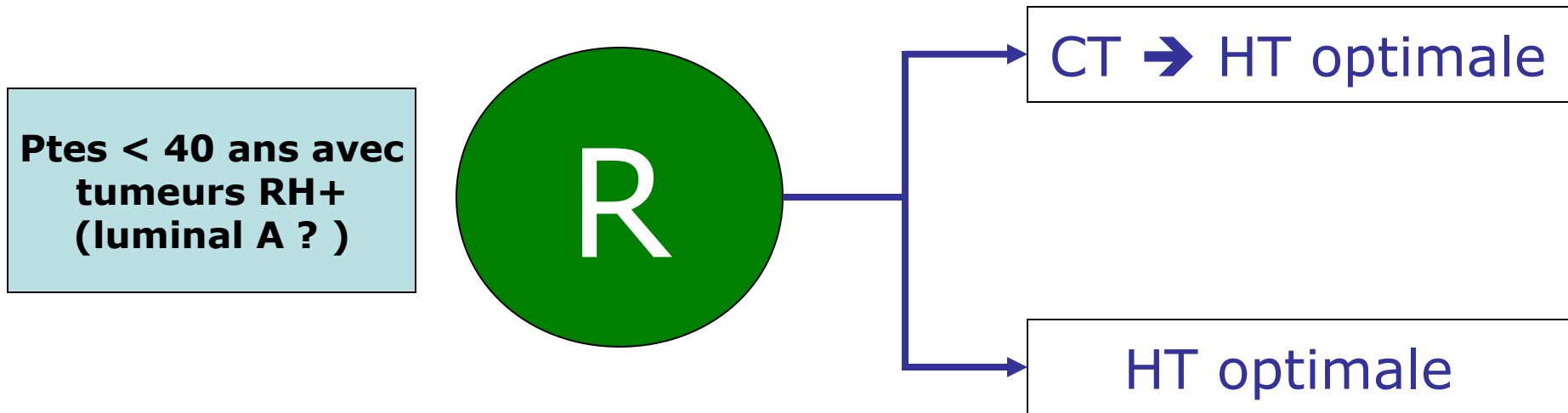


**Peut-on, dans certains cas, faire
l'impasse de la chimiothérapie ?
*.... pour les tumeurs RH+...***

**Marc Debled – Louis Mauriac
Hervé Bonnefoi**

**Institut Bergonié
Bordeaux**

Faire l'impasse de la chimiothérapie adjuvante ?



Aucune étude significative !

**L'âge jeune est-il un facteur pronostique
péjoratif ?**

**L'âge jeune est-il un facteur prédictif de
chimiosensibilité ?**

**Quel impact de la chimiothérapie en
association à un traitement hormonal
optimal ?**

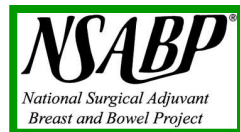
Pour conclure ...

Un pronostic plus péjoratif ?

