Particularités biologiques, chimiothérapie, Hormonothérapie,des cancers du sein de la femme jeune au stades précoces

Pr Luis Teixeira
Centre des maladies du Sein
Hôpital Saint Louis

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Plan

- **Plan**
  - Définition/données épidémiologiques
  - Particularités biologiques
  - Particularités cliniques
  - Traitement de chimiothérapie
  - Hormonothérapie
  - Préservation de la fertilité

Une individualisation grandissante: BCY 4

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESO—ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4)

Palush-Shimin S et al, Ann Oncol 2020

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

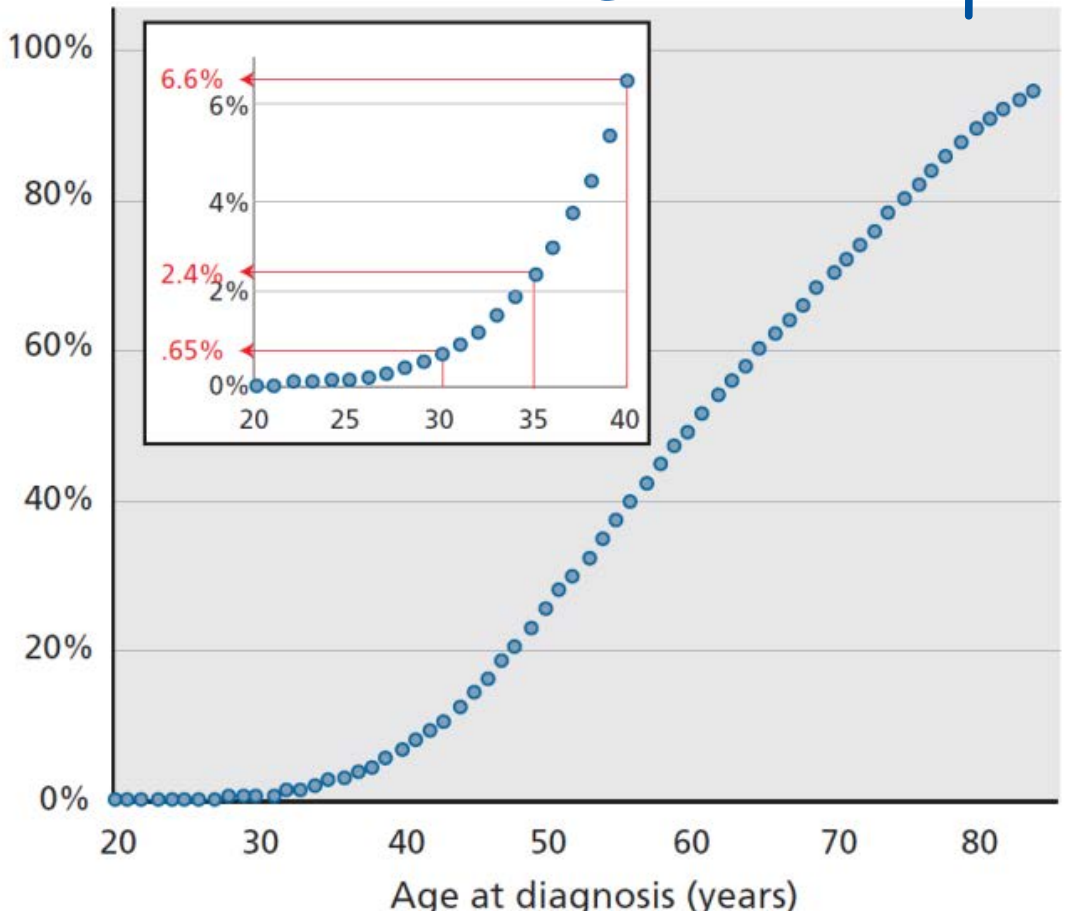
Définitions

- **Plusieurs définitions dans le temps**

- Auparavant femmes < 35 ans

- Actuellement: **Femmes <40 ans** , groupe des très jeunes <35 ans (EUSOMA, BCY)

Données épidémiologiques



Représentent 6.6% des nouveaux cas diagnostiqués/an aux USA

Tichy J.R et al JNCCN 2013

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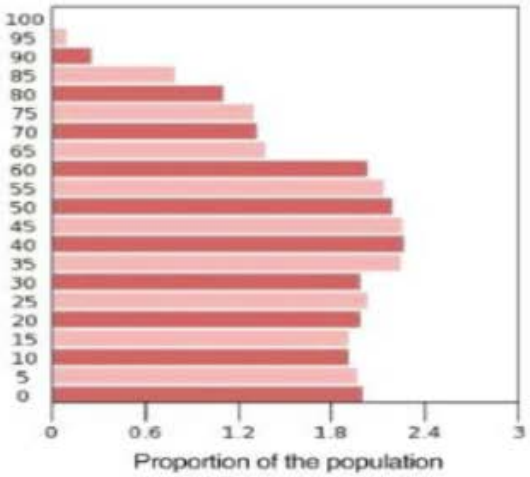
Données épidémiologiques

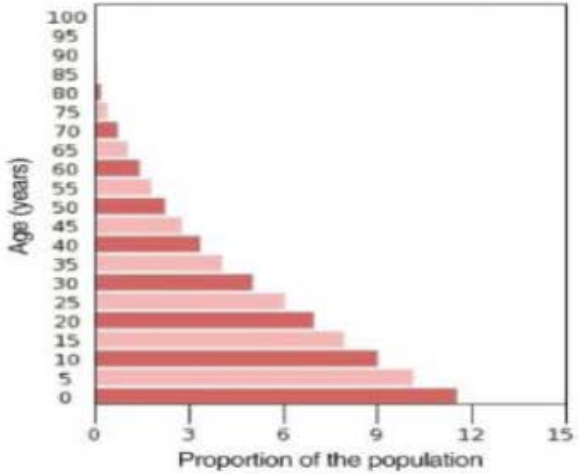
US - Europe

~ 6 % of BC < 40



Middle East - Africa

~ 20-25% of BC < 40



SINGAPORE 2018 ESMO ASIA

Kroman N et al; BMJ 2000, Elkum N et al; BMC Cancer 2006
Brinton L et al; JNCI 2008, Akarolo-Anthony S et al; BCR 2010

Progressivement

1- Est-ce lié à l'âge?

Indication à traiter différemment.

2- Est-ce lié aux caractéristiques tumorales?

Traitement selon le type de tumeur

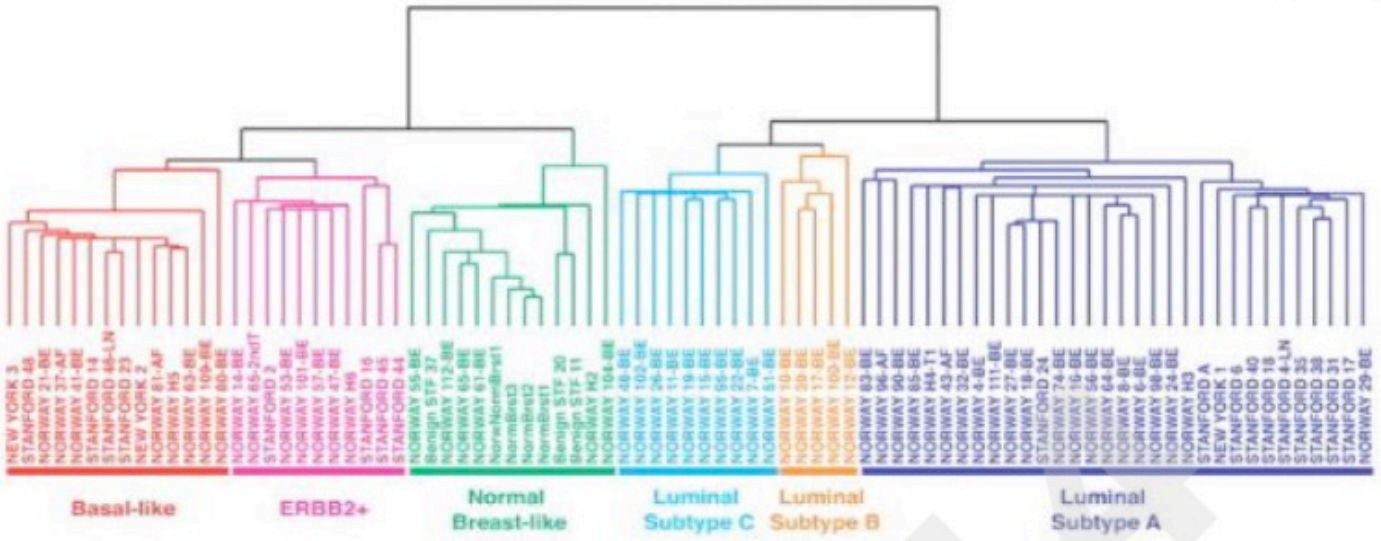
A ce jour question non complètement résolue

Sous-types histologiques

Breast cancer intrinsic subtypes

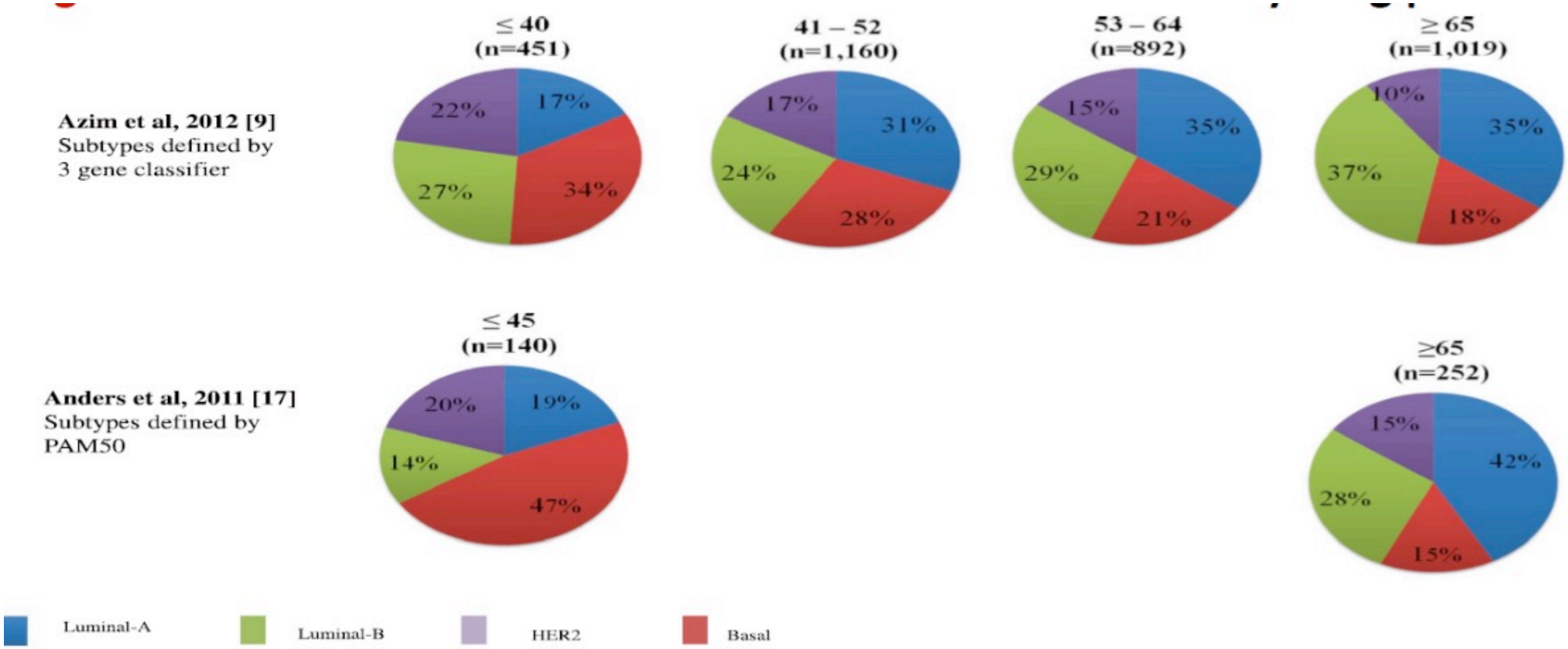
Subsequently developed into PAM50 assay

Parker *et al* JCO 2009

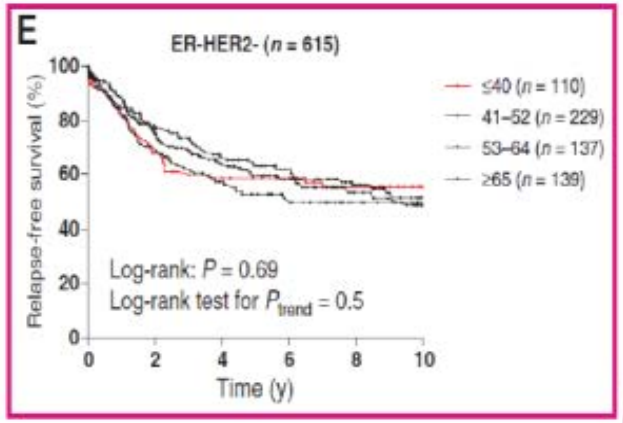


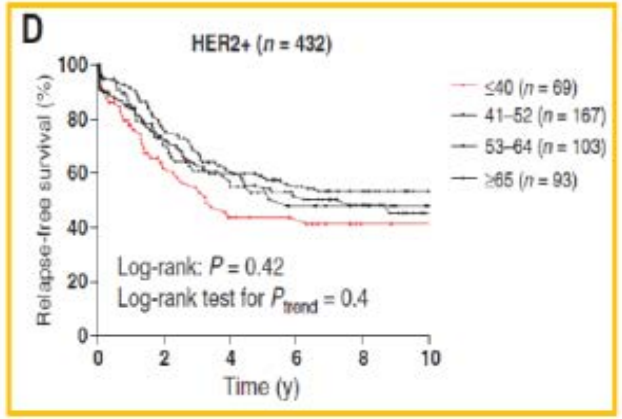
Basal-like HER2 Luminal B Luminal A

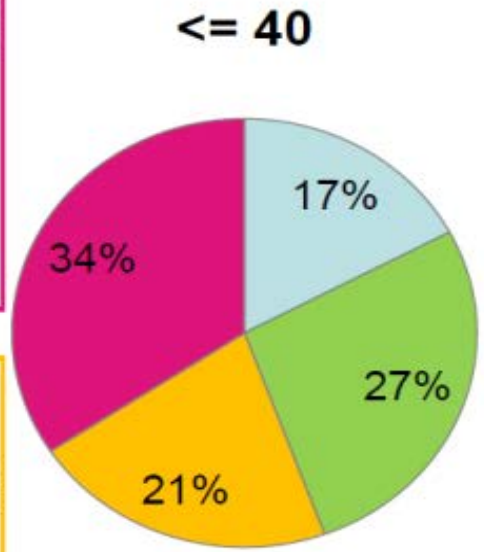
Répartition selon les sous-types histologiques

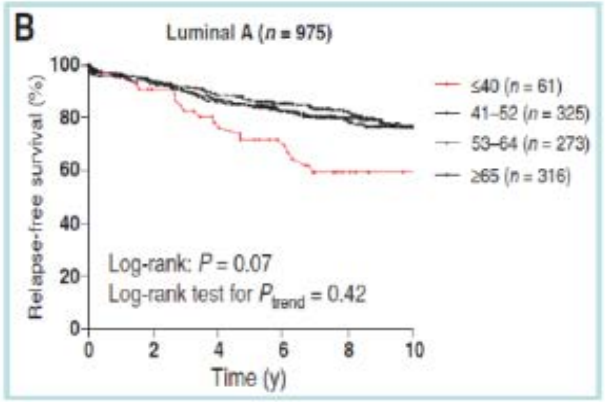


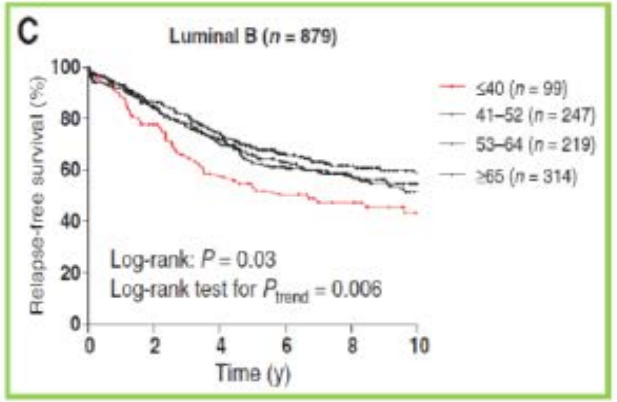
Survie globale selon les sous-types histologiques











Plus fréquemment Triples négatives HER2+
< 40 ans Plus mauvais pronostic

Signature gènes du stroma
« cellules mammaires immatures »

Azim et al Clin can res 2012

Plus mauvais pronostic chez les femmes jeunes en comparaison des plus âgées
Surtout vrai pour le luminales

