Acquis et limites en oncologie médicale en situation non métastatique

Les thérapies anti-HER2

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Centre Paul Strauss
Strasbourg

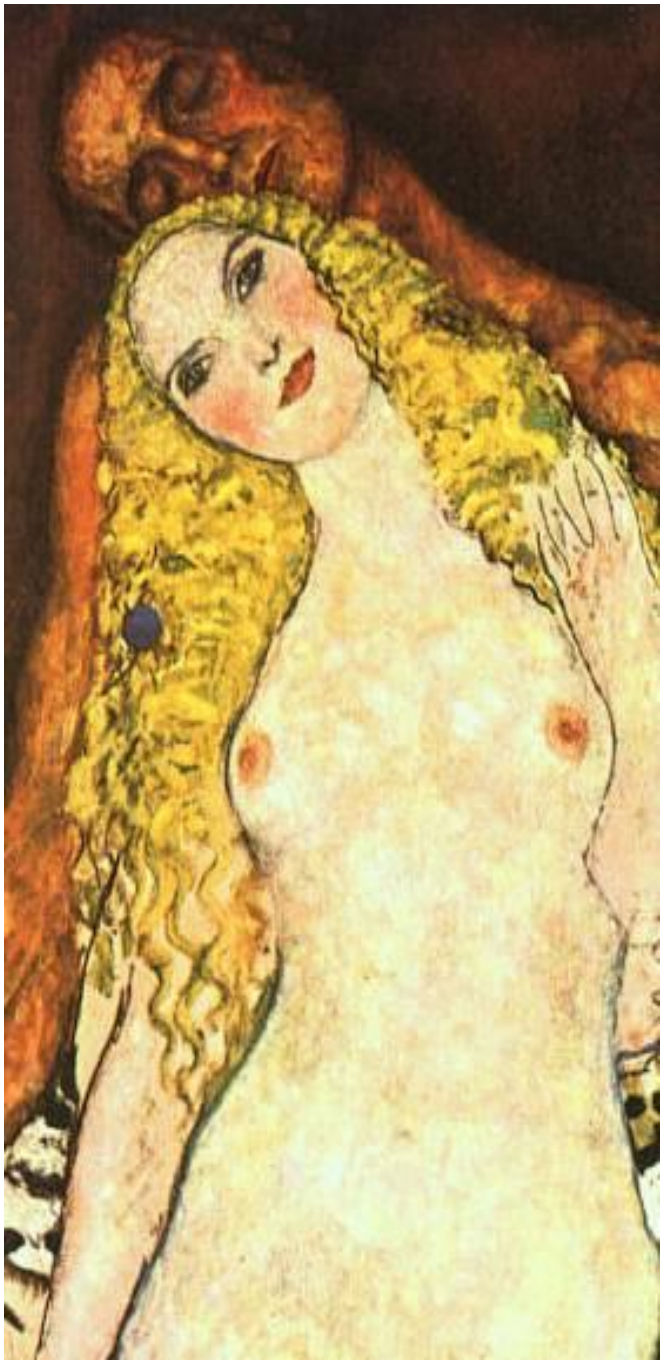
Conflits d'intérêt
en rapport avec cette présentation

– ***Le Laboratoire ROCHE***

Questions et réponses

- *Le traitement de référence est CT + trastuzumab 12 mois*
- *Le bénéfice du trastuzumab dépend-il des RH ?*
- *Peut-on aussi traiter les tumeurs pT1 N0 ?*
- *Peut-on raccourcir la durée du trastuzumab ?*
- *Doit-on prolonger la durée du trastuzumab ?*
- *Doit-on prescrire le trastuzumab concomitamment à la CT, à la RT ?*
- *Peut-on prescrire le trastuzumab sans CT ?*
- *Peut-on administrer le trastuzumab différemment ?*
- *Peut-on remplacer le trastuzumab ?*
- *Faut-il associer le trastuzumab avec une autre thérapie anti-HER2 ?*

Le traitement de référence est CT + Trastuzumab pendant 12 mois



AMM du trastuzumab en phase adjuvante

Herceptin est indiqué dans le traitement du cancer du sein précoce HER2 positif : après chirurgie, chimiothérapie et radiothérapie (si indiquée) :

⟶ après une chimiothérapie adjuvante avec la doxorubicine et le cyclophosphamide, en association avec le paclitaxel ou le docétaxel.

⟶ en association à une chimiothérapie adjuvante associant le docétaxel et le carboplatine.

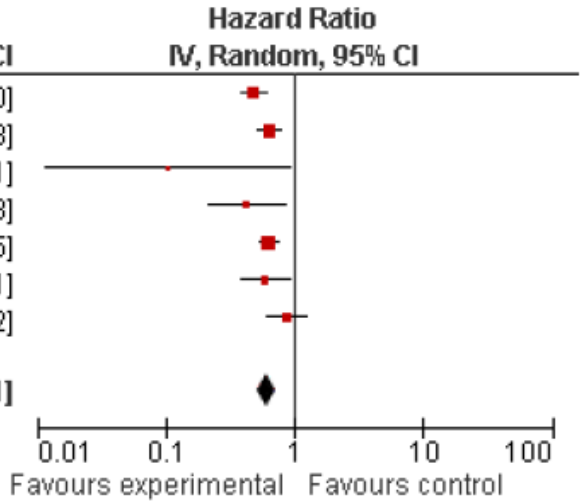
⟶ en association à une chimiothérapie néoadjuvante, suivie d'un traitement adjuvant avec Herceptin, chez les patients ayant une maladie localement avancée (y compris inflammatoire) ou des tumeurs mesurant plus de 2 cm de diamètre.

Méta-analyse des essais adjuvants avec trastuzumab

Figure 7. Disease-free survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.73	0.11	1672	1679	21.8%	0.48 [0.39, 0.60]
BCIRG006	-0.45	0.1	1074	1073	23.2%	0.64 [0.52, 0.78]
Buzdar	-2.27	1.11	23	19	0.6%	0.10 [0.01, 0.91]
FinHer	-0.87	0.35	115	116	5.2%	0.42 [0.21, 0.83]
HERA	-0.46	0.09	1703	1698	24.7%	0.63 [0.53, 0.75]
NOAH	-0.53	0.22	117	118	10.7%	0.59 [0.38, 0.91]
PACS-04	-0.15	0.18	260	268	13.8%	0.86 [0.60, 1.22]
Total (95% CI)			**4964**	**4971**	**100.0%**	**0.60 [0.50, 0.71]**

Heterogeneity: Tau² = 0.02; Chi² = 12.25, df = 6 (P = 0.06); I² = 51%
Test for overall effect: Z = 5.89 (P < 0.00001)



(1) B31+N9831

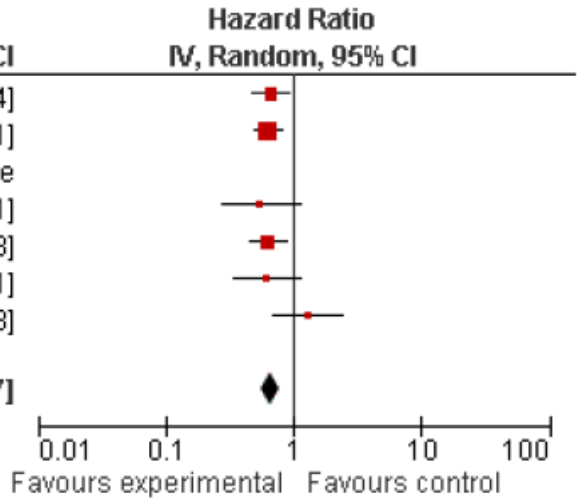
The Cochrane Library 2012, Issue 4

Méta-analyse des essais adjuvants avec trastuzumab

Figure 4. Overall survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.4	0.17	1672	1679	22.0%	0.67 [0.48, 0.94]
BCIRG006	-0.46	0.13	1074	1073	37.7%	0.63 [0.49, 0.81]
Buzdar	0	0	23	19		Not estimable
FinHer	-0.6	0.36	115	116	4.9%	0.55 [0.27, 1.11]
HERA	-0.46	0.17	1703	1698	22.0%	0.63 [0.45, 0.88]
NOAH	-0.48	0.3	117	118	7.1%	0.62 [0.34, 1.11]
PACS-04	0.24	0.32	260	268	6.2%	1.27 [0.68, 2.38]
Total (95% CI)			**4964**	**4971**	**100.0%**	**0.66 [0.57, 0.77]**