.... Une chimiothérapie ; pas de TRT anti-hormonal



N = 2 233



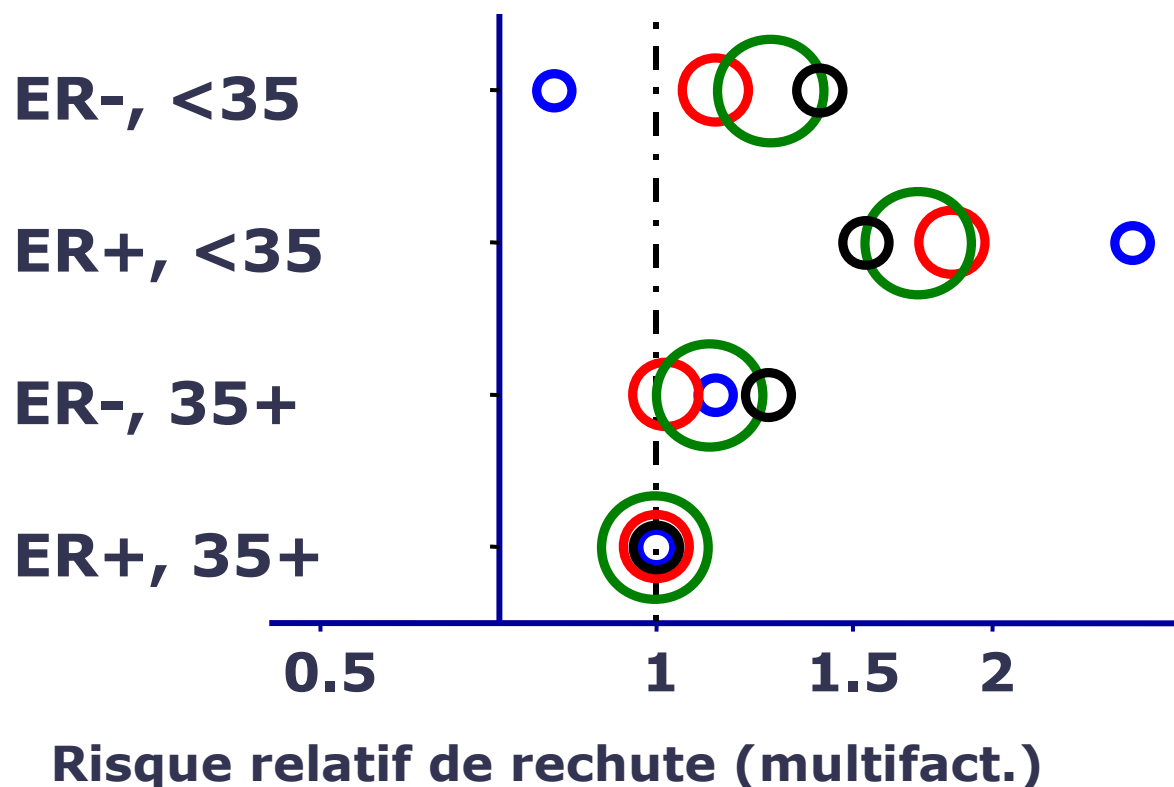
N = 5 849



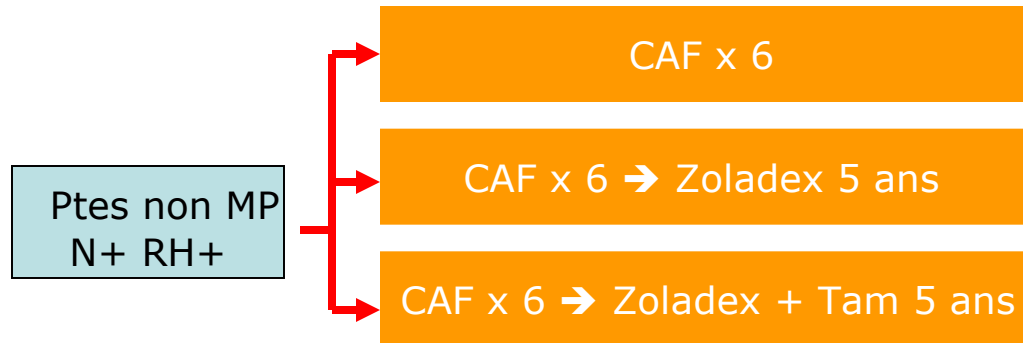
N = 1 112



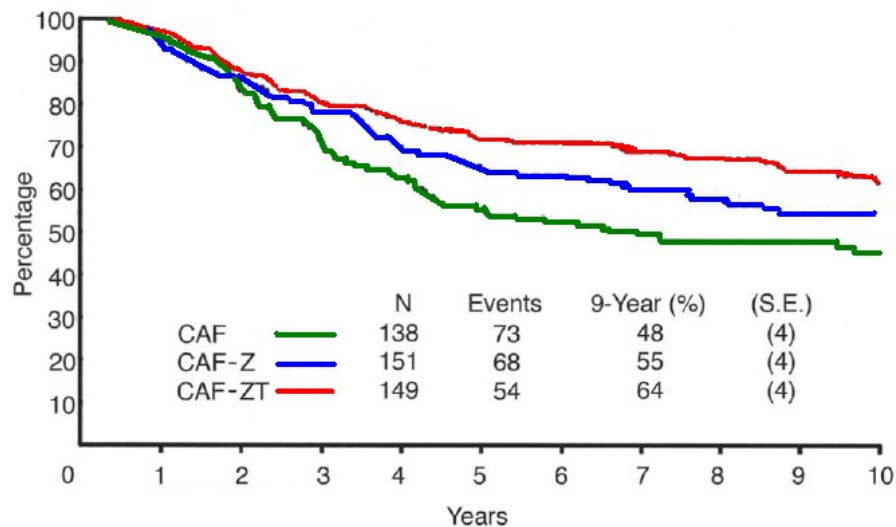
N = 670



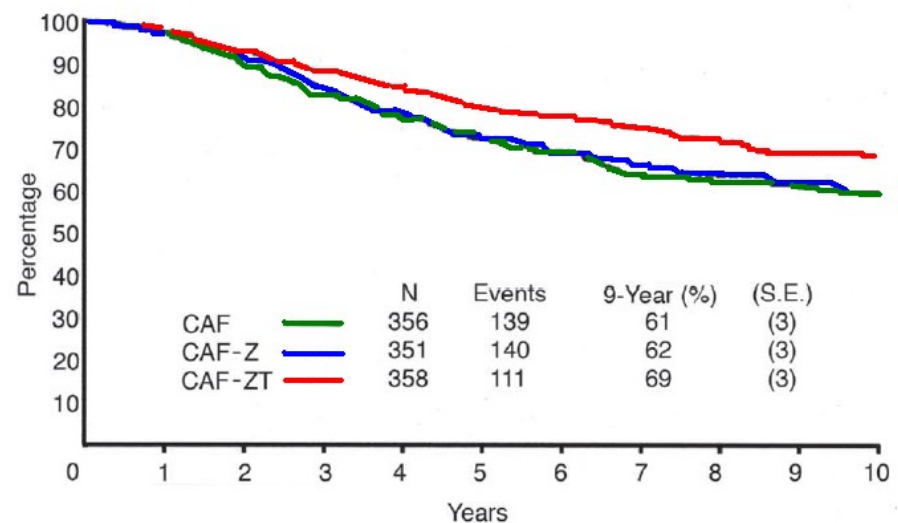
Valeur pronostique de l'aménorrhée (Int 0101 ; E5188)



Ptes < 40 ans



Ptes > 40 ans



L'âge jeune : Un facteur pronostique indépendant ?



Institut Bergonié

Centre Régional de Lutte Contre le Cancer
de Bordeaux et du Sud-Ouest

	< 40 ans N = 255	40 – 49 ans N = 979	p
CCI	81 %	74 %	0,01
pT1	60 %	67 %	ns
pN0	52 %	55 %	ns
mSBR III	41 %	21 %	

→ De multiples facteurs confondants
(stade, grade, embols, ménopause, aménorrhée CT-induite)

Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007

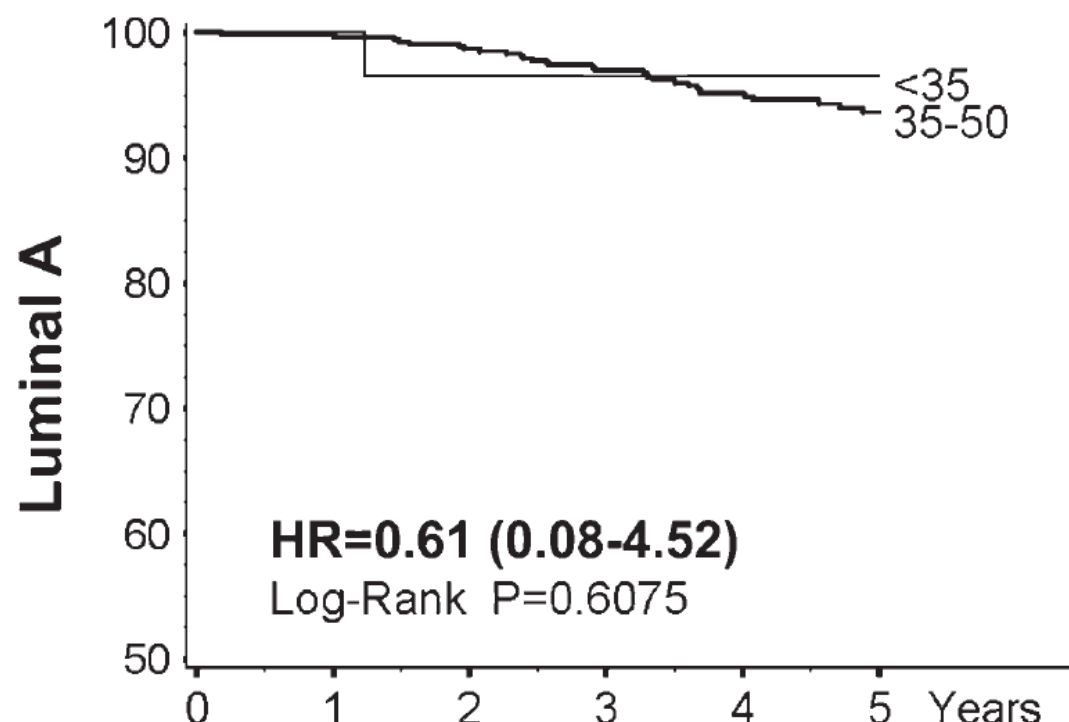
Risk category	
Low risk ^a	Node negative AND all of the following features: - pT* ≤2 cm, AND - Grade 1**, AND - Absence of extensive peritumoral vascular invasion^b, AND - ER and/or PgR*** expressed^c, AND - HER2/<i>neu</i> gene neither overexpressed nor amplified^d, AND - Age ≥35 years
Intermediate risk ^e	Node negative AND at least one of the following features: - pT* >2 cm, OR - Grade 2-3**, OR - Presence of extensive peritumoral vascular invasion^b, OR - ER and PgR absent^c, OR - HER2/<i>neu</i> gene overexpressed or amplified^d, OR - Age <35 years Node positive (1-3 involved nodes) AND - ER and/or PgR expressed, AND - HER2/<i>neu</i> gene neither overexpressed nor amplified^d
High risk	Node positive (1-3 involved nodes) AND - ER and PgR absent, OR - HER2/<i>neu</i> gene overexpressed or amplified^d Node positive (4 or more involved nodes)

Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009

A. Goldhirsch^{1,2*}, J. N. Ingle³, R. D. Gelber⁴, A. S. Coates⁵, B. Thürlimann⁶, H.-J. Senn⁷
& Panel members[†]

	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
Clinicopathological features			
ER and PgR	Lower ER and PgR level		Higher ER and PgR level
Histological grade	Grade 3	Grade 2	Grade 1
Proliferation	High ^a	Intermediate ^a	Low ^a
Nodes	Node positive (four or more involved nodes)	Node positive (one to three involved nodes)	Node negative
PVI	Presence of extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1–5 cm	≤2 cm
Patient preference	Use all available treatments		Avoid chemotherapy-related side-effects
Multigene assays			
Gene signature ^b	High score	Intermediate score	Low score

L'âge jeune dans les tumeurs luminal A : N'est pas un facteur pronostique indépendant



	Luminal A		<i>P</i> ^a
	<35	35–50	
ALL	29	563	
Hormonal therapy, <i>n</i> (%)			
None	2 (6.9)	12 (2.1)	
TAM alone	1 (3.4)	84 (14.9)	
LH-RH alone	3 (10.3)	18 (3.2)	
TAM + LHRH	22 (75.9)	431 (76.6)	
Other/NOS	1 (3.4)	18 (3.2)	0.036
Chemotherapy, <i>n</i> (%)			
None	22 (75.9)	430 (76.4)	
Anthracycline	7 (24.1)	102 (18.1)	
CMF	0 (0.0)	17 (3.0)	
Other/NOS	0 (0.0)	14 (2.5)	0.76

**L'âge jeune n'est pas un facteur pronostique
péjoratif (majeur) démontré**

**L'âge jeune est-il un facteur prédictif de
chimiosensibilité ?**

**Quel impact de la chimiothérapie en
association à un traitement hormonal
optimal ?**

Quelles conclusions ?

