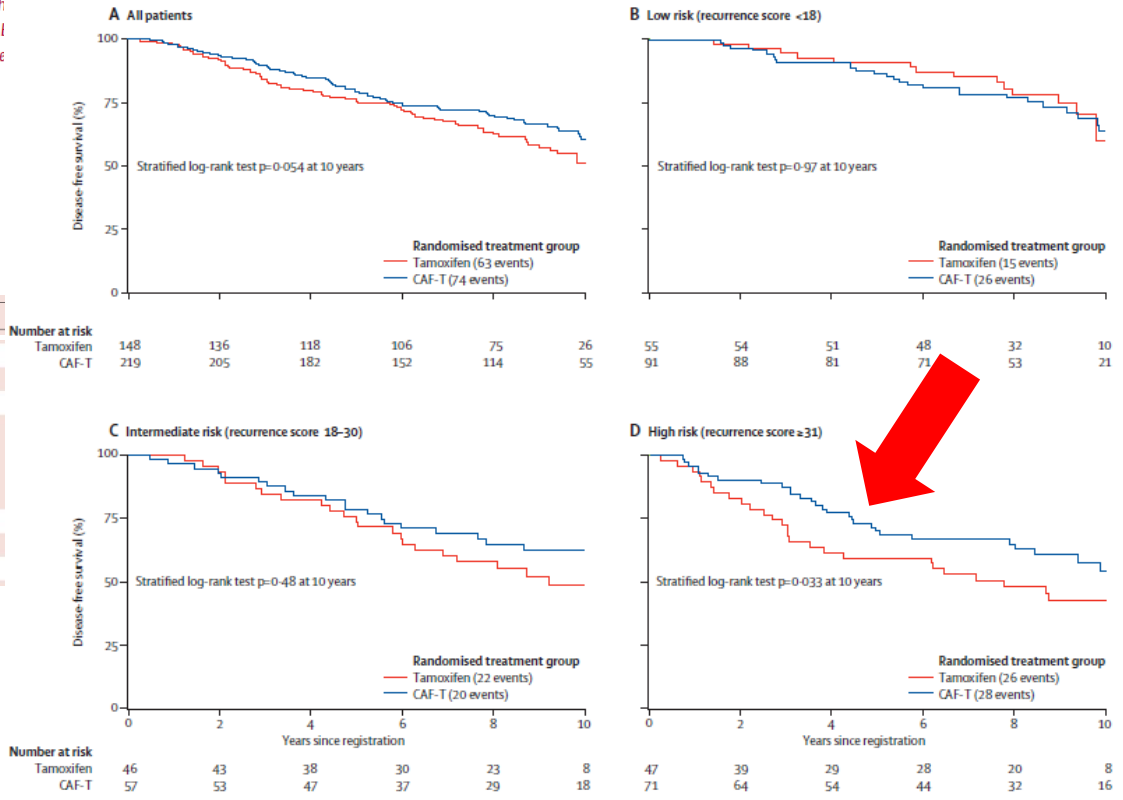
Lips, Breast Cancer Res Treat 2013

Quelle chimio pour les ‘luminaux’ ?

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial

Kathy S Albain, William E Barlow, Steven Shak, Gabriel N Hortobagyi, Robert B Livingston, I-Tien Yeh, Frederick L Baehner, Nancy E Davidson, George W Sledge, Eric P Winer, Clifford Hudis, James N Ingle, [illegible] Lois Shepherd, Julie R Gralow, Carl Yoshizawa, D Craig Allred, C Kent Osborne, Daniel F Hayes, for The

	Tamoxifen alone (n=148)	CAF-T (n=219)	Overall (n=367)
1–3 positive nodes	94 (63·5)	133 (60·7)	227 (61·9)
ER-positive by RT-PCR assay	145 (98·0)	210 (95·9)	355 (96·7)
Ethnic origin (black)	12 (8·1)	15 (6·8)	27 (7·4)
Tumour size			
<2 cm	46 (31·1)	74 (33·8)	120 (32·7)
2–5 cm	94 (63·5)	136 (62·1)	230 (62·7)
>5 cm	8 (5·4)	9 (4·1)	17 (4·6)
PgR-negative by RT-PCR assay	27 (18·2)	49 (22·4)	76 (20·7)
PgR-negative by local institution	30 (20·3)	45 (20·5)	75 (20·4)
HER2-positive by RT-PCR assay	13 (8·8)	30 (13·7)	43 (11·7)



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Albain, Lancet Oncol 2010

Plan

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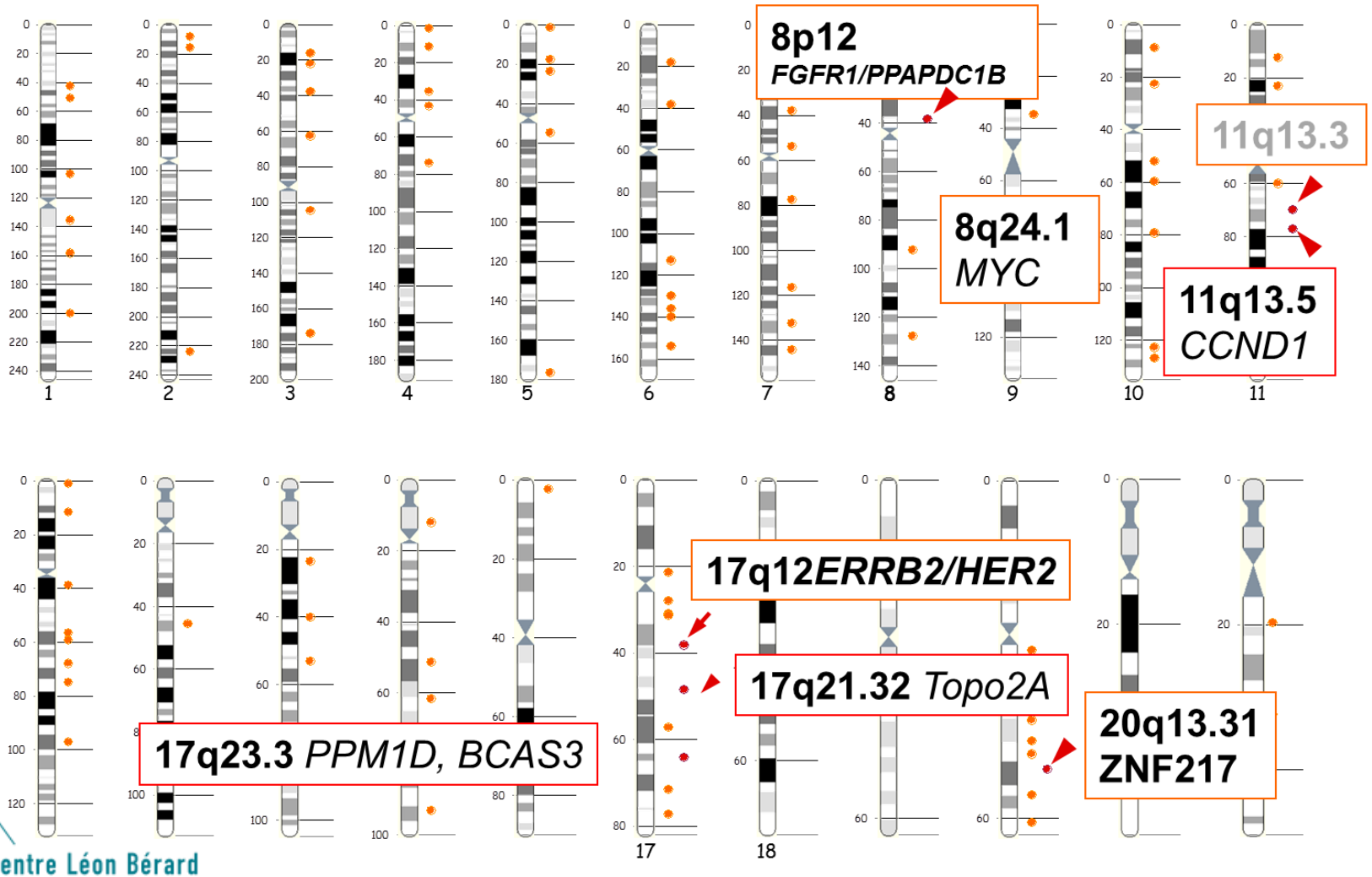
Quelle chimio pour les ‘HER2 positif’ ?



