Journée Laurence Leroyer 2018

Des études marquantes depuis l'an dernier …

Christelle Levy
Centre François Baclesse, Caen

Situation adjuvante

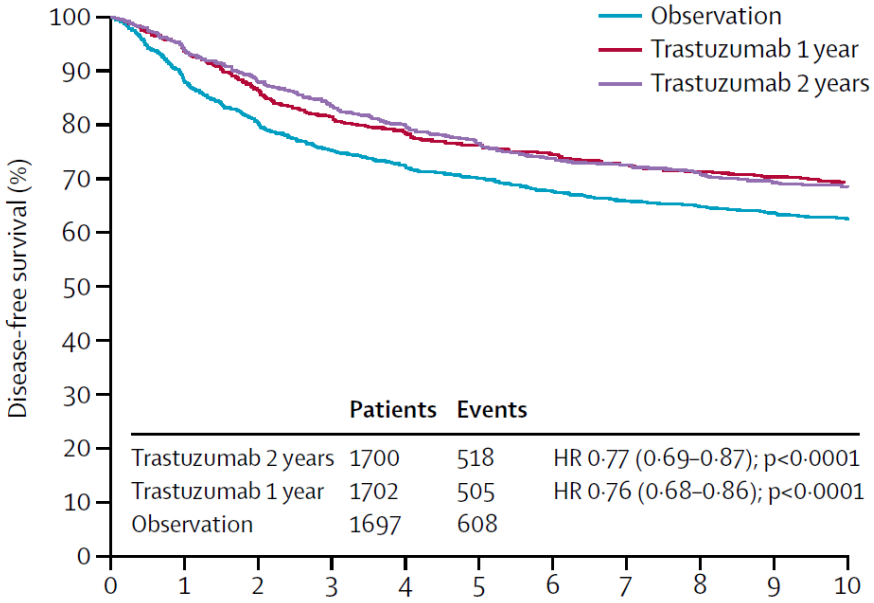
- HER2+
  - APHINITY
  - EXTENET
- RH+
  - SOFT-TEXT
- Dose dense

The **APHINITY** Study

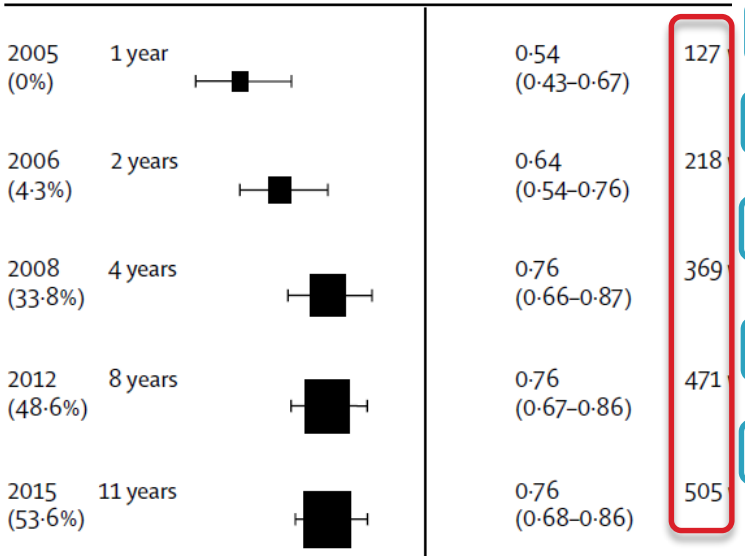
Adjuvant Pertuzumab and Herceptin in Initial Therapy

BIG 4-11 / BO25126 / TOC4939g

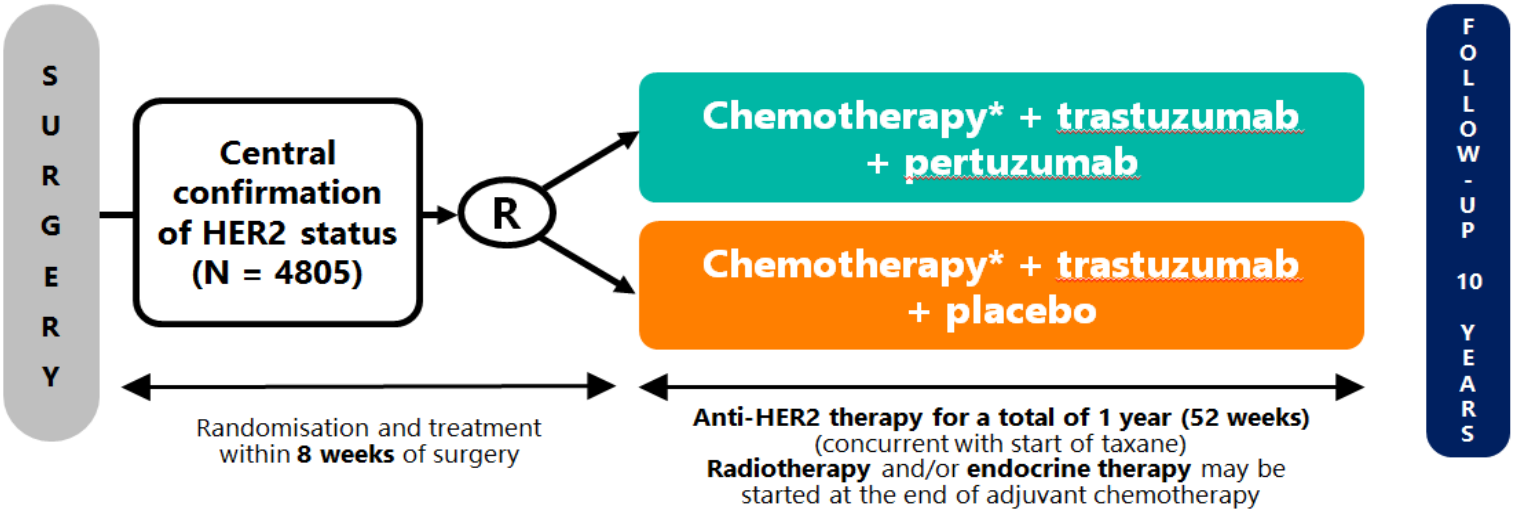
HERA



Comment améliorer ces résultats ?



Cameron D, *Lancet* 2017; 389: 1195–205



Critères d'inclusion

N+

N- > 10 mm (ou > 5mm et grade 3 / RH négatifs / < 35 ans)

FEVG > 55%

- Amendement en Nov 2012 pour inclure 1000 nouvelles patientes **N+** (3800 ➔ 4800)
- 4804 patientes (Nov 2011 à Août 2013)

- Critère de jugement: survie sans récidive invasive (autres cancers exclus)

  hypothèse à 3 ans

  91,8 % vs 89.2% (Δ=2.6%) HR=0.75

- Résultats présentés avec un FU médian de 45 mois

Population

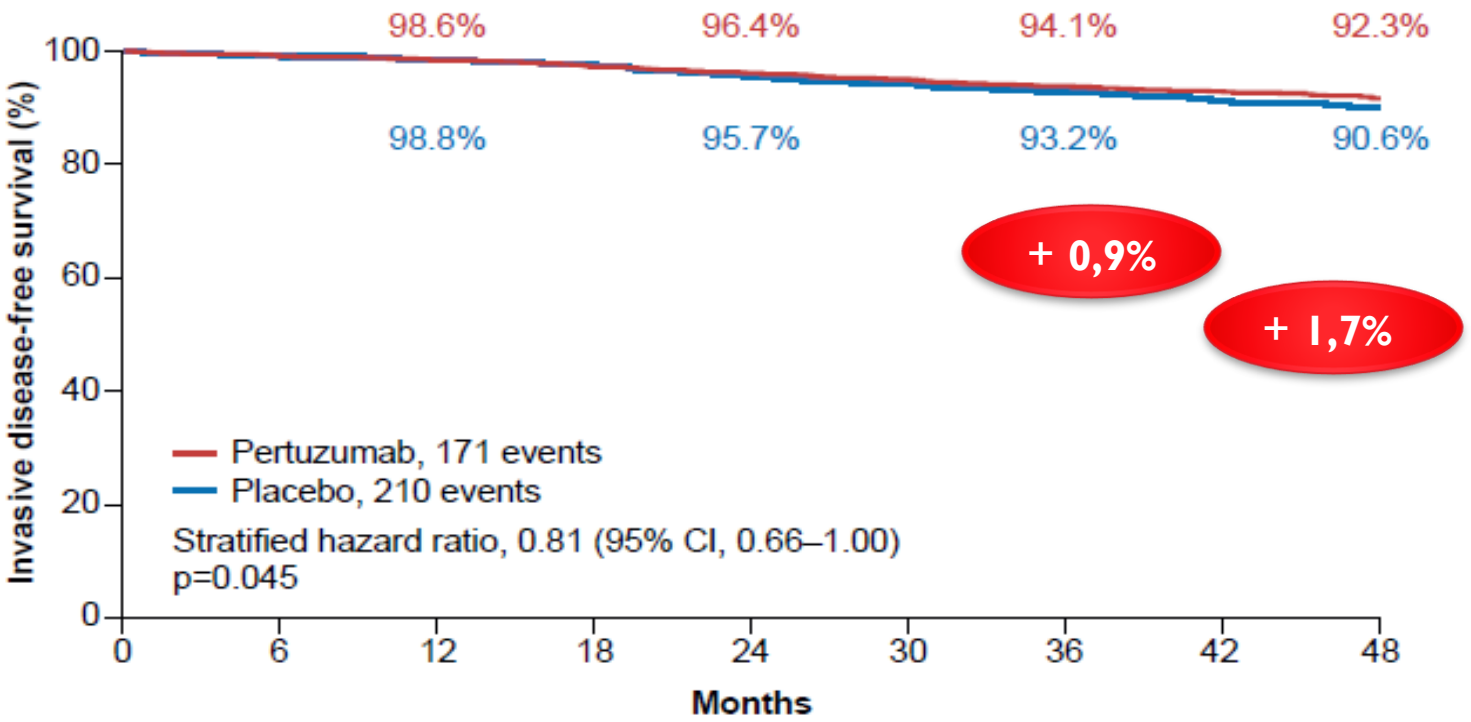
Characteristic, n (%)	Pertuzumab (n = 2400)	Placebo (n = 2404)
Nodal status		
▪ 0 positive nodes + T ≤ 1 cm	90 (3.8)	84 (3.5)
▪ 0 positive nodes + T > 1 cm	807 (33.6)	818 (34.0)
▪ 1-3 positive nodes	907 (37.8)	900 (37.4)
▪ ≥ 4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant CT regimen (randomized)		
▪ Anthracycline containing	1865 (77.7)	1877 (78.1)
▪ Nonanthracycline containing	535 (22.3)	527 (21.9)
HR status (central determination)		
▪ Negative (ER- and PgR-)	864 (36.0)	858 (35.7)
▪ Positive (ER+ and/or PgR+)	1536 (64.0)	1546 (64.3)