L'âge : un facteur prédictif indépendant ?

Quelque soient
les RH

(b) Polychemotherapy (trend $\chi^2_1=34.8$; $2p<0.00001$)

Age <40	395/7077 (5.6%/y)	479/5595 (8.6%/y)	-88.7	173.8	0.60 (SE 0.06)
40-49	832/19553 (4.3%/y)	1045/16629 (6.3%/y)	-174.9	397.2	0.64 (SE 0.04)
50-59	1965/33600 (5.8%/y)	2389/31644 (7.5%/y)	-219.5	823.9	0.77 (SE 0.03)
60-69	2004/31655 (6.3%/y)	2221/30332 (7.3%/y)	-112.9	803.5	0.87 (SE 0.03)
≥70	194/3388 (5.7%/y)	253/3835 (6.6%/y)	-9.3	70.6	0.88 (SE 0.11)
Age unknown	7/130	12/74	-1.4	2.4	
(b) subtotal	5397/ 95403 (5.7%/y)	6399/ 88109 (7.3%/y)	-606.7	2271.4	0.77 (SE 0.02) $2p<0.00001$

■ 99% or ◊ 95% CIs

0 0.5 1.0 1.5 2.0
Chemotherapy better | Chemotherapy worse

RE négatif ou
< 10 fmol/mg

(a) Polychemotherapy alone versus no adjuvant (trend*: $\chi^2_1=0.2$; $2p=0.69$; NS)

<50	307/915 (33.6%)	374/807 (46.3%)	-60.6	133.6	0.64 (SE 0.07)
50-59	180/464 (38.8%)	230/479 (48.0%)	-25.7	78.5	0.72 (SE 0.10)
60-69	117/264 (44.3%)	134/275 (48.7%)	-16.9	46.1	0.69 (SE 0.12)
≥70	5/14	8/21	-2.3	1.8	
Unknown	2/4	0/1			
(a) subtotal	611/1661 (36.8%)	746/1583 (47.1%)	-105.6	260.0	0.67 (SE 0.05) $2p<0.00001$

■ 99% or ◊ 95% CIs

0 0.5 1.0 1.5 2.0
Polychemotherapy better | Polychemotherapy worse

**L'âge jeune n'est pas un facteur pronostique
péjoratif (majeur) démontré**

**L'âge jeune n'est pas un facteur prédictif de
chimiosensibilité démontré**

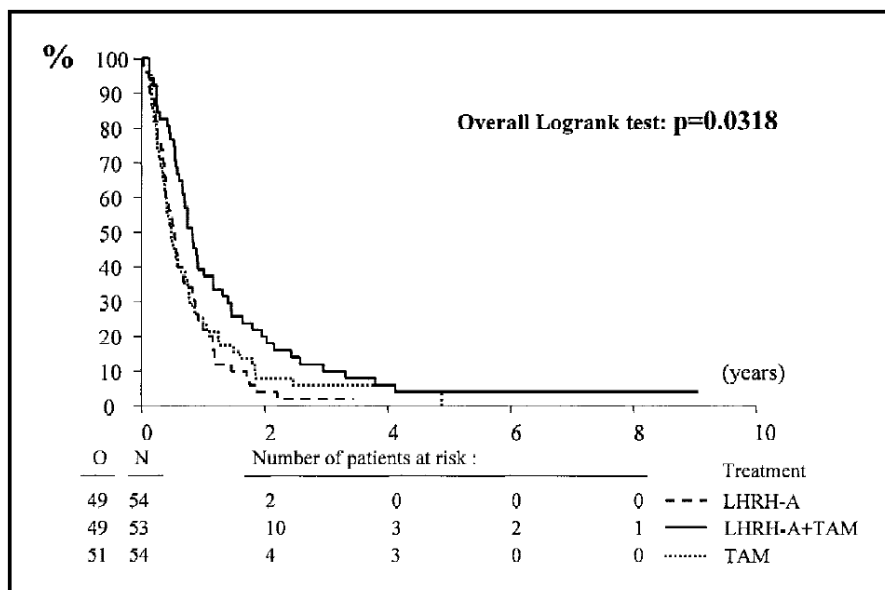
**Quel impact de la chimiothérapie en
association à un traitement hormonal
optimal ?**

Quelles conclusions ?