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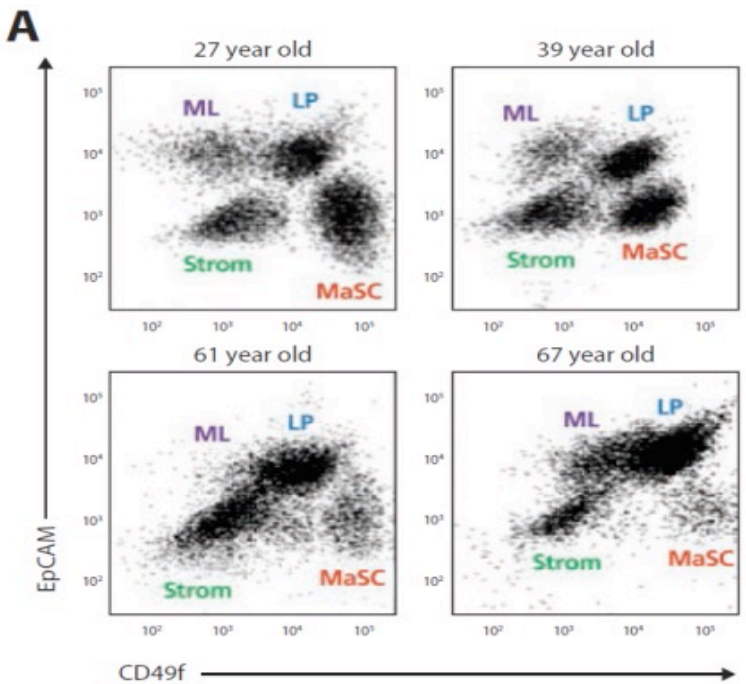
Age at Diagnosis (years)	No. of Patients	Breast Cancer Deaths, No. (%)	HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡	HR (95% CI)§
≤ 40	1,916	242 (12.6)	1.9 (1.6 to 2.3)	1.5 (1.3 to 1.8)	1.4 (1.2 to 1.7)	1.3 (1.1 to 1.5)
41-50	4,654	321 (6.9)	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.0 (0.8 to 1.2)	0.9 (0.8 to 1.1)
51-60	5,249	343 (6.5)	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	3,477	164 (4.7)	0.7 (0.6 to 0.9)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)	0.8 (0.7 to 1.0)
> 70	2,279	112 (4.9)	0.7 (0.5 to 1.0)	1.2 (0.8 to 1.6)	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.4)

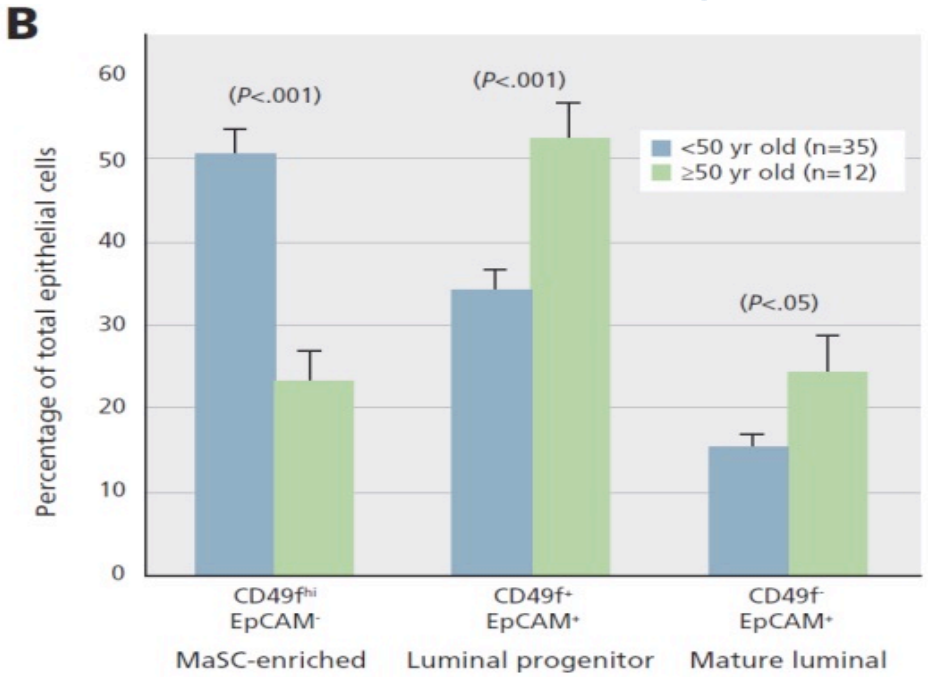
The effect of age on survival varies by breast cancer subtype: young age is particularly prognostic in women with luminal disease

Breast cancer subtype	Results in young patients
Luminal A	HR, 1.7; 95% CI, 1.1 – 2.7
Luminal B	HR, 1.2; 95% CI, 0.9 – 1.7
HER2-positive	HR, 1.1; 95% CI, 0.7 – 1.7
Triple negative	HR, 1.3; 95% CI, 0.9 – 1.7

Partridge AH et al, J Clin Oncol 2016;34:3308-14

Répartition des « progéniteurs/cellules souches » différente en fonction de l'âge

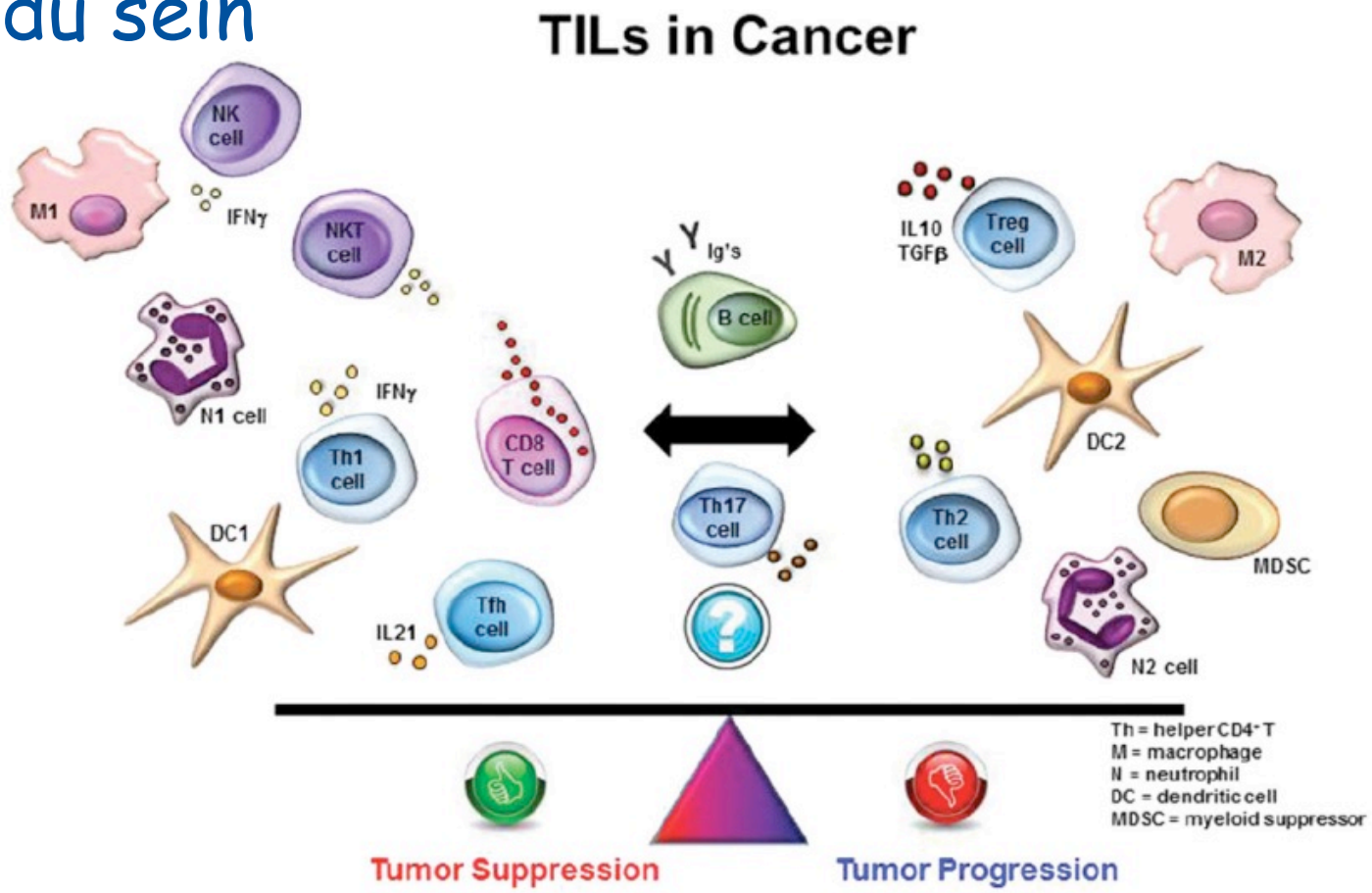




Transformation à partir de cellules « souches » différentes chez les patientes jeunes?

Tichy et al JNCCN 2013

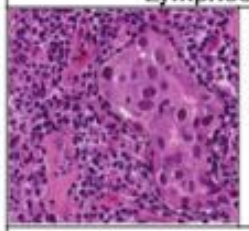
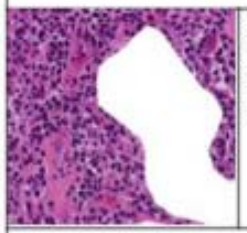
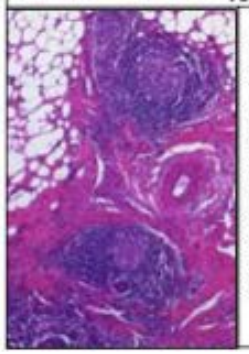
Rôle de l'infiltrat inflammatoire
Lymphocytes infiltrant les tumeurs ou « Tils » dans le cancer du sein



Différent types de
Lymphocytes infiltrant les tumeurs
ou « Tils » dans le cancer du sein

LPBC: (sTILS>50-60% des cellules)
Bon pronostic
Triples négatives
HER2+ (prédictif de réponse sous Trastuzumab)

Loi S

Morphology	Definition and biological relevance	Diagnostic relevance
Lymphocyte-predominant breast cancer (LPBC)		
	Working category to describe tumors with "more lymphocytes than tumor cells".	Definitions vary across studies with stromal TILs of 50-60% used as a threshold. LPBC can be used for predefined subgroup analyses and for description of tumors with a particularly high immune infiltrate, however, keep in mind that TILs are a continuous parameter and the threshold for LPBC is still arbitrary.
Stromal TILs		
	Indicator of increased accumulation of immune-cells in tumor tissue	Stromal TILs have been shown to be predictive for increased response to neoadjuvant chemotherapy as well as improved outcome after adjuvant chemotherapy. **Based on current data, this parameter is the best parameter for characterization of TILs.**
Intratumoral TILs		
	TILs with direct cell-cell contact with carcinoma cells, might be an indicator of direct cell-based anti-tumor effects.	Several studies have shown that intratumoral TILs are more difficult to evaluate and do not provide additional predictive/prognostic information compared to stromal TILs.
TILs at the invasive margin		
The localization of TILs are the invasive edge is included in the evaluation approach presented in this guideline.		For breast cancer there are no studies with a separate evaluation of TILs at the invasive edge. For practical purposes, the reliable evaluation of the invasive edge might be difficult when using core biopsies in the neoadjuvant setting.
Tertiary lymphoid structures (TLS)		
	Typically localized in the surrounding area of the tumor, TLS might be localized in normal tissue directly adjacent to the tumor, consisting of a T cell zone next to a B cell follicle, often with germinal centers.	While these structures may be important for the biology of tumor-immune reactions, they are not yet optimized for non-research based assessments. The main problem is that TLS have a spatial heterogeneity and are principally localized in areas surrounding the tumor. They might not be in the plane of the tissue section that is being evaluated, in particular when using core biopsies. Furthermore, it might be difficult to distinguish lymphoid aggregates from true TLS, in particular when the germinal center is not in the plane of the section.

Salgado et al, Ann Oncol 2014

Infiltrat lymphocytaire plus important chez les femmes jeunes

Table 1 Clinicopathologic characteristics and distribution of FOXP3+ intratumoral lymphocytes (iTILs) in the study population

Characteristics	Number of patients	FOXP3+ iTILs (≥2)	
	(%)	Prevalence %	*P* value
Age at diagnosis (year)			<0.001
<40	294 (7.4)	41.6 (106/255)	
40-49	844 (21.1)	38.5 (264/685)	
50-65	1,425 (35.7)	29.5 (350/1186)	
>65	1,429 (35.8)	27.0 (311/1150)	

Liu *et al. Breast Cancer Research* 2014, **16**:432

Depuis l'ère des sous-types histologiques

Box 3 | Clinical characteristics in women <40

- High risk of local recurrence
- Short median time from diagnosis to local recurrence
- High risk of mortality following local recurrence
- High risk of contralateral breast cancer
- High proportion oestrogen receptor-negative or progesterone receptor-negative disease
- High proportion of HER2-positive disease
- High proportion *TP53*-positive tumours

Narod S, Nat Rev Clin oncol 2012

Cancer du sein Triples négatifs chez les femmes jeunes/formes génétiques

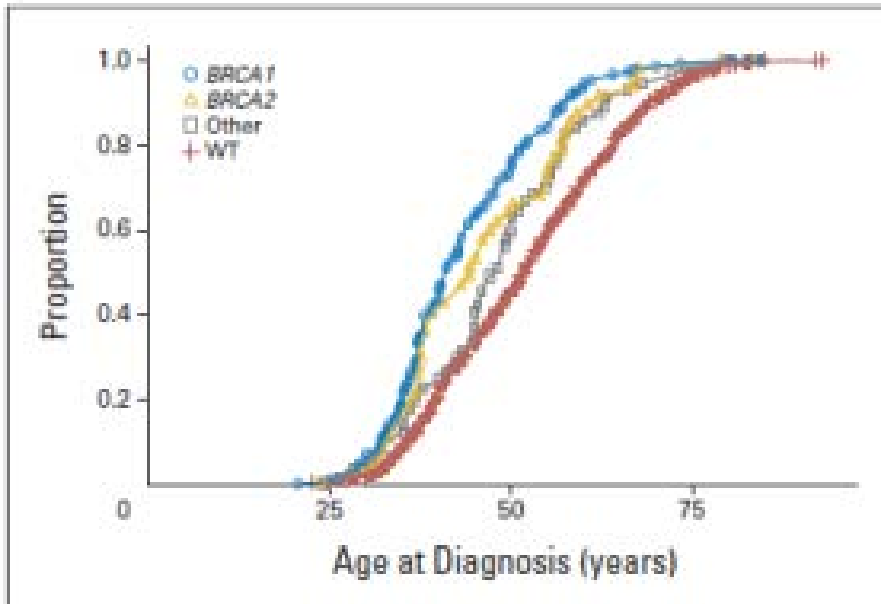
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

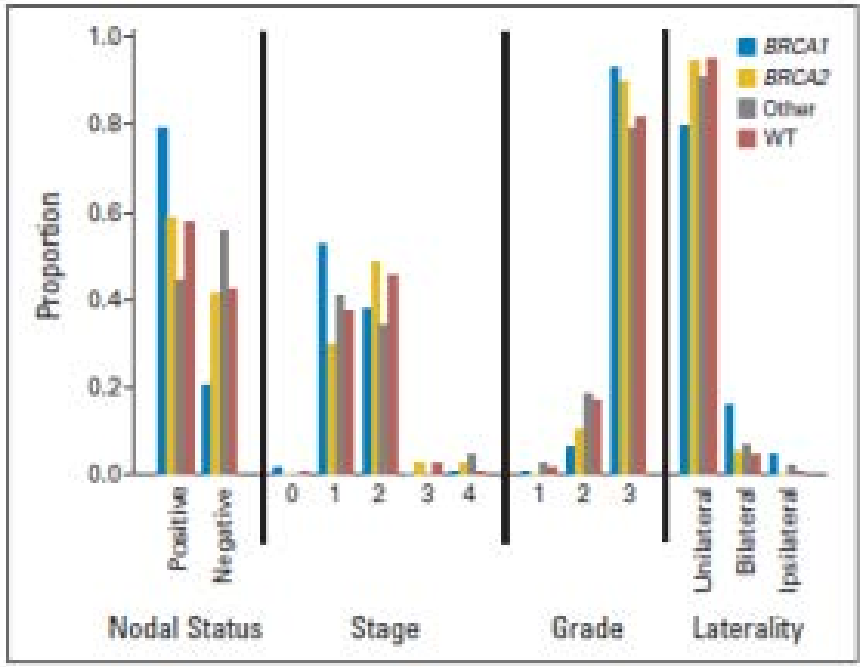
Inherited Mutations in 17 Breast Cancer Susceptibility Genes Among a Large Triple-Negative Breast Cancer Cohort Unselected for Family History of Breast Cancer

Fergus J. Couch, Steven N. Hart, Priyanka Sharma, Amanda Ewart Toland, Xianshu Wang, Penelope Miron, Janet E. Olson, Andrew K. Godwin, V. Shane Pankratz, Curtis Olswold, Seth Slettedahl, Emily Hallberg, Lucia Guidugli, Jaime I. Davila, Matthias W. Beckmann, Wolfgang Janni, Brigitte Rack, Arif B. Ekici, Dennis J. Slamon, Irene Konstantopoulou, Florentia Fostira, Athanassios Vratimos, George Fountzilas, Liisa M. Pelttari, William J. Tapper, Lorraine Durcan, Simon S. Cross, Robert Pilarski, Charles L. Shapiro, Jennifer Klemp, Song Yao, Judy Garber, Angela Cox, Hiltrud Brauch, Christine Ambrosone, Heli Nevanlinna, Drakoulis Yannoukakos, Susan L. Slager, Celine M. Vachon, Diana M. Eccles, and Peter A. Fasching

Patientes non sélectionnées sur l'histoire familiale; 1824 patientes
Taux de mutation de 14.6% dans 14 gènes BRCA1/BRCA2 représentent à eux seuls 11.2% des mutations.