> 60% N+

évènements

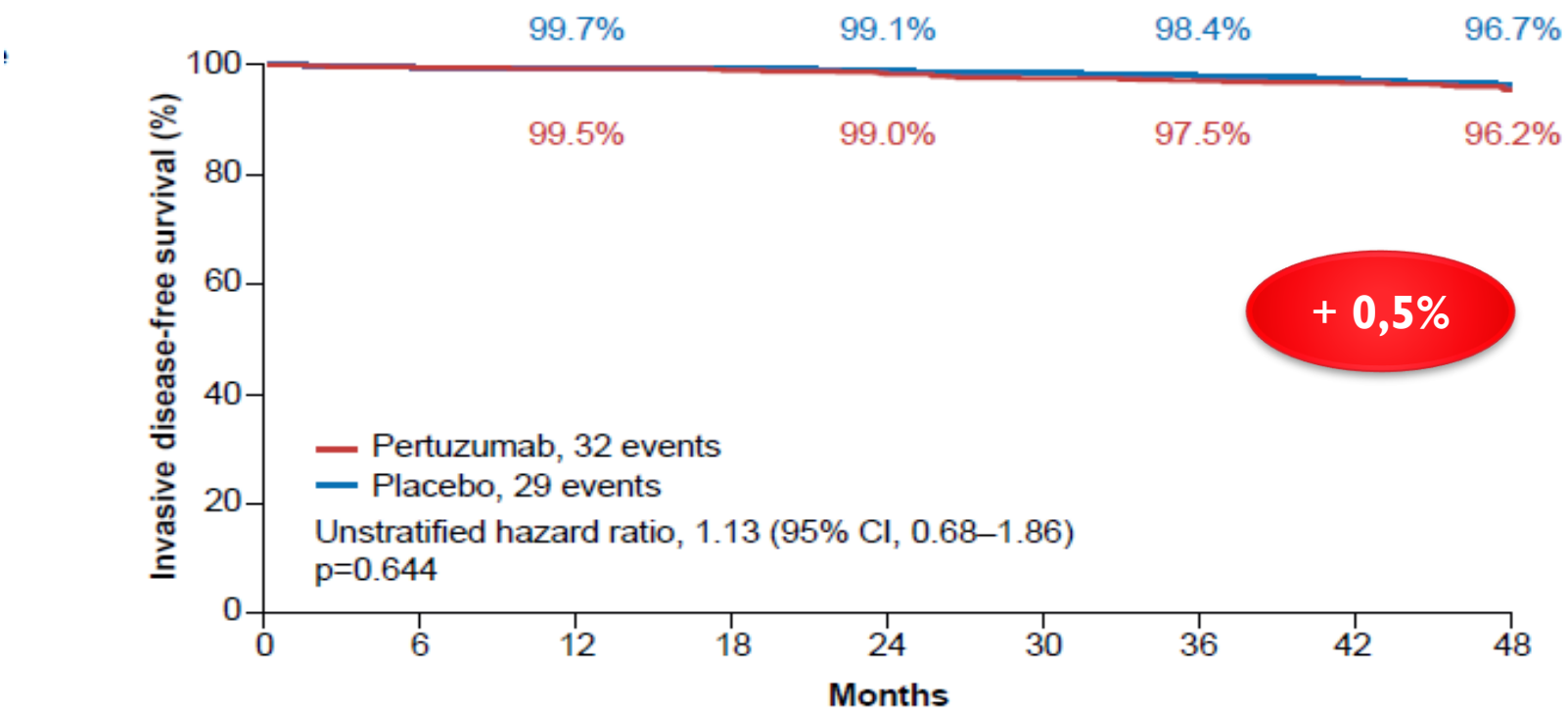
	Ptz n=2400	Pla n=2404
Total patients with IDFS event, n (%)	171 (7.1)	210 (8.7)
Category of first IDFS event, n (%)		
Distant recurrence	112 (4.7)	139 (5.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without prior event	28 (1.2)	26 (1.1)
All patients with a distant recurrence at any time during the study, n (%)	119 (5.0)	145 (6.0)
Site of first distant recurrence n (%)		
Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
CNS	46 (1.9)	45 (1.9)
Other	9 (0.4)	9 (0.4)
Bone	21 (0.9)	30 (1.2)

iDFS



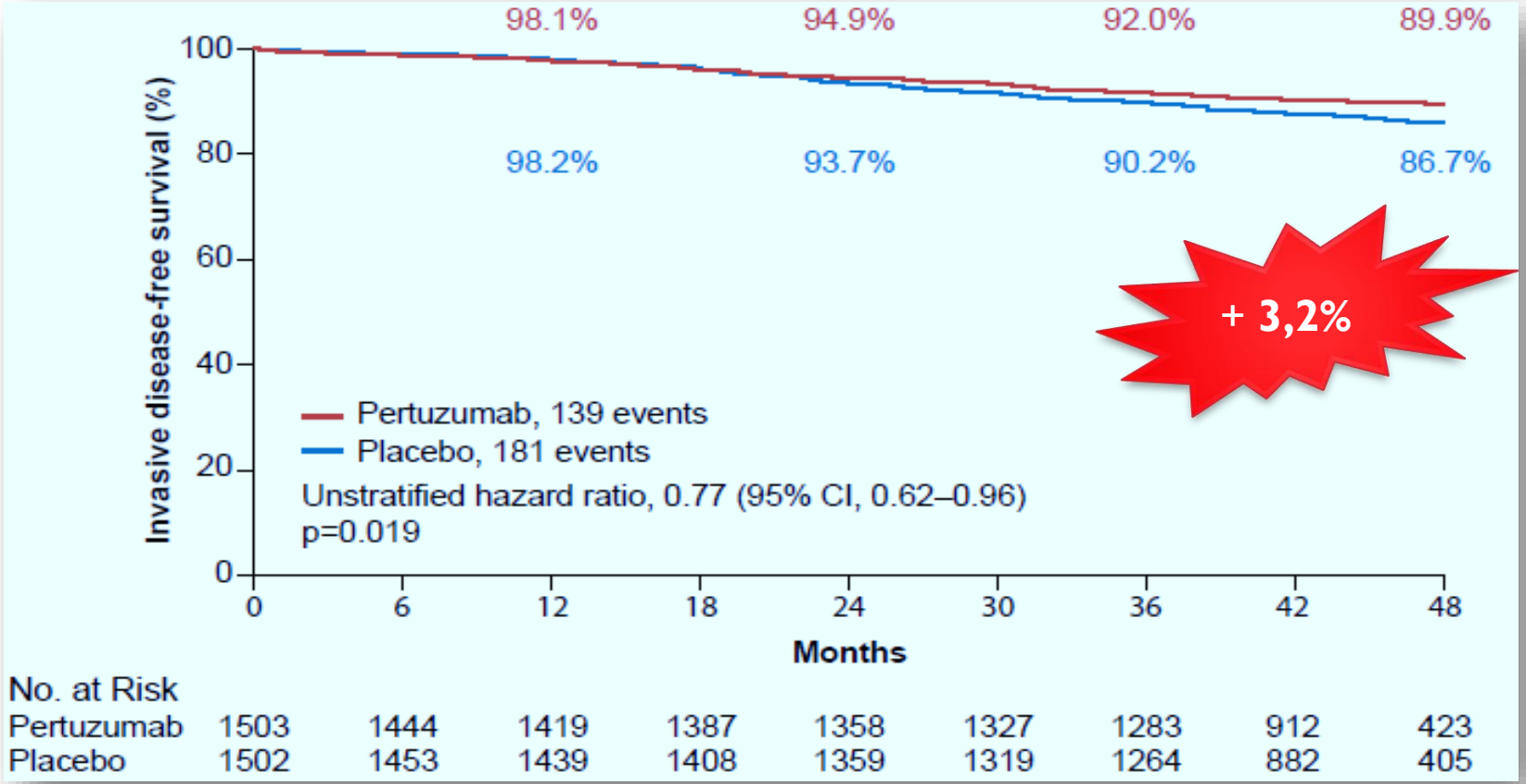
No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