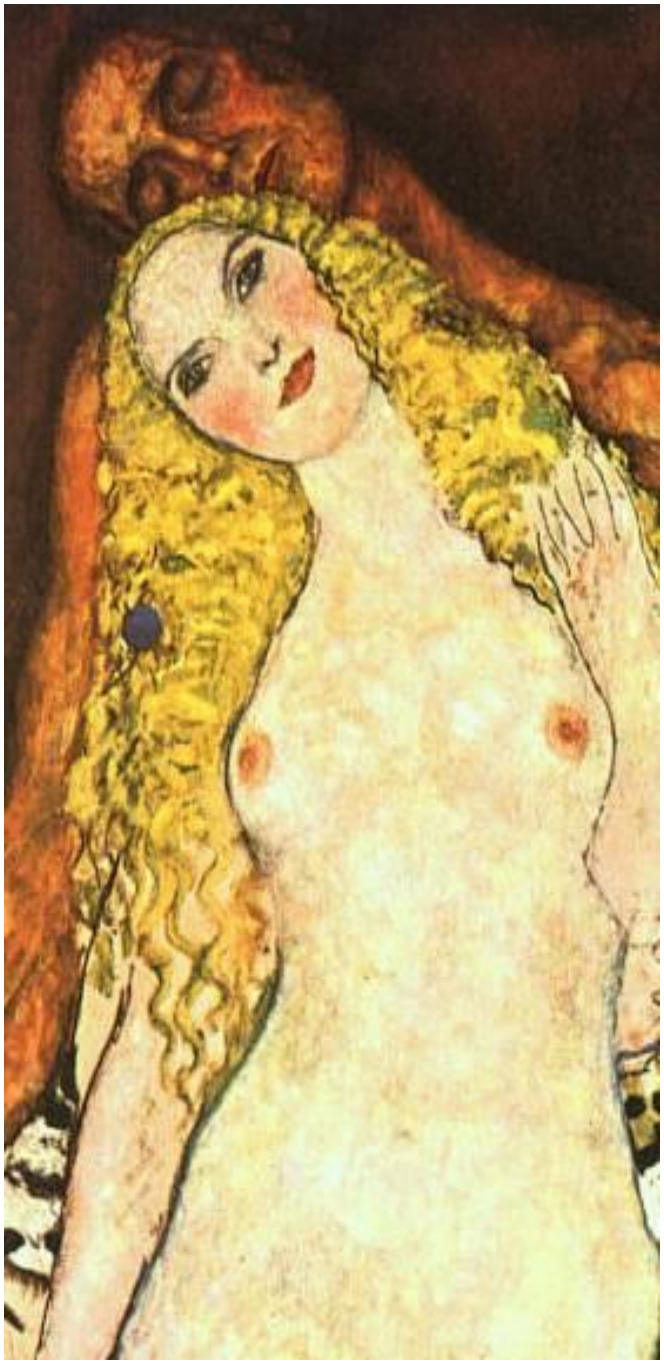
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)



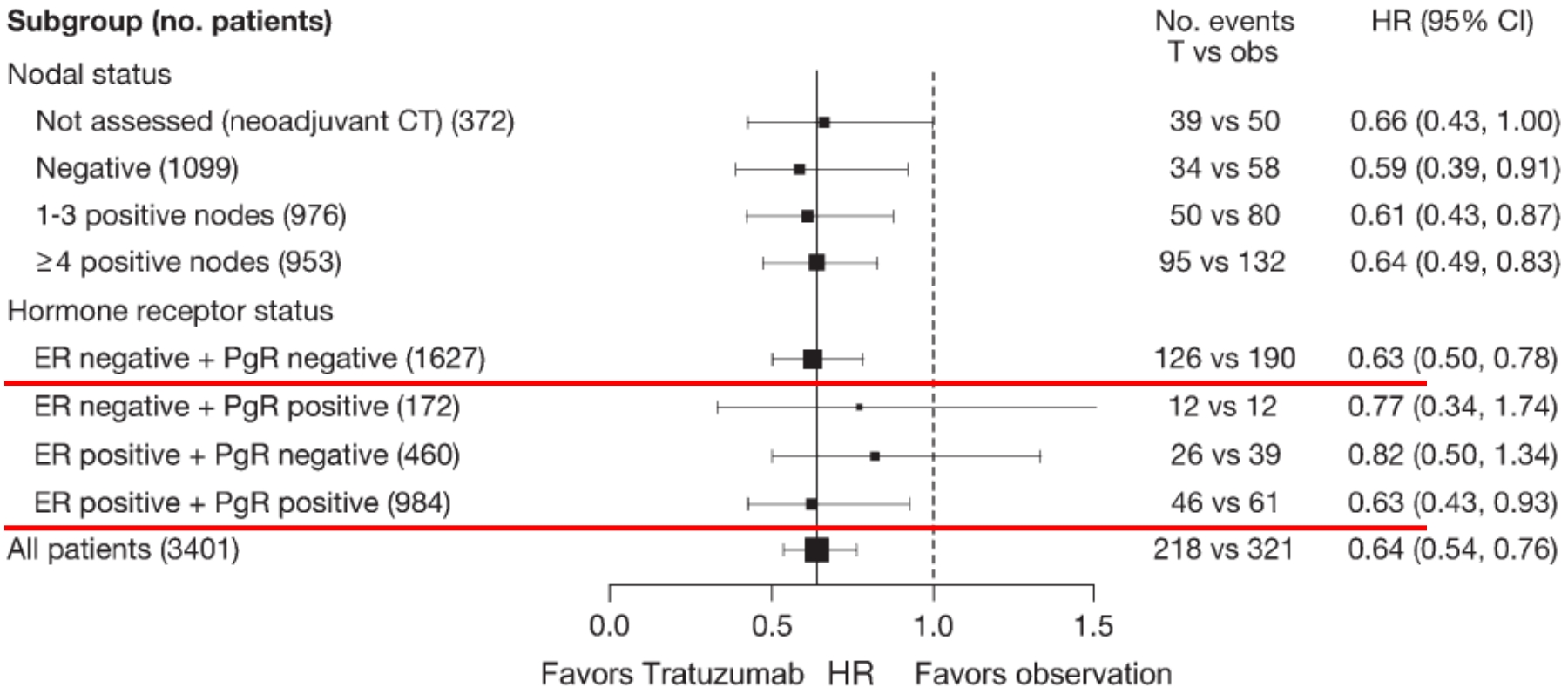
(1) B31+N9831

The Cochrane Library 2012, Issue 4

Le bénéfice du trastuzumab dépend-il des RH ?



Etude HERA
DFS à 3 ans selon les sous-groupes

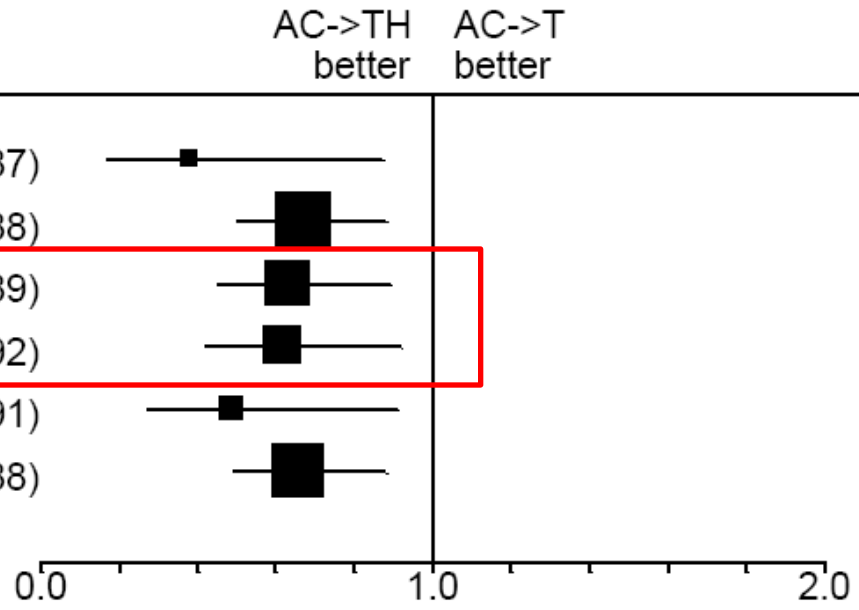


T, trastuzumab; obs, observation; HR, hazard ratio

Untch M . Ann Onc 2008

Etude BCIRG 006 AC→T versus AC→TH
OS à 5 ans selon les sous-groupes

Subgroup	AC->T O/N	AC->TH O/N	HR (CI)
Nodes -	22 / 309	8 / 310	0.38(0.17,0.87)
Nodes +	119 / 764	86 / 764	0.67(0.50,0.88)
HR -	81 / 500	54 / 500	0.63(0.45,0.89)
HR +	60 / 573	40 / 574	0.62(0.42,0.92)
Tsize<2cm	31 / 361	16 / 329	0.49(0.27,0.91)
Tsize>=2cm	110 / 712	78 / 745	0.66(0.49,0.88)