Cancer du sein Triples négatifs chez les femmes jeunes mutées





Plus souvent N+, Plus souvent de haut grade

Traitement par chimiothérapie

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4)

There is no evidence to recommend a specific chemotherapy regimen for young women requiring neo/adjuvant chemotherapy

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Ann Oncol 2020

Signatures moléculaires et patients pré-ménopausées

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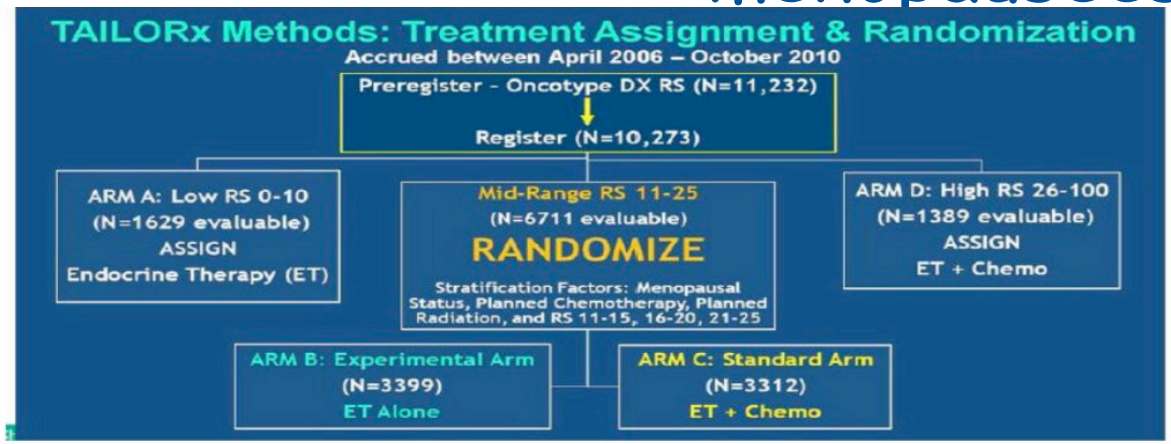


rding to Recurrence Score and Assigned Treatment in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	94.0±0.6	84.0±1.3
Score of 11–25, endocrine therapy	92.8±0.5	83.3±0.9
Score of 11–25, chemoendocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemoendocrine therapy	87.6±1.0	75.7±2.2

Table 3. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	95.1±1.1	87.4±2.0
Score of 11–15, endocrine therapy	95.1±1.1	85.7±2.2
Score of 11–15, chemoendocrine therapy	94.3±1.3	89.2±1.9
Score of 16–20, endocrine therapy	92.0±1.3	80.6±2.5
Score of 16–20, chemoendocrine therapy	94.7±1.1	89.6±1.7
Score of 21–25, endocrine therapy	86.3±2.3	79.2±3.3
Score of 21–25, chemoendocrine therapy	92.1±1.8	85.5±3.0
Score of ≥26, chemoendocrine therapy	86.4±1.9	80.3±2.9

Pts ≤ 50 years: 46%

CONCLUSIONS

Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger. (Funded

SINGAPORE ESMO ASI

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Signatures moléculaires et patients pré-ménopausées

EORTC

The future of cancer therapy

San Antonio Breast Cancer Symposium, December 10-14, 2009

SUMMARY OF RESULTS

DMFS

	Patients ≤50y old N = 452			Patients > 50y old N = 865		
ITT1 population	Events / total	Kaplan Meier 5Y DMFS (95% CI)	HR (95%CI)	Events / total	Kaplan Meier 5Y DMFS (95% CI)	HR (95%CI)
No chemotherapy	17/225	93.3% (88.6-95.8%)	Reference	23/440	95.4% (92.8 ; 97.1)	Reference
Chemotherapy	9/227	96.3% (91.9-98.2%)	0.54 (0.24-1.22)	23/345	95.2% (92.4; 97.0)	1.11 (0.62-1.98)

Absolute difference 3% 0.2%

DMFI

	Patients ≤50y old N = 452			Patients > 50y old N = 865		
ITT1 population	Events / total	Kaplan Meier 5Y DMFI (95% CI)	HR (95%CI)	Events / total	Kaplan Meier 5Y DMFI (95% CI)	HR (95%CI)
No chemotherapy	16/225	93.6% (89.3-96.3%)	Reference	18/440	96.7% (94.3-98.1%)	Reference
Chemotherapy	8/227	96.1% (91.9-98.2%)	0.54 (0.24-1.22)	19/425	96.3% (93.9-97.8%)	1.17 (0.61-2.23)

Absolute difference 2.5% 0.4%

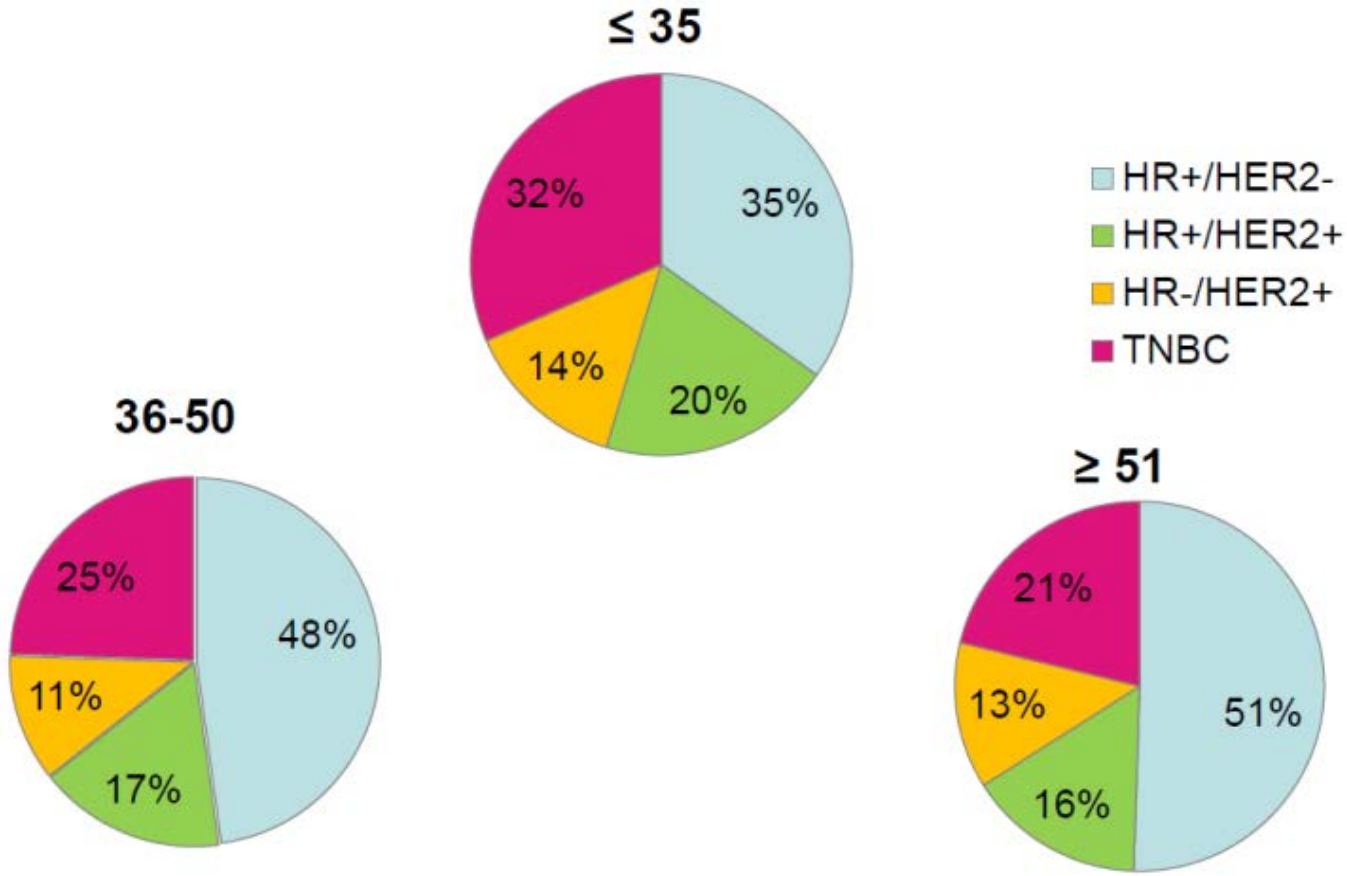
ET for patients ≤ 50y consisted mostly in tamoxifen.
Only 8.3% of the ≤50 cH/gL patients received OFS

- C-High/G-low patients, ≤ 50y have a small numeric benefit of CT (DMFS 3%, DMFI 2.5%) (stats descriptive only)
- Observed absolute difference is smaller than seen in TailorX
- Median FU in the 2 trials is different (MINDACT: 5 years; TailorX: 7.5 years)

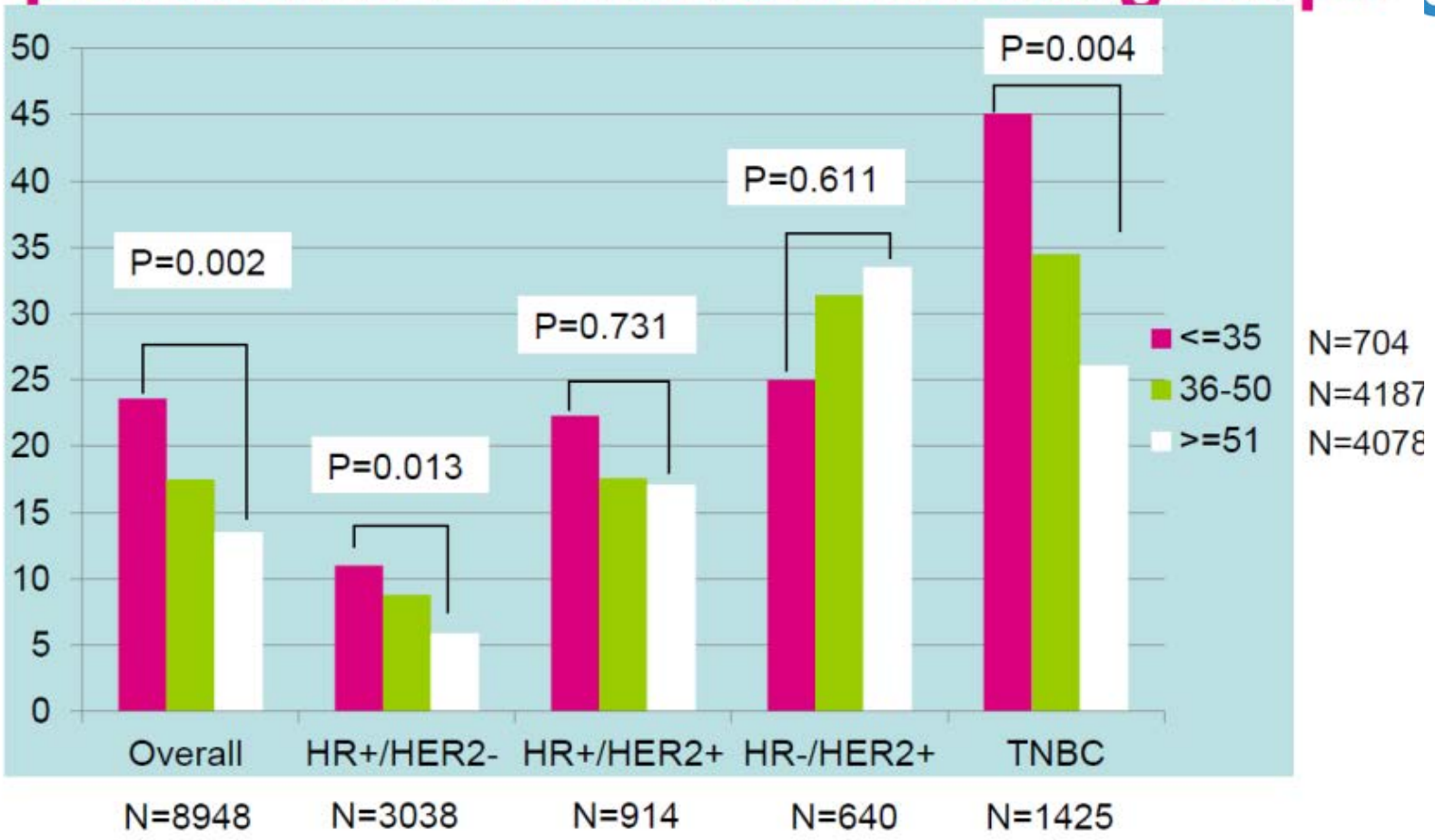
Pas de spécificité du type de traitement selon l'age

The indications for and the choice of adjuvant systemic treatment for invasive breast cancer should be driven, as for women in other age categories, by extent of disease and the biological characteristics of the tumour (including, but not limited to, ER/PR and HER-2 receptors, proliferation, and grade) and patient's comorbidities.	[I, A]	
For the time being, the type of systemic treatment of EBC is independent of *BRCA* or any other constitutional genetic status.	Expert opinion	
The optimal (neo)adjuvant CT regimen specifically for young women in terms of efficacy and long-term toxicity is currently unknown. As for all stage I—III breast cancer patients, the preferred regimens are standard anthracycline, alkylating and taxane-based regimens.	[I, A]	100%
The indication for dose-dense chemotherapy is independent of age.		
Standard duration of treatment (minimum of 4 and maximum of 8 cycles) should be prescribed.	[I, A]	
Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated.	[I, A]	
Young age by itself should not be an indication to prescribe a combination of cytotoxic agents.		
In patients with TNBC or *BRCA*-associated tumours the incorporation of platinum agents increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated.	[I, B]	
Data on the impact of incremental increases in pCR on long-term outcome are not conclusive.		
The use of platinum derivatives has potential additional impact on fertility and increased toxicity that may compromise standard duration and dosing of systemic treatment, and this needs to be clearly communicated to patients.		
For patients with TNBC not achieving a pCR after standard neoadjuvant regimens, the routine addition of adjuvant chemotherapy with 6—8 cycles of capecitabine may be considered	[I, A]	
There are no data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended.	[I, A]	100%

Répartition des différents sous-types histologiques en fonction de l'âge
Etudes en néoadjuvant du groupe GEPAR



pCR rates overall and in subgroups



*adjusted for age, tumor size, nodal status, histological type, grading, trial

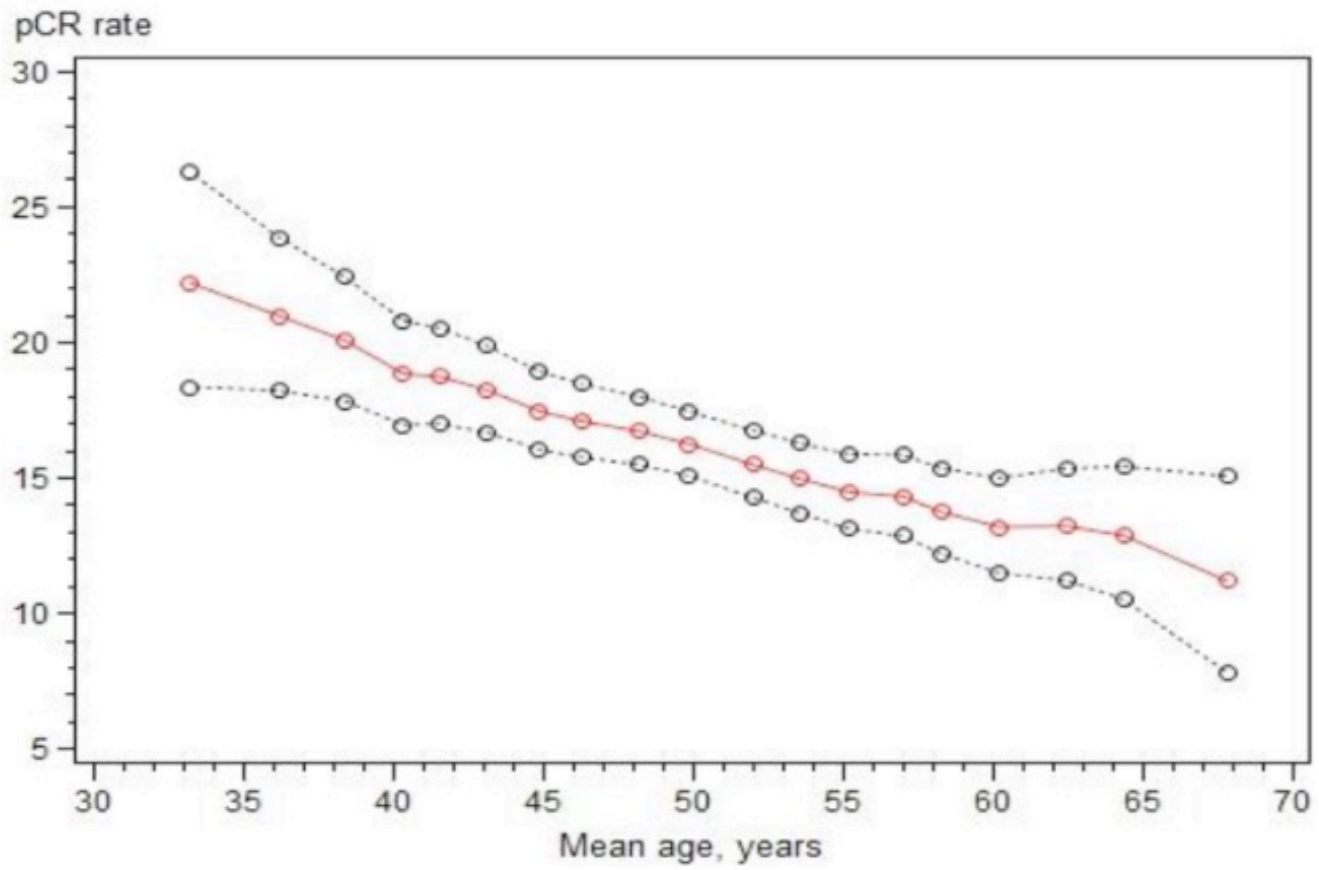
Loibl S, et al. Cancer Res 2012;72: #S3-1