Aphinity: N-

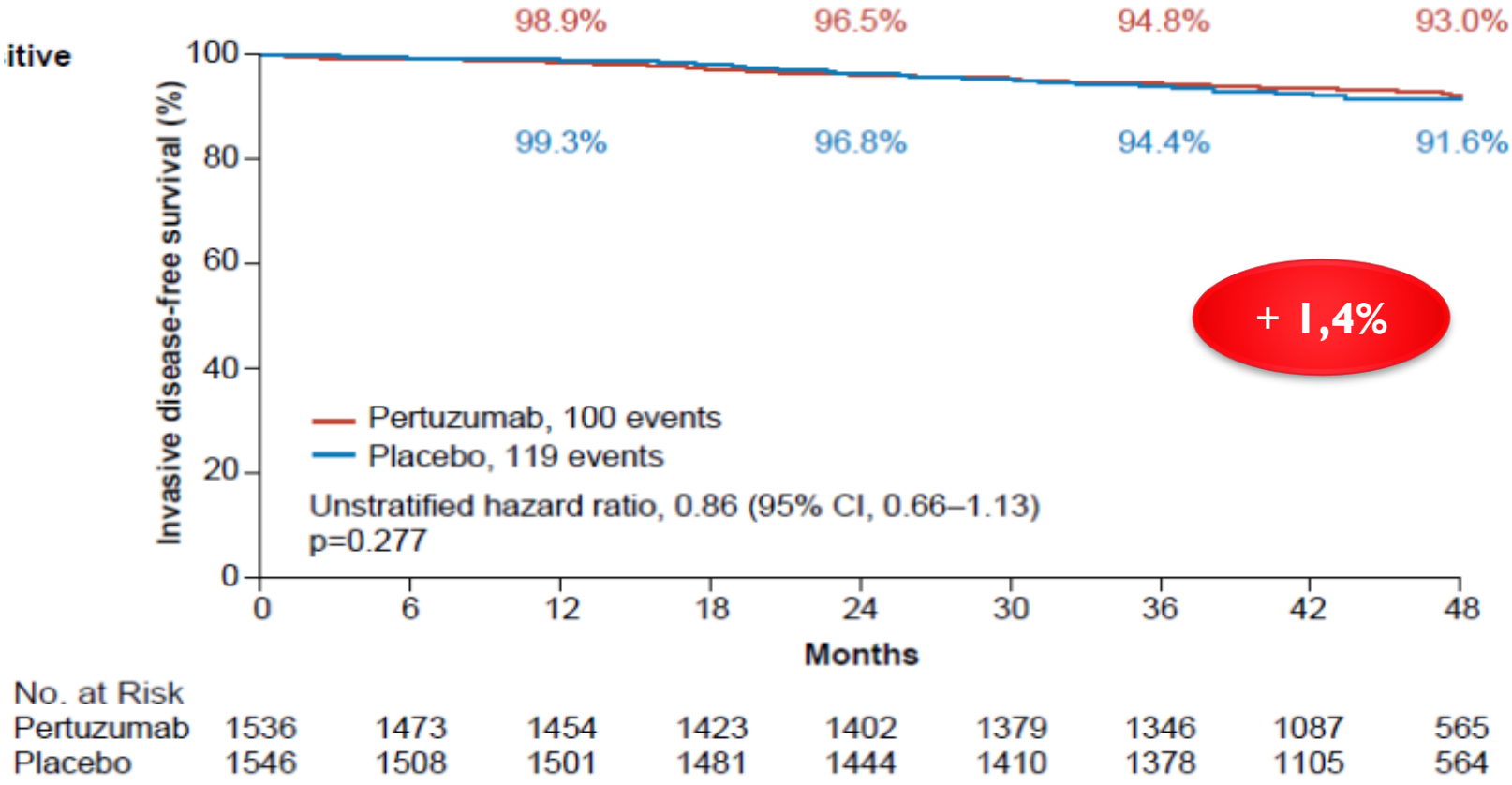


No. at Risk									
Pertuzumab	897	865	856	849	841	826	818	775	456
Placebo	902	882	873	866	856	849	844	792	461

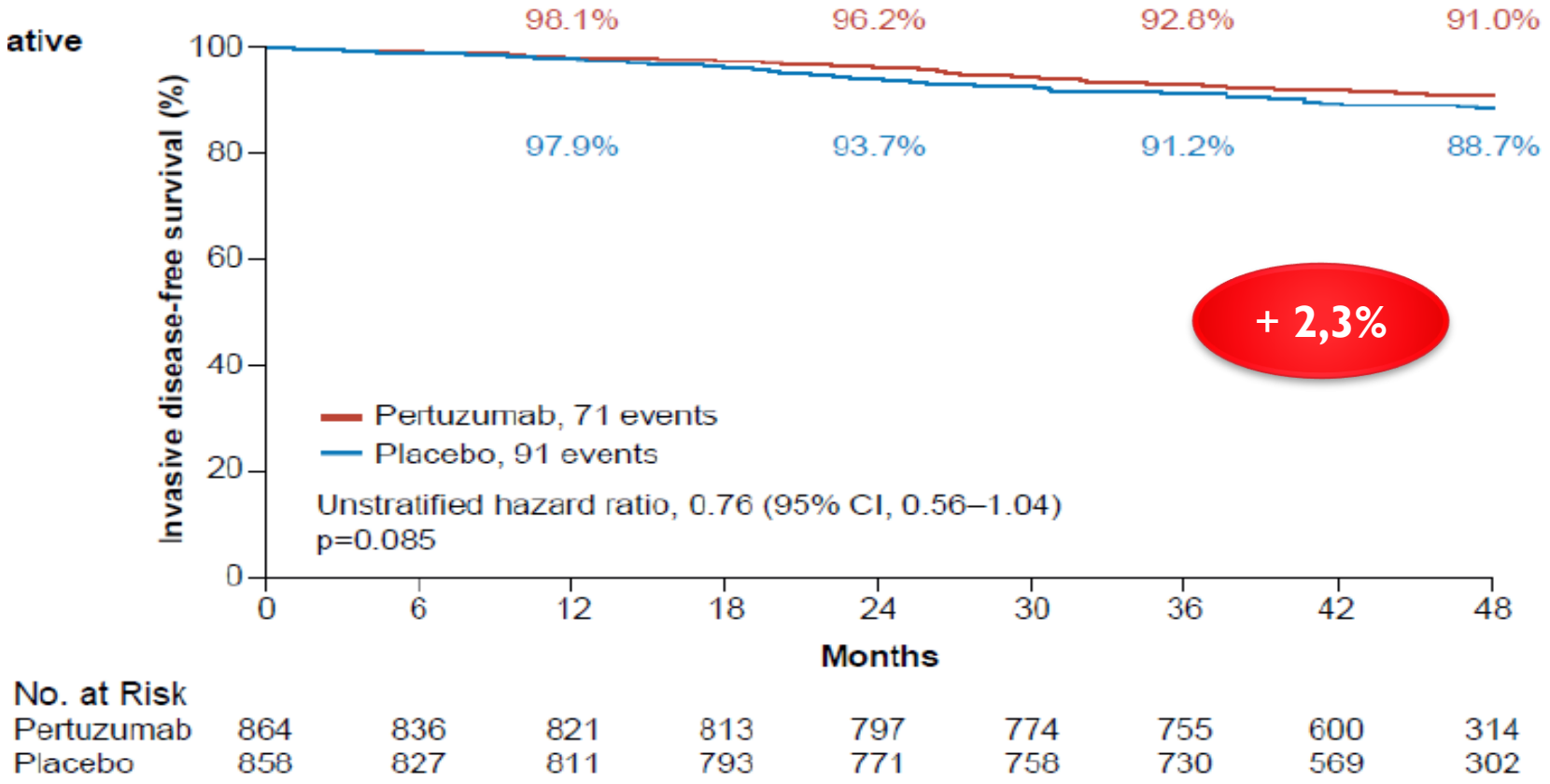
Aphinity: N+


98.1%
94.9%
92.0%
89.9%
98.2%
93.7%
90.2%
86.7%
+ 3,2%
Invasive disease-free survival (%)
100
80
60
40
20
0
Pertuzumab, 139 events
Placebo, 181 events
Unstratified hazard ratio, 0.77 (95% CI, 0.62–0.96)
p=0.019
0
6
12
18
24
30
36
42
48
Months
No. at Risk
Pertuzumab 1503 1444 1419 1387 1358 1327 1283 912 423
Placebo 1502 1453 1439 1408 1359 1319 1264 882 405

Aphinity: RH+


itive
98.9%
96.5%
94.8%
93.0%
99.3%
96.8%
94.4%
91.6%
100
80
60
40
20
0
Invasive disease-free survival (%)
+ 1,4%
Pertuzumab, 100 events
Placebo, 119 events
Unstratified hazard ratio, 0.86 (95% CI, 0.66–1.13)
p=0.277
0
6
12
18
24
30
36
42
48
Months
No. at Risk
Pertuzumab 1536 1473 1454 1423 1402 1379 1346 1087 565
Placebo 1546 1508 1501 1481 1444 1410 1378 1105 564

Aphinity: RH-


ative
98.1%
96.2%
92.8%
91.0%
97.9%
93.7%
91.2%
88.7%
+ 2,3%
Invasive disease-free survival (%)
100
80
60
40
20
0
Pertuzumab, 71 events
Placebo, 91 events
Unstratified hazard ratio, 0.76 (95% CI, 0.56–1.04)
p=0.085
0
6
12
18
24
30
36
42
48
Months
No. at Risk
Pertuzumab 864 836 821 813 797 774 755 600 314
Placebo 858 827 811 793 771 758 730 569 302

Tolérance

	Pertuzumab n=2364		Placebo n=2405	
	All grade	Grade ≥3	All grade	Grade ≥3
Diarrhoea	71.2	9.8	45.2	3.7
• Onset after chemotherapy during targeted therapy	18.1	0.5	9.2	0.2
• Anthracycline-based chemotherapy	67.3	7.5	40.8	3.1
• Non-anthracycline-based (TCH) chemotherapy	84.7	18.0	61.6	6.1
Nausea	69.0	2.4	65.5	2.5
Fatigue	48.8	3.9	44.3	2.5
Arthralgia	28.7	0.9	32.5	1.1
Myalgia	26.0	0.9	29.5	1.3
Stomatitis	28.4	2.0	24.0	1.0
Anaemia	27.8	6.9	23.3	4.7
Dysgeusia	26.0	0.1	21.5	<0.1
Rash	25.8	0.4	20.3	0.2
Decreased appetite	23.9	0.8	19.9	0.4
Mucosal inflammation	23.4	1.7	18.4	0.7
Epistaxis	18.2	<0.1	13.6	0.0
Oedema peripheral	17.1	0	20.1	0.2
Pruritus	14.0	0.1	9.0	<0.1

Tolérance cardiaque

N (%)	Pertuzumab n=2364	Treatment difference ptz vs. pla (95% CI)	Placebo n=2405
Primary cardiac endpoint	17 (0.7)	0.4 (0.0, 0.8)	8 (0.3)
• Heart failure NYHA III/IV + LVEF drop* • Cardiac death**	15 (0.6) 2 (0.08)		6 (0.2) 2 (0.08)
• Anthracycline-based chemo (N=3728) • Non-anthracycline-based chemo (N=1038)	13 (0.7) 2 (0.4)		5 (0.3) 1(0.2)
• Recovered according Investigator or LVEF	9 (0.4)		4 (0.2)
Secondary cardiac endpoint Asymptomatic or mildly symptomatic LVEF drop*	64 (2.7)	-0.1 (-1.0, 0.9)	67 (2.8)

Conclusions

- Avec un suivi médian de 45 mois, le double blocage Pertuzumab-Trastuzumab **réduit le risque de rechute invasive de 19%** (HR 0.81; 95% CI 0.66, 1.00; p=0.0446)
- Le bénéfice du double blocage concerne **principalement les patientes N+** (HR=0.77; 95% CI=0.62–0.96; p=0.0188)
- Les patientes du bras contrôle (Trastuzumab seul) ont eu une évolution plus favorable que prévu dans l'hypothèse statistique (iDFS à 3 ans de 93.2%, vs 89.2%)
- nécessité d'une mise à jour des résultats avec un suivi prolongé

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 Avril 2018

The CHMP adopted an extension to the existing indication as follows: the **adjuvant** treatment of adult patients with **HER2-positive early breast cancer** **at high risk of recurrence**