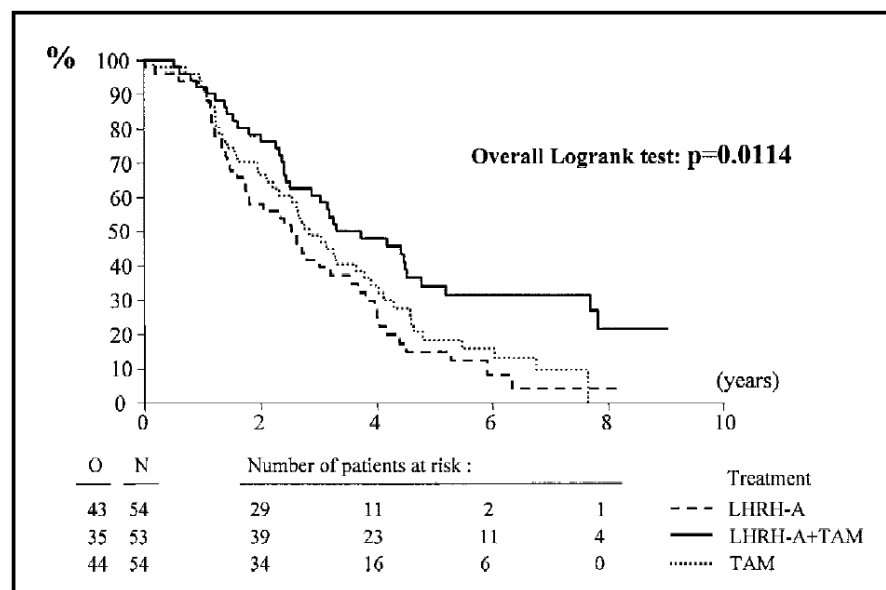
Quelle hormonothérapie optimale

En phase M+ : Ag LHRH + TAM > Tam ou Ag LHRH

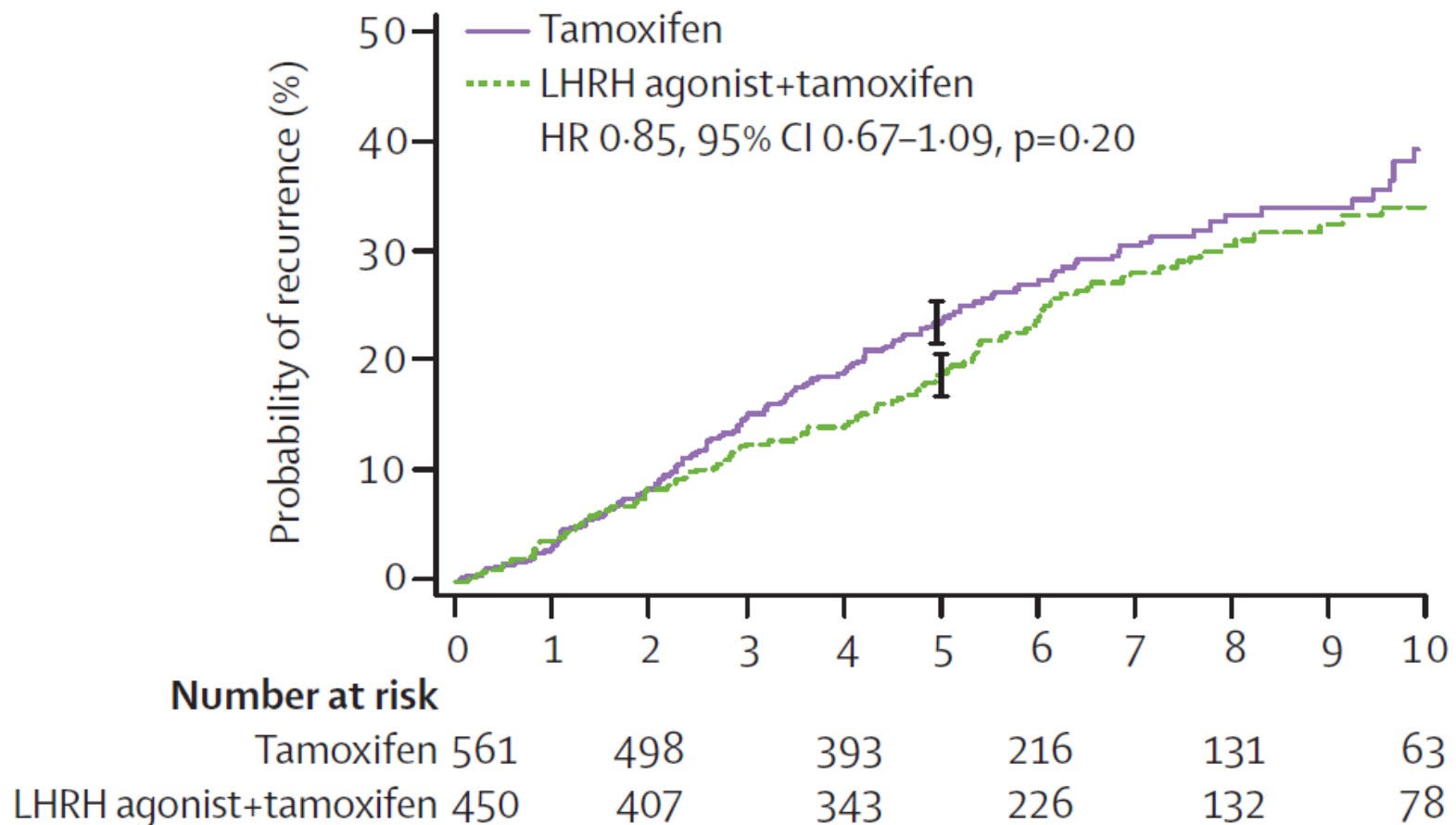
Survie sans progression



Survie globale



Situation adjuvante : Tam VS suppression ovarienne + Tam



SOFT [IBCSG 24-02, BIG 2-02]

- Activité ovarienne
8 mois après la CT
- RH+

N = 3,000

IBCSG Trial 24-02 (BIG 2-02) SOFT
Cumulative Accrual through 30 Sep 2010
Goal: 3000 patients (50/month)

North America BIG Target (since 1/1/2006)