GBG GERMAN BREAST GROUP

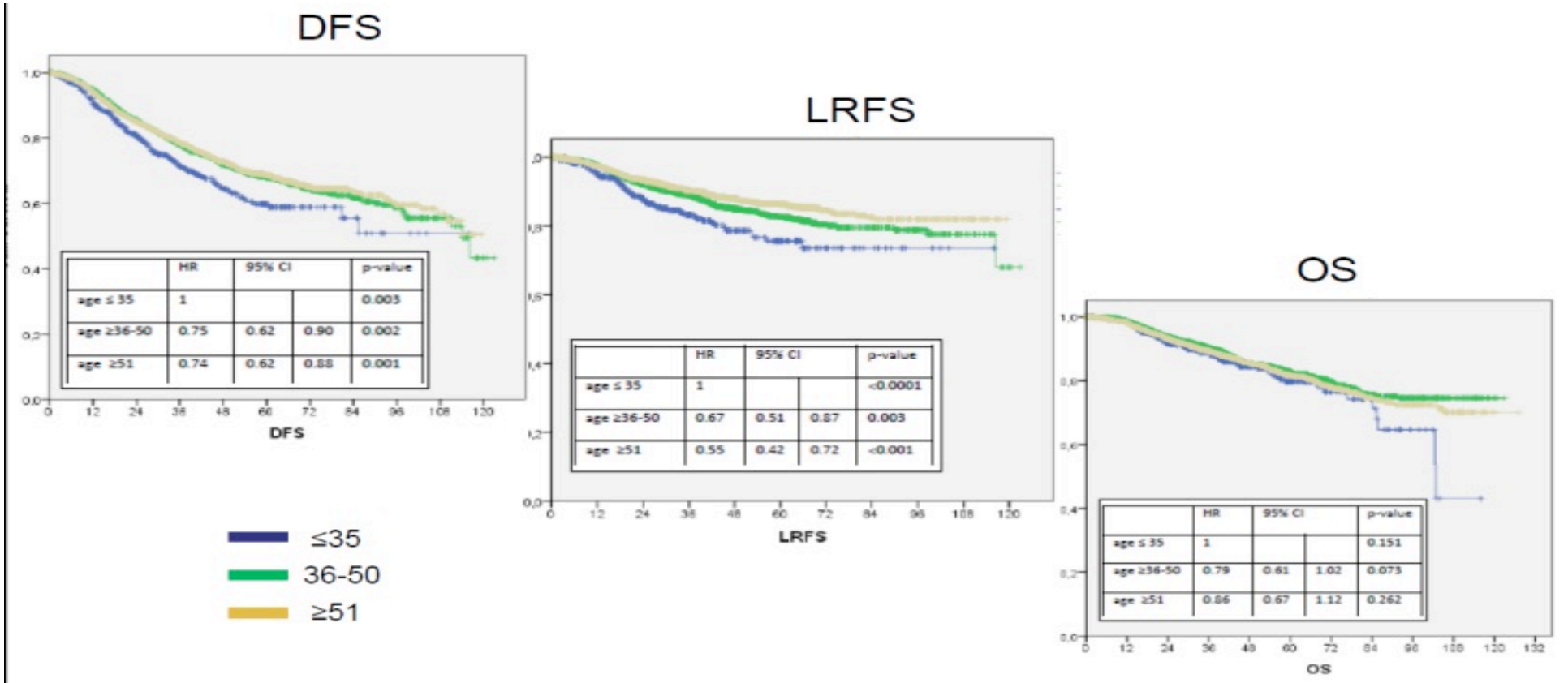
Vrai quelque soit le sous type histologique

Taux de pCR plus élevé chez les plus jeunes

Taux de réponse complète histologique en fonction de l'âge



Moins bon pronostic lorsqu'il existe une maladie résiduelle post chimiothérapie néoadjuvante



	HR	95% CI		p-value
age ≤ 35	1			0.003
age ≥36-50	0.75	0.62	0.90	0.002
age ≥51	0.74	0.62	0.88	0.001

	HR	95% CI		p-value
age ≤ 35	1			<0.0001
age ≥36-50	0.67	0.51	0.87	0.003
age ≥51	0.55	0.42	0.72	<0.001

	HR	95% CI		p-value
age ≤ 35	1			0.151
age ≥36-50	0.79	0.61	1.02	0.073
age ≥51	0.86	0.67	1.12	0.262

Loibl S, et al. Cancer Res 2012;72: #S3-1

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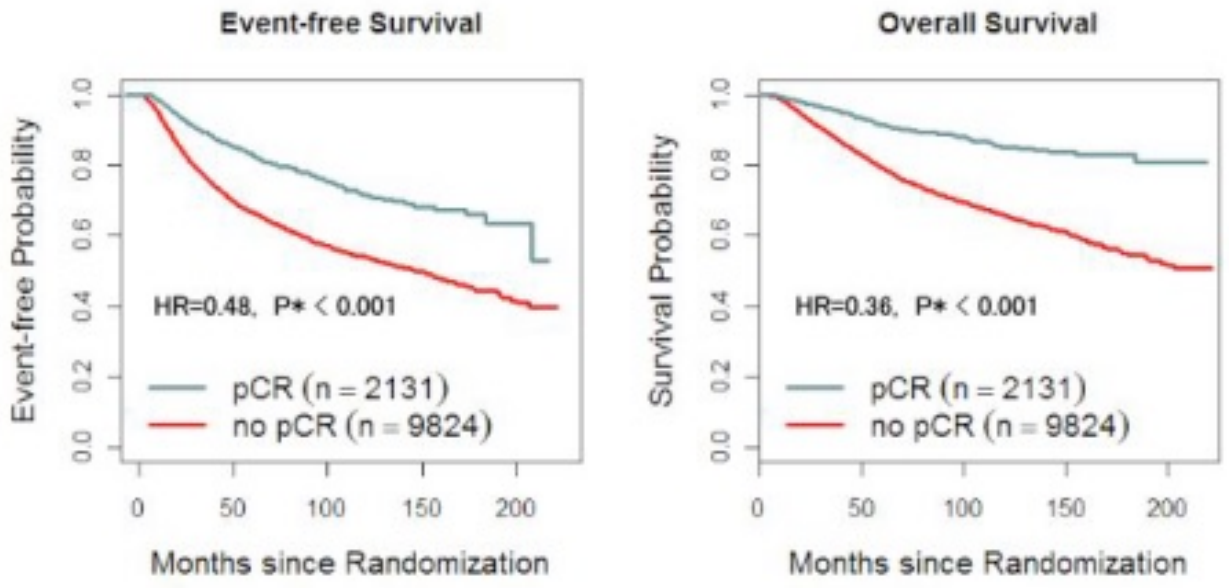
pCR corrélée à la survie pour les triples négatives

Association of pCR and Survival



pCR=ypT0/is ypN0

* Nominal p-value

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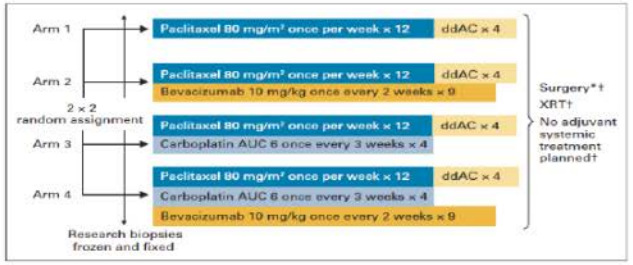
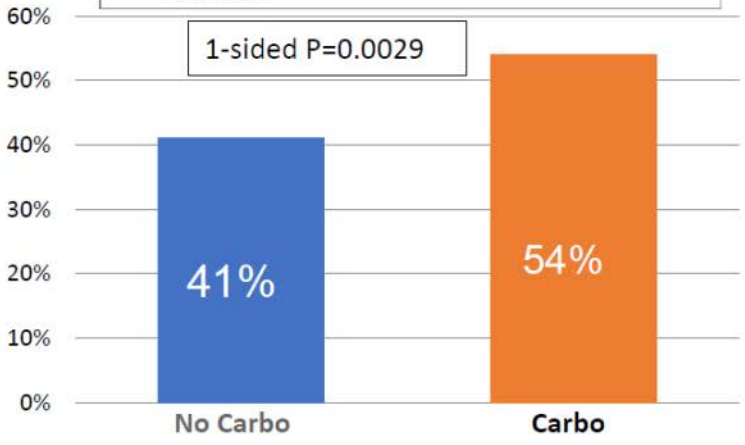
cortaza et al Lancet 2014

Dérivés platines: carboplatine

pCR Rates (ypTis/ypN0) in TNBC with platinum

CALGB 40603

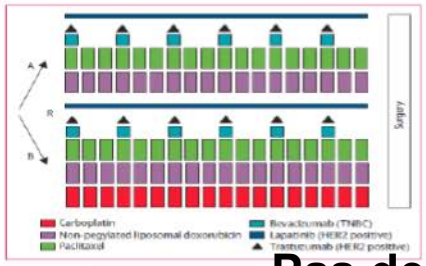


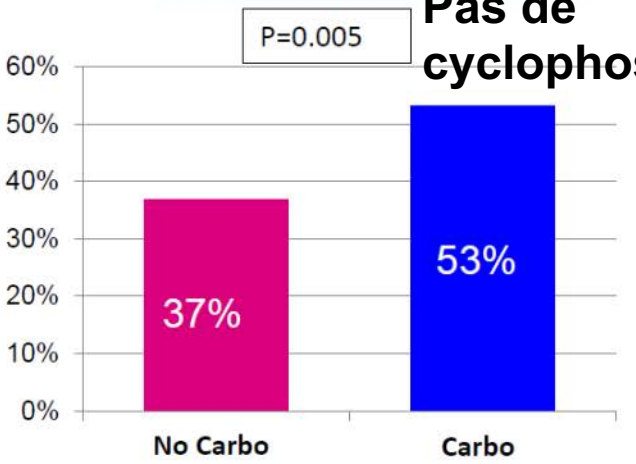


N=157 N=158

Sikov W, et al. J Clin Oncol 2014

GeparSixto





Pas de cyclophosphamide

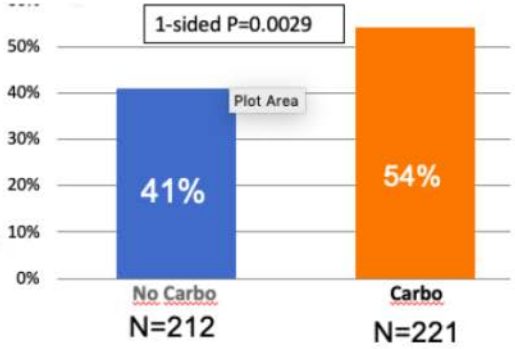
N=212 N=221

von Minckwitz G, et al. Lancet Oncol 2014

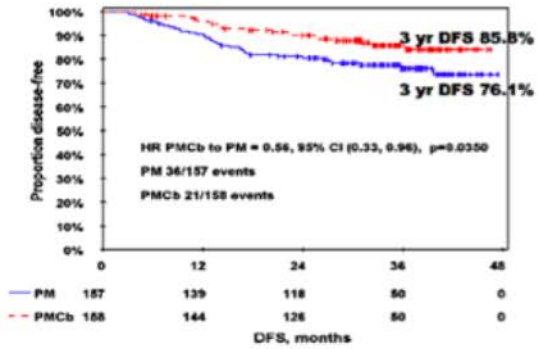
Amélioration de l'EFS pour GeparSixto

GeparSixto

CARBO AUC 1.5-2 weekly



Sikov W, et al. J Clin Oncol 2014



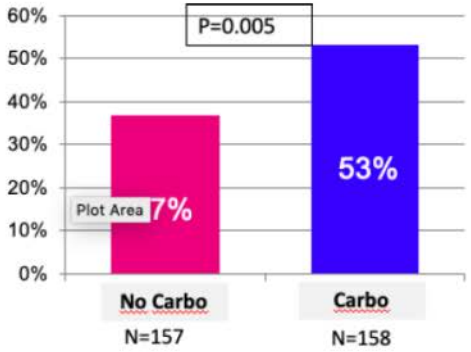
EFS
HR = 0.56
p = 0.0350

9.7 %

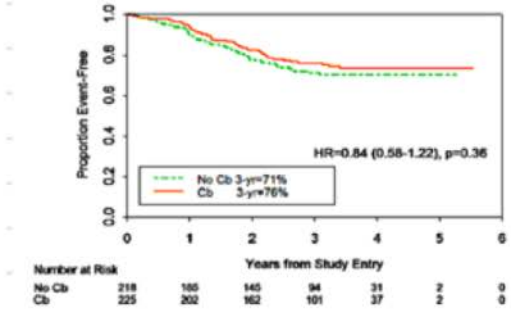
Significatif

CALGB 40603

CARBO AUC 6 q3 weeks



von Minckwitz G, et al. Lancet Oncol 2014



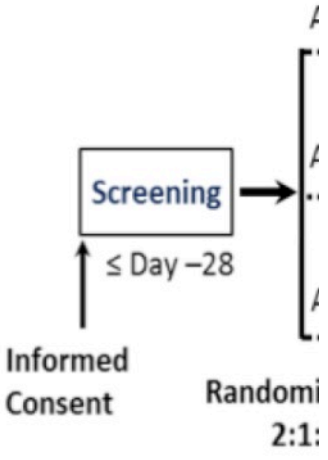
EFS
HR = 0.84
p = 0.38

4.9%

Non Significatif

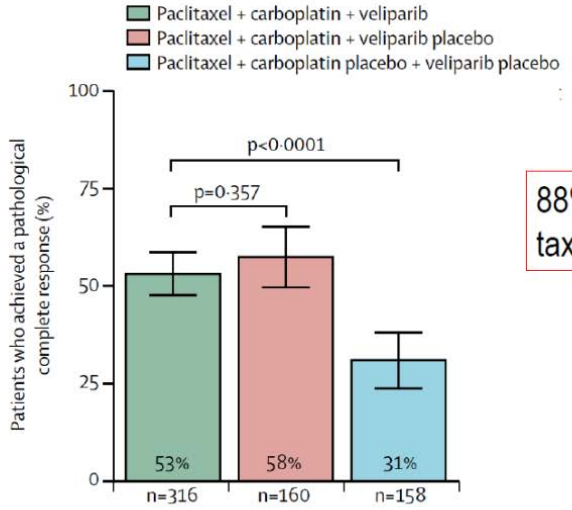
Etude Brightness: Parpinh+ carboplatine

BrighTNesS TRIAL



~27% pCR

Await EFS and OS



88% pts completed taxol/carbo

Loibl S, et al. Lancet Oncol 2018

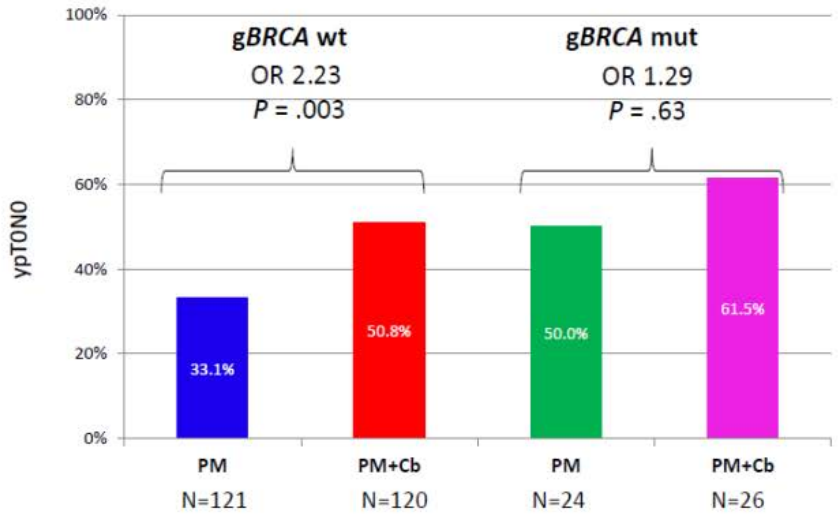
BARCELONA 2019 ESMO congress

q3 weeks

Echec du véliparib, **intérêt du carboplatine confirmé**

Bénéfice du carboplatine non lié au statut BRCA

GeparSixto: pCR in TNBC by g*BRCA* status



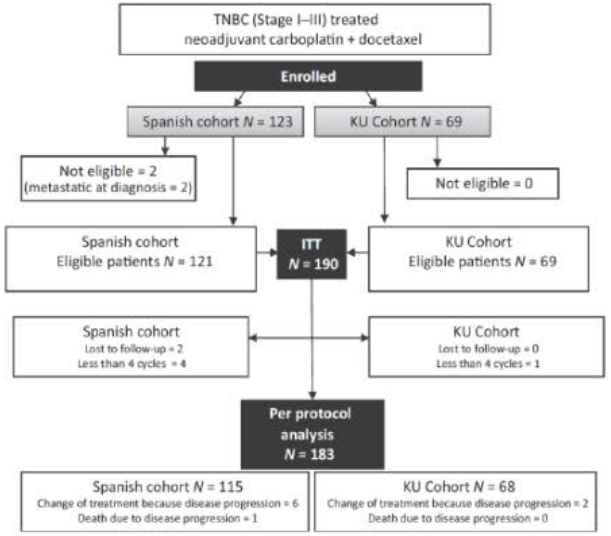
g*BRCA* predicts higher pCR

g*BRCA* does not predict higher benefit from platinum in early breast cancer

Hahnen E et al, JAMA Oncol 2017

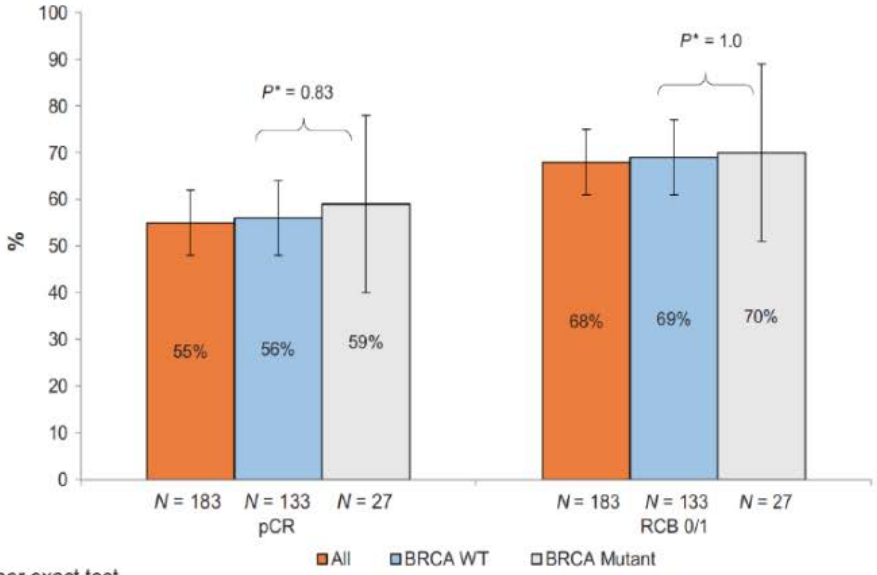
Bénéfice du carboplatine non lié au statut BRCA

Efficacy of Neoadjuvant Carboplatin plus Docetaxel in Triple-Negative Breast Cancer: Combined Analysis of Two Cohorts



Docetaxel 75 mg/m2
Carboplatin AUC 6
q3w x 6 cycles

pCR rate with platinum similar in WT BRCA and BRCA Mutant



*Fisher exact test

Hormonothérapie

Hormonothérapie; questions

- Avant la ménopause en cas de tumeur RH+ quels sont les traitements optimaux, à quel prix?
- Quelle doit être la durée de l'hormonothérapie

- Toutes les femmes doivent-elles avoir une suppression ovarienne?
  Essai SOFT

- En cas de suppression ovarienne faut-il y associer
  Du Tamoxifène ?
  Des inhibiteurs de l'aromatase?