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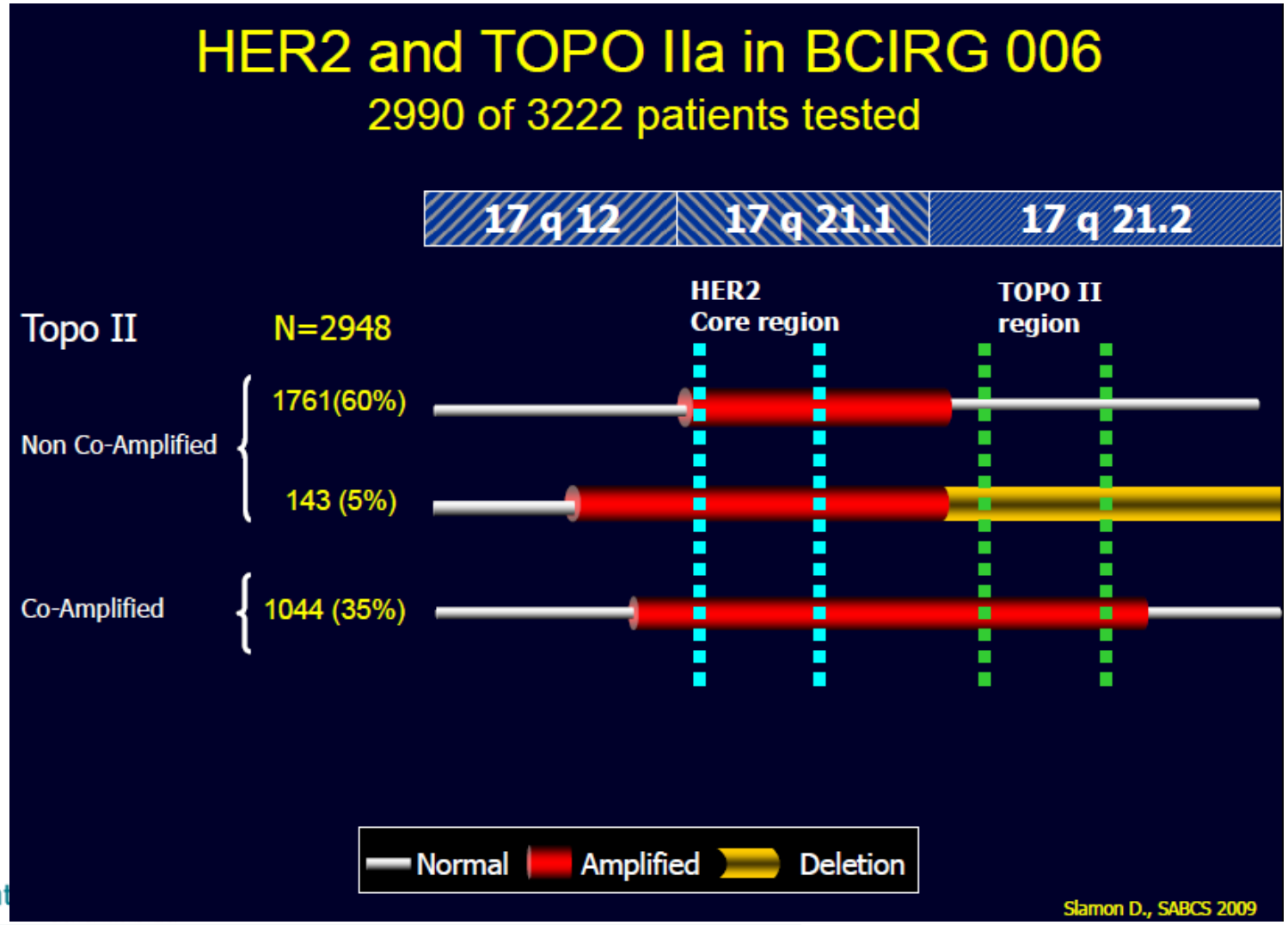
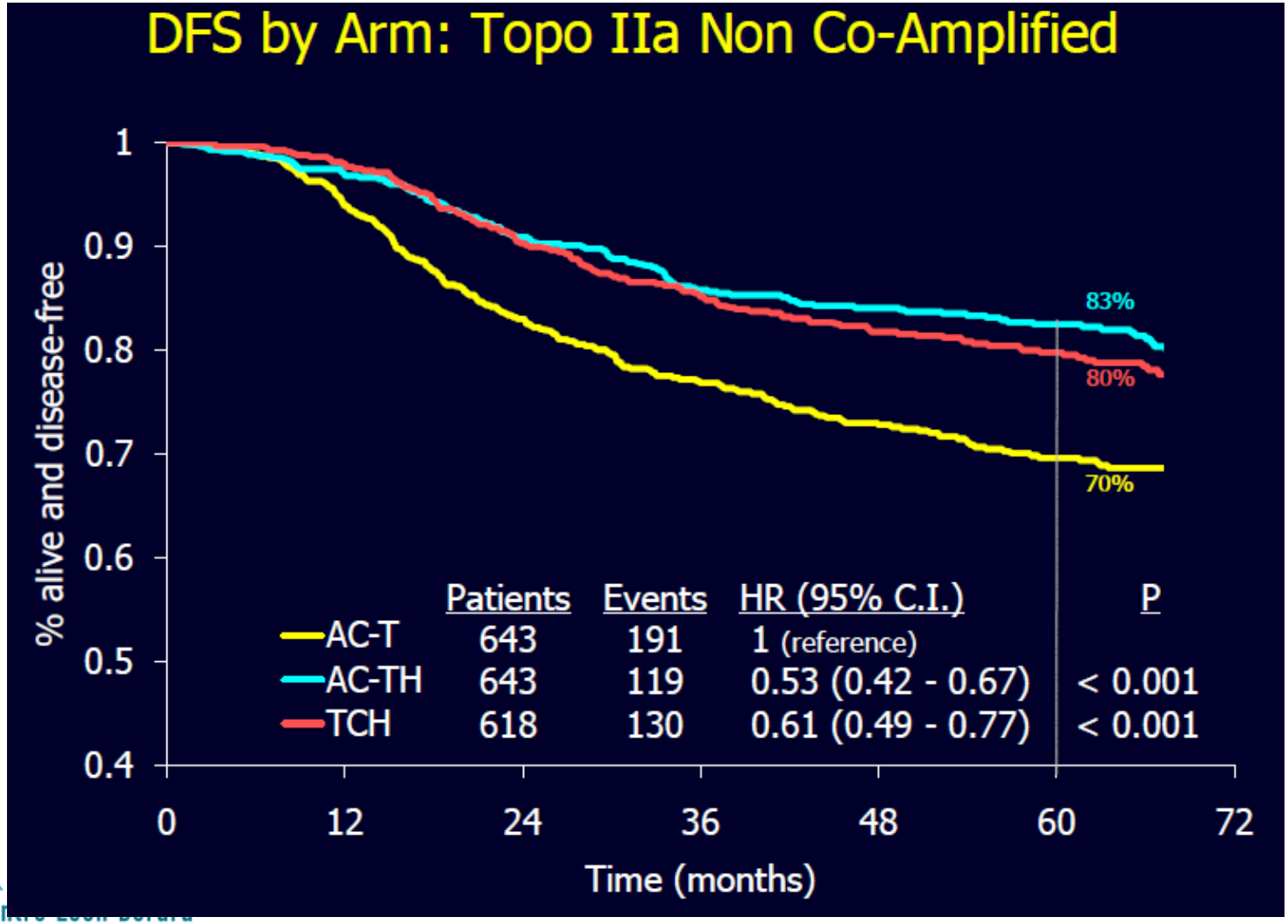
Vincent-Salomon, Clin Cancer Res 2008