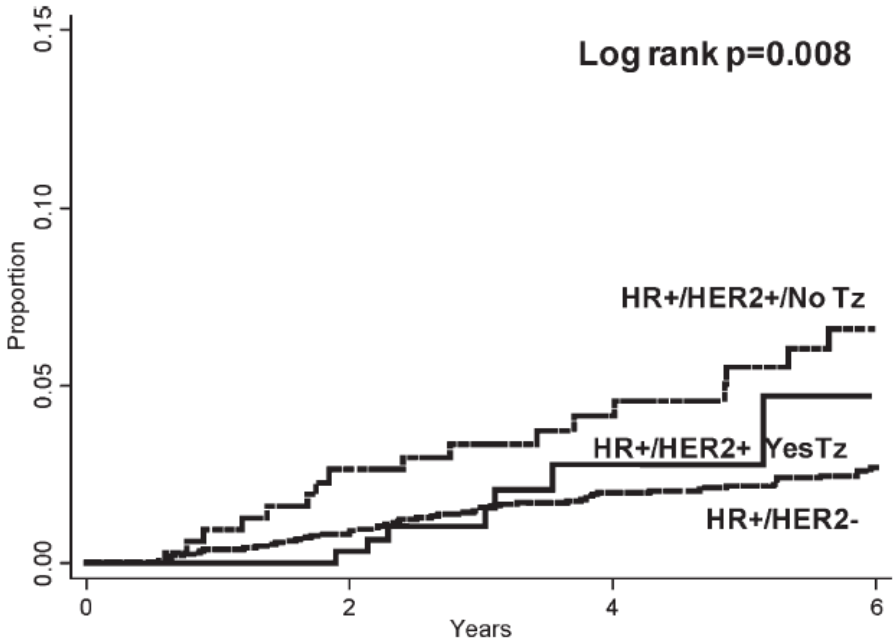


Slamon D. NEJM 2011

Taux de rechute locale selon RH, HER2, trastuzumab

322 pts RH+ HER2+ sans trastu
314 pts RH+ HER2+ avec Trastu

257 pts RH- HER2+ sans trastu
292 pts RH- HER2+ avec trastu



Kim MM . Cancer 2012

Doit-on traiter les tumeurs pT1ab N0 ?

Bénéfice du trastuzumab selon le T et le N dans l'étude HERA

	Patients, n		Outcome (3-year DFS)		
	Trastuzumab	Observation	Trastuzumab	Observation	HR (95% CI)
Overall	1703	1698	80·6%	74·3%	0·64 (0·54–0·76)
Node negative*	544	555	90·8%	84·9%	0·59 (0·39–0·91)
Node negative (1·1–2·0 cm)	252	258	91·3%	86·7%	0·53 (0·26–1·07)

Follow-up 23·5 months. DFS=disease-free survival. HR=hazard ratio. *Node-negative group of 1099 patients includes 60 with tumours <1 cm, 33 with tumour s 1·0 cm, 510 with tumours 1·1–2·0 cm, 484 with tumours >2·1 cm, and 12 with tumours of unknown size.

Banerjee S, lancet 2010

Etude BCIRG 006 AC→T versus AC→TH
OS à 5 ans selon les sous-groupes

Subgroup	AC->T O/N	AC->TH O/N	HR (CI)
Nodes -	22 / 309	8 / 310	0.38(0.17,0.87)
Nodes +	119 / 764	86 / 764	0.67(0.50,0.88)
HR -	81 / 500	54 / 500	0.63(0.45,0.89)
HR +	60 / 573	40 / 574	0.62(0.42,0.92)
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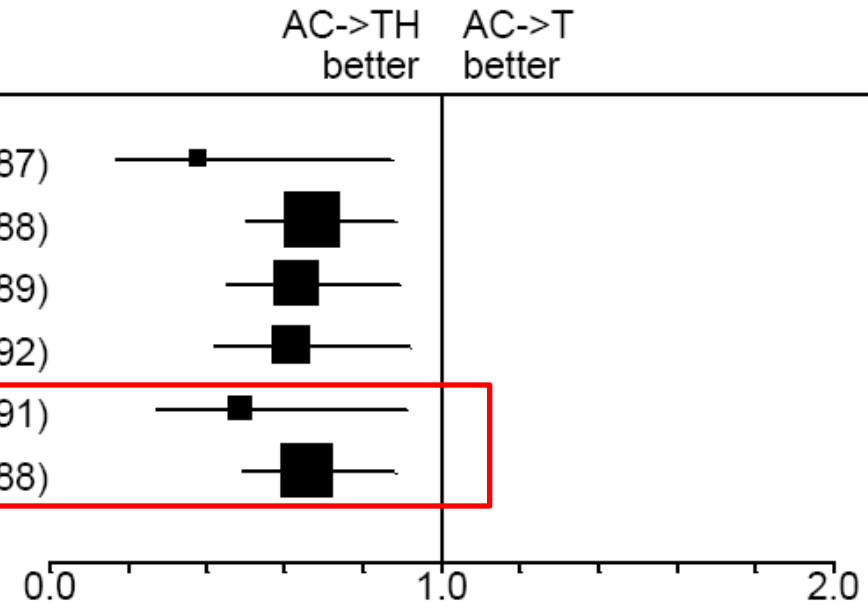
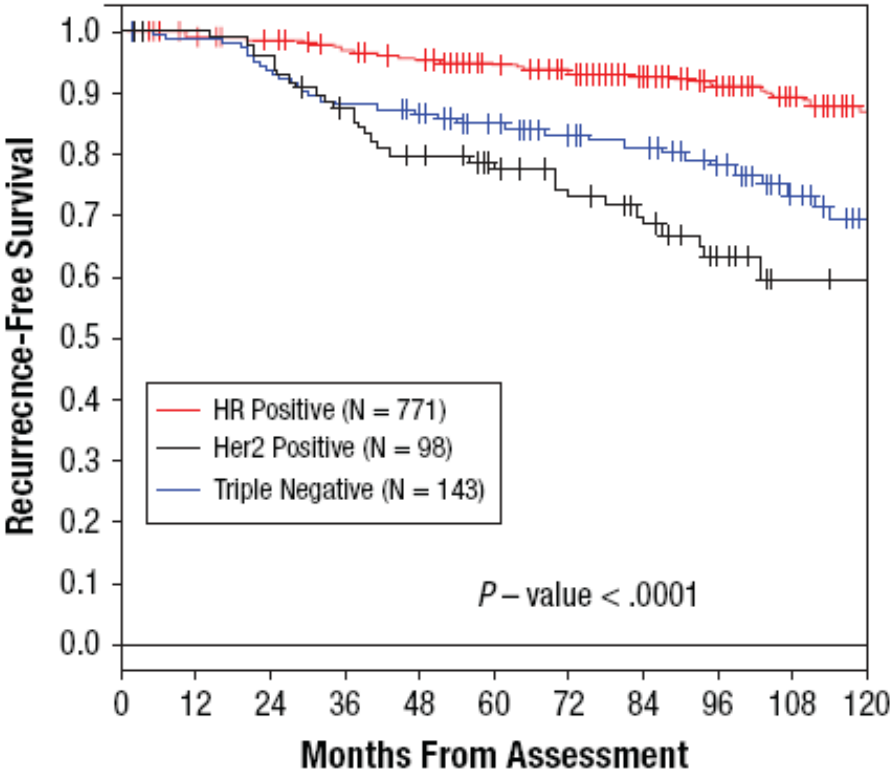
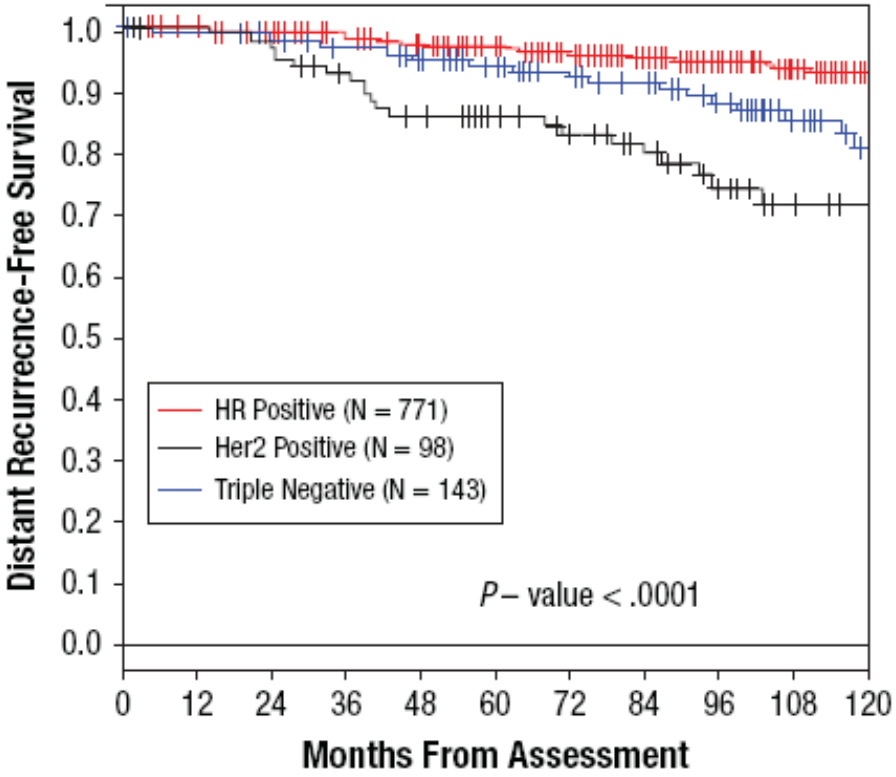