R
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T x 5y

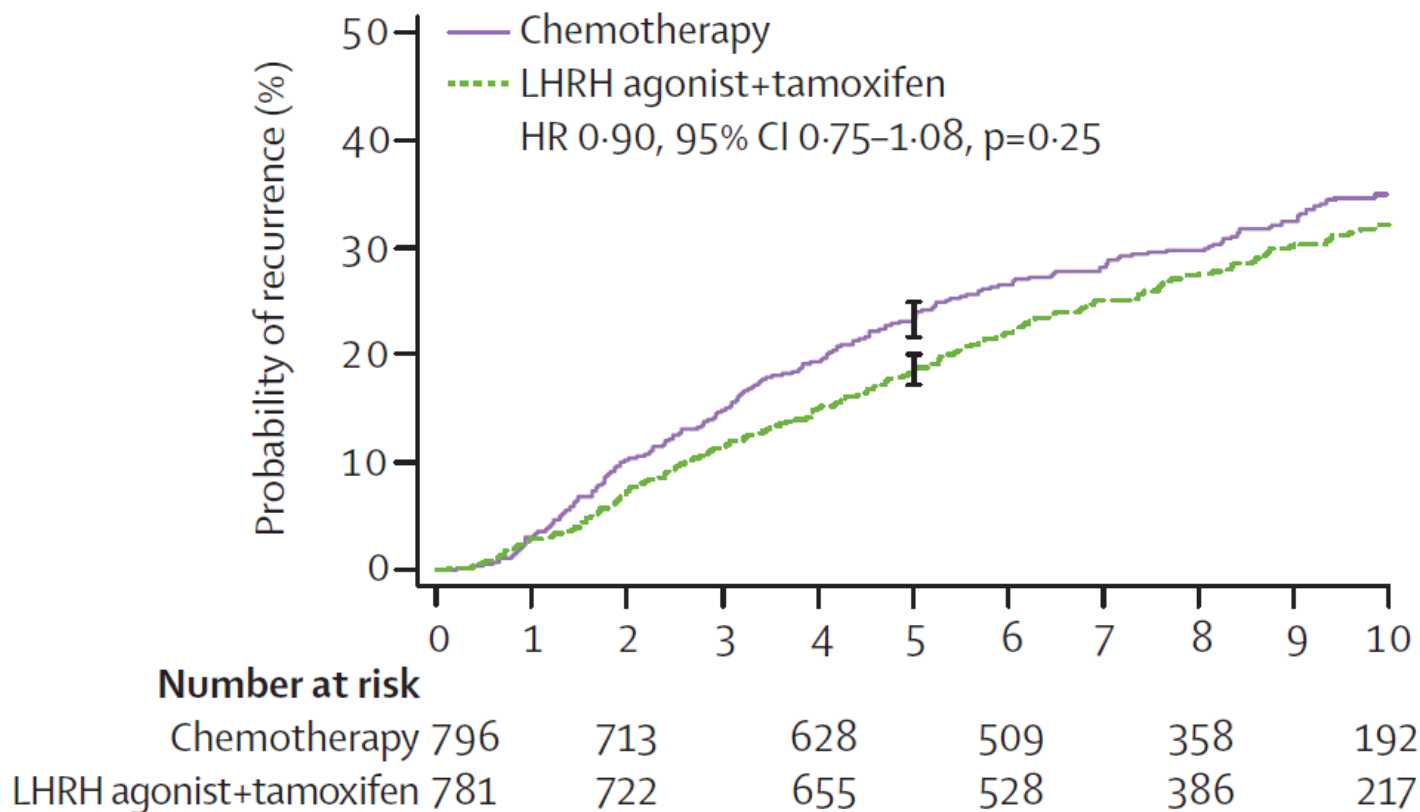
Supp ovar. + Tam x 5 a

Supp ovar. + Exe x 5a

→ Les inclusions sont terminées

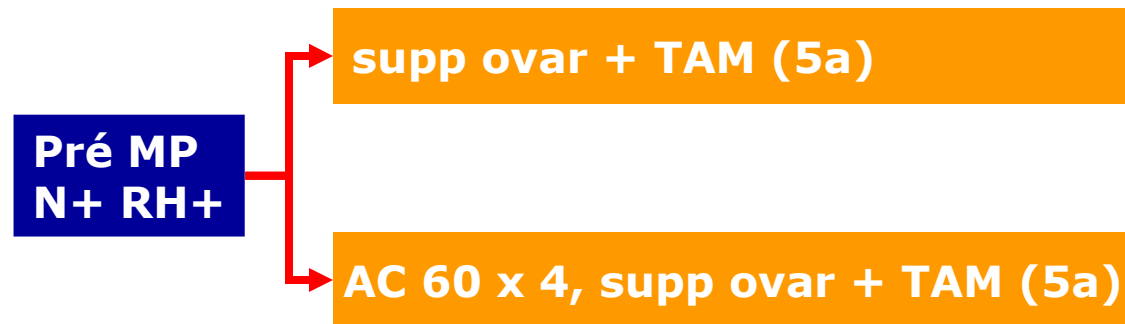
Place relative de la CT et de l'HT

Adjuvant : CT VS suppression ovarienne + Tam



→ 'chemotherapy' n'est pas le standard !
→ Une comparaison qui n'a pas de logique !

Bénéfice de la chimiothérapie ? L'étude IBCSG 11-93



Arrêt après 174 ptes incluses sur 760

Age médian	45 ans
Tumeur > 2 cm	42 %
Grade 1 / 2 / 3	22% / 54 % / 23%
1 – 3 N+	97 %

Bénéfice de la chimiothérapie ? L'étude IBCSG 11-93

supp ovar + TAM (5a)

Pré MP
N+ RH+

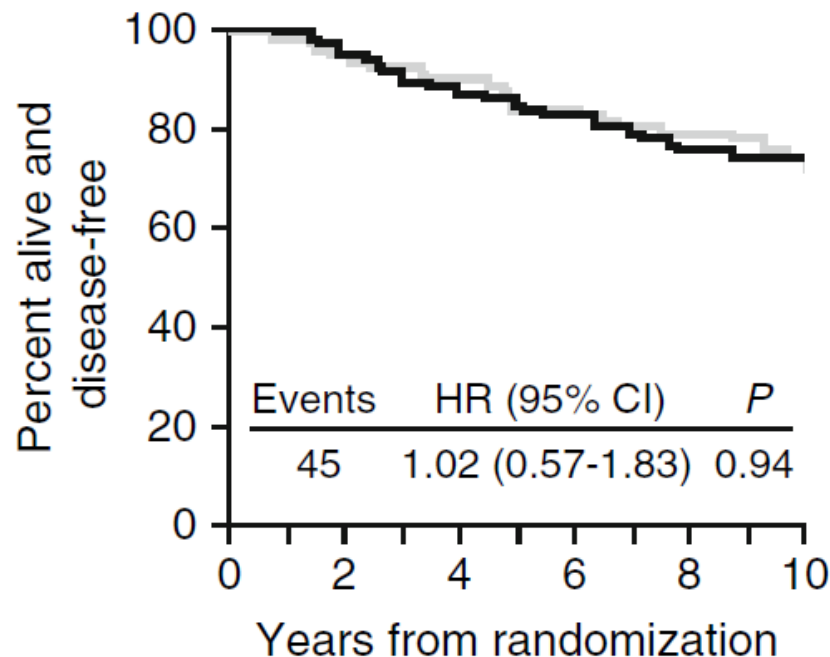
OFS+Tam

OFS+AC+Tam

AC 60 x 4, supp ovar + TAM (5a)

Age médian	45 ans
Tumeur > 2 cm	42 %
Grade 1 / 2 / 3	22% / 54 % / 23%
1 – 3 N+	97 %

Pts	DFS % ± Standard Error	
	5-yr	10-yr
OFS+Tam	85	84 ± 4
OFS+AC+Tam	89	85 ± 4
		73 ± 5



Arrêt après 174 ptes incluses sur 760 !!!

Thurlimann, BCRT 2009

LA CT systématique avt 40 ans : un standard ?

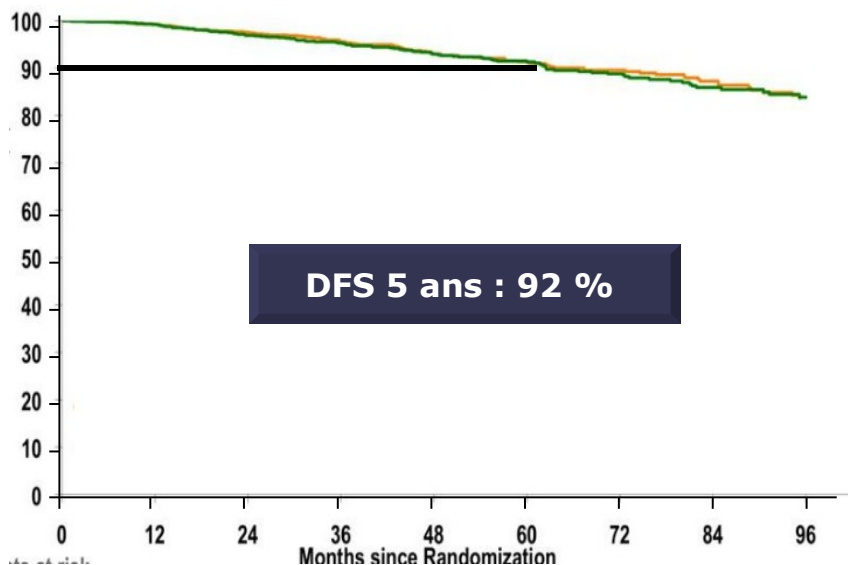
Ptes non MP
RH+

Agoniste-Tam x 3a

Agoniste – Tam x 3a
+ Zoledronate 4 mg/ 6m

Agoniste – Anastroz. x 3a

Agoniste – Anastroz. X 3 a
+ Zoledronate 4 mg/ 6m



Gnant, NEJM, 2009 ; ASCO 2010

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D., Gero Luschin-Ebengreuth, M.D., Sabine Pöstlberger, M.D., Christian Menzel, M.D., Raimund Jakesz, M.D., Michael Seifert, M.D., Michael Hubalek, M.D., Vesna Bjelic-Radisic, M.D., Hellmut Samonigg, M.D., Christoph Tausch, M.D., Holger Eidtmann, M.D., Günther Steger, M.D., Werner Kwasny, M.D., Peter Dubsky, M.D., Michael Fridrik, M.D., Florian Fitzal, M.D., Michael Stierer, M.D., Ernst Rücklinger, Ph.D., and Richard Greil, M.D., for the ABCSG-12 Trial Investigators*

ABSTRACT

BACKGROUND

Ovarian suppression plus tamoxifen is a standard adjuvant treatment in premenopausal women with endocrine-responsive breast cancer. Aromatase inhibitors are superior to tamoxifen in postmenopausal patients, and preclinical data suggest that zoledronic acid has antitumor properties.

METHODS

We examined the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in premenopausal women with endocrine-responsive early breast cancer. We randomly assigned 1803 patients to receive goserelin (3.6 mg given subcutaneously every 28 days) plus tamoxifen (20 mg per day given orally) or anastrozole (1 mg per day given orally) with or without zoledronic acid (4 mg given intravenously every 6 months) for 3 years. The primary end point was disease-free survival; recurrence-free survival and overall survival were secondary end points.