- Quid des toxicités?

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Référentiels hormonothérapie

	St Gallen 2013	ASCO 2014
Pré ménopause	TAM 5 ans	TAM 5 à 10 ans
Ménopause	TAM 5 à 10 ans ou IA 5 ans ou IA puis TAM ou TAM puis IA	IA 5 ans ou TAM 5 à 10 ans ou TAM 5 ans puis IA 5 ans

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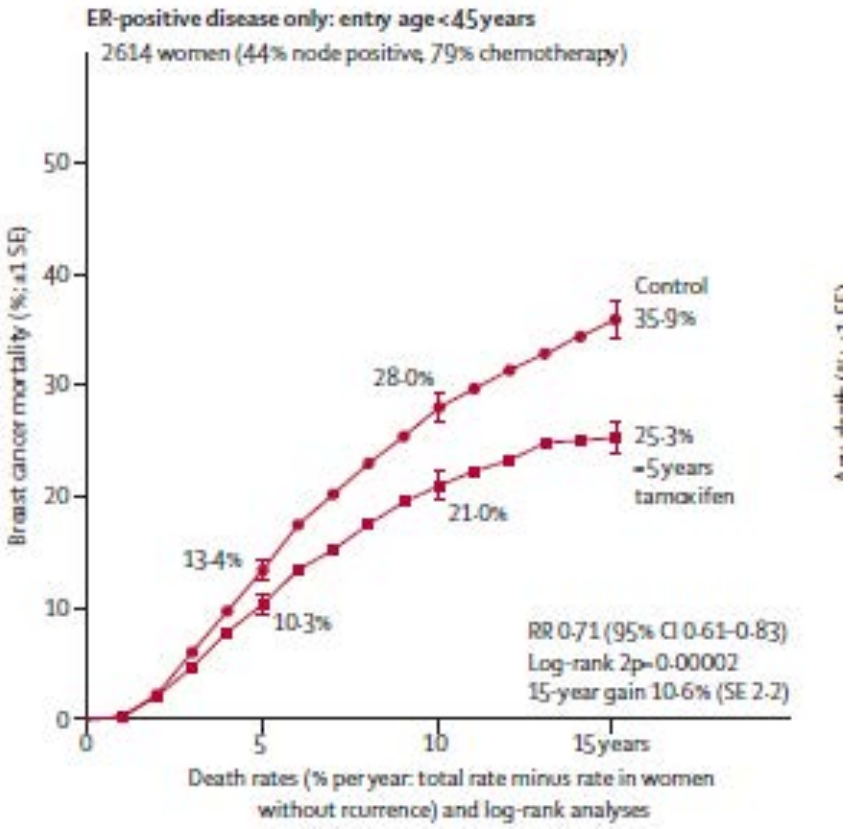
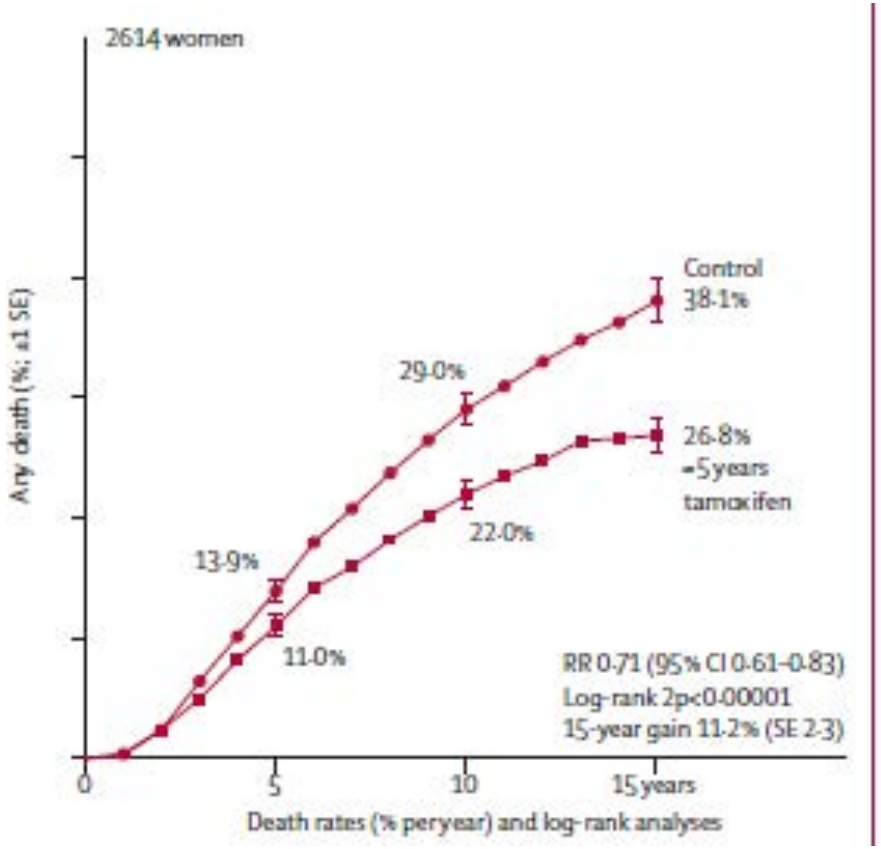
Tamoxifène 5 ans: à 15 ans < 45 ans RE+

79% traitées par chimiothérapie N= 2614, Lancet 2011 EBCTCG





Mortalité par cancer du sein: réduction de 10,6%

Mortalité toutes causes: 11,2%

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Essais portant sur la durée 5 ans versus 10 ans de tamoxifène

Essais	Nombre de patientes
ECOG, Scottish, NSABP B 14	1568
ATLAS	11646
ATOM	6953
TOTAL	20187

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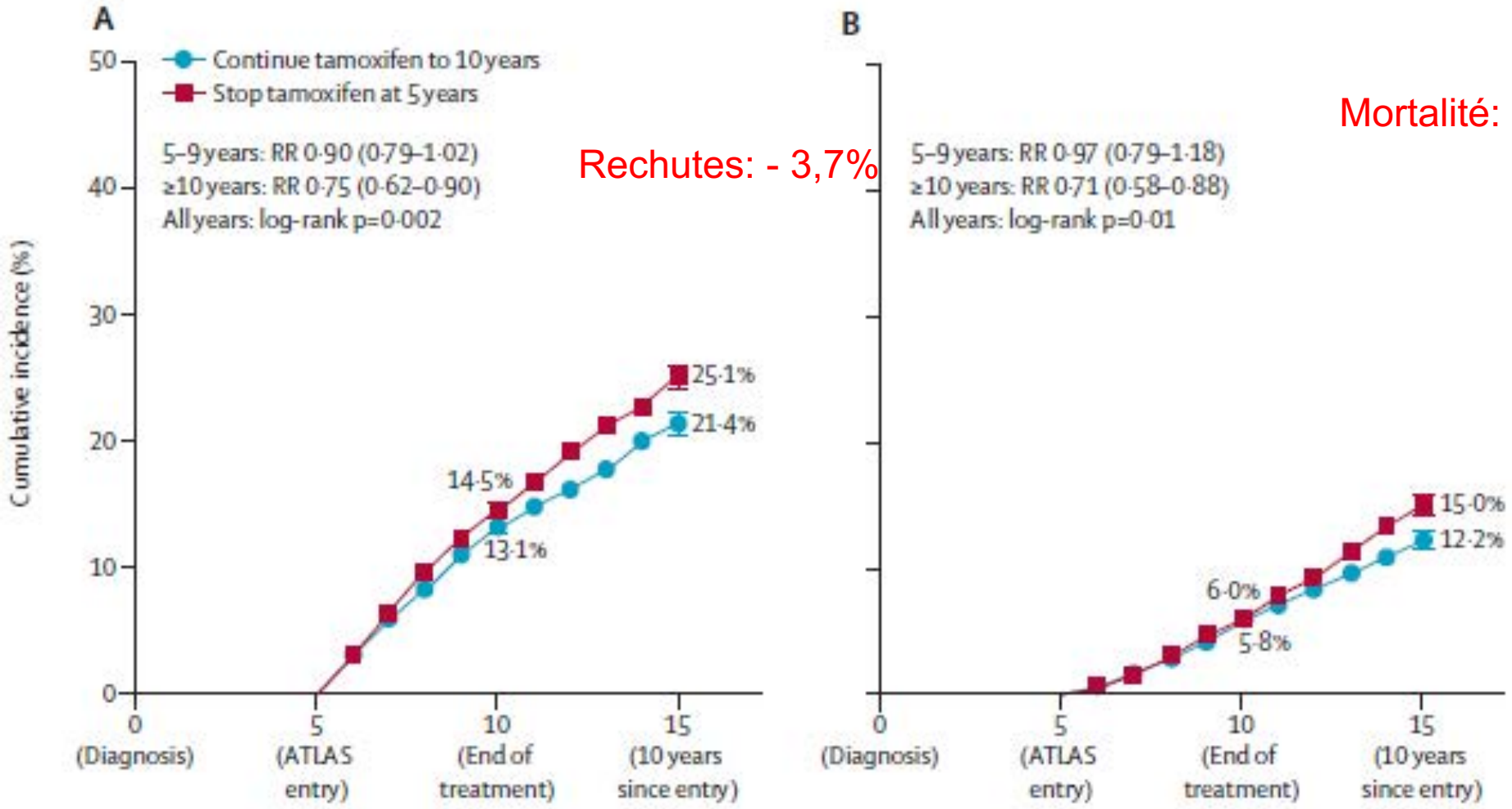
ATLAS 10 vs 5 ans de tamoxifène, 6846 patientes RE+



Rechutes: - 3,7%

Mortalité: - 2,8%

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Attom: 10 versus 5 ans

6953 patientes randomisées
Survie sans rechute: 4% de bénéfice, HR = 0,85 (0,76-0,85)
Survie globale: 1% de différence NS p= 0,2, RR = 0,94 (0,86-1,03)

Gray ASCO 2013

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ATLAS + ATTOM

	Mortalité par cancer du sein	Mortalité globale
Années 5-9	0,97 (0,84-1,15)	0,99 (0,89-1,10)
Années ≥ 10	0,75 (0,65-0,86)*	0,84 (0,77-0,93)*
TOTAL	0,85 (0,77-0,94)*	0,91 (0,84-0,97)*

* $p<0,05$ en faveur des 10 ans

Gray ASCO 2013

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Durée: MA17 létrozole en fonction de la ménopause

Au diagnostic 877 patientes pré ménopausées et 4289 ménopausées

4 à 5 ans de tamoxifène **puis** randomisation entre létrozole ou placebo,
à 2,5 ans arrêt de l'étude en raison du bénéfice **en SSR en faveur du létrozole,** choix proposé de poursuivre de permuter ou d'arrêter

Gain en SSR à l'extension du létrozole

Pré ménopausées: HR = 0,26 (0,13-0,55)

Ménopausées: HR = 0,67 (0,51-0,89)

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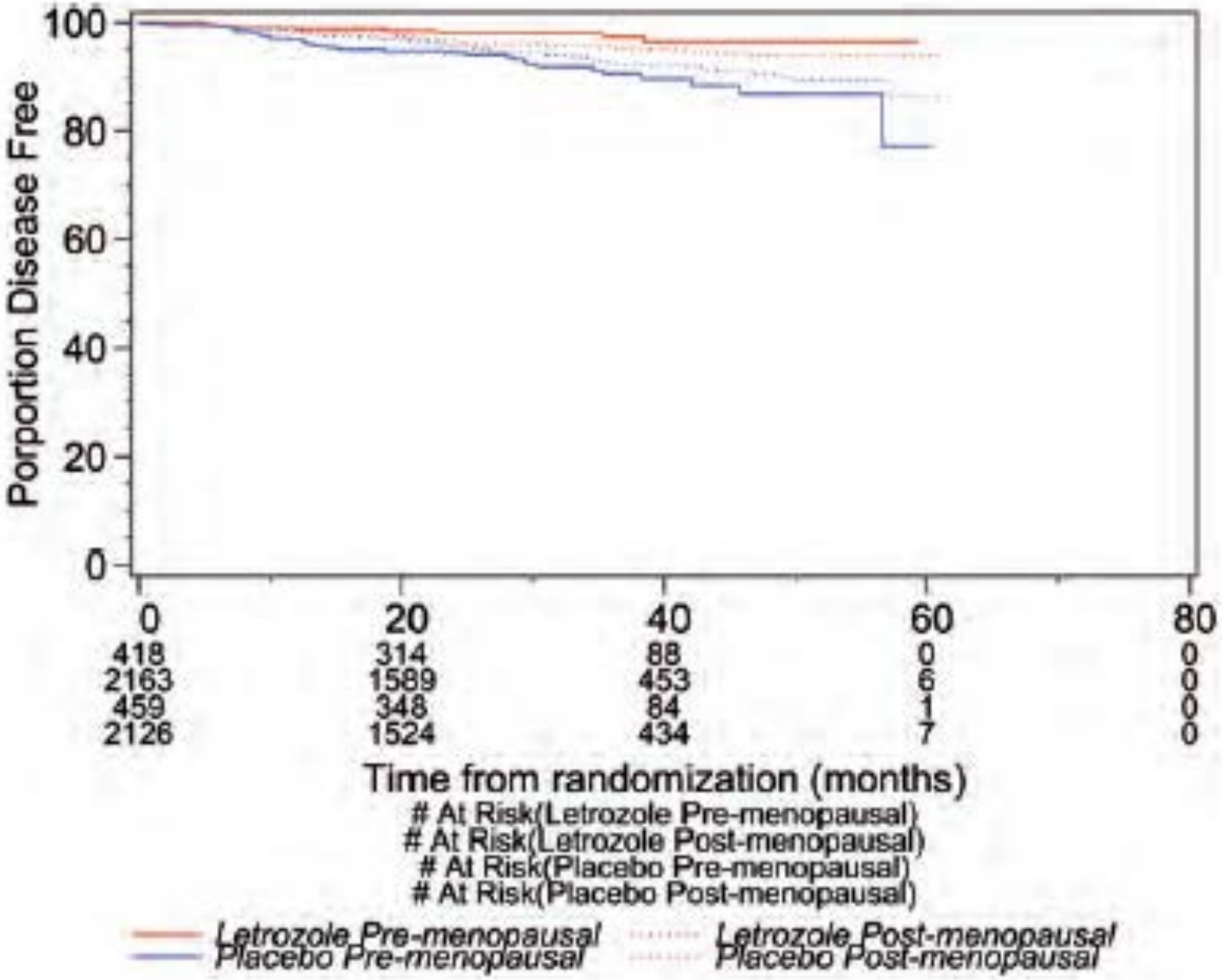
Goss PE Ann Oncol 2013, 24:355-361

Bénéfice du létrozole
En fonction de la ménopause au diagnostic: SSR



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Tamoxifène, Inhibiteurs de l'aromatase et Agonistes de la LHRH

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Tamoxifène ± castration: ECOG E3193

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345 patientes pré ménopausées RE ou RP +
Pas de chimiothérapie
T< 3 cm N0

Médiane de suivi 9,9 ans

Pas de bénéfice ni en SSR ni en SG

Majoration des effets indésirables sous T + SO (grades 3 et 4: 22,4% versus 12,3% p = 0,004)

Davantage de troubles climatériques, moindre activité sexuelle, moins bonne qualité de vie (p< 0,01)

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Tevaarwerk A, JCO 2014; 32: 3948-3958