Quelle chimio pour les ‘HER2 positif’ ?



Slamon, NEJM 2011

Quelle chimio pour les ‘HER2 positif’ ?



Slamon, NEJM 2011

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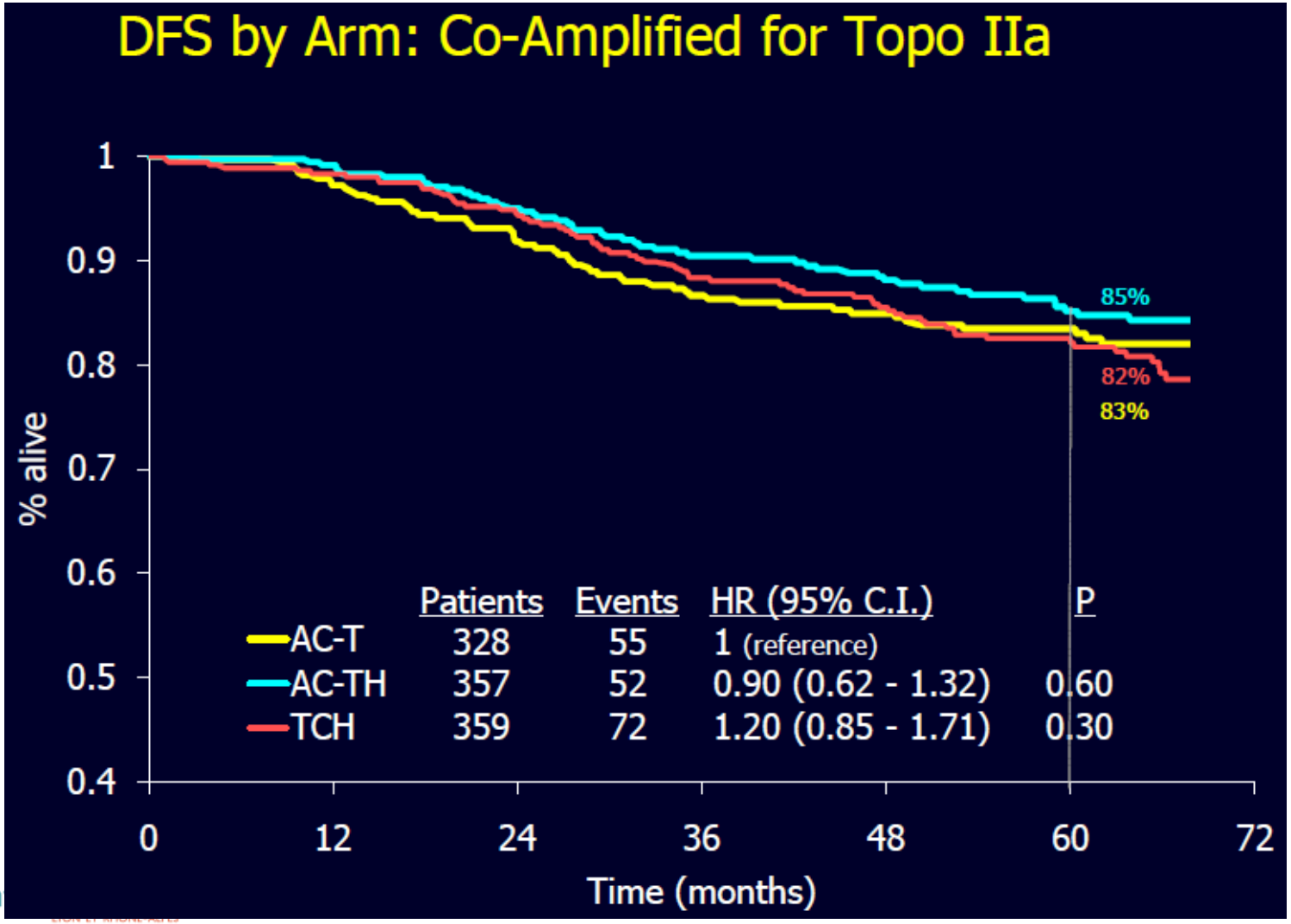