EXTENET

. trastuzumab adjuvant interrompu ≤ 1 an avant inclusion

. N+

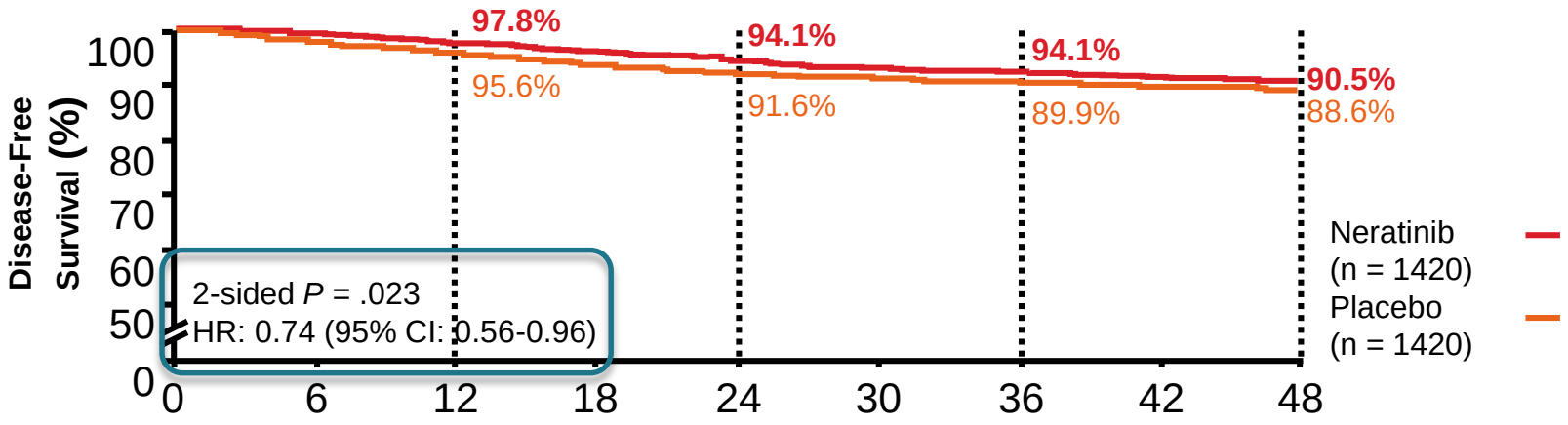
. ou absence de pCR après CNA

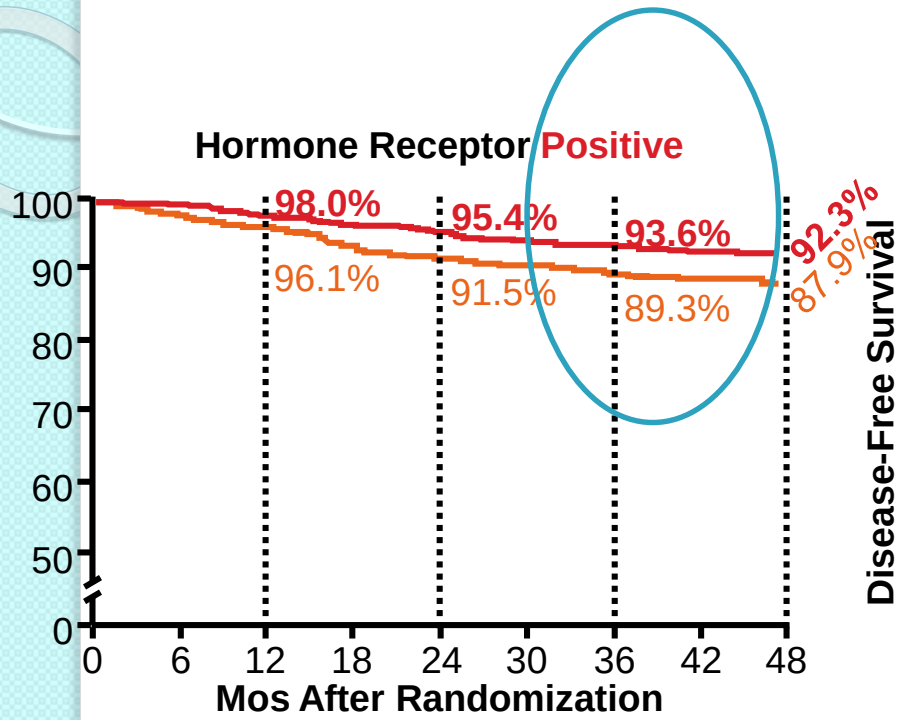
Neratinib 240 mg/day

N = 2840

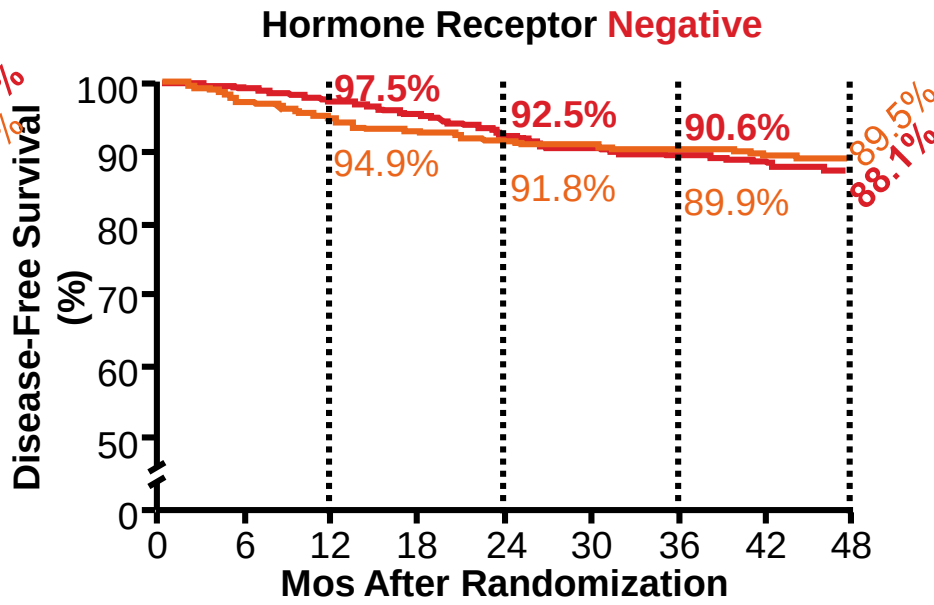
Placebo

objectif principal = iDFS:
2- and 5-yr F/U
OS: 5-yr F/U





2-sided *P* = .003
HR: 0.57 (95% CI: 0.39-0.82)



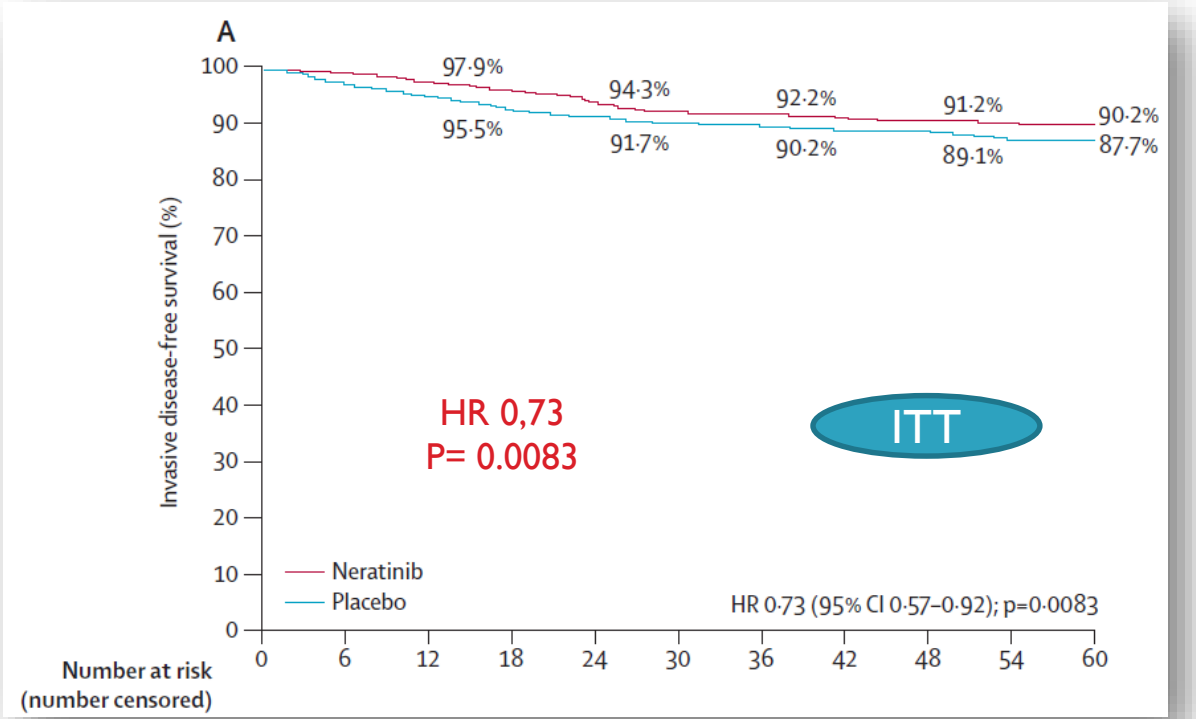
2-sided *P* = .938
HR: 0.57 (95% CI: 0.67-1.45)