Slamon D. NEJM 2011

Evolution des pT1ab N0 sans CT et trastuzumab adjuvant

1012 patientes traitées entre 1990 et 2002





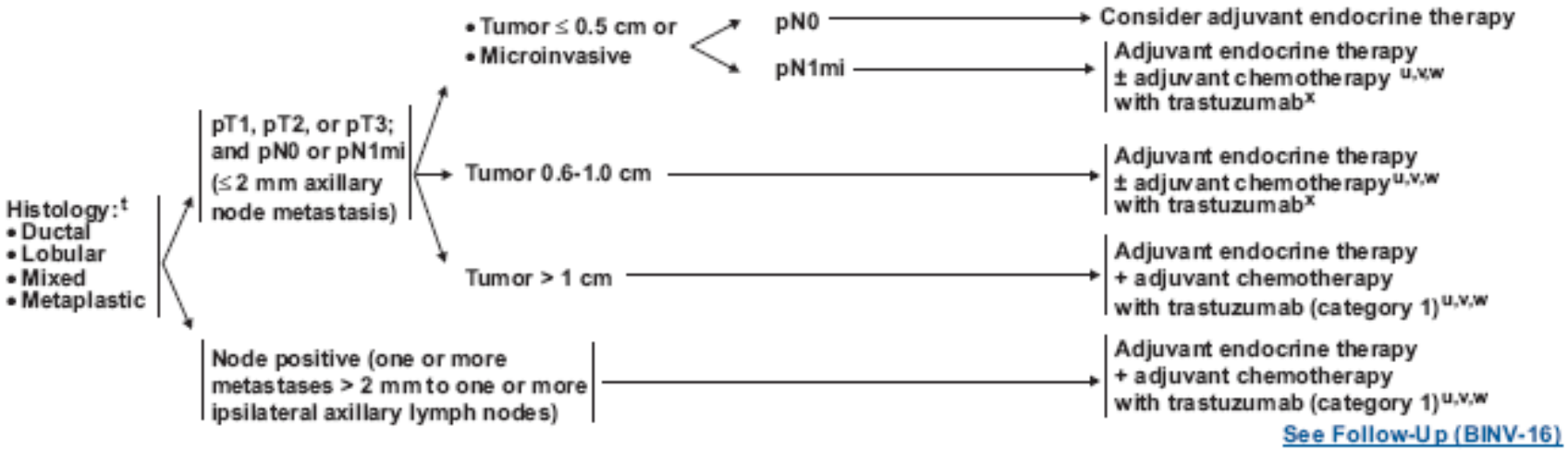
Theriault RL, Cl Breast Cancer, 2011

Les recommandations de l'INCA

- L'association de chimiothérapie et trastuzumab dans les tumeurs pT1ab N0 n'est pas contre indiquée mais, à elle seule, la surexpression de HER2 ne peut pas la justifier.

- Son indication doit tenir compte des autres facteurs pronostiques utilisés pour prescrire une chimiothérapie.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE[b]



See Follow-Up (BINV-16)

See Adjuvant Endocrine Therapy (BINV-J) and Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).

[t] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[u] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[v] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in those with a favorable prognosis where the incremental benefit of chemotherapy may be smaller. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[w] There are limited data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

[x] The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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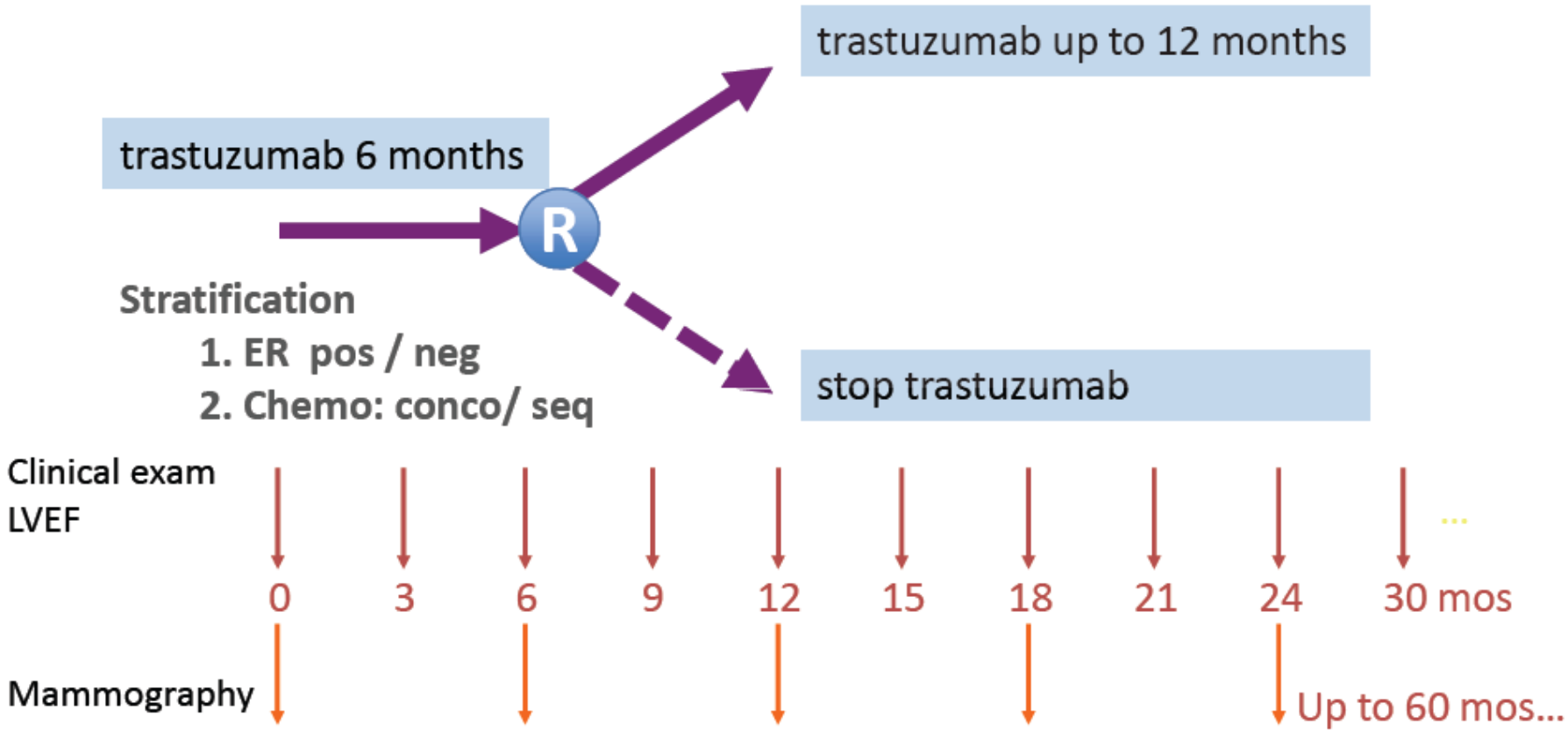
Peut-on raccourcir la durée du trastuzumab ?