Slamon, NEJM 2011

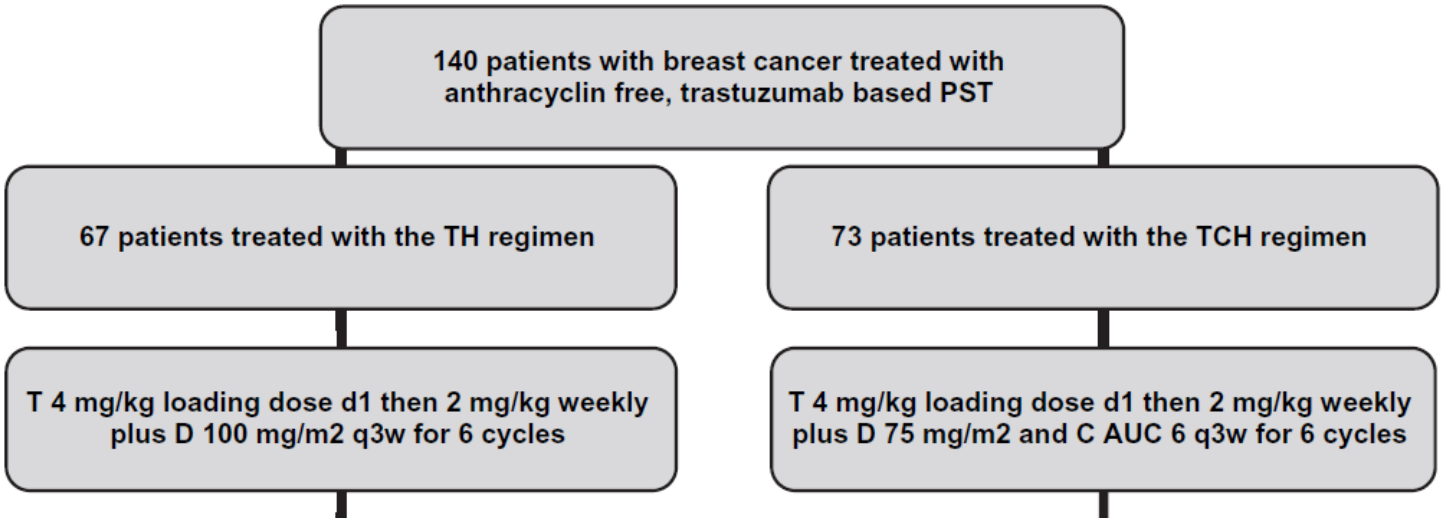
Quelle chimio pour les 'HER2 positif' ?

original article

Annals of Oncology 22: 321–328, 2011
doi:10.1093/annonc/mdq397
Published online 6 August 2010

Long-term follow-up of HER2-overexpressing stage II or III breast cancer treated by anthracycline-free neoadjuvant chemotherapy

S. Guiu[1], M. Liegard[1], L. Favier[1], I. van Praagh[2], R. Largillier[3], B. Weber[4], D. Coeffic[5], L. Moreau[6], F. Priou[7], M. Campone[8], J. Gligorov[9], L. Vanlemmens[10], V. Trillet-Lenoir[11], L. Arnould[1] & B. Coudert[1*]



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Guiu, Ann Oncol 2011

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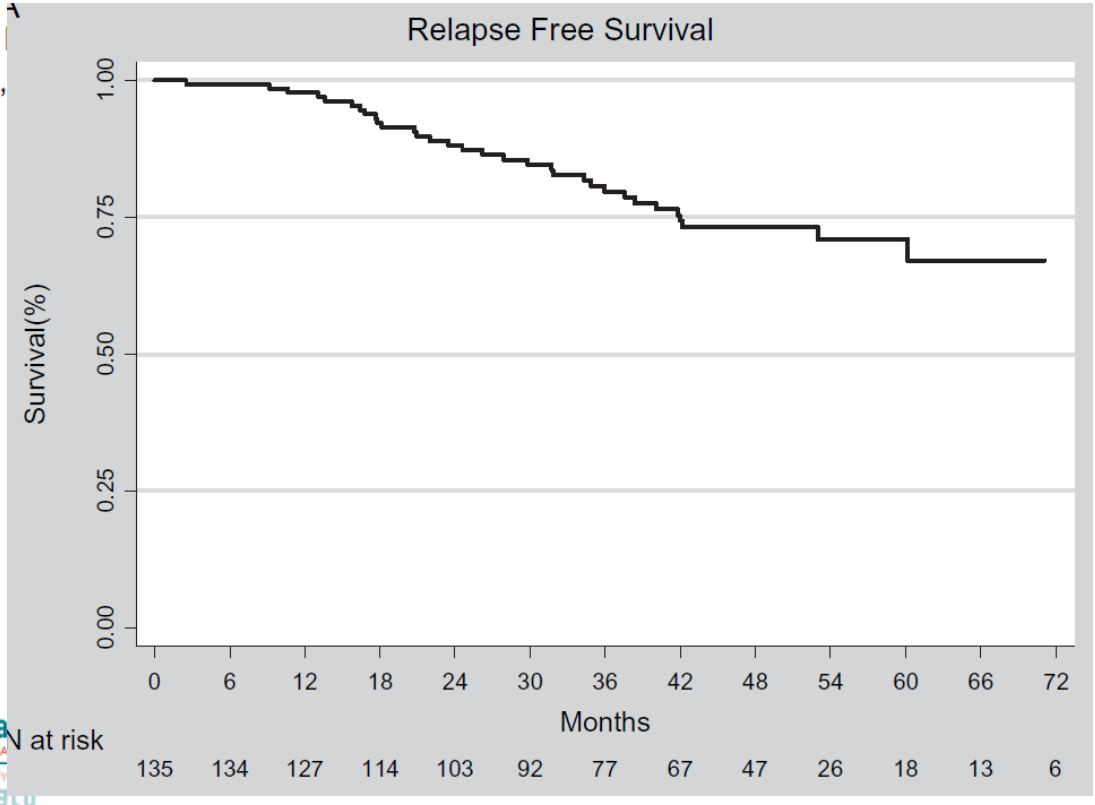