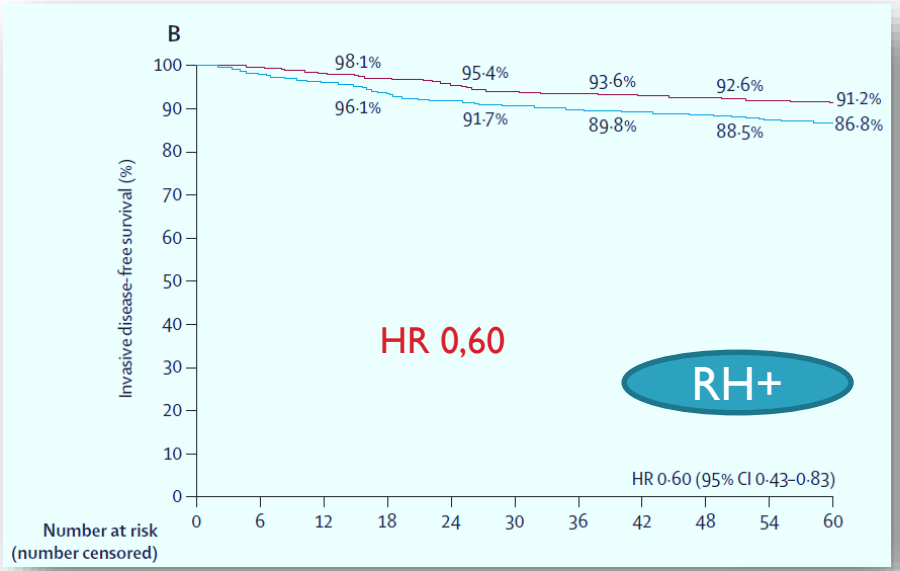
ExteNET: Baseline Characteristics

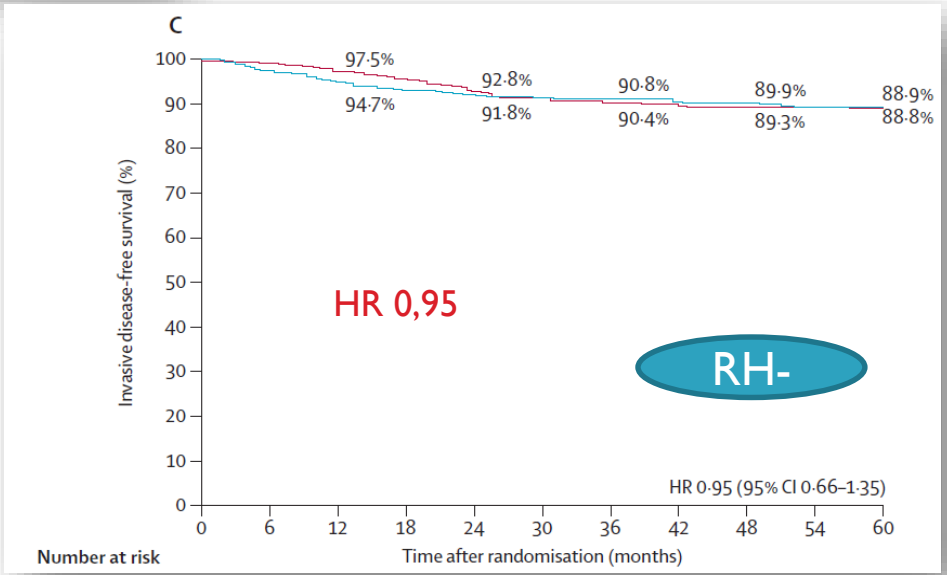
Characteristic, %	Neratinib (n = 1420)	Placebo (n = 1420)
Median age, yrs (range)	52 (25-83)	53 (24-81)
Negative nodal status	23.6	23.7
Positive hormone receptor status	57.7	57.3
Earlier trastuzumab regimen concurrent with chemo	60.3	63.3
Neoadjuvant anthracycline or anthracycline + taxane	80.6	79.7
Median time from trastuzumab, mos (range)	4.2 (0.4-30.9)	4.3 (0.3-40.6)

Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2017; 18: 1688–700



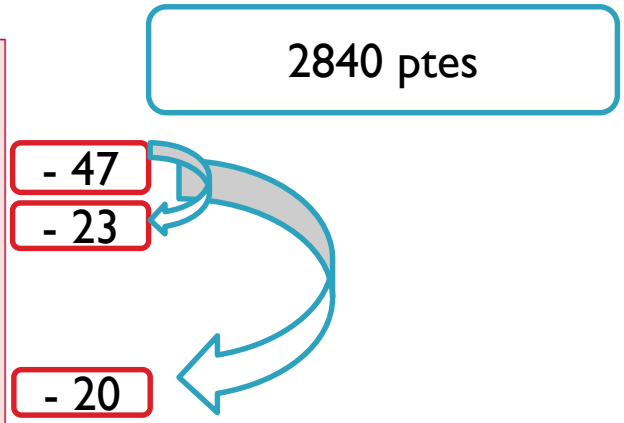

B
98·1%
95·4%
93·6%
92·6%
91·2%
96·1%
91·7%
89·8%
88·5%
86·8%
Invasive disease-free survival (%)
HR 0,60
RH+
HR 0·60 (95% CI 0·43–0·83)
Number at risk
(number censored)
0 6 12 18 24 30 36 42 48 54 60


C
97·5%
92·8%
90·8%
89·9%
88·9%
94·7%
91·8%
90·4%
89·3%
88·8%
Invasive disease-free survival (%)
HR 0,95
RH-
HR 0·95 (95% CI 0·66–1·35)
Number at risk
Time after randomisation (months)
0 6 12 18 24 30 36 42 48 54 60

	Neratinib (n=1420)	Placebo (n=1420)
Any invasive disease-free survival event	116 (8%)	163 (11%)
Local or regional invasive recurrence	12 (1%)	35 (2%)
Invasive ipsilateral breast tumour recurrence	5 (<1%)	7 (1%)
Invasive contralateral breast cancer	4 (<1%)	11 (1%)
Distant recurrence*	91 (6%)	111 (8%)
Bone	31 (2%)	31 (2%)
Brain	15 (1%)	17 (1%)
Distant lymph node	11 (1%)	18 (1%)
Liver	24 (2%)	24 (2%)
Lung	14 (1%)	25 (2%)
Other	11 (1%)	6 (<1%)
Other abdominal viscera	0	2 (<1%)
Pleura	1 (<1%)	7 (1%)
Subcutaneous tissue	2 (<1%)	1 (<1%)
Unspecified	1 (<1%)	0
Death without previous recurrence	4 (<1%)	5 (<1%)

Data are n (%). *Event types are not mutually exclusive.

Table 3: Site of first invasive disease-free survival event in the intention-to-treat population



	Neratinib (n=1408)			Placebo (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	0
Abdominal						0
Headache						0
Upper abd						0
Rash						0
Decreased appetite						0
Muscle spasms	157 (11%)	1 (<1%)	0	44 (3%)	1 (<1%)	0
Dizziness	143 (10%)	3 (<1%)	0	125 (9%)	3 (<1%)	0
Arthralgia	84 (6%)	2 (<1%)	0	158 (11%)	4 (<1%)	0

Durée médiane: 5 jours (1-139)
Dans la majorité des cas < 30 jours
1.4% pts hospitalisés

FDA U.S. FOOD & DRUG ADMINISTRATION

"On July 17, 2017, the U.S. Food and Drug Administration approved neratinib (NERLYNX, Puma Biotechnology, Inc.) for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy."

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"On 22 February 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Nerlynx , intended for the treatment of breast cancer."

Chimiothérapie adjuvante: place du dose-dense

méta-analyse de l'EBCTCG

méthodologie

□ **Méta-analyse sur <u>données individuelles</u> à partir de 25 essais (34 122 pts) parmi 31 essais randomisés avec chimiothérapie adjuvante par anthracyclines et taxanes**

Objectifs: Récidive & Mortalité spécifique

1- Dose-dense (/ **2** semaines) *vs* standard (/ **3** semaines)

- → même CT, mêmes doses : **7 essais, N=10004**
- → quelques différences (CT ou doses) : **5 essais, N=5508**

2- Séquentiel (/ **3** semaines) *vs* concomitant (/ **3** semaines)

- → même CT : **5 essais, N=9644**
- → quelques différences dans CT : **1 essai, N=1384**

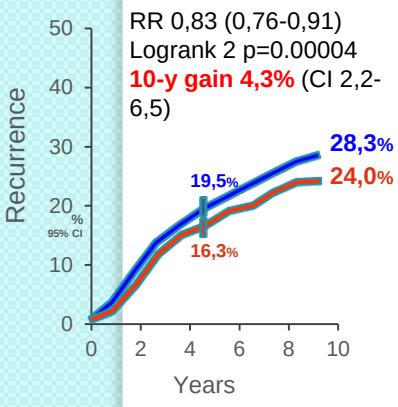
3- Séquentiel (/ **2** semaines) *vs* concomitant (/ **3** semaines)

- quelques différences dans CT : **6 essais, N=6532**

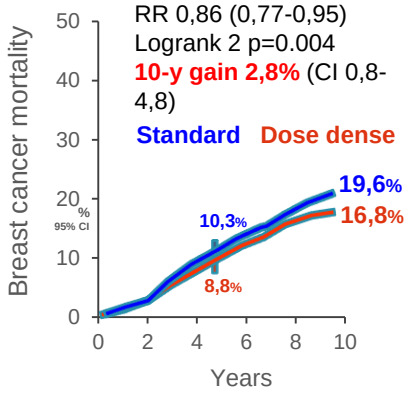
Méta-analyse EBCTCG - dose densité

CT/2 semaines (dose dense) *vs* CT/3 semaines (CT identiques) N = 10 004

Rechute

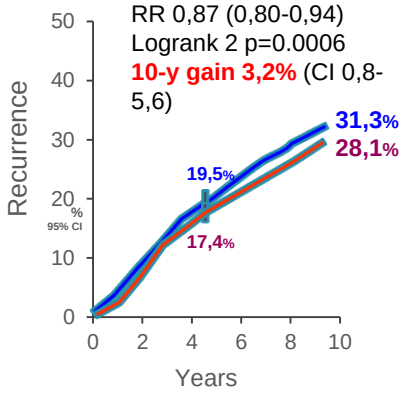


Mortalité spécifique

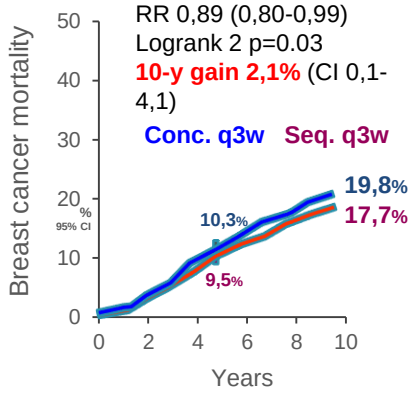


CT séquentielle (/3 semaines) *vs* CT concomitante (/3 semaines) N = 11 028

Rechute



Mortalité spécifique



réduction du risque de rechute et de décès/cancer du sein par réduction de l'intervalle entre les cycles ou par l'utilisation d'un schéma séquentiel

Gray R., et al., SABCS 2017, GS1-01

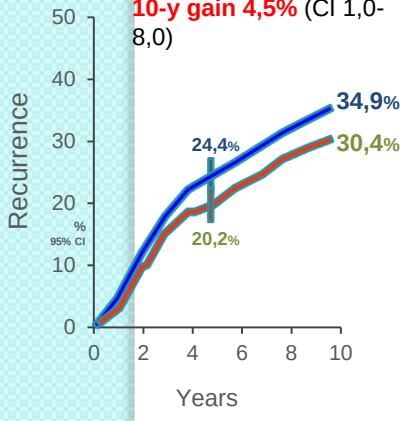
Méta-analyse EBCTCG - dose densité

CT séquentielle (/-2semaines) *vs* CT concomitante (/-3 semaines)