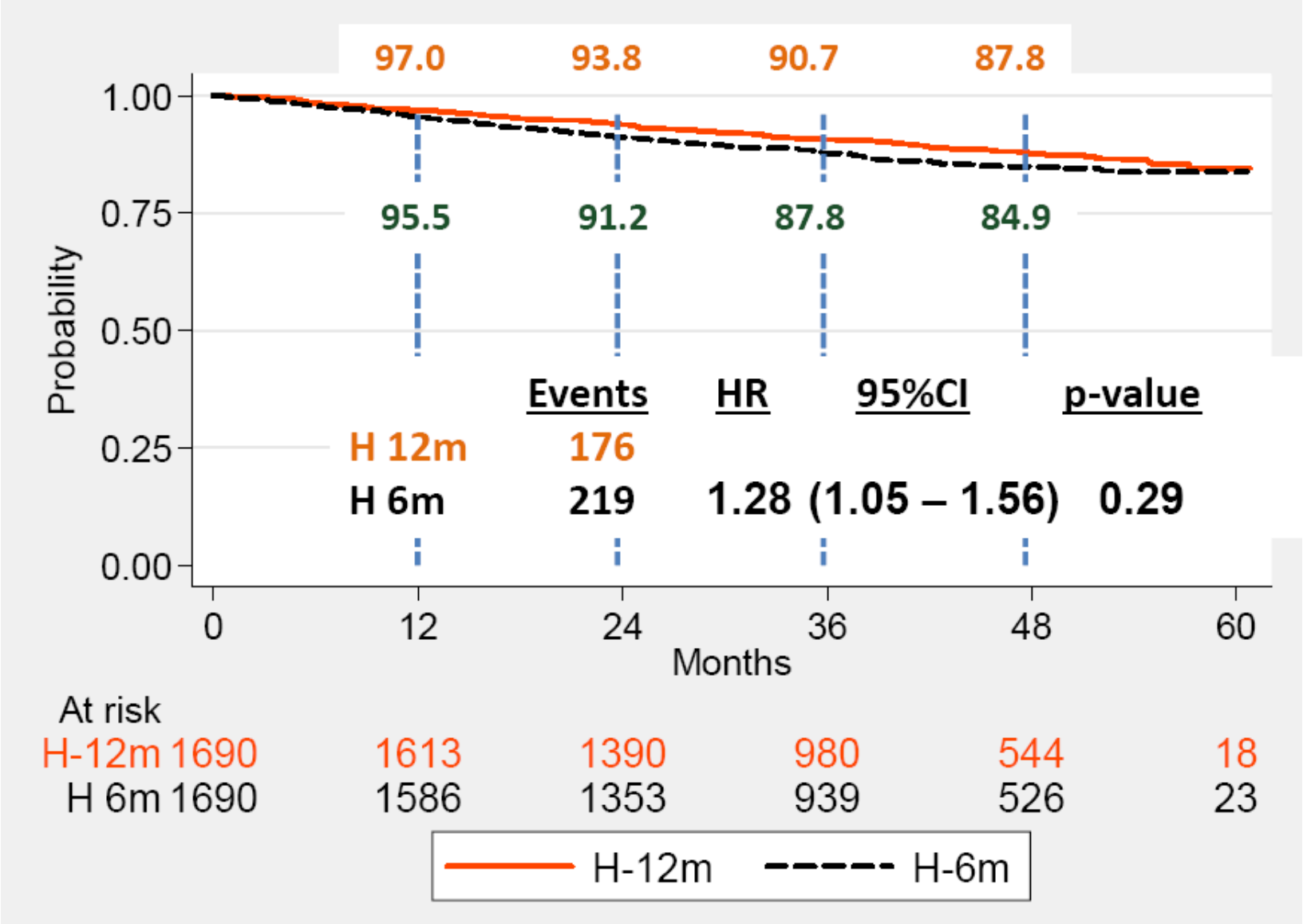
Etude PHARE

Study design

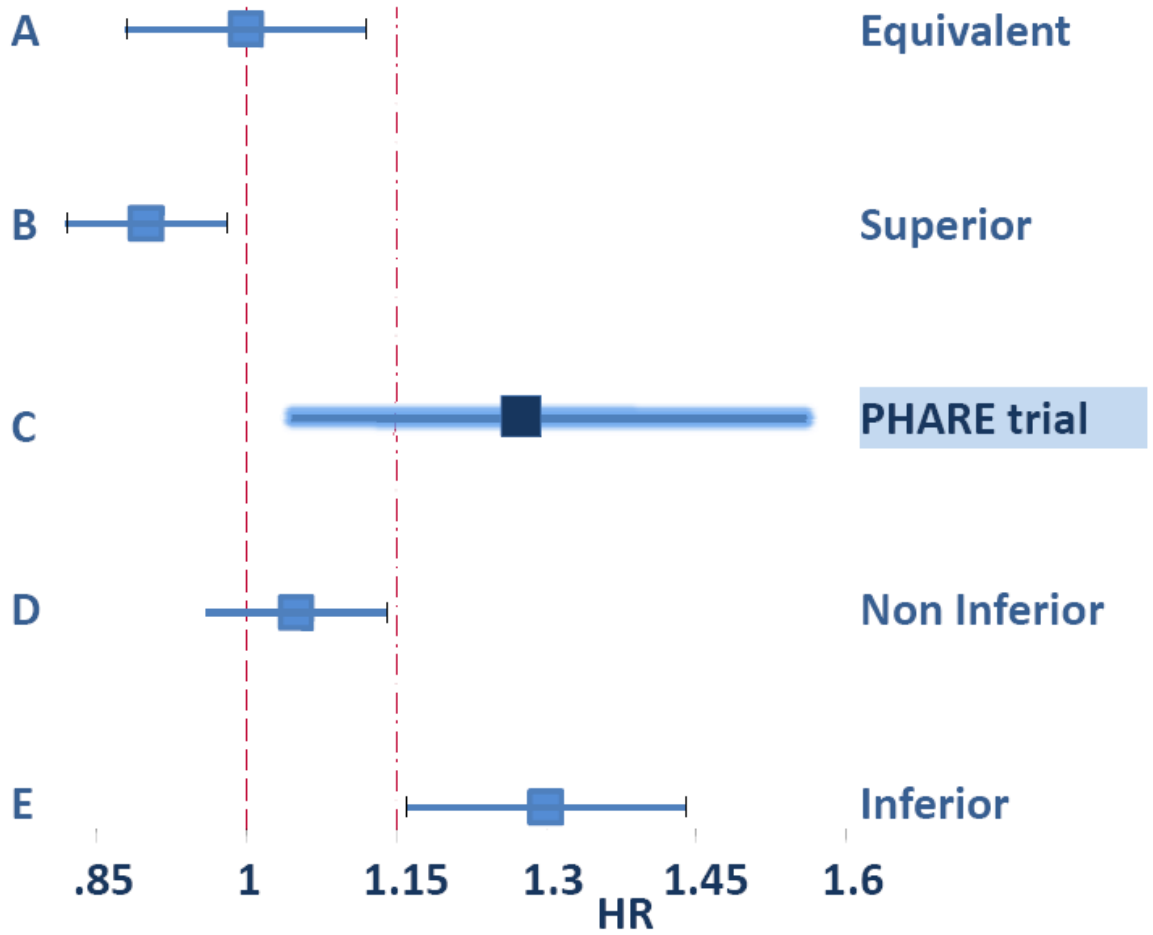


Etude PHARE – DFS

Suivi médian = 42,5 mois



Etude PHARE – DFS
Suivi médian = 42,5 mois

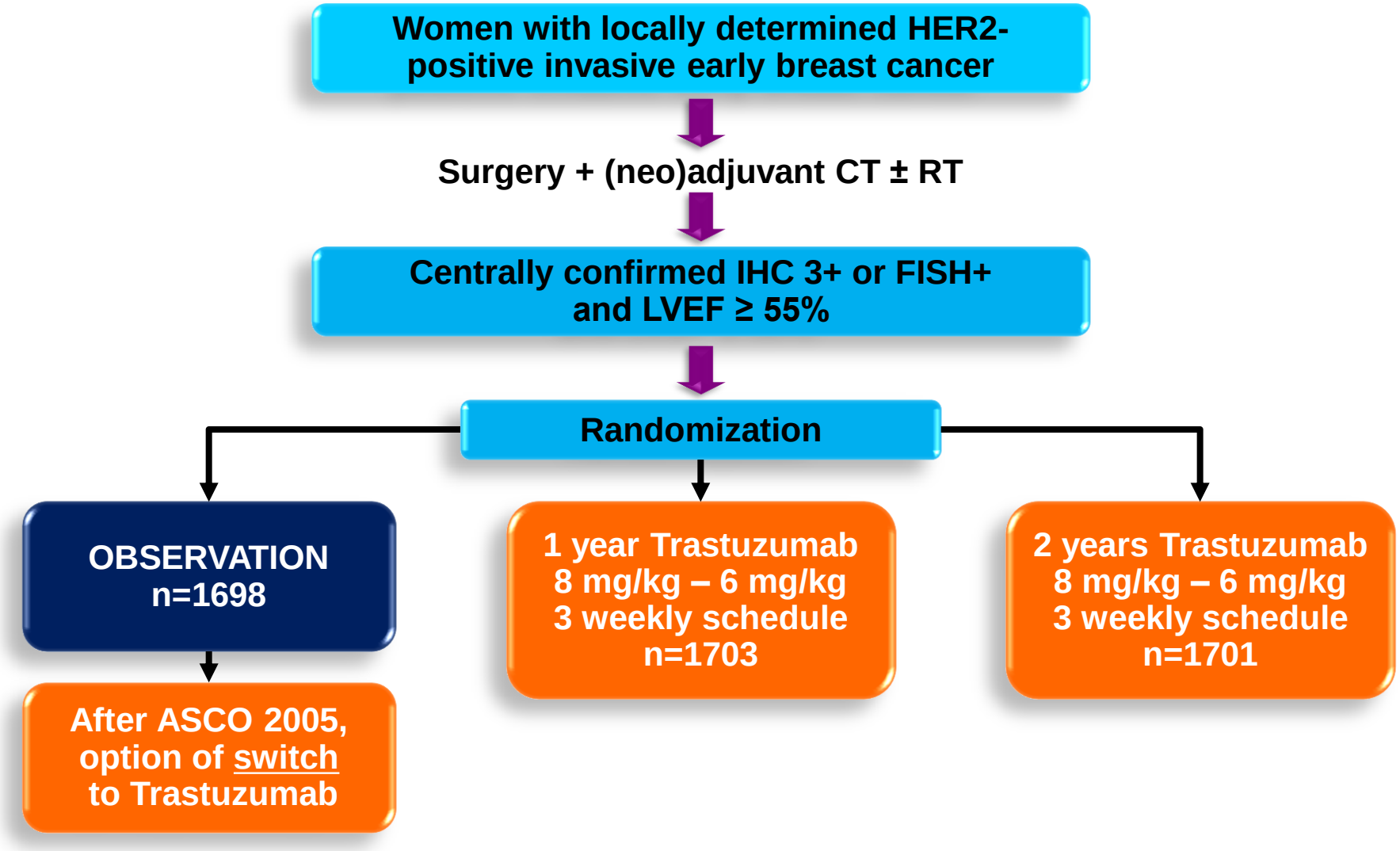


"After careful thought and lengthy debate we recommend that entry to the trial be suspended. We do