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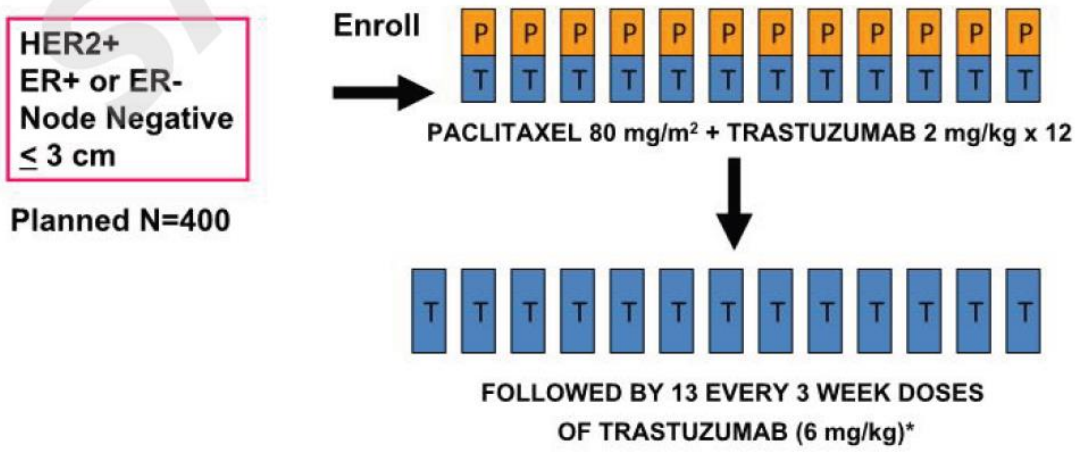
Guiu, Ann Oncol 2011

Quelle chimio pour les ‘HER2 positif’ ?

	N	%	
Age			
<50	132	33	
50-70	233	57	
≥70	41	10	
Size of Primary Tumor			
T1a ≤0.5 cm	77	19	50%
T1b >0.5-≤1.0	124	31	
T1c >1.0-≤2.0	169	42	50%
T2 >2.0-≤3.0	36	9	
Histologic Grade			
I Well differentiated	44	11	
II Moderately differentiated	131	32	
III Poorly differentiated	228	56	
HR Status (ER and/or PR)			
Positive	272	67	
Negative	134	33	



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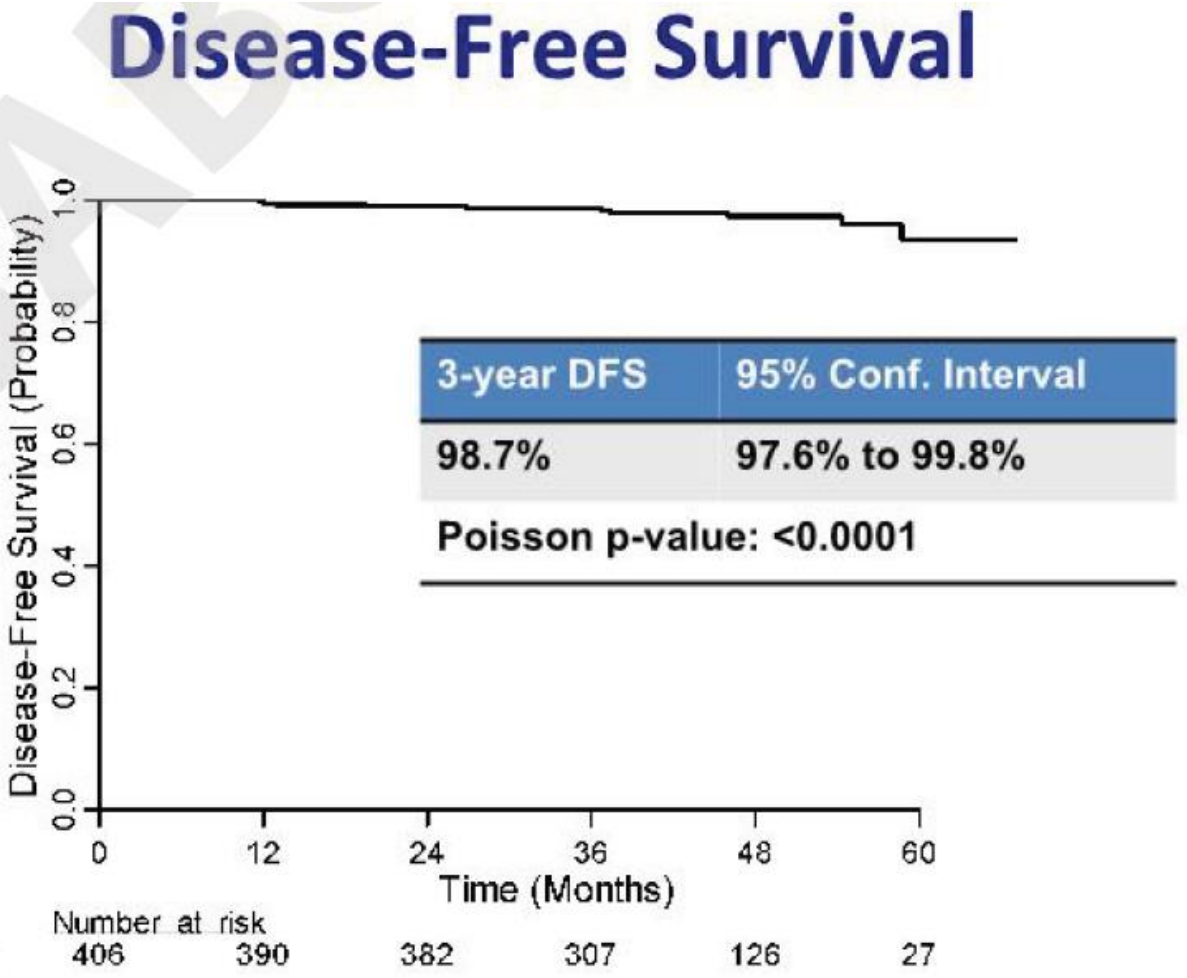
Tolaney, SABCS 2013

Quelle chimio pour les ‘HER2 positif’ ?