RESULTS

After a median follow-up of 47.8 months, 137 events had occurred, with disease-free survival rates of 92.8% in the tamoxifen group, 92.0% in the anastrozole group, 90.8% in the group that received endocrine therapy alone, and 94.0% in the group that received endocrine therapy with zoledronic acid. There was no significant difference in disease-free survival between the anastrozole and tamoxifen groups (hazard ratio for disease progression in the anastrozole group, 1.10; 95% confidence interval [CI], 0.78 to 1.53; $P=0.59$). The addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy without zoledronic acid, resulted in an absolute reduction of 3.2 percentage points and a relative reduction of 36% in the risk of disease progression (hazard ratio, 0.64; 95% CI, 0.46 to 0.91; $P=0.01$); the addition of zoledronic acid did not significantly reduce the risk of death (hazard ratio, 0.60; 95% CI, 0.32 to 1.11; $P=0.11$). Adverse events were consistent with known drug-safety profiles.

CONCLUSIONS

The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer. (ClinicalTrials.gov number, NCT00295646.)

From the Medical University of Vienna (M.G., R.J., M. Seifert, G.S., P.D., F.F.), Hansch Hospital (M. Stierer), and the Austrian Breast and Colorectal Cancer Study Group (E.R.)—all in Vienna; Paracelsus Medical University Salzburg, Salzburg (B.M., C.M., R.G.); Medical University of Graz, Graz (W.S., G.L.E., V.B.R., H.S.); Hospital of the Sisters of Mercy (S.P., C.T.) and General Hospital Linz (M.F.)—both in Linz; Medical University of Innsbruck, Innsbruck (M.H.); and Wiener Neustadt Hospital, Wiener Neustadt (W.K.)—all in Austria; and the University of Schleswig-Holstein, Kiel, Germany (H.E.). Address reprint requests to Dr. Gnant at the Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria, or at michael.gnant@meduniwien.ac.at.

*The investigators participating in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) are listed in the Appendix.

N Engl J Med 2009;360:679-91.
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LA CT systématique avt 40 ans : un standard ?

Ptes non MP
RH+

Agoniste-Tam x 3a

Agoniste – Tam x 3a
+ Zoledronate 4 mg/ 6m

Agoniste – Anastroz. x 3a

Agoniste – Anastroz. X 3 a
+ Zoledronate 4 mg/ 6m

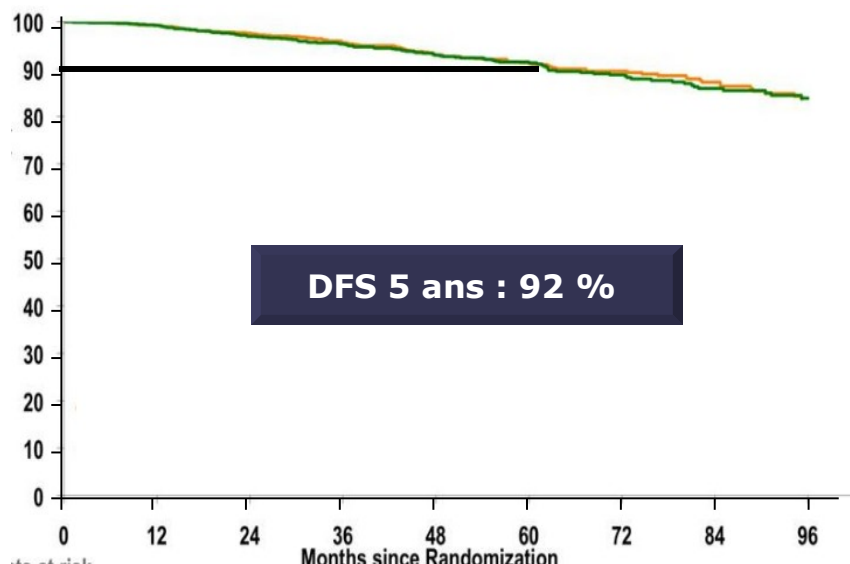


Table 1. Demographic and Baseline Disease Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Tamoxifen (N = 451)	Tamoxifen plus Zoledronic Acid (N = 449)	Anastrozole (N = 453)	Anastrozole plus Zoledronic Acid (N = 450)
Age at study entry				
Median — yr	45.5	45.3	45.0	44.5
Range — yr	27.6–56.5	27.5–56.3	25.9–56.3	28.8–56.4
≤40 yr — no. (%)	80 (17.7)	67 (14.9)	88 (19.4)	91 (20.2)
>40 yr — no. (%)	370 (82.0)	382 (85.1)	364 (80.4)	358 (79.6)
Cancer stage — no. (%)				
T1	338 (74.9)	335 (74.6)	348 (76.8)	339 (75.3)
≥T2	99 (22.0)	98 (21.8)	93 (20.5)	97 (21.6)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	13 (2.9)
Nodal status — no. (%)				
Negative	301 (66.7)	295 (65.7)	303 (66.9)	302 (67.1)
Positive	136 (30.2)	138 (30.7)	139 (30.7)	135 (30.0)
Unknown	13 (2.9)	16 (3.6)	10 (2.2)	12 (2.7)
Histologic grade — no. (%)				
1 or 2	344 (76.3)	344 (76.6)	344 (75.9)	339 (75.3)
3	93 (20.6)	89 (19.8)	97 (21.4)	98 (21.8)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	12 (2.7)
Estrogen-receptor status — no. (%)†				
Negative	16 (3.5)	19 (4.2)	15 (3.3)	17 (3.8)
Low expression	51 (11.3)	61 (13.6)	54 (11.9)	58 (12.9)
Medium expression	166 (36.8)	149 (33.2)	167 (36.9)	153 (34.0)
High expression	204 (45.2)	204 (45.4)	206 (45.5)	210 (46.7)
Unknown‡	14 (3.1)	16 (3.6)	11 (2.4)	12 (2.7)
Progesterone-receptor status — no. (%)†				
Negative	40 (8.9)	32 (7.1)	34 (7.5)	36 (8.0)
Low expression	52 (11.5)	64 (14.3)	58 (12.8)	59 (13.1)
Medium expression	160 (35.5)	142 (31.6)	149 (32.9)	131 (29.1)
High expression	185 (41.0)	195 (43.4)	200 (44.2)	212 (47.1)
Unknown‡	14 (3.1)	16 (3.6)	12 (2.6)	12 (2.7)
Preoperative chemotherapy — no. (%)				
No	406 (90.0)	404 (90.0)	408 (90.1)	405 (90.0)
Yes	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Unknown	21 (4.7)	22 (4.9)	21 (4.6)	19 (4.2)

* All patients received goserelin. Percentages may not total 100 because of rounding.

† Hormone-receptor status was defined by the Reiner score for staining,²³ which is based on a scale of 10 to 100%, with 10 to 50% indicating low expression of the estrogen and progesterone receptors, 51 to 80% indicating medium expression, and 81 to 100% indicating high expression.

‡ Patients in this category were identified as having protocol violations; they were included in the intention-to-treat analysis but excluded from the per-protocol analysis.

The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 13, 2009

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

Nancy Lee Harris, M.D., *Editor*
Jo-Anne O. Shepard, M.D., *Associate Editor*
Sally H. Ebeling, *Assistant Editor*

Eric S. Rosenberg, M.D., *Associate Editor*
Alice M. Cort, M.D., *Associate Editor*
Christine C. Peters, *Assistant Editor*



Case 25-2009: A 36-Year-Old Woman with Hormone-Receptor-Positive Breast Cancer

Harold J. Burstein, M.D., Ph.D., Irene Souter, M.D., Helen Anne D'Alessandro, M.D.,
and Dennis C. Sgroi, M.D.