6532 women

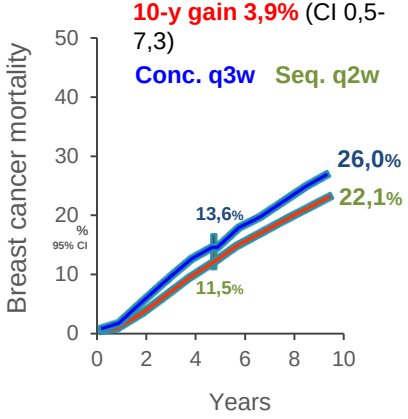
Rechute

RR 0,82 (0,74-0,91)
Logrank 2 p=0.0001
10-y gain 4,5% (CI 1,0-8,0)



Mortalité spécifique

RR 0,82 (0,73-0,93)
Logrank 2 p=0.001
10-y gain 3,9% (CI 0,5-7,3)

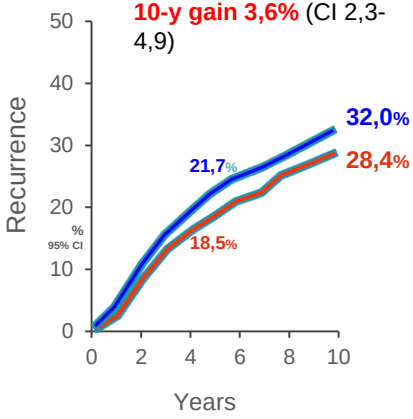


CT dose dense *vs* CT conventionnelle (analyse poolée des 25 essais)

34122 women

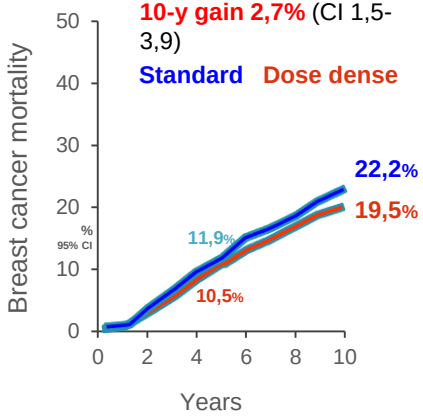
Rechute

RR 0,85 (0,81-0,89)
Logrank 2 p<0.00001
10-y gain 3,6% (CI 2,3-4,9)



Mortalité spécifique

RR 0,87 (0,82-0,92)
Logrank 2 p<0.00001
10-y gain 2,7% (CI 1,5-3,9)



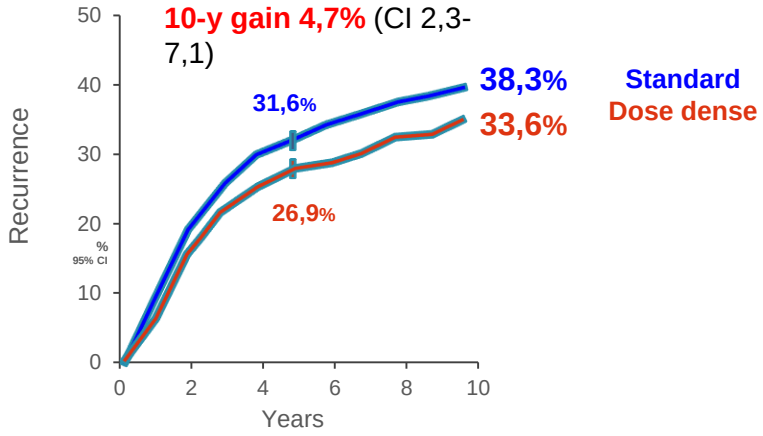
Gray R., et al., SABCS 2017, GS1-01

Méta-analyse EBCTCG - dose densité

CT dose dense *vs* CT conventionnelle (analyse poolée des 25 essais) selon statut ER

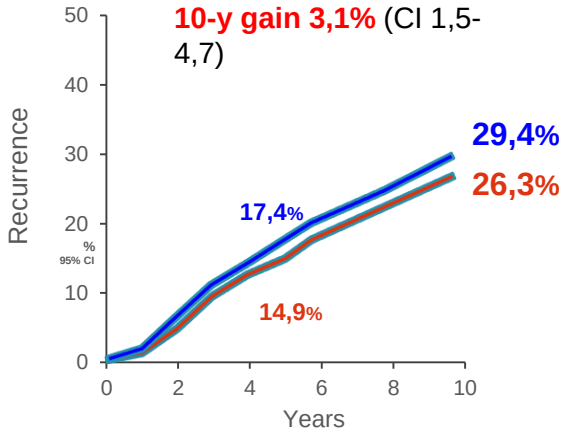
ER-Negative - **9209 women**

RR 0,82 (0,76-0,88)
Logrank 2 p<0.00001
10-y gain 4,7% (CI 2,3-7,1)



ER-Positive -**23495 women**

RR 0,86 (0,81-0,91)
Logrank 2 p<0.00001
10-y gain 3,1% (CI 1,5-4,7)



Gray R., et al., SABCS 2017, GS1-01

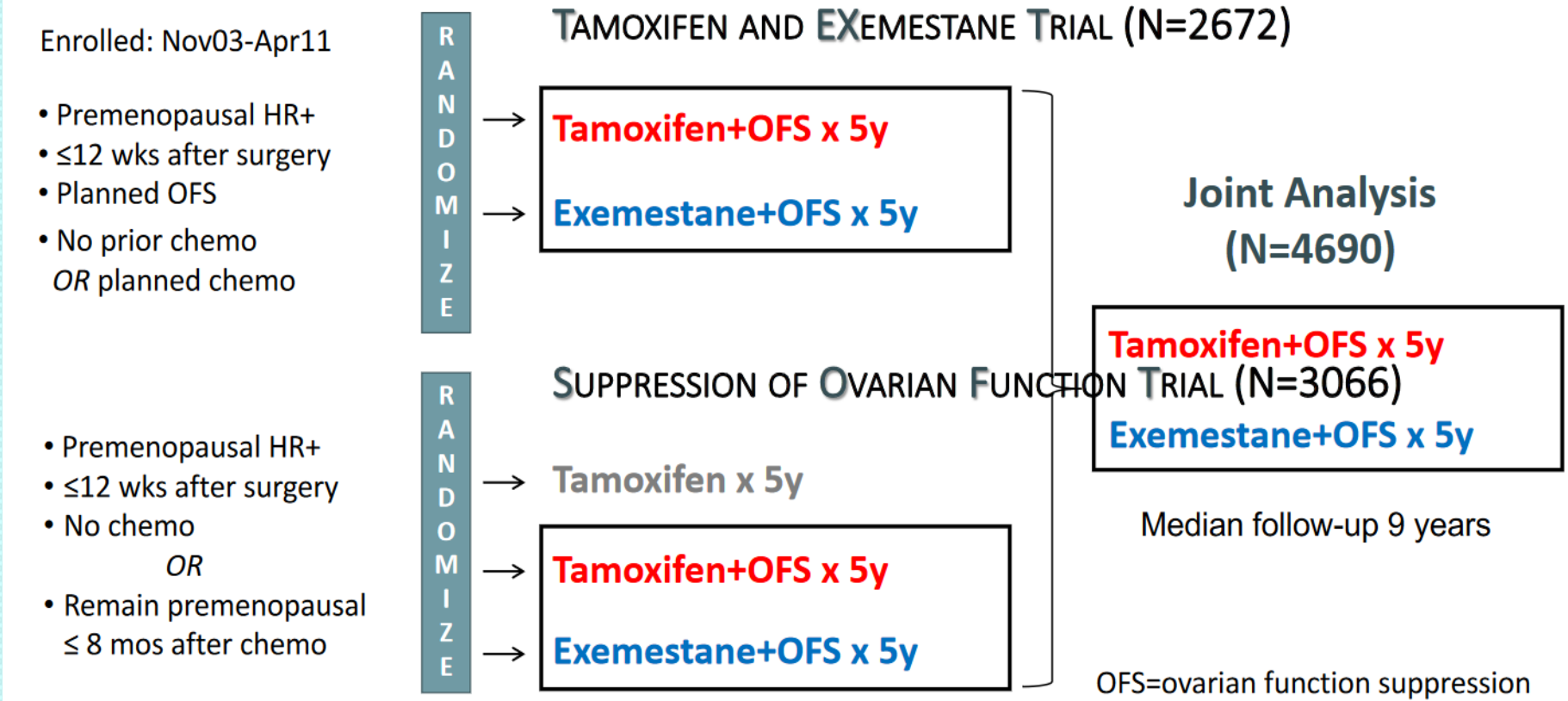
Questions subsidiaires …

- Toxicité ??? …
  - Précoce
  - Tardive (risque cardiaque, leucémies)

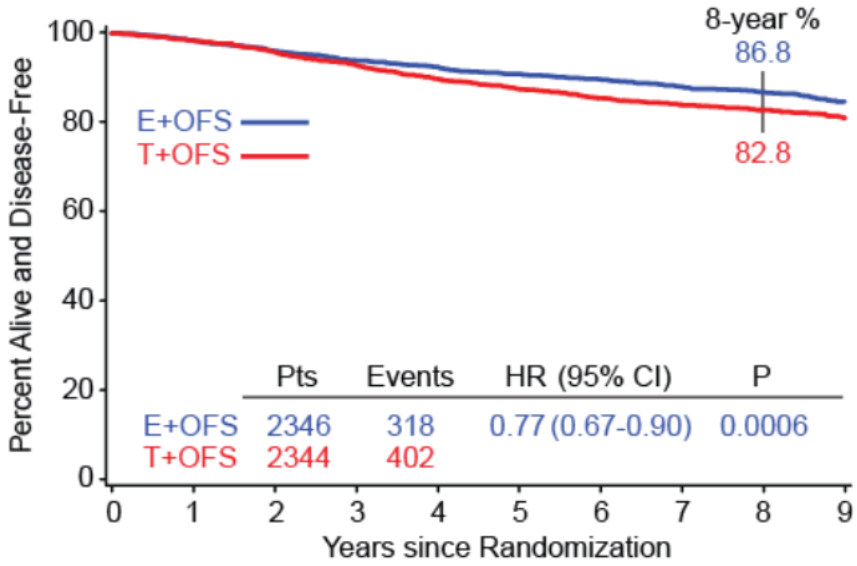
- Comment définir la population qui tirera le bénéfice optimal d'un schéma dose-dense ("high risk")?
  - N2 ?
  - RH neg / Triple négatif ?
  - Prolifération élevée
  - Femmes "jeunes" ?