not recommend, at this time, a crossover to a longer duration of intervention for the 6 month group but would reserve the option of such a recommendation for the future, dependent on how the data develop"

Peut-on prolonger la durée du trastuzumab ?

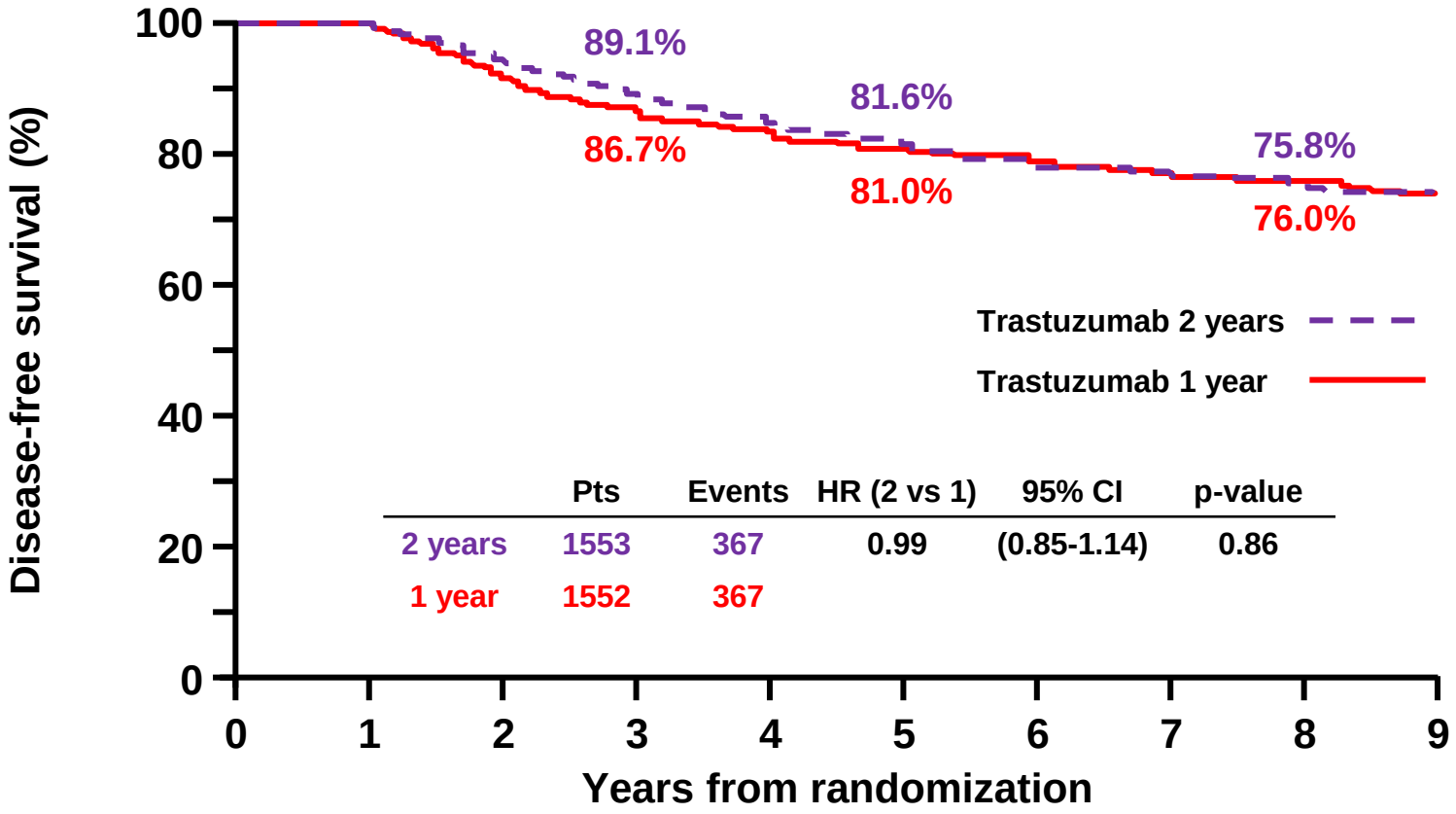
HERA TRIAL DESIGN

Accrual 2001 – 2005 (n=5102)