PRESENTATION OF CASE

- 36 ans - pT1c (14 mm), pN1mi (0,2 - 1,8 mm, HES- CK+)
- LVI- ; curage 13 N -
- RE+, RP+, Her2-
- Mammaprint 'low risk' ; Oncotype : 16 (M+ 10 ans : 10%)

(H.A.D.), and Pathology (D.C.S.), Massachusetts General Hospital; and the Departments of Medicine (H.J.B.), Obstetrics, Gynecology, and Reproductive Biology (I.S.), Radiology (H.A.D.), and Pathology (D.C.S.), Harvard Medical School — all in Boston.

N Engl J Med 2009;361:699-707.
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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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DISCUSSION OF MANAGEMENT

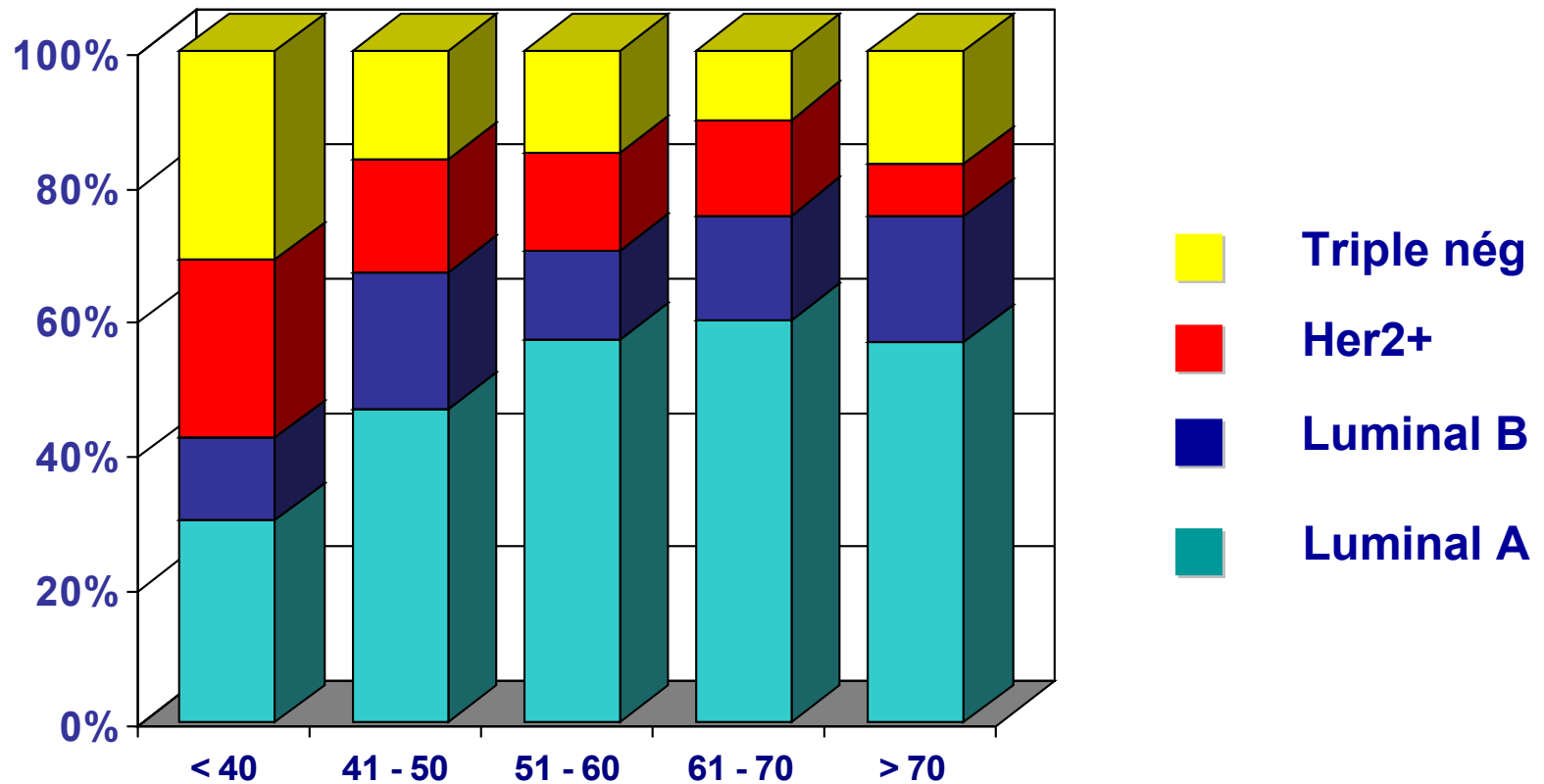
In summary, this patient with early-stage breast cancer has a generally favorable prognosis, despite her young age and regardless of her nodal status. For adjuvant treatment, I would recommend tamoxifen and ovarian suppression

but not chemotherapy, recommendations that are consistent with international treatment guidelines.^{33,34} Consultation with an expert in fertility and reproductive medicine would be indicated if the patient is interested.

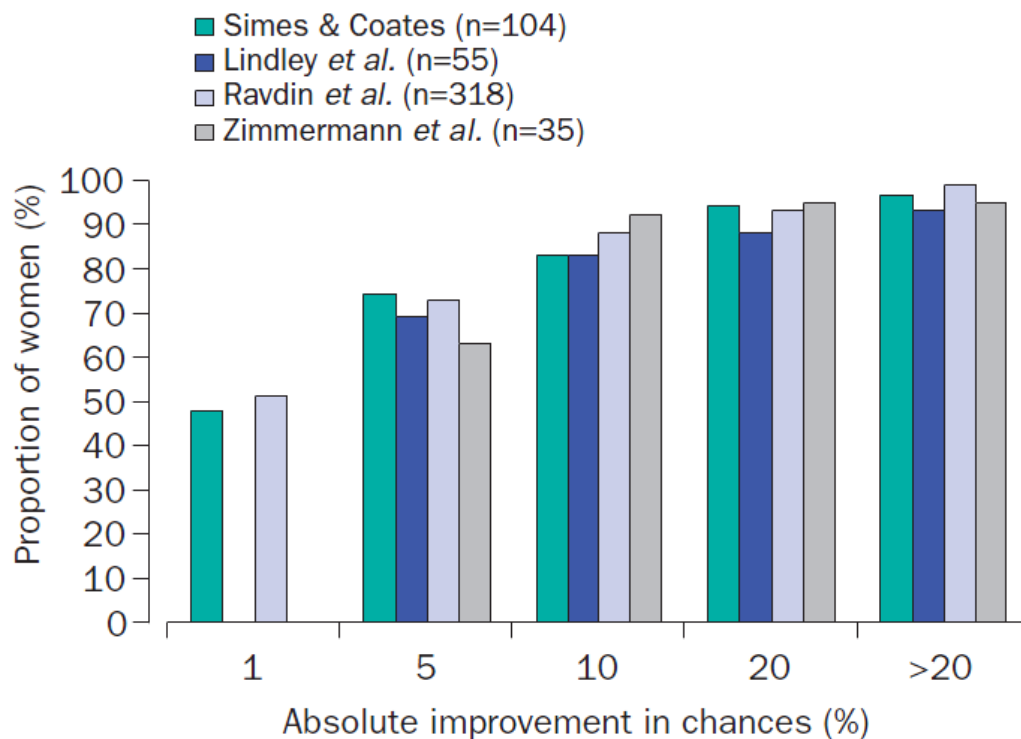
33. NCCN Clinical Practice Guidelines in Oncology: breast cancer, Fort Washington, PA: National Comprehensive Cancer Network (<http://www.nccn.org>.)

34. Goldhirsch A, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of early Breast Cancer 2009. Ann Oncol 2009

Une situation peu fréquente ...