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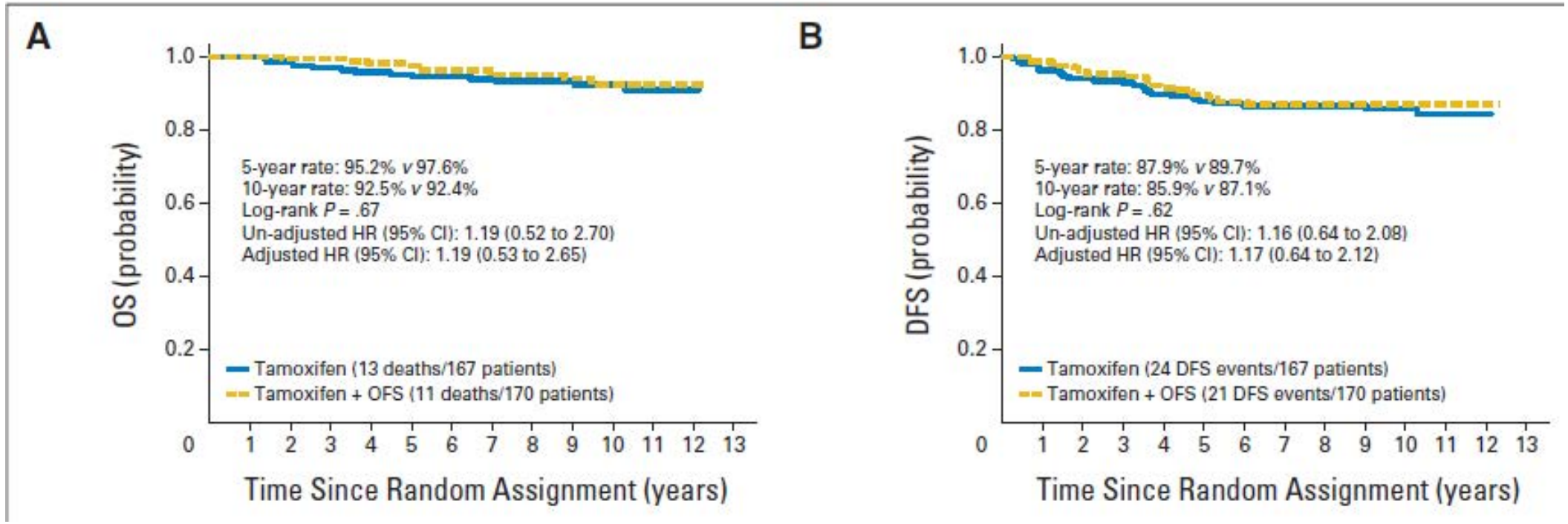
Tamoxifène ± castration: ECOG E3193



Tevaarwerk JCO 2014

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Etude ABCSG

1803 patientes pré-ménopausées de bon pronostic (76% T1, 70% N-, 80% de grade I ou II)

23% de moins de 40 ans,
Pas de chimiothérapie
Toutes traitées par analogues LHRH (3 ans) et randomisées entre:

Tamoxifène

Tamoxifène + ac zolédronique

Anastrozole

Anastrozole + ac zolédronique

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Gnant Ann Oncol 11-2014

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Etude ABCSG-12

94,4 mois de médiane de suivi: SG 95,2%
86 décès, 65 rechutes loco-régionales, 125 métastases, 26 cancers controlatéraux) 36 autres cancers
Pas de différence de survie sans rechute entre le tamoxifène et l'anastrozole
Mais risque accru de décès sous anastrozole: HR = 1,63 (1,05-1,45) ??

Réduction non statistiquement significative du risque de rechute (3,4%) et de décès (2,2%) sous acide zolédronique

➢Le tamoxifène reste la molécule de référence en association avec les analogues

Essais TEXT et SOFT

4690 patientes pré ménopausées RH+ randomisées dans 2 essais de phase III entre :

Castration + Exemestane

Castration + Tamoxifène

Certaines d'entre elles traitées antérieurement par chimiothérapie

Médiane de suivi de 68 mois

SSR à 5 ans :

Bras exemestane: 91,1%

Bras tamoxifène: 87,3%

Pas de différence en survie globale: HR = 1,14 (0,86-1,51)

Pagani O, N Engl J Med 2014;371:107-18

Caractéristiques des patientes

	SOFT		TEXT	
	Pas de chimio 47%	Chimio 53%	Pas de chimio 40%	Chimio 60%
Âge (médiane)	46	40	45	43
N+	9%	57%	21%	66%
T> 2 cm	14%	47%	19%	53%
Grade 1	41%	14%	26%	12%
Grade 3	7%	35%	12%	37%
HER2+	4%	18%	5%	17%

Avant 35 ans 90% de chimiothérapie

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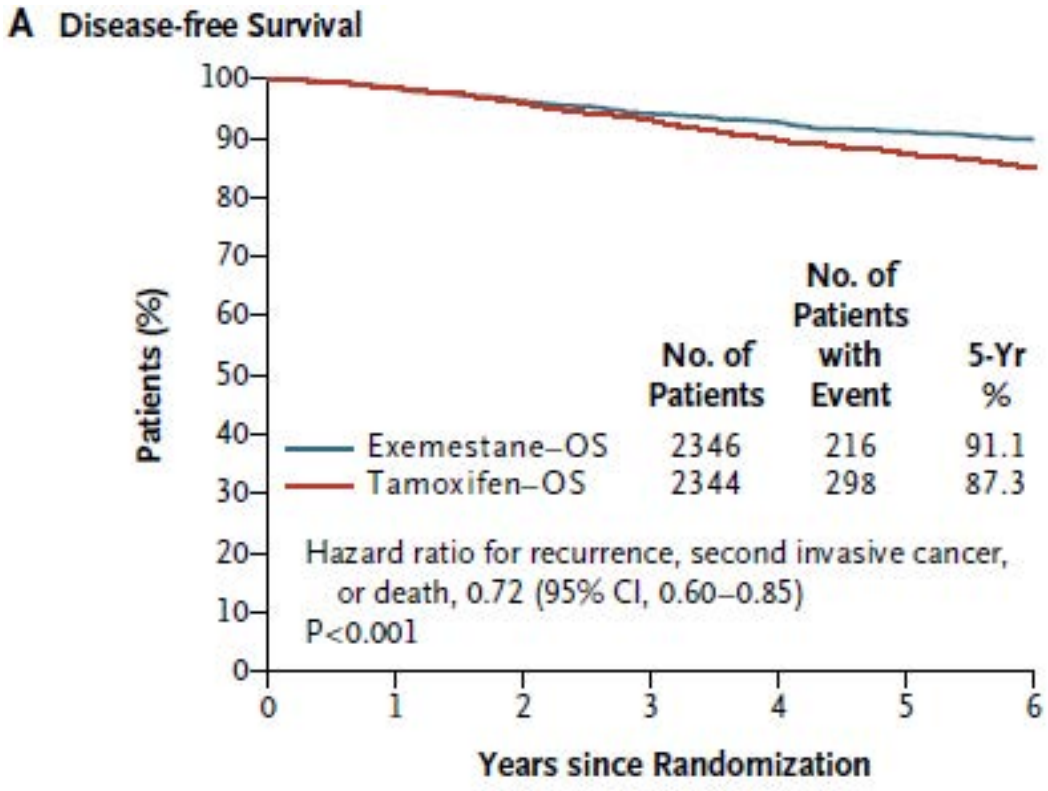
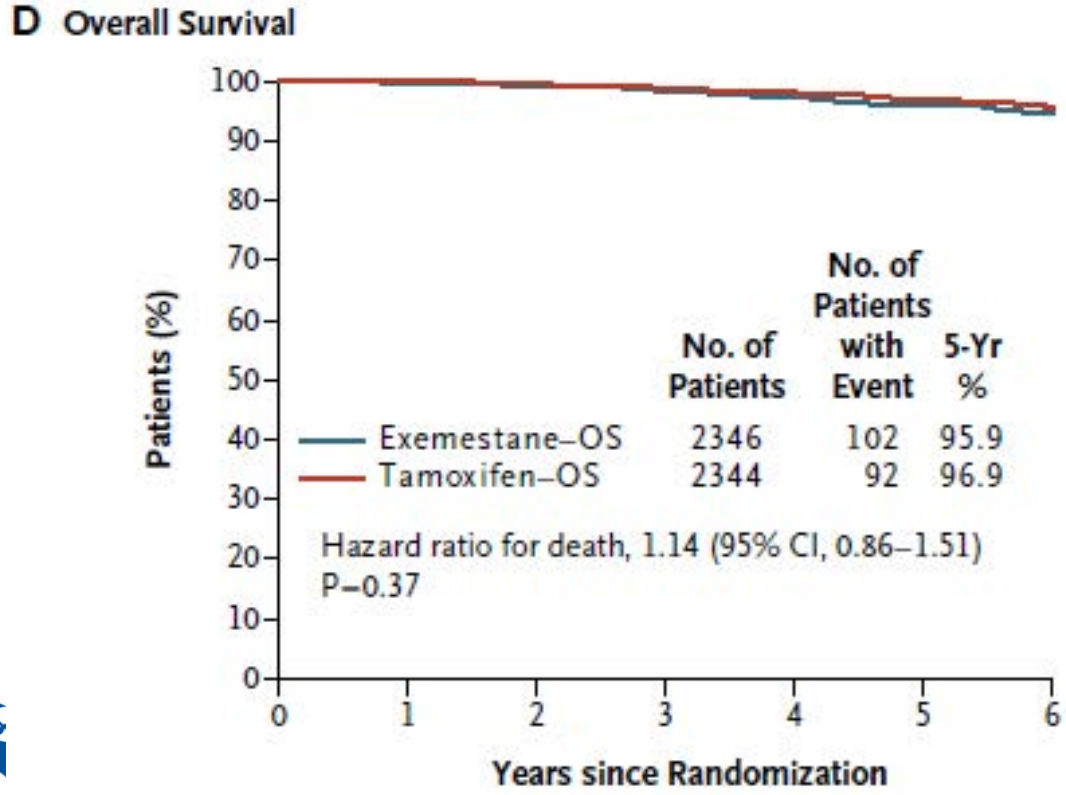
Essais TEXT et SOFT





ASSISTANCE PUBLIQUE

Essai TEXT + SOFT

*Breast cancer free interval , Distant relapse free interval

Gains en valeur absolue à 5 ans	E + SO versus T + SO
BCFI	4%
DRFI	1,8%
Sans chimio (TEXT) BCFI	3%
Survie globale	HR = 1,14 (0,86-1,51) p = 0,37
	TEXT vs SOFT
Pré méno après chimio BCFI	5,5% vs 3,9%
Pré méno après chimio DRFI	3,4% vs 2,6%

Dans TEXT, pas de chimiothérapie, 21% de N+, 16% < 40 ans, 19% T>2 cm

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Essai SOFT

Randomisation entre:
Tamoxifène 5 ans (n= 1018)
Tamoxifène + castration 5 ans (n=1015)
Exemestane + castration 5 ans (n=1014)

Médiane de suivi 5,6 ans

Pas de bénéfice à l'ajout de la castration au tamoxifène en SSR (p = 0,10)
Supériorité du bras exemestane + castration par rapport au bras tamoxifène seul: 4,3% en valeur absolue (HR = 0,68) en SSR

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Bénéfice de la castration chez les patientes non ménopausées par la chimiothérapie

En termes de BCFI et DRFI*

Bénéfice à 5 ans	T + SO vs T	E + SO vs T
BCFI	4,5% 0,78 (0,60-1,02)	7,7% 0,65 (0,49-0,87)
DRFI	1,2% 0,87 (0,64-1,17)	4,2% 0,72 (0,52-0,98)
BFCI avant 35 ans	11,2%	15,7%

*Breast cancer free interval , Distant relapse free interval

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Effets indésirables

15% d'arrêt de la SO à 2 ans, 22% à 4 ans

16% d'arrêt de traitement dans le bras exemestane, 11% sous tamoxifène

30,6% d'EI de grade 3 ou 4 sous exemestane + SO
29,4% sous tamoxifène + SO

50% de dépression (4% sévères)
Bouffées de chaleur, insomnie, HTA, ostéoporose 13% sous exemestane vs 6,4% sous tamoxifène, arthralgies, fractures, sécheresse vaginale, dyspareunie, diminution de la libido

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Effets indésirables

	T + SO	T
BVM	93%	80%
Sueurs	62%	48%
Diminution libido	47%	42%
Sécheresse vaginale	50%	42%
Dépression	52%	47%
Insomnie	57%	46%
Arthralgies myalgies	75%	69%
Ostéoporose	20%	12%
HTA	5%	2%
Troubles glucidiques	8%	4%

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Mise à jour de l'étude SOFT

Randomized comparison of adjuvant tamoxifen plus ovarian suppression versus tamoxifen in premenopausal women with hormone receptor-positive early breast cancer:

Update of the SOFT trial.

Fleming G. et al., SABCS 2017, GS4-03

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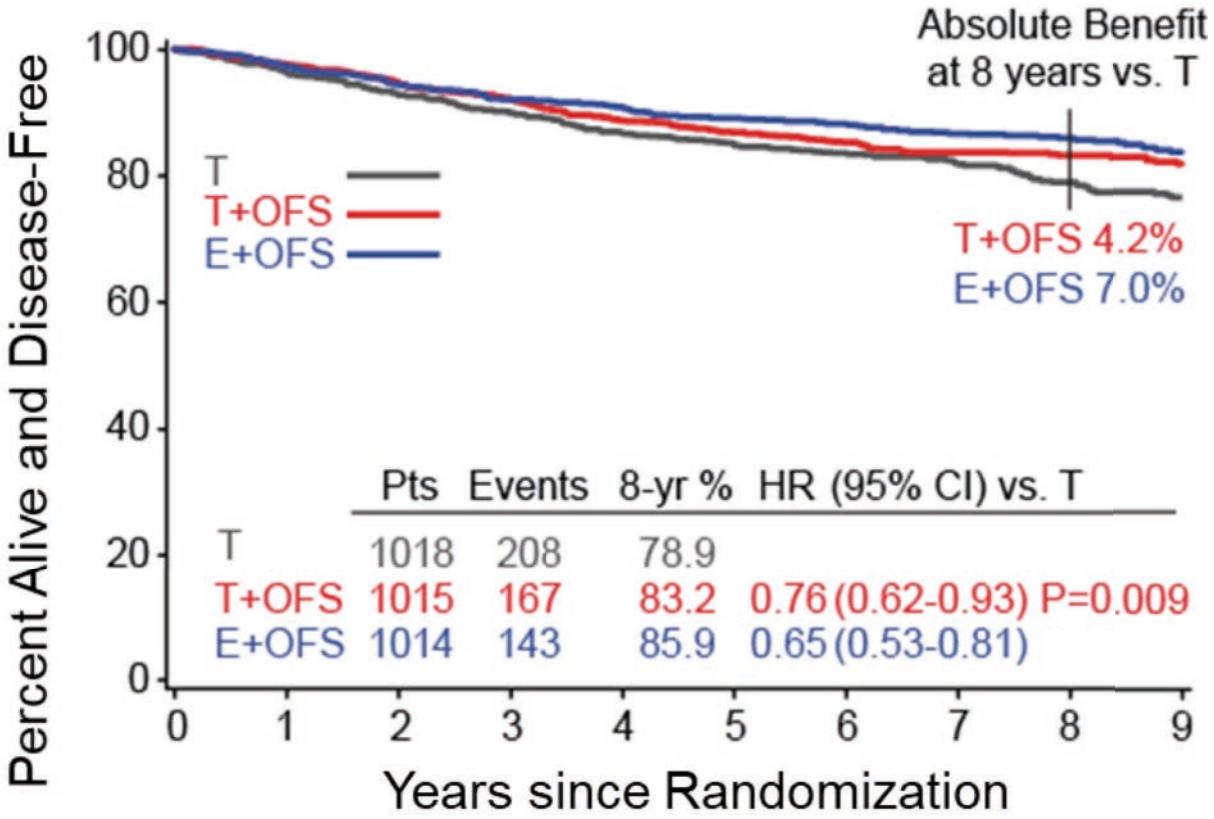
→ Amélioration significative de la SSM dans le bras E ou TAM + SO



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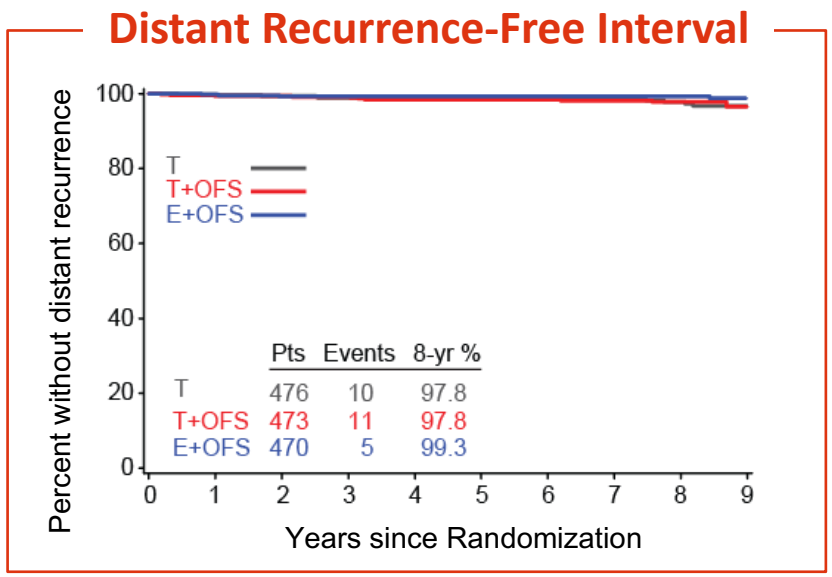
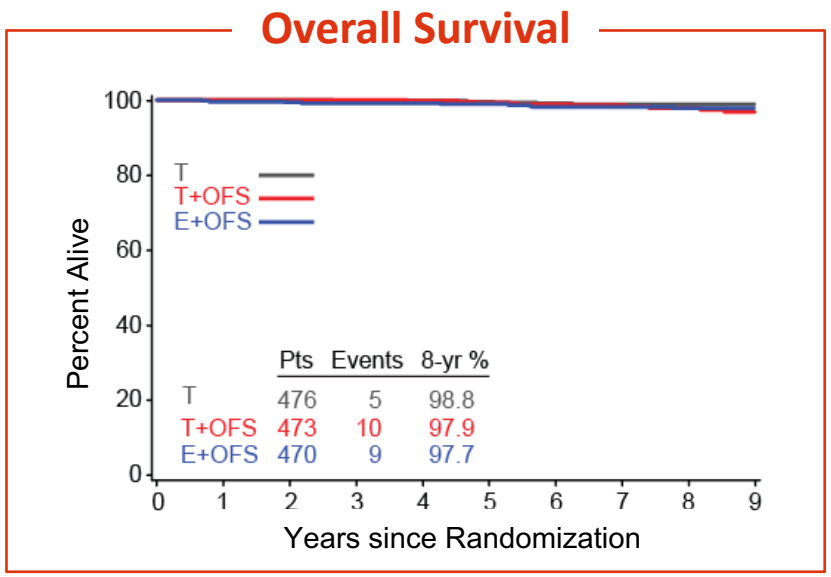
Etude SOFT: Patientes **sans CT adjuvante**