SOFT & TEXT

Actualisation des résultats SABCS 2017 (> 8 ans FU)



Analyse combinée SOFT-TEXT: TAM + SO vs EXE +SO (5 ans)



Bénéfice absolu de 4% sur la DFS à 8 ans pour SO + Exemestane
Sans bénéfice sur la survie globale
Bénéfice absolu de 8% en DFS pour les femmes < 35 ans

SOFT: Suppression of Ovarian Function Trial Planned Update

Enrolled: Dec 2003-Jan 2011

Stratification

Receipt of (neo)adjuvant chemotherapy

-No chemo, enrolled within 12 weeks of surgery (47%)
-Prior chemo, premenopausal E2 level within 8 months (53%)

Nodal status

-Positive (34.5%)

OFS method intended

-Triptorelin (91%)

Median follow-up 8 years

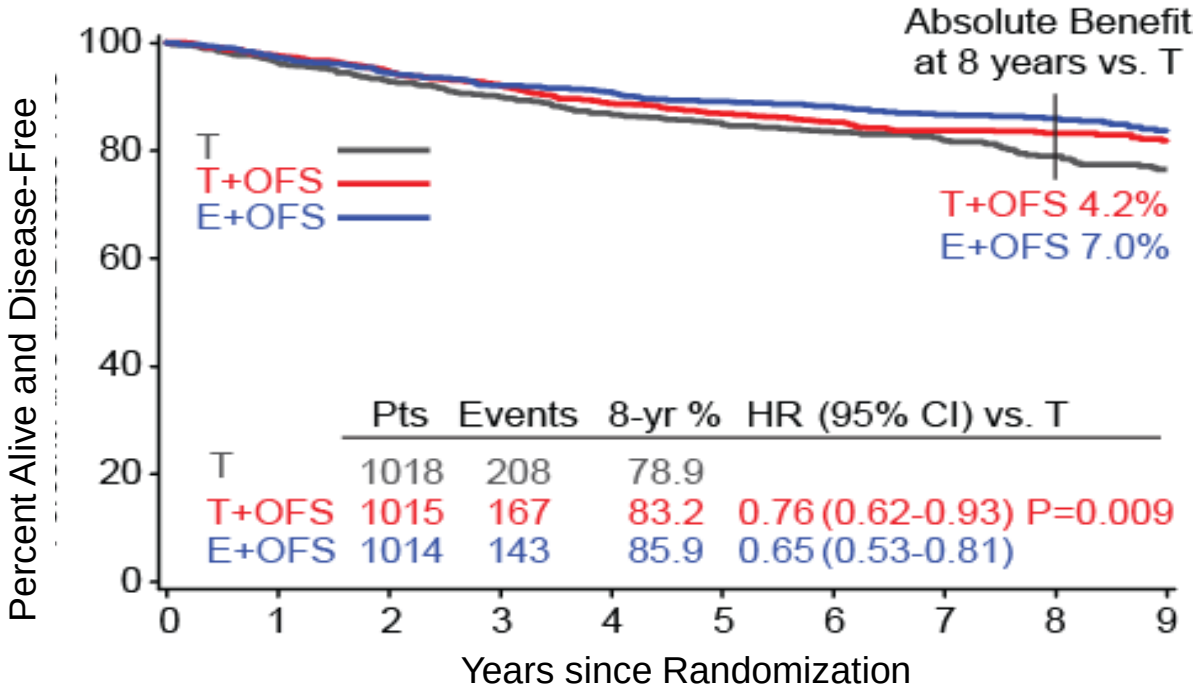
Tamoxifen x 5y (n=1018)

Tamoxifen+OFS x 5y (n=1015)

Exemestane+OFS x 5y (n=1014)

OFS=Ovarian Function Suppression

SOFT : survie sans maladie (8 ans)

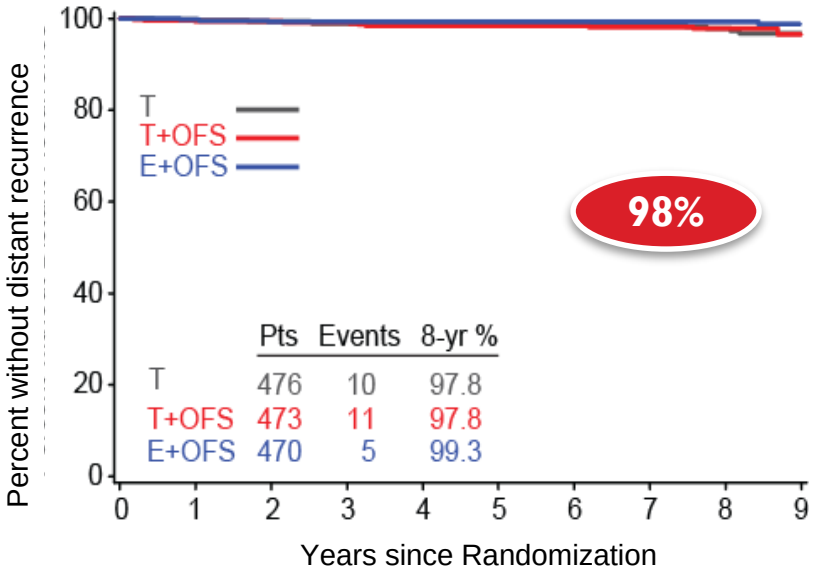


Amélioration significative de la suppression ovarienne sur la SSM

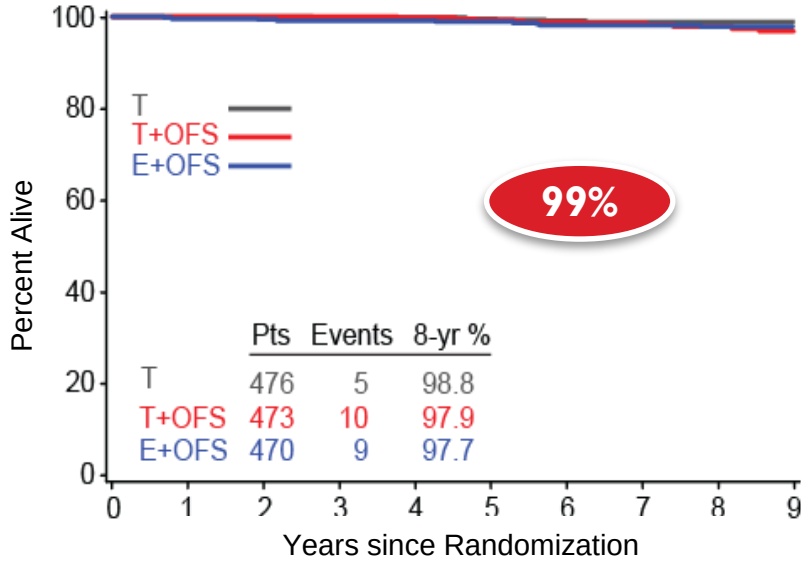
Fleming G. et al., SABCS 2017, GS4-03

SOFT: en l'absence de CT adjuvante

SSMéta



Survie globale

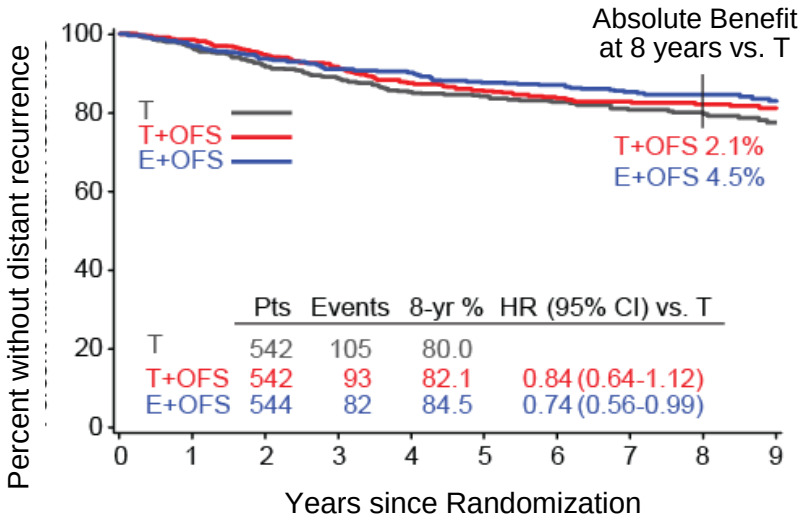


Population à très faible risque de rechute ….

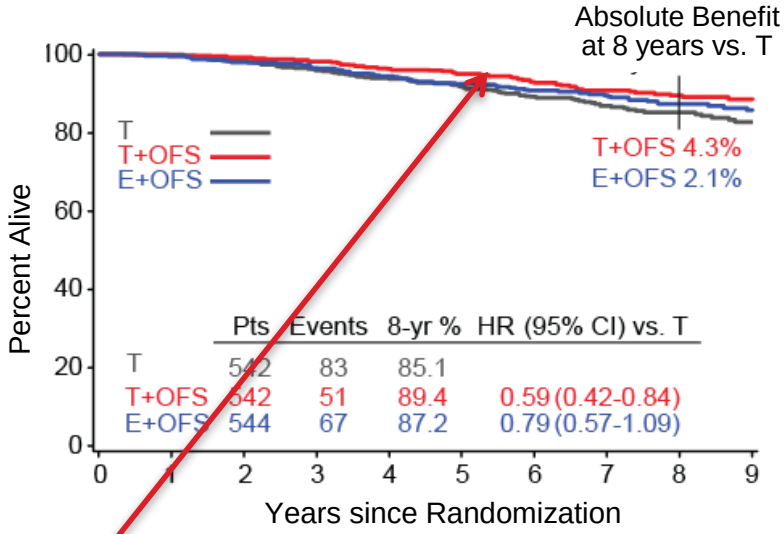
Fleming G. et al., SABCS 2017, GS4-03

SOFT: avec CT adjuvante

Distant Recurrence-Free Interval



Overall Survival



Amélioration significative de la survie globale dans le bras TAM + SO (89,4%)

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

2018 ASCO® ANNUAL MEETING

Abstract 503: absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with hormone receptor positive (HR+) HER2-negative breast cancer (BC): Results from TEXT and SOFT.