CT adjuvante ... pour quel bénéfice ?



→ Un critère important de plus grande acceptation :
avoir la responsabilité d'une personne dépendante

Pour conclure

- **L'âge jeune**
 - n'est pas un facteur pronostique indépendant (à mon avis)
 - n'est pas un facteur prédictif indépendant
- **Peut-on dans certains cas faire l'impasse de la CT ?**
 - oui, pour les tumeurs luminales A (20 – 30% des cas)
- **Quelle hormonothérapie proposer alors ?**
 - Tam, traitement de référence
 - Supp. Ovarienne + Tam : HR 0,85 (p = 0,20)
- **L'attente des patientes est sans doute un peu différente**
- **Qu'en est-il de la toxicité, Jean-Paul ?**

... Merci de votre attention ...





Etudes randomisées : CT VS suppression ovarienne

Etude	Nbre ptes	TRT	Résultats
ZEBRA	1 600 N+ RH+/-	• CMF x 6 (oral ou iv) • Ag LHRH x 2 ans	CMF = ag LHRH (RH+)
Scandinave	762 N+ ou N-> 5cm RH+	• CMF x 9 (iv) • Irradiation ovarienne	CMF = Irrad. ovar.
Scottish	332 N+ RH+/-	• CMF x 6-8 (iv) • Chir ovar / irradiation	CMF = Supp. ovar.
TABLE	599 N+ RE+	• CMF x 6 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH
IBCSG VIII	1063 N- RE+/-	• CMF x 6 (oral) • Ag LHRH x 2 ans • CMF x 6 → Ag LHRH	CMF = ag LHRH
GABG IV-A-93	771 N- RE+	• CMF x 3 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH

→ Suppression ovarienne = CT

Etudes randomisées : CT VS suppression ovarienne

Etude	Nbre ptes	TRT	Résultats
ZEBRA	1 600 N+ RH+/-	• CMF x 6 (oral ou iv) • Ag LHRH x 2 ans	CMF = ag LHRH (RH+)
Scandinave	762 N+ ou N-> 5cm RH+	• CMF x 9 (iv) • Irradiation ovarienne	CMF = Irrad. ovar.
Scottish	332 N+ RH+/-	• CMF x 6-8 (iv) • Chir ovar / irradiation	CMF = Supp. ovar.
TABLE	599 N+ RE+	• CMF x 6 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH
IBCSG VIII	1053 N- RE+/-	• CMF x 6 (oral) • Ag LHRH x 2 ans • CMF x 6 → Ag LHRH	CMF = ag LHRH
GABG IV-A-93	771 N- RE+	• CMF x 3 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH

**Le CMF seul n'est pas le standard !
Une comparaison qui n'a pas de logique !**

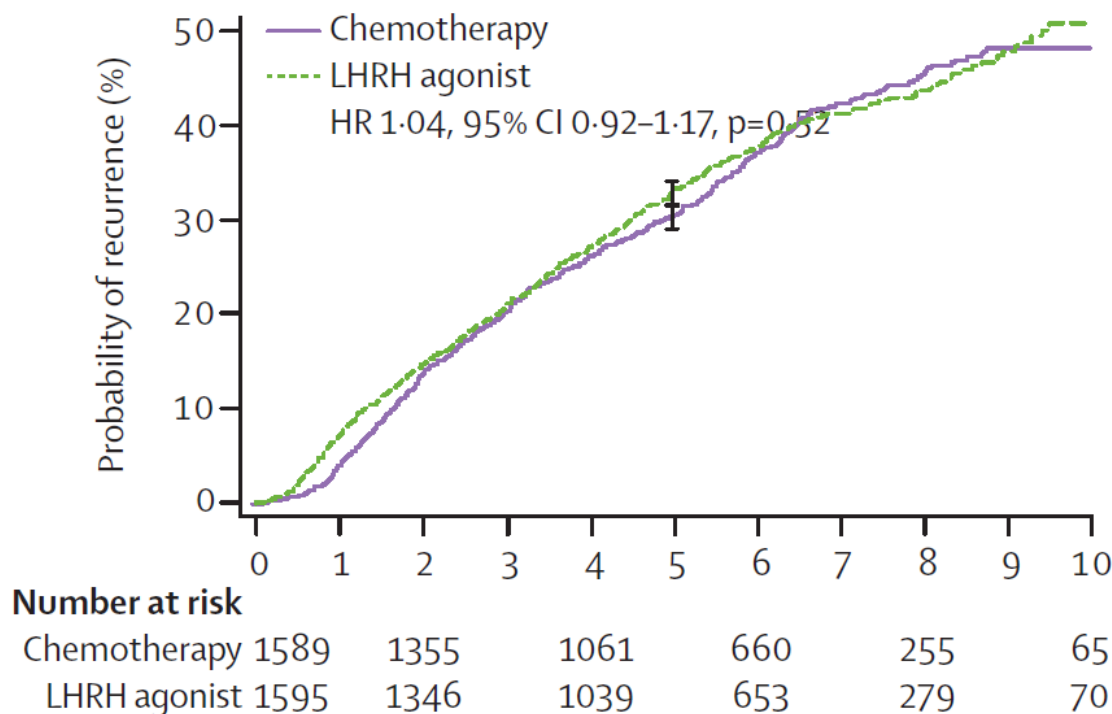
→ Suppression ovarienne = CT

Etudes randomisées : CT VS suppression ovarienne

Etude	Nbre ptes	TRT	Résultats
ZEBRA	1 600 N+ RH+/-	CMF vs supp ovar.	Pas de différence (RH+)
Scandinave	762 N+ ou N-> 5cm RH+	CMF vs RxT ovar.	Pas de différence
Scottish	332 N+ RH+/-	CMF vs Chir/RxT ovar.	CMF = Supp. ovar.
TABLE	599 N+ RE+	CMF vs Ag LHRH x 2 ans	CMF = ag LHRH
IBCSG VIII	1063 N- RE+/-	CMF vs Ag LHRH x 2 ans	Pas de différence
GABG IV-A-93	771 N- RE+	CMF vs Ag LHRH x 2 ans	Pas de différence
GROCTA 02	224 N+/- RE+	CMF vs supp ovar + TAM	Pas de différence
ABCSG 05	1034 N- RE+	CMF vs Ag LHRH + TAM	supp ovar + TAM >
FASG 05	162 N+ RE+	FAC vs supp ovar + TAM	Pas de différence
FASG 06	333 N+ RE+	FEC50 vs supp ovar + TAM	Pas de différence

➔ **Suppression ovarienne = CT**

Etudes randomisées : CT VS suppression ovarienne



→ Le CMF seul n'est pas le standard !
→ Une comparaison qui n'a pas de logique !

Etudes randomisées : CT VS suppression ovarienne

Etude	Nbre ptes	TRT	Résultats
ZEBRA	1 600 N+ RH+/-	• CMF x 6 (oral ou iv) • Ag LHRH x 2 ans	CMF = ag LHRH (RH+)
Scandinave	762 N+ ou N-> 5cm RH+	• CMF x 9 (iv) • Irradiation ovarienne	CMF = Irrad. ovar.
Scottish	332 N+ RH+/-	• CMF x 6-8 (iv) • Chir ovar / irradiation	CMF = Supp. ovar.
TABLE	599 N+ RE+	• CMF x 6 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH
IBCSG VIII	1063 N- RE+/-	• CMF x 6 (oral) • Ag LHRH x 2 ans • CMF x 6 → Ag LHRH	CMF = ag LHRH
GABG IV-A-93	771 N- RE+	• CMF x 3 (iv) • Ag LHRH x 2 ans	CMF = ag LHRH