CT, chemotherapy; RT, radiotherapy

DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU

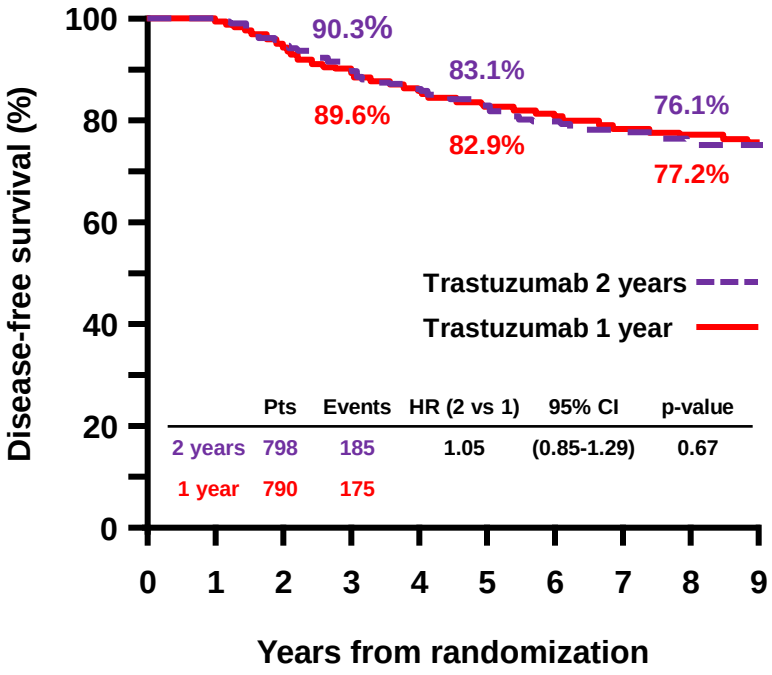


	Pts	Events	HR (2 vs 1)	95% CI	p-value
2 years	1553	367	0.99	(0.85-1.14)	0.86
1 year	1552	367			

No. at risk										
Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

DFS BY HORMONE RECEPTOR STATUS AT 8 YRS MFU

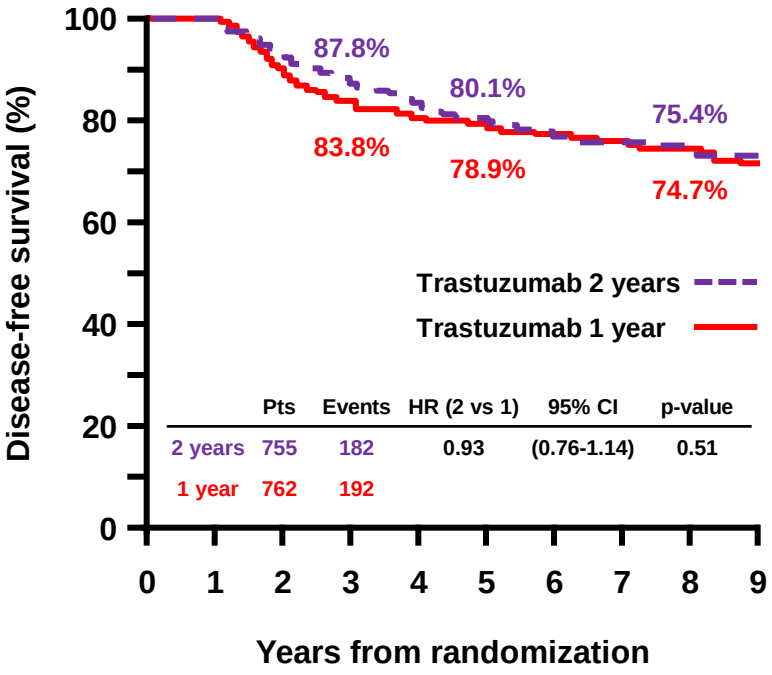
Hormone receptor positive
92.6% received endocrine therapy



No. at risk

Trastuzumab 2 years	798	798	747	710	673	642	597	544	321	97
Trastuzumab 1 year	790	790	736	691	663	634	617	559	337	106

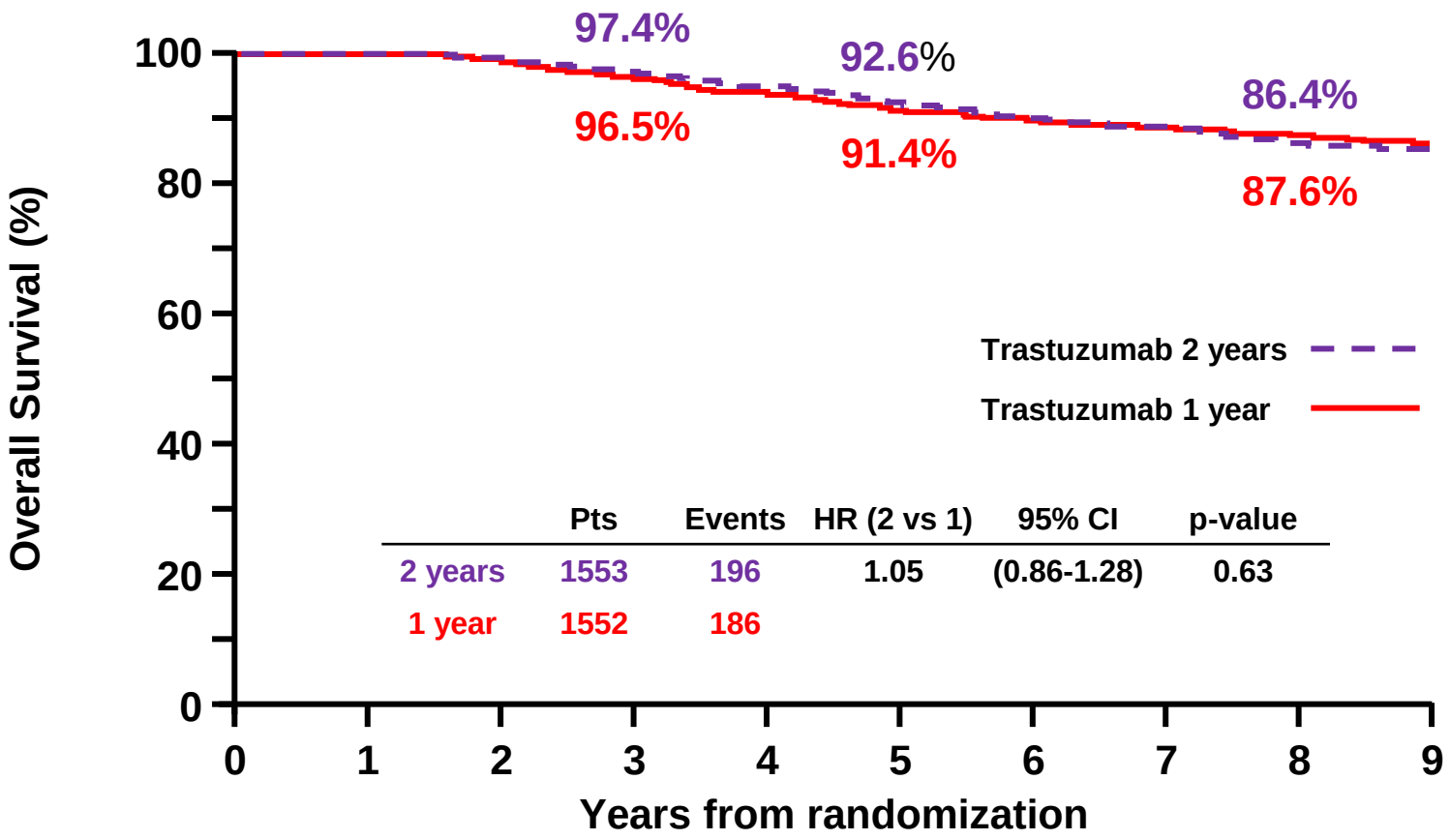
Hormone receptor negative
2.8% received endocrine therapy



No. at risk

Trastuzumab 2 years	755	755	695	651	619	581	556	507	312	97
Trastuzumab 1 year	762	762	677	628	602	580	563	512	312	99