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Tolaney, SABCS 2013

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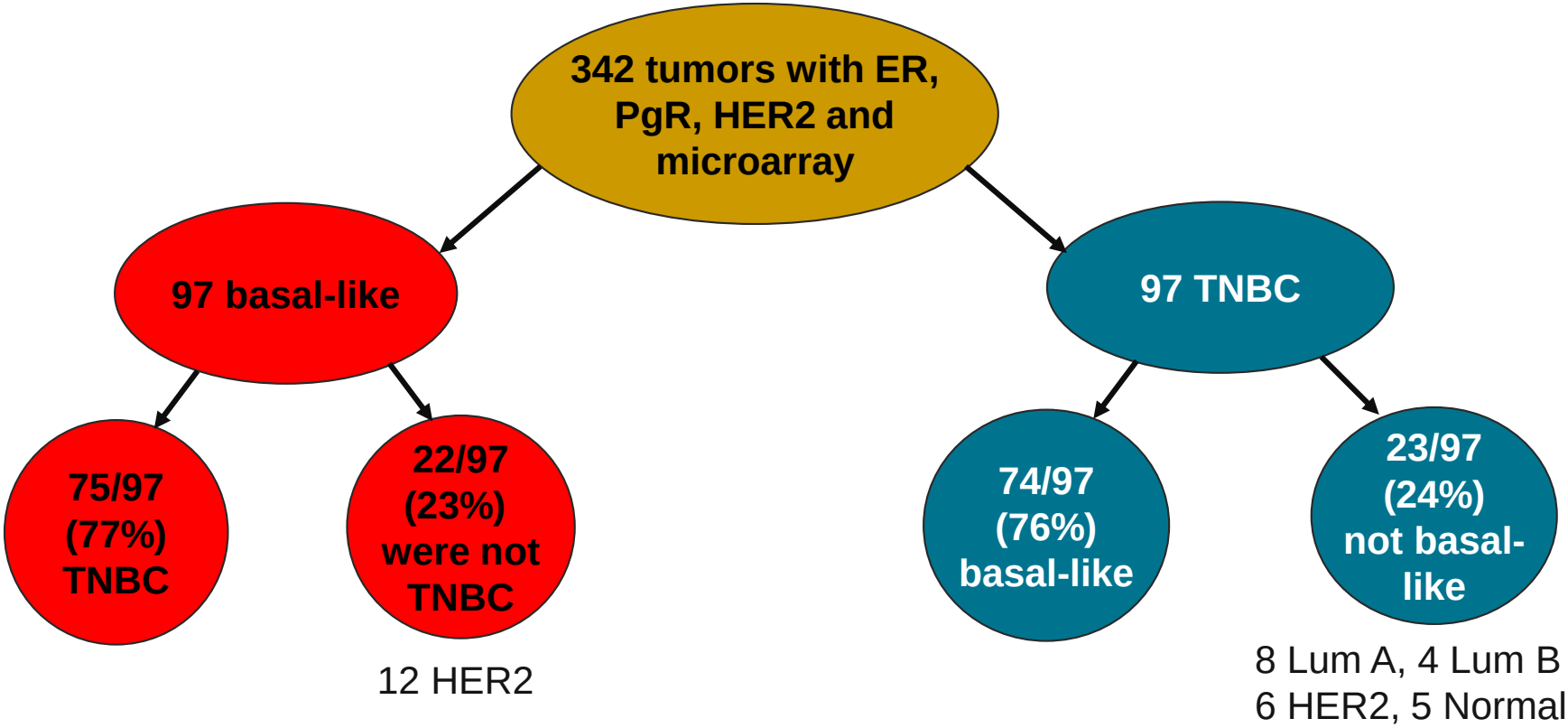
Quelle chimio pour les ‘triple-négatifs’ ?



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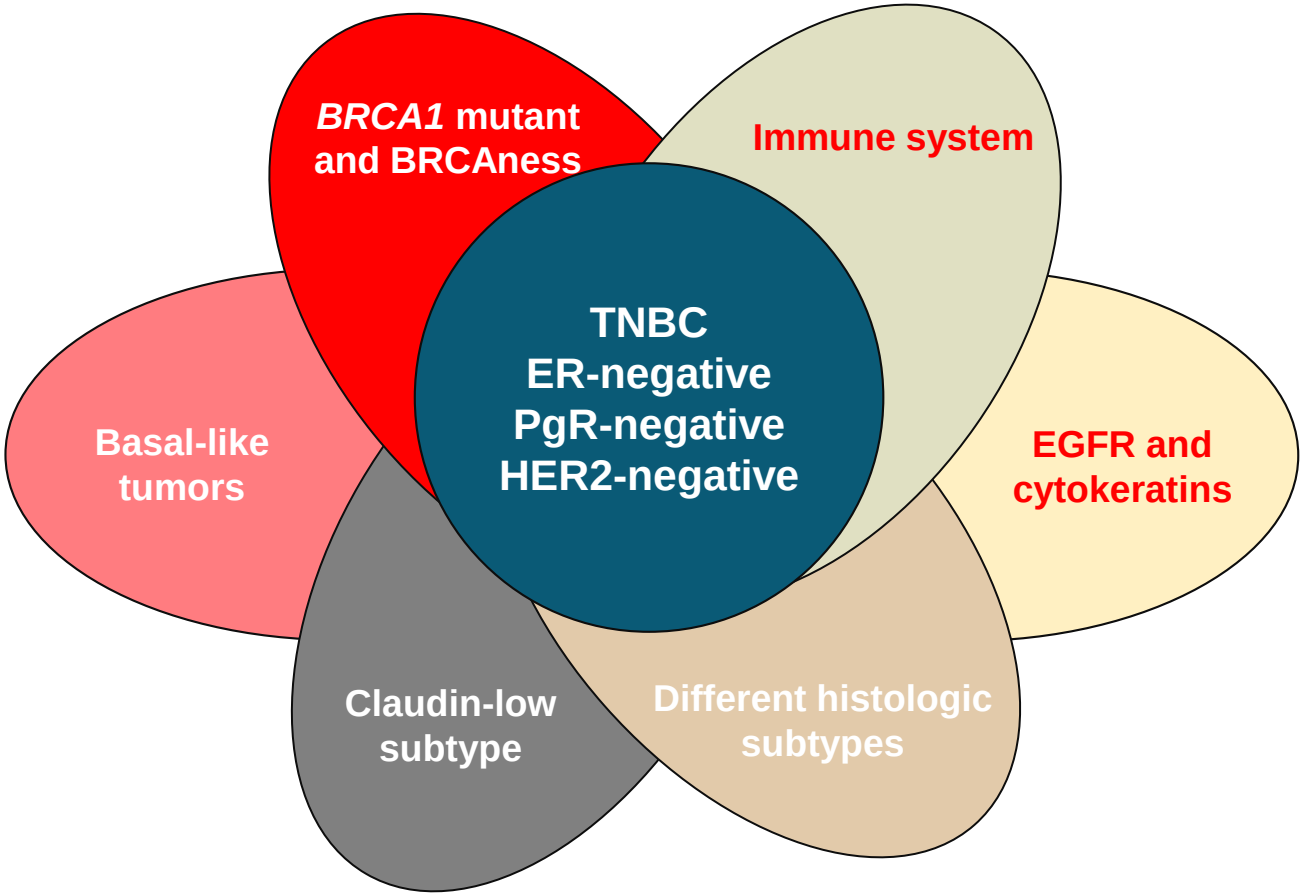
Parker, JCO 2009

Quelle chimio pour les ‘triple-négatifs’ ?



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Metzger-Filho, JCO 2012

Quelle chimio pour les ‘triple-négatifs’ ?

place du carboplatine (situation néoadj) ?