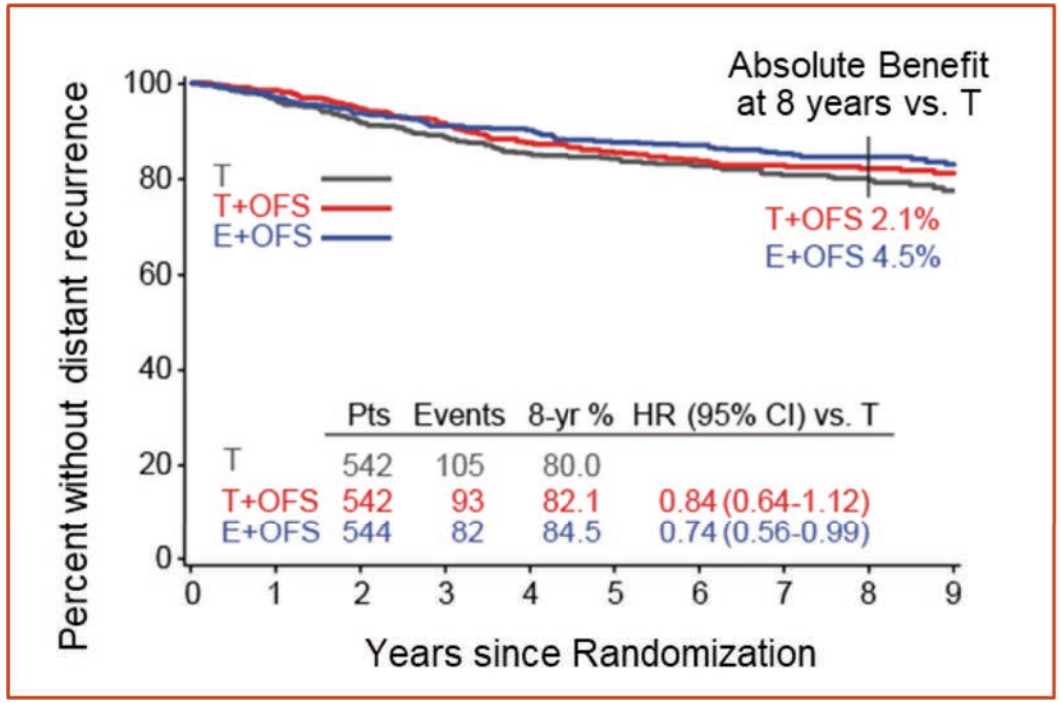


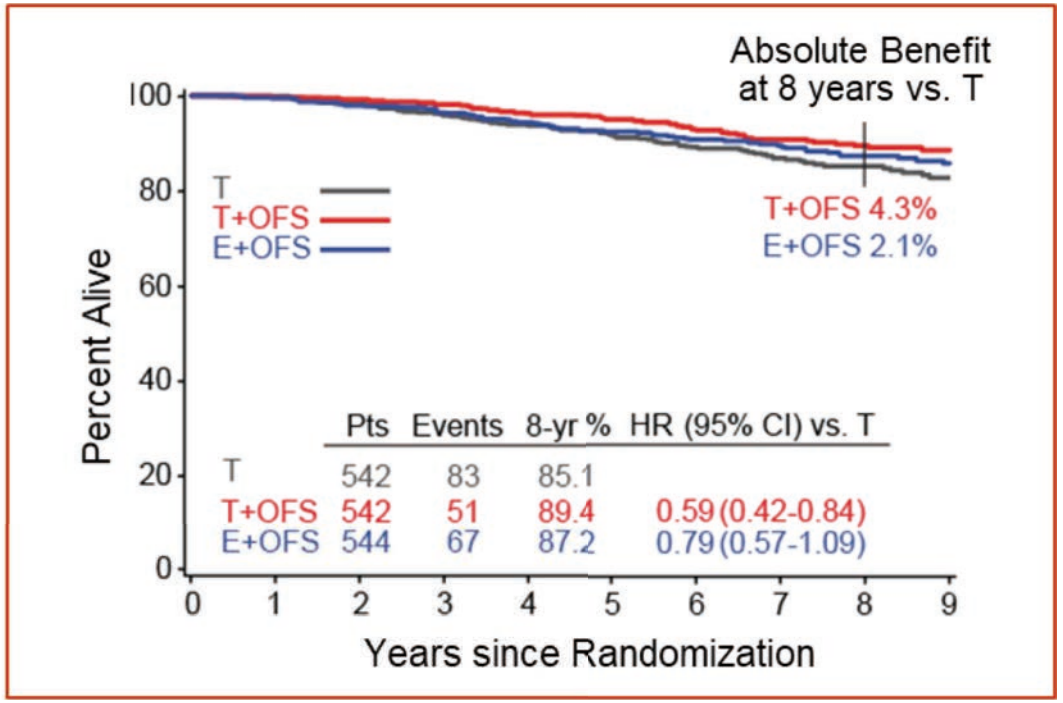


Population **à très faible risque de rechute**.
Parmi les 24 décès, 12 décès non reliés à la pathologie cancéreuse.

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Etude SOFT: Patientes **avec CT adjuvante**





→ **Amélioration significative de la survie globale dans le bras TAM + SO.**

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PB1: Hormonothérapie et observance

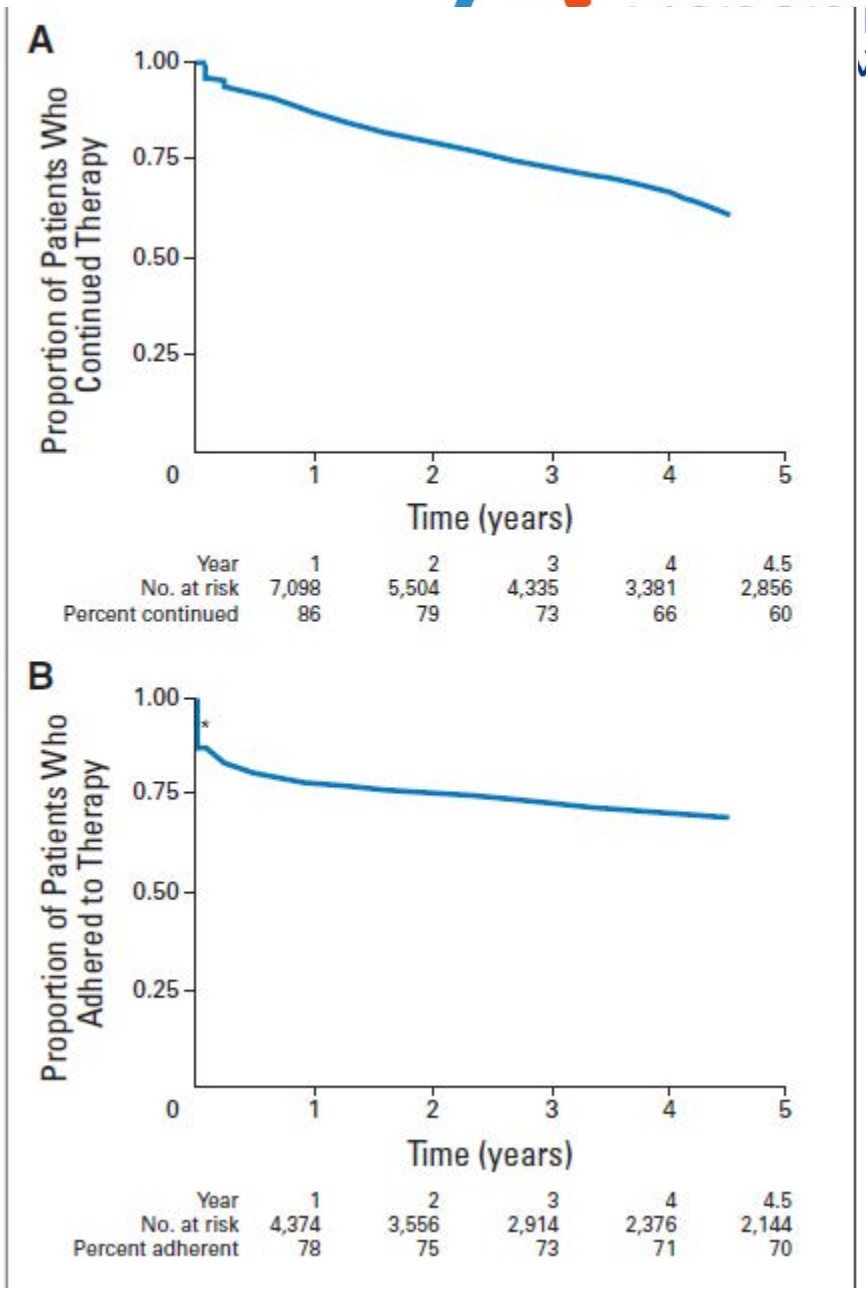
8769 patientes (base de données de la Caroline du nord)

Au bout de 4,5 ans:

32% d'arrêt

28% de prises aléatoires

49% de traitements pris comme prescrits



Hershman D, JCO 2010; 28: 4120-4128

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

PB1: Hormonothérapie et observance

MUNICH 2018 ESMO congress

GUSTAVE ROUSSY

SERUM ASSESSMENT OF NON-ADHERENCE TO ADJUVANT ENDOCRINE THERAPY (ET) AMONG PREMENOPAUSAL PATIENTS IN THE PROSPECTIVE MULTICENTER CANTO COHORT

B.Pistilli[1], A.Paci[2], S.Michiels[3], A.Ferreira[4], A.Di Meglio[4], V.Poinsignon[2], P.Cottu[5], F.Lerebours[5], C.Coutant[6], A.Lesur[7], D.Tredan[8], P.Soulie[9], L.Vanlemmens[10], C.Jouannaud[11], C.Levy[12], S.Everhard[13], P.Arveux[13], A.Partridge[14], S.Delaloge[1], F.André[1,15], L.Vaz Luis[1,4,15]

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UNICANCER canto

Increased risk of non-adherence

1

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journal homepage: www.ejconline.com

ELSEVIER EJC

Early discontinuation of tamoxifen intake in younger women with breast cancer: Is it time to rethink the way it is prescribed?

Laetitia Huiart [a,b,c,*], Anne-Déborah Bouhnik [b,c], Dominique Rey [b,c,d], Carole Tarpin [e], Camille Cluze [b,c,d], Marc Karim Bendiane [b,c,d], Patrice Viens [e,f], Roch Giorgi [g,h]

JOURNAL OF CLINICAL ONCOLOGY — ASCO SPECIAL ARTICLE

2

Importance of OFS in higher-risk patients

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression

Harold J. Burstein, Christina Lacchetti, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggs

SINGAPORE 2018 ESMO ASIA

Pistilli B et al, ESMO 2018. Huiart L et al, Eur J Cancer 2012;48:1939-46
Burstein HJ et al, J Clin Oncol 2016;34:1689-701

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

PB2 Ovariectomie bilatérale et mortalité cardiovasculaire

Étude de cohorte de la Mayo Clinic:

1274 femmes avec une ovariectomie unilatérale
1091 femmes avec une ovariectomie bilatérale avant 45 ans
2383 femmes sans ovariectomie

Mortalité cardiovasculaire:
Groupe I: HR = 0,82 (0,67-0,99) p= 0,04
Groupe II: HR = 1,44 (1,01-2,05) p=0,04
Sans THS : HR = 1,84 (1,27-2,68) p = 0,01
Avec THS: HR = 0,65 (0,30-1,41) p=0,28

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Riveira C, Menopause. 2009 ; 16(1): 15–23

Suppression ovarienne et qualité de vie

Stérilité
Sécheresse vaginale
Altération de la sexualité
Bouffées de chaleur, sueurs nocturnes
Insomnie
Infections urinaires
Ostéoporose
La ménopause chimio-induite est une cause importante de l'altération de la qualité de vie chez les femmes ayant eu une chimiothérapie (Ganz 1998, Meyerowitz 1999, Schover 1994, Gupta 2000)

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Pré ménopausée RH+ ?

Pré ménopausées RH+		
Pas de chimiothérapie		Chimiothérapie
Bas risque: T1, N-,grade 1	Risque intermédiaire: Bas grade mais T>1 ou N+	Haut risque ≥ T2, N++, grade 3, < 35 ans
Tamoxifène 5 ans	Chimiothérapie + Tam ou SO + T ou E	SO +T ou E (<35 ans)
Durée?	SO + T OU E?	OS + E > OS + T

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Recommandations St Gallen 2015

ER positive & HER2-negative (“luminal disease”)		
Without markers of less endocrine responsiveness (“luminal A-like”)	Endocrine therapy alone according to menopausal status	See Table 2 Consider chemotherapy if 4 or more nodes involved
Premenopausal low risk	Tamoxifen 5 years	
Premenopausal other	Tamoxifen 5 – 10 years or OFS plus tamoxifen or OFS plus exemestane	See criteria in papers [3,4,116]

More generally, the Panel considered that factors arguing for inclusion of OFS were age 35 or less; persisting premenopausal oestrogen level after adjuvant chemotherapy; or the involvement of 4 or more axillary nodes. A lesser majority would add grade 3 disease or an adverse result from a multi-parameter molecular marker test as indications for OFS.

Factors arguing for the use of an AI plus OFS rather than tamoxifen plus OFS were (overwhelmingly) the involvement of 4 or more nodes, with lesser majorities accepting age 35 or less; grade 3; or the adverse result of a multi-parameter molecular marker test as supporting such treatment. The Panel was almost evenly divided as to whether a persisting premenopausal estrogen level after adjuvant chemotherapy should favour an AI rather than tamoxifen. As a supplementary question the Panel was asked, “if you decide to give OFS are you more likely to recommend tamoxifen or an AI?” with a majority favouring AI.

The Panel considered that if OFS were included the optimal duration of such therapy should be 5 years, and that extended endocrine therapy for a total of 10 years should be considered for premenopausal patients initially node-positive or with other adverse pathology. .

SO + Tam ou AI pour haut risques:
Toujours Préménopausiques après chimiothérapie
N+ (>3)
<35 ans

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Coates et al Ann Oncol 2015

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESO—ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4)

S. Paluch-Shimon[1*†], F. Cardoso[2†], A. H. Partridge[11†], O. Abulkhair[3], H. A. Azim Jr[4], G. Bianchi-Micheli[5], M.-J. Cardoso[2,20], G. Curigliano[6,7], K. A. Gelmon[8], N. Harbeck[9], J. Merschdorf[10], P. Poortmans[12], G. Pruneri[13], E. Senkus[14], T. Spanic[15], V. Stearns[16], Y. Wengström[17], F. Peccatori[18‡] & O. Pagani[19‡]

Recommendations for adjuvant GnRH agonist use are based on data from trials with monthly administration. Thus, current guidelines support monthly use to optimize ovarian function suppression, particularly in very young women (<35 years of age) and in those receiving an AI.	Expert opinion
3-monthly use may be considered on a case-by-case basis with very close monitoring of ovarian function, when monthly use is not feasible or accepted by the patient.	
Estradiol levels should be checked if there are concerns ovarian function is not suppressed, especially if a breakthrough bleeding occurs and/or the patient is on an AI; if done, the analysis should preferably be performed in the same laboratory, and when possible in a central reference laboratory. In cases of inadequate suppression alternative strategies should be discussed (oophorectomy or continuation of tamoxifen alone).	Expert opinion
The method of ovarian suppression (surgical versus medical) requires balancing patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time and cost/availability.	Expert opinion
The addition of a GnRH agonist to tamoxifen can be considered in women at higher risk of relapse resuming ovarian function within 2 years after chemotherapy completion.	[II, B]

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Adjuvant systemic treatment

Endocrine therapy

All young women should be counselled, before the onset of systemic therapy (either CT or ET), about the risks, associated symptoms and outcomes of treatment-related amenorrhea and premature menopause, referred for special fertility counselling/consultation and informed of available and approved ameliorative therapies.	Expert opinion
Neoadjuvant ET should not be used in young women outside clinical trials.	Expert opinion
All patients with HR-positive disease should receive adjuvant ET.	[I, A]
Tamoxifen alone for 5 years is indicated for low-risk patients.	[I, A]
Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively postmenopausal.	[I, A]
Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.	[I, A]
The addition of a GnRH agonist (or ovarian ablation) to tamoxifen or an aromatase inhibitor is indicated in patients at higher risk of relapse.	[I, A]
AIs without ovarian function suppression contraindicated in premenopausal women.	[I, A]
	[I, A]

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Recommandations ASCO

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression

Harold J. Burstein, Christina Lacchetti, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggs

1.2 Women with stage II or stage III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy.

1.3 Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy.