OS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU

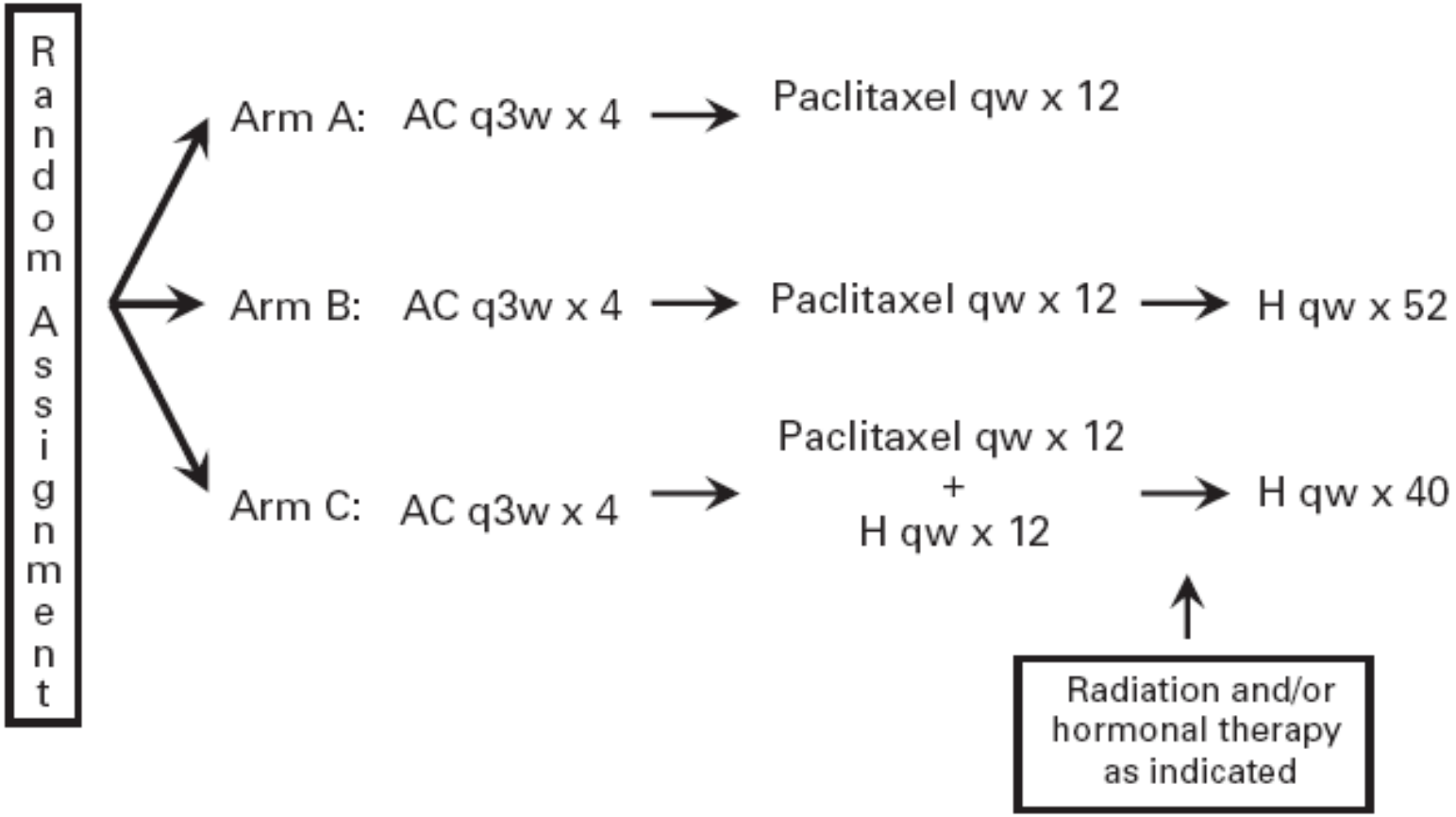


	Pts	Events	HR (2 vs 1)	95% CI	p-value
2 years	1553	196	1.05	(0.86-1.28)	0.63
1 year	1552	186			

No. at risk										
Trastuzumab 2 years	1553	1553	1525	1485	1438	1382	1317	1193	708	208
Trastuzumab 1 year	1552	1552	1513	1461	1413	1364	1329	1218	732	225

Peut-on prescrire le trastuzumab concomitamment à la CT, à la RT?

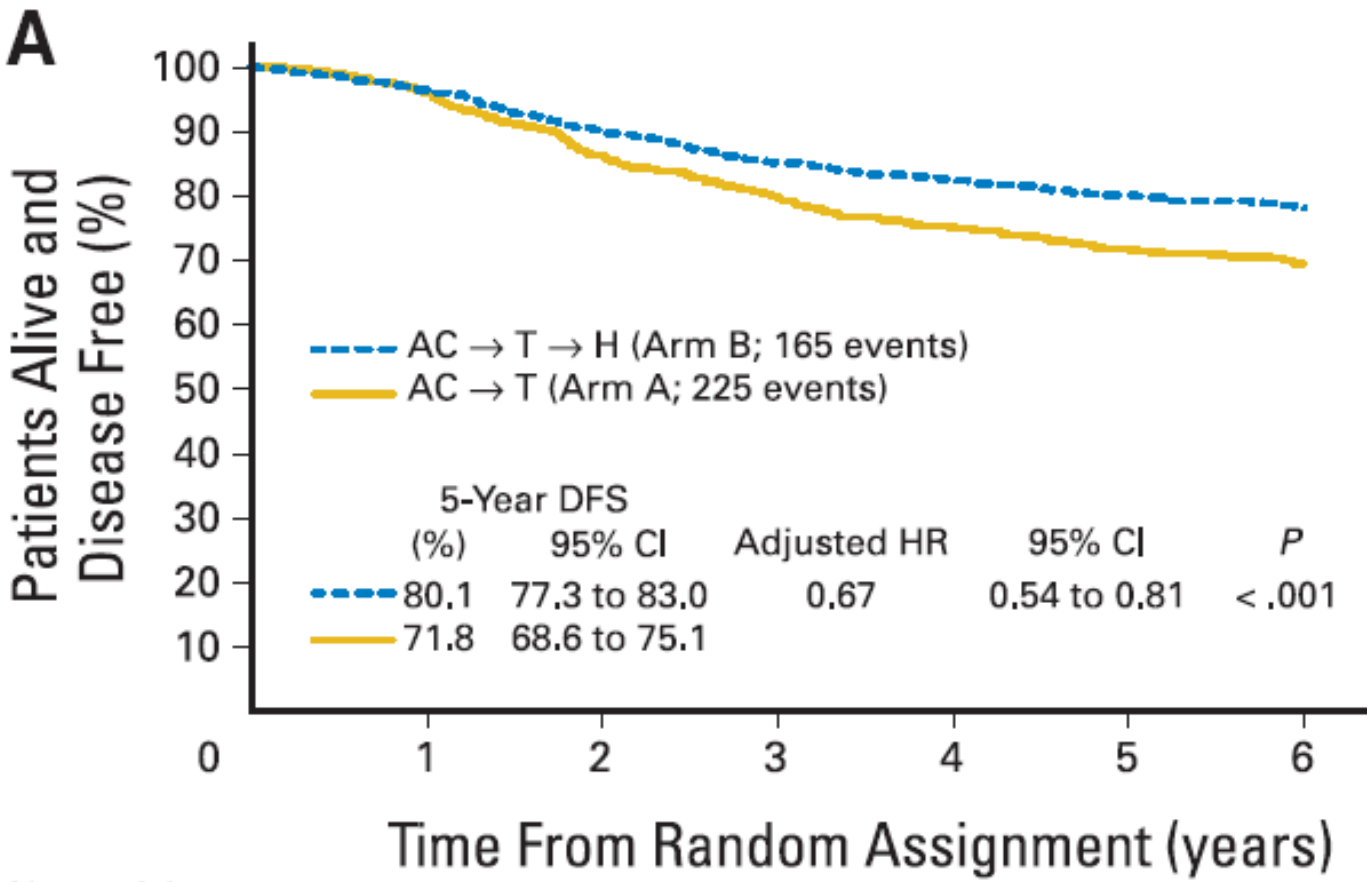
Etude de phase III N9831



⟶ Pas d'irradiation de la CMI

Perez EA et al. JCO 2011

Etude N9831 – Survie sans maladie bras A versus bras B