études	shémas	N	pCR contrôle	pCR carbo
GeparSixto	AC/paclitaxel/beva +/- carbo hebdo AUC 1,5	595 (315 TN)	43 %	**57 %**
CALGB 40603	2x2 paclitaxel +/- beva +/- carbo AUC 6	433	41 %	**54 %**
GEICAM 2006-03	EC > docetaxel +/- carbo AUC 6	94	30 %	**30 %**
IPSY-2	paclitaxel +/- carbo/veliparib	71	~ 26 %	**~ 52 %**

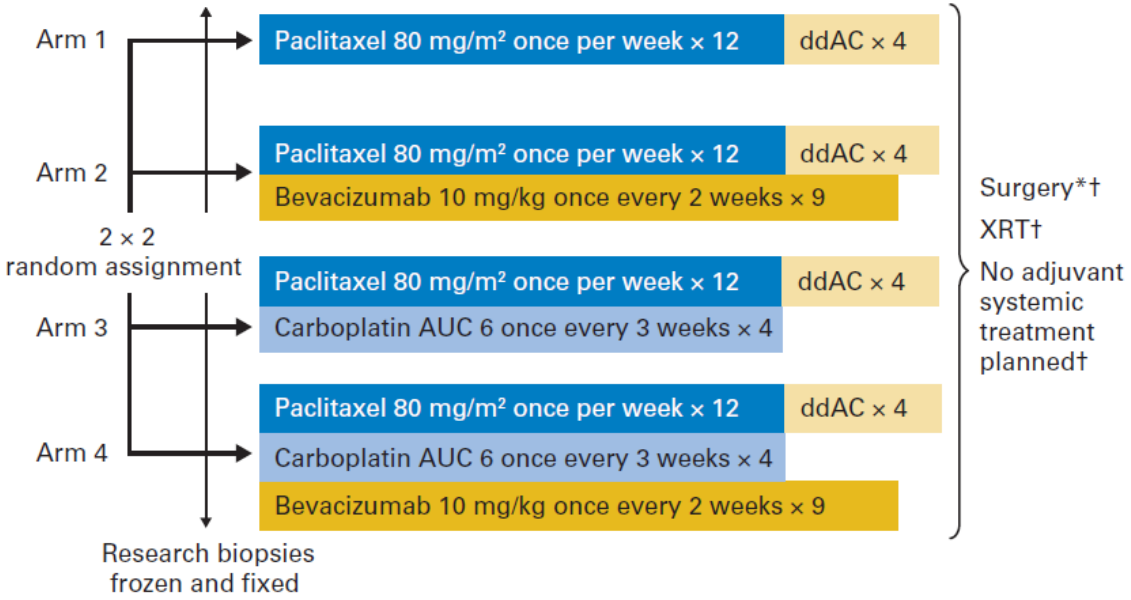
Quelle chimio pour les ‘triple-négatifs’ ?

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance)

William M. Sikov, Donald A. Berry, Charles M. Perou, Baljit Singh, Constance T. Cirrincione, Sara M. Tolaney, Charles S. Kuzma, Timothy J. Pluard, George Somlo, Elisa R. Port, Mehra Golshan, Jennifer R. Bellon, Deborah Collyar, Olwen M. Hahn, Lisa A. Carey, Clifford A. Hudis, and Eric P. Winer



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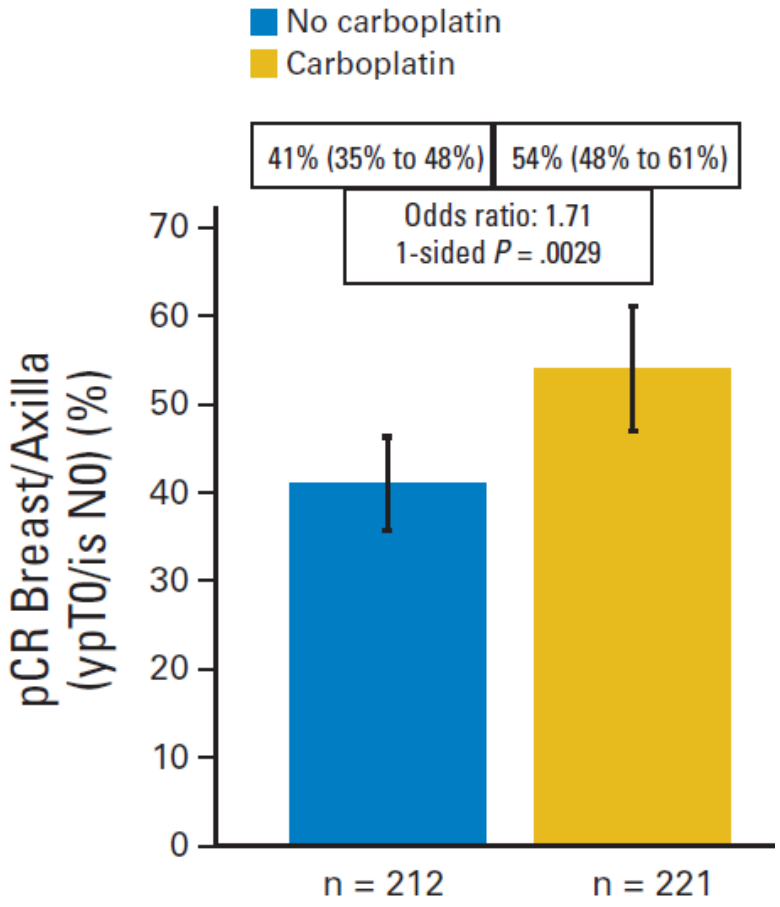
Sikov, JCO 2014

Quelle chimio pour les ‘triple-négatifs’ ?