1.4 Women with stage I breast cancers not warranting chemotherapy should receive endocrine therapy but not receive ovarian suppression.

1.5 Women with node-negative cancers 1 cm or less (T1a, T1b) should receive endocrine therapy but not receive ovarian suppression.

2. If ovarian suppression is recommended, should ovarian suppression be administered in combination with tamoxifen or an AI?

- Ovarian suppression may be administered with either tamoxifen or an AI.

Préservation de la fertilité: +++

Population de femmes jeunes, préoccupation fréquente.

Proposition de préservation de fertilité pour toute femme de moins de 40

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Etude POEMS

Phase 3

Tumeurs Triples négatives

Chimiothérapie Néo/adjuvante comp endoxan +/- Goserilin 3.6mg/mois début 1 semaine avant chimiothérapie fin 2 semaines après dernier cycle

Obj principal: ménopauses précoces à 2 ans

Obj secondaire: nombre de grossesses, DFS, OS, ins ovariennes

Moore H.C.F et al NEJM 2015

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Etude POEMS

Ménopauses précoces à 2 ans

Chimio seule 22%

Chimio + Gosereline 8%

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Plus de grossesses

Table 3. Pregnancy Outcomes.

Outcome	Chemotherapy Alone (N=113)	Chemotherapy plus Goserelin (N=105)	Odds Ratio with Goserelin	P Value*
Attempted pregnancy — no. of patients (%)	18 (16)	25 (24)	1.78	0.12
Achieved pregnancy — no. of patients (%)	12 (11)	22 (21)	2.45	0.03
≥1 delivery — no. of patients (%)	8 (7)	16 (15)	2.51	0.05
Delivery or ongoing pregnancy — no. of patients (%)	10 (9)	19 (18)	2.45	0.04
Babies born — no.†	12	18		
Ongoing pregnancies at last report — no.	3	5		
Adverse pregnancy event — no. of events				
Miscarriage	5	4		
Elective termination	3	2		
Delivery complication	2	2		

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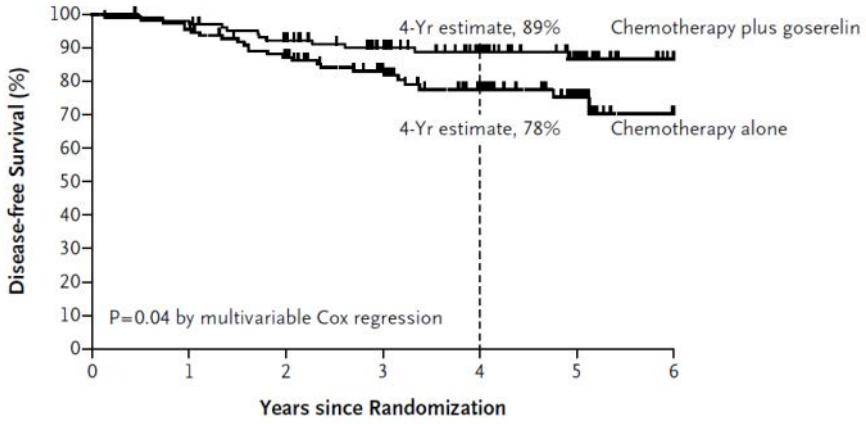
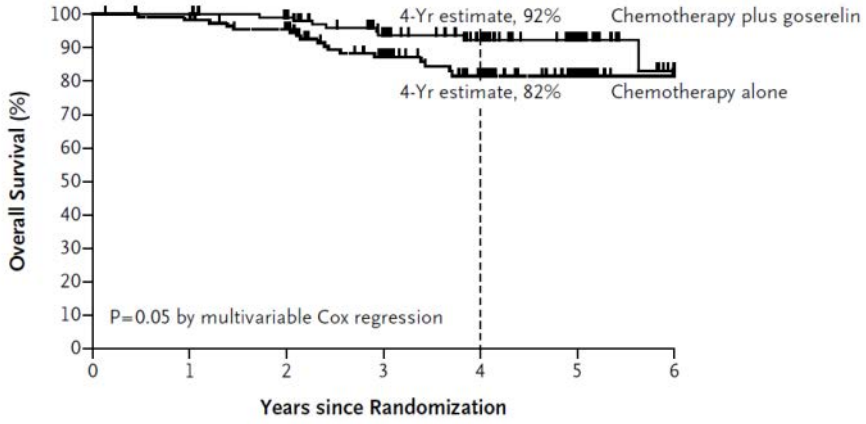
DFS et OS semblables (voir mieux)



No. at Risk							
Chemotherapy plus goserelin	105	103	94	80	59	37	5
Chemotherapy alone	113	109	94	72	49	26	5



No. at Risk							
Chemotherapy plus goserelin	105	105	101	83	61	37	6
Chemotherapy alone	113	111	102	77	53	28	6

Effectifs faibles, mais pas d'aggravation

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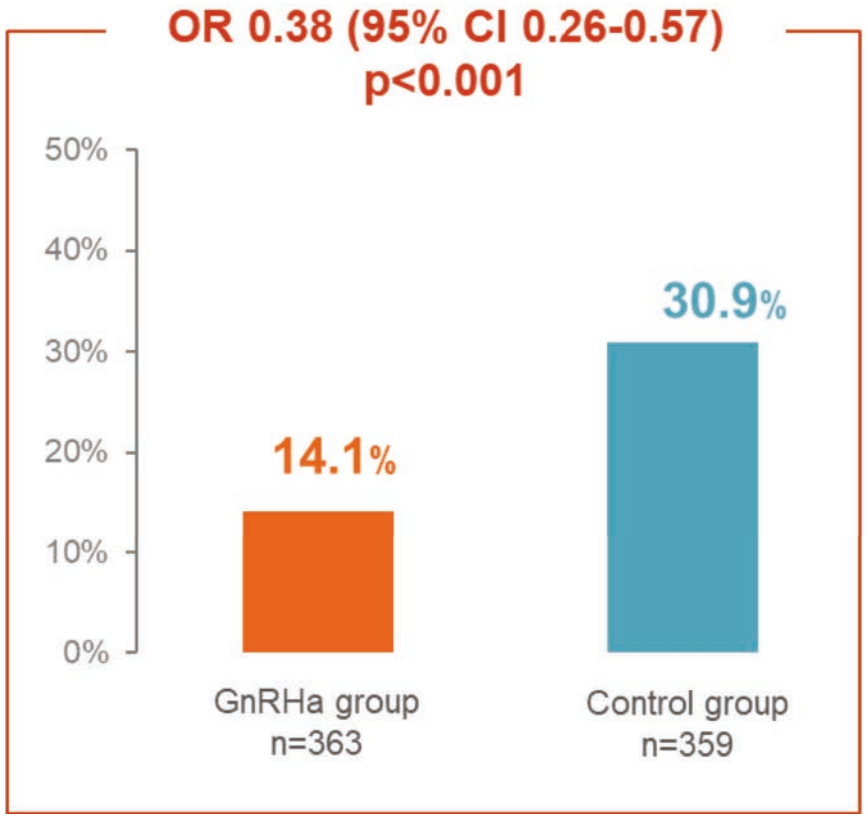
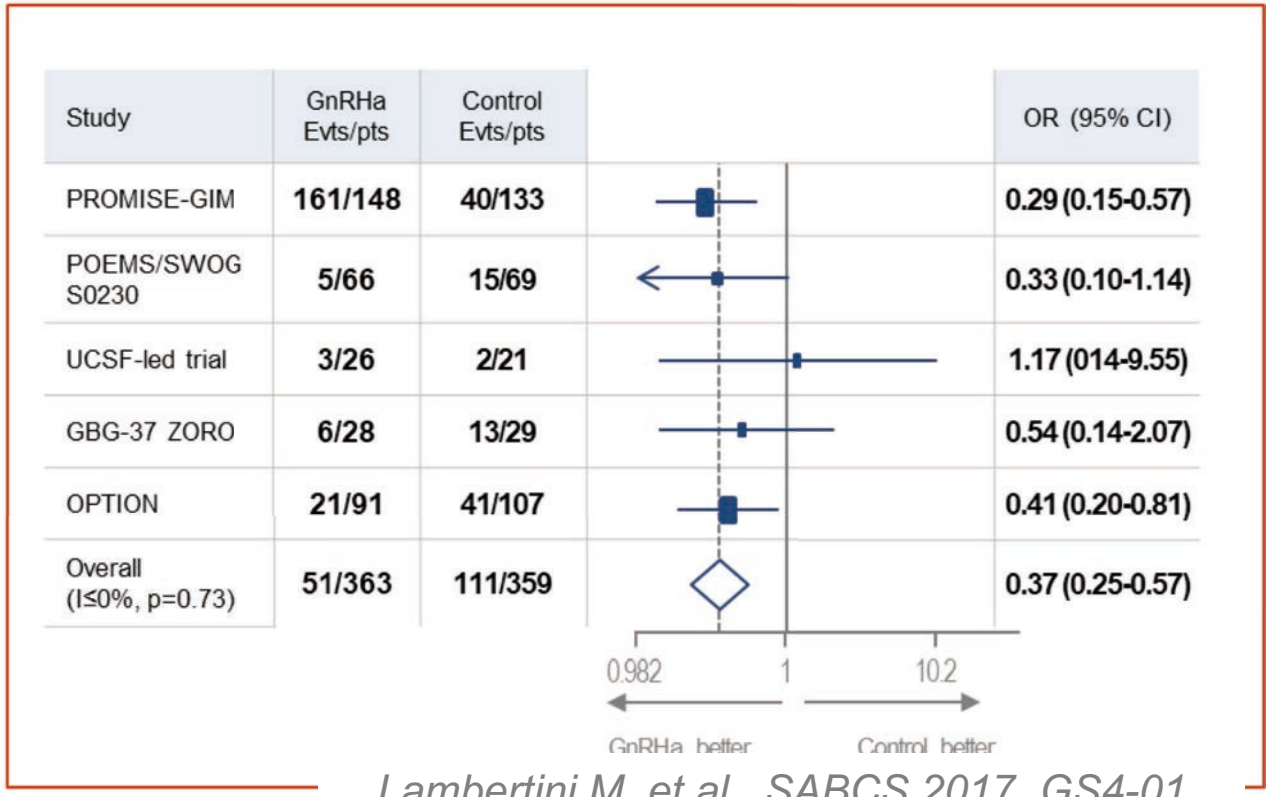
Long-term follow-up of pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients

Lambertini M. et al., SABCS 2017, GS4-01

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Insuffisance ovarienne précoce avec ou sans GnRH



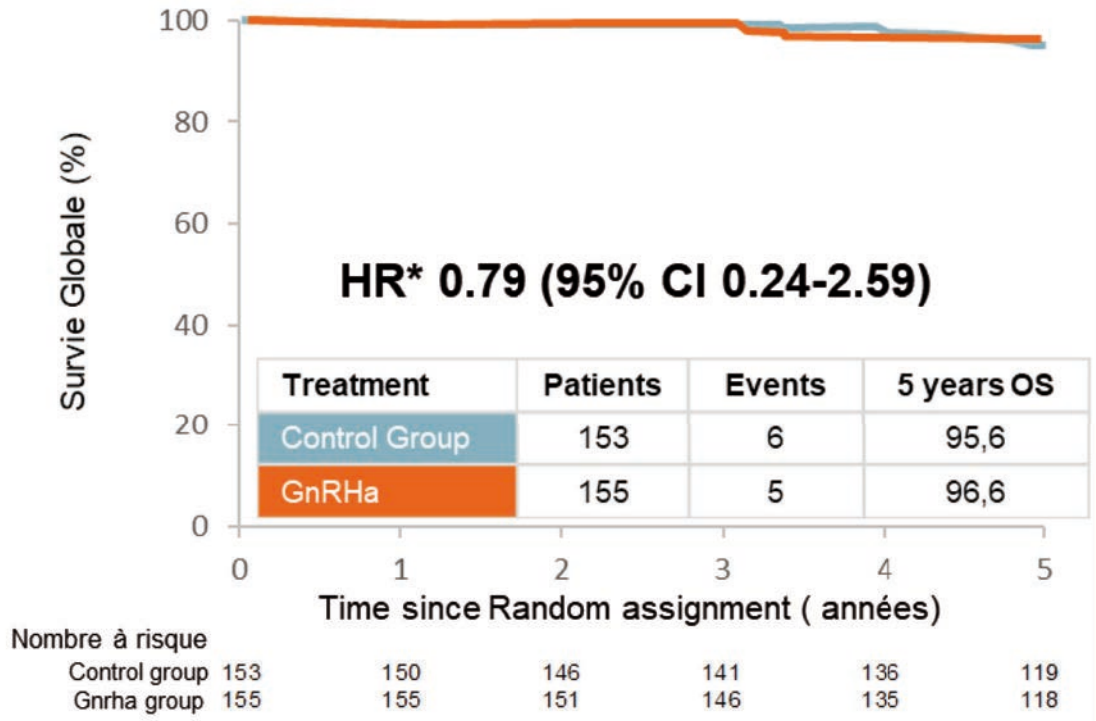


Study	GnRHa Evts/pts	Control Evts/pts	OR (95% CI)
PROMISE-GIM	161/148	40/133	0.29 (0.15-0.57)
POEMS/SWOG S0230	5/66	15/69	0.33 (0.10-1.14)
UCSF-led trial	3/26	2/21	1.17 (014-9.55)
GBG-37 ZORO	6/28	13/29	0.54 (0.14-2.07)
OPTION	21/91	41/107	0.41 (0.20-0.81)
Overall (I≤0%, p=0.73)	51/363	111/359	0.37 (0.25-0.57)

Lambertini M. et al., SABCS 2017, GS4-01

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Survie globale avec ou sans GnRH

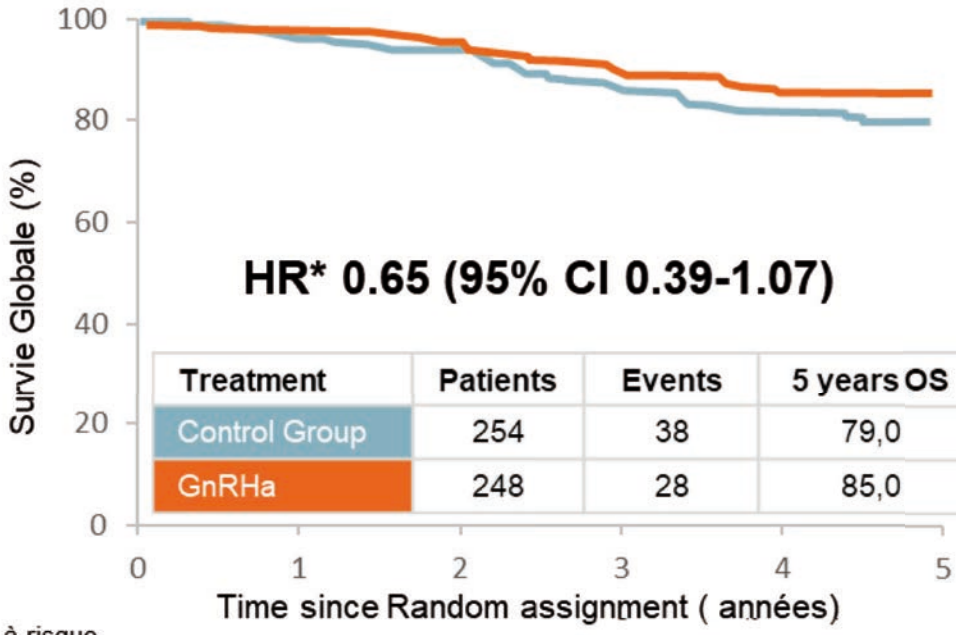


Treatment	Patients	Events	5 years OS
Control Group	153	6	95,6
GnRHa	155	5	96,6

Nombre à risque

Control group	153	150	146	141	136	119
Gnrha group	155	155	151	146	135	118

Estrogen receptor-negative disease



Treatment	Patients	Events	5 years OS
Control Group	254	38	79,0
GnRHa	248	28	85,0

Nombre à risque

Control group	254	211	195	149	118	69
Gnrha group	248	214	198	166	129	80

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Recommandations St Gallen 2015

The Panel considered that fertility preservation by ovarian tissue or oocyte conservation should be offered upon request for patients aged less than 40.

The Panel strongly supported the use of OFS during chemotherapy for receptor-negative disease to preserve ovarian function and fertility.

INCa 2020

En conclusion, le seul effet bénéfique démontré des agonistes de la GnRH est un bénéfice sur l'incidence de la reprise des cycles au cours de la première année post-chimiothérapie dans le sous-groupe de femmes jeunes avec cancer du sein, alors qu'elles n'auront pas encore à ce moment de leur prise en charge l'autorisation pour une grossesse. En revanche, les effets bénéfiques sur la fertilité à long terme ne sont pas objectivables en raison de l'absence de données suffisantes qui pourraient renseigner sur le nombre de femmes ayant conçu dans une population de femmes souhaitant concevoir.

Recommandations du groupe de travail

R1. Les agonistes de la GnRH ne peuvent pas être recommandés en tant que méthode de préservation de la fertilité (Grade A).

R2. Il n'existe pas de données pour recommander l'utilisation des agonistes de la GnRH ni pour préserver la réserve ovarienne des effets de la chimiothérapie ni pour améliorer les chances de grossesse spontanée (Grade A).