En conclusion

- Avantage à la suppression ovarienne associée à Tam (ou IA) vs Tam seul
- Impact plus important
  - après chimio adjuvante
  - avant 35 ans

- En (i)SSM, SO + EXE > SO + Tam

- mais supériorité de SO + Tam en survie globale

- Chez les femmes les plus jeunes, association plus “secure” en cas de défaut de suppression ovarienne

Back-up

APHINITY: Primary endpoint

Invasive Disease-Free Survival (IDFS)

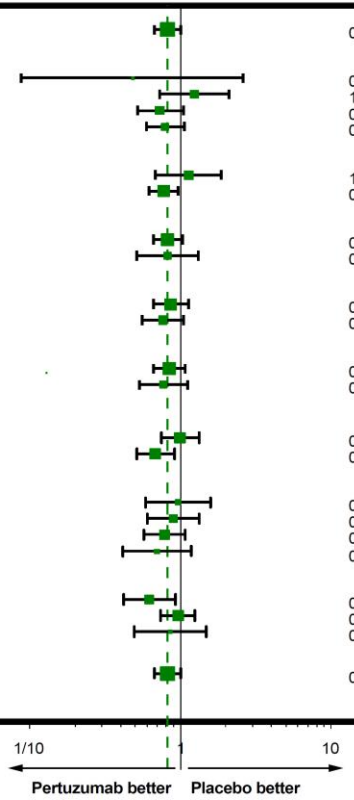
- **IDFS**: Time from randomisation until the date of the first occurrence of one of the following events:
  - Ipsilateral invasive breast tumour recurrence
  - Ipsilateral local-regional invasive breast cancer recurrence
  - Distant recurrence
  - Contralateral invasive breast cancer
  - Death attributable to any cause including breast cancer, non-breast cancer, or unknown cause

Excludes second primary NON breast cancer events

	PLANNED 3-year IDFS rate Placebo vs. Pertuzumab
HR=0.75*	89.2% vs. 91.8% (Δ=2.6%)

iDFS Forest Plot by Subgroup

Subgroup	Pertuzumab No. of Patients	Placebo No. of Patients	Pertuzumab No. of Events	Placebo No. of Events	Hazard Ratio (95% CI)	Pertuzumab 3-year IDFS Rate, %	Placebo 3-year IDFS Rate, %	Interaction test p-value
All patients	2400	2404	171	210	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status								
0 positive nodes, tumor ≤1cm	90	84	2	4	0.48 (0.09–2.60)	97.7	97.5	0.374
0 positive nodes, tumor >1cm	807	818	30	25	1.23 (0.72–2.10)	97.5	98.5	
1–3 positive nodes	907	900	55	75	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	596	602	84	106	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	897	902	32	29	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	1503	1502	139	181	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen								
Anthracycline	1865	1877	139	171	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	535	527	32	39	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status								
Positive (ER- and/or PgR-positive)	1536	1546	100	119	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	864	858	71	91	0.76 (0.56–1.04)	92.8	91.2	
Protocol version								
Protocol A	1828	1827	120	143	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	572	577	51	67	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening								
Pre-menopausal	1152	1173	93	96	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	1242	1220	78	113	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)								
<40	326	327	30	32	0.96 (0.59–1.59)	93.4	93.1	0.781
40–49	708	702	48	53	0.89 (0.60–1.32)	94.5	94.3	
50–64	1051	1082	69	91	0.78 (0.57–1.07)	94.3	93.3	
≥65	315	293	24	34	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)								
<2	977	944	41	64	0.62 (0.42–0.92)	97.0	94.6	0.203
2–<5	1273	1283	108	115	0.96 (0.74–1.24)	92.5	93.0	
≥5	147	174	22	31	0.85 (0.49–1.47)	87.5	87.5	
Sex								
Female	2397	2396	171	209	0.82 (0.67–1.01)	94.1	93.2	NA



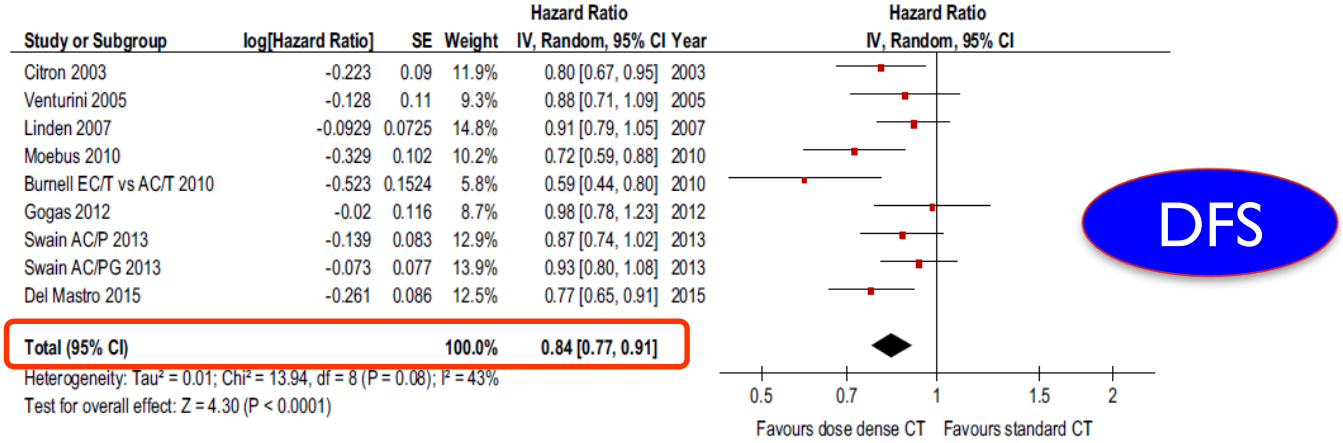
Breast Cancer Res Treat (2015) 151:251–259
DOI 10.1007/s10549-015-3405-4

REVIEW

Adjuvant dose-dense chemotherapy in breast cancer: a systematic review and meta-analysis of randomized trials

Fausto Petrelli[1] · Mary Cabiddu[1] · Andrea Coinu[1] · Karen Borgonovo[1] · Mara Ghilardi[1] · Veronica Lonati[1] · Sandro Barni[1]

. 8 essais retenus (8/0S et 7/DFS)
. N = 17 889
. 6/8 utilisaient anthracyclines + taxanes
. Majorité de patientes N+ (52 à 100%)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Citron 2003	-0.223	0.09	11.9%	0.80 [0.67, 0.95]	2003
Venturini 2005	-0.128	0.11	9.3%	0.88 [0.71, 1.09]	2005
Linden 2007	-0.0929	0.0725	14.8%	0.91 [0.79, 1.05]	2007
Moebus 2010	-0.329	0.102	10.2%	0.72 [0.59, 0.88]	2010
Burnell EC/T vs AC/T 2010	-0.523	0.1524	5.8%	0.59 [0.44, 0.80]	2010
Gogas 2012	-0.02	0.116	8.7%	0.98 [0.78, 1.23]	2012
Swain AC/P 2013	-0.139	0.083	12.9%	0.87 [0.74, 1.02]	2013
Swain AC/PG 2013	-0.073	0.077	13.9%	0.93 [0.80, 1.08]	2013
Del Mastro 2015	-0.261	0.086	12.5%	0.77 [0.65, 0.91]	2015
Total (95% CI)			**100.0%**	**0.84 [0.77, 0.91]**	

Heterogeneity: Tau² = 0.01; Chi² = 13.94, df = 8 (P = 0.08); I² = 43%
Test for overall effect: Z = 4.30 (P < 0.0001)

Hazard Ratio IV, Random, 95% CI

0.5 0.7 1 1.5 2
Favours dose dense CT Favours standard CT

DFS

OS

RE - → HR = 0,20 (p= 0.002)
RE +→ HR= 0,93 (p= 0,25)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Citron 2003	-0.163	0.114	12.5%	0.85 [0.68, 1.06]	2003
Venturini 2005	-0.1257	0.1345	9.0%	0.88 [0.68, 1.15]	2005
Linden 2007	-0.1021	0.0887	20.7%	0.90 [0.76, 1.07]	2007
Moebus 2010	-0.274	0.129	9.8%	0.76 [0.59, 0.98]	2010
Gogas 2012	-0.114	0.142	8.1%	0.89 [0.68, 1.18]	2012
Swain AC/PG 2013	-0.151	0.105	14.8%	0.86 [0.70, 1.06]	2013
Swain AC/P 2013	0.01	0.106	14.5%	1.01 [0.82, 1.24]	2013
Del Mastro 2015	-0.431	0.124	10.6%	0.65 [0.51, 0.83]	2015
Total (95% CI)			**100.0%**	**0.86 [0.79, 0.93]**	

Heterogeneity: Chi² = 8.72, df = 7 (P = 0.27); I² = 20%
Test for overall effect: Z = 3.85 (P = 0.0001)

Hazard Ratio IV, Fixed, 95% CI

0.5 0.7 1 1.5 2
Favours dose dense CT Favours standard CT

VOLUME 34 · NUMBER 20 · JULY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2) –Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline

Neelima Denduluri, Mark R. Somerfield, Andrea Eisen, Jamie N. Holloway, Arti Hurria, Tari A. King, Gary H. Lyman, Ann H. Partridge, Melinda L. Telli, Maureen E. Trudeau, and Antonio C. Wolff

Acceptable adjuvant chemotherapy regimens for patients with higher-risk early breast cancer (CCO recommendation 13)

- Dose-dense doxorubicin-cyclophosphamide → paclitaxel (once every 2 weeks)
- Dose-dense epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 weeks 4 cycles → paclitaxel 175 mg/m^2 every 2 weeks for 4 cycles

Summary SOFT and TEXT SABCS17 updates

- Adjuvant E+OFS, compared with T+OFS, shows a sustained absolute improvement in DFS (4%) and reduction in distant recurrence (2.1%) with longer median follow-up of 9 years; greatest benefit very young women
- No difference in TEXT/SOFT combined overall survival (93%) after 9 years
- Addition of OFS to tamoxifen now significantly improves DFS at 8 years median follow-up vs tamoxifen alone (overall, prior chemo cohort)
  - 8.7% absolute DFS benefit < age 35, therefore consider OFS
  - DFS improved vs tam if exemestane used with OFS
  - Beware of incomplete OFS with GnRH; best to use tamoxifen, if in doubt
- Lower clinical risk (no chemo) 98% 8 year DRFI and 99% OS tam alone
- Follow-up continues for both trials - will need beyond 20 years