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT



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Sikov, JCO 2014

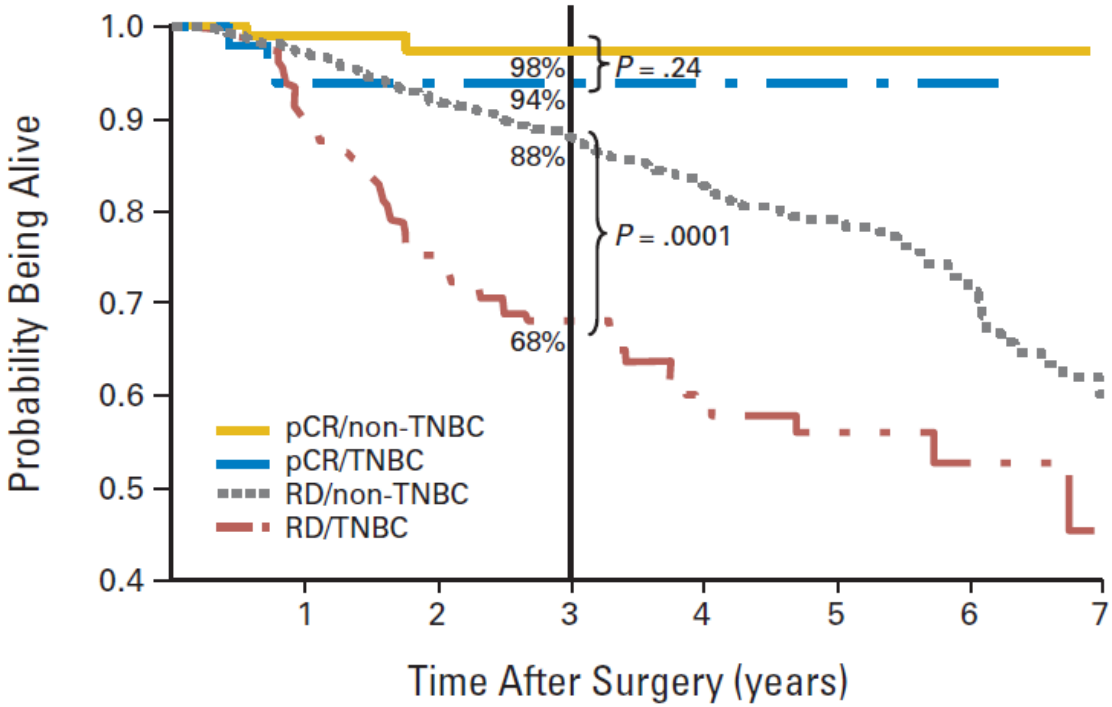
Quelle chimio pour les ‘triple-négatifs’ ?

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, and Lajos Pusztai



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Liedtke, JCO 2008

Quelle chimio pour les ‘triple-négatifs’ ?

Gene Pathways Associated With Prognosis and Chemotherapy Sensitivity in Molecular Subtypes of Breast Cancer

Takayuki Iwamoto, Giampaolo Bianchini, Daniel Booser, Yuan Qi, Charles Coutant, Christine Ya-Hui Shiang, Libero Santarpia, Junji Matsuoka, Gabriel N. Hortobagyi, William Fraser Symmans, Frankie A. Holmes, Joyce O’Shaughnessy, Beth Hellerstedt, John Pippen, Fabrice Andre, Richard Simon, Lajos Pusztai

Neoadjuvant datasets					
MDACC/MAQC		MDACC/IGR		USO 02103	
ER+/HER2−	ER−/HER2−	ER+/HER2−	ER−/HER2−	ER+/HER2−	ER−/HER2−
133	65	41	41	32	29
51.9 (26–79)	51.4 (29–75)	49.7 (31–78)	47.3 (31–75)	47.5 (26–60)	50.0 (32–66)
20.1 (0–80)	13.6 (0–100)	—	—	63.8 (23–140)	69.0 (20–175)
7.5	13.8	7.3	—	—	3.4
60.2	49.2	56.1	51.2	34.4	31.0
16.5	13.8	12.1	39.0	65.6	65.5
15.0	21.5	24.4	9.8	—	—
—	—	—	—	—	—
32.3	23.1	31.7	17.1	34.4	34.5
67.7	76.9	43.9	22.0	65.6	65.5
—	—	24.4	61.0	—	—
9.8	—	7.3	—	3.1	—
56.4	21.5	46.3	14.6	46.9	13.8
33.8	78.5	19.5	70.3	46.9	75.9
—	—	26.8	14.6	—	10.3
T/FAC	T/FAC	FAC or FEC		FEC/wTX	FEC/wTX

High sensitivity to chemotherapy in triple negative cancers was consistently associated with higher expression of gene sets that included

- microtubule spindle formation
- DNA repair
- cellular aging Gene Ontology

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Iwamoto, JNCI 2010

Conclusions

- chimiothérapie pour les cancers ‘luminaux’ : anthracyclines + taxanes (uniquement pour les lum. B ?)

- chimiothérapie pour les cancers ‘HER2-positif’ : anthracyclines + taxanes (ou taxanes seuls ?)

- chimiothérapie pour les cancers ‘triple-négatifs’ : anthracyclines + taxanes (association avec carboplatine ?)

Perspectives

- obtenir de vraies signatures génomiques prédictives de la réponse à telle ou telle chimiothérapie !

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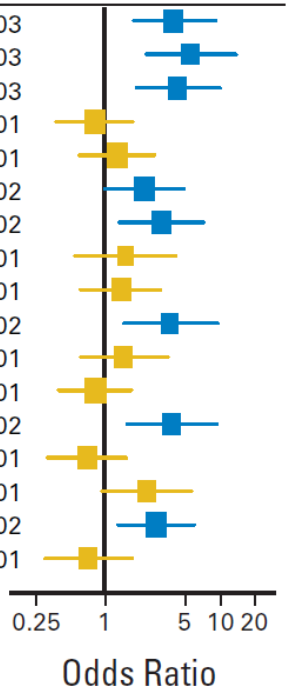
Perspectives

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Gene Modules and Response to Neoadjuvant Chemotherapy in Breast Cancer Subtypes: A Pooled Analysis

Michail Ignatiadis, Sandeep K. Singhal, Christine Desmedt, Benjamin Haibe-Kains, Carmen Criscitiello, Fabrice Andre, Sherene Loi, Martine Piccart, Stefan Michiels, and Christos Sotiriou

	OR	95% CI	*P*	FDR
GGI	3.16	1.62 to 6.36	8.8E-04	5.0E-03
Gene70	4.19	2.01 to 8.96	1.6E-04	2.7E-03
CIN70	3.37	1.71 to 6.89	5.8E-04	4.9E-03
Stroma1	0.86	0.45 to 1.6	6.4E-01	6.4E-01
Stroma2	1.24	0.65 to 2.31	5.1E-01	5.7E-01
Immune1	1.95	1.01 to 3.75	4.4E-02	9.4E-02
Immune2	2.58	1.29 to 5.2	7.4E-03	1.8E-02
RAS	1.43	0.61 to 3.28	4.0E-01	5.4E-01
MAPK	1.32	0.67 to 2.55	4.1E-01	5.4E-01
PTEN	2.98	1.38 to 6.62	6.0E-03	1.8E-02
AKTmTOR	1.37	0.68 to 2.87	3.9E-01	5.4E-01
PIK3CA	0.86	0.47 to 1.57	6.3E-01	6.4E-01
IGF1	3.05	1.46 to 6.49	3.2E-03	1.4E-02
SRC	0.75	0.39 to 1.45	3.9E-01	5.4E-01
MYC	2.02	0.96 to 4.27	6.3E-02	1.2E-01
E2F3	2.36	1.26 to 4.46	7.5E-03	1.8E-02
BetaCatenin	0.77	0.37 to 1.59	4.7E-01	5.7E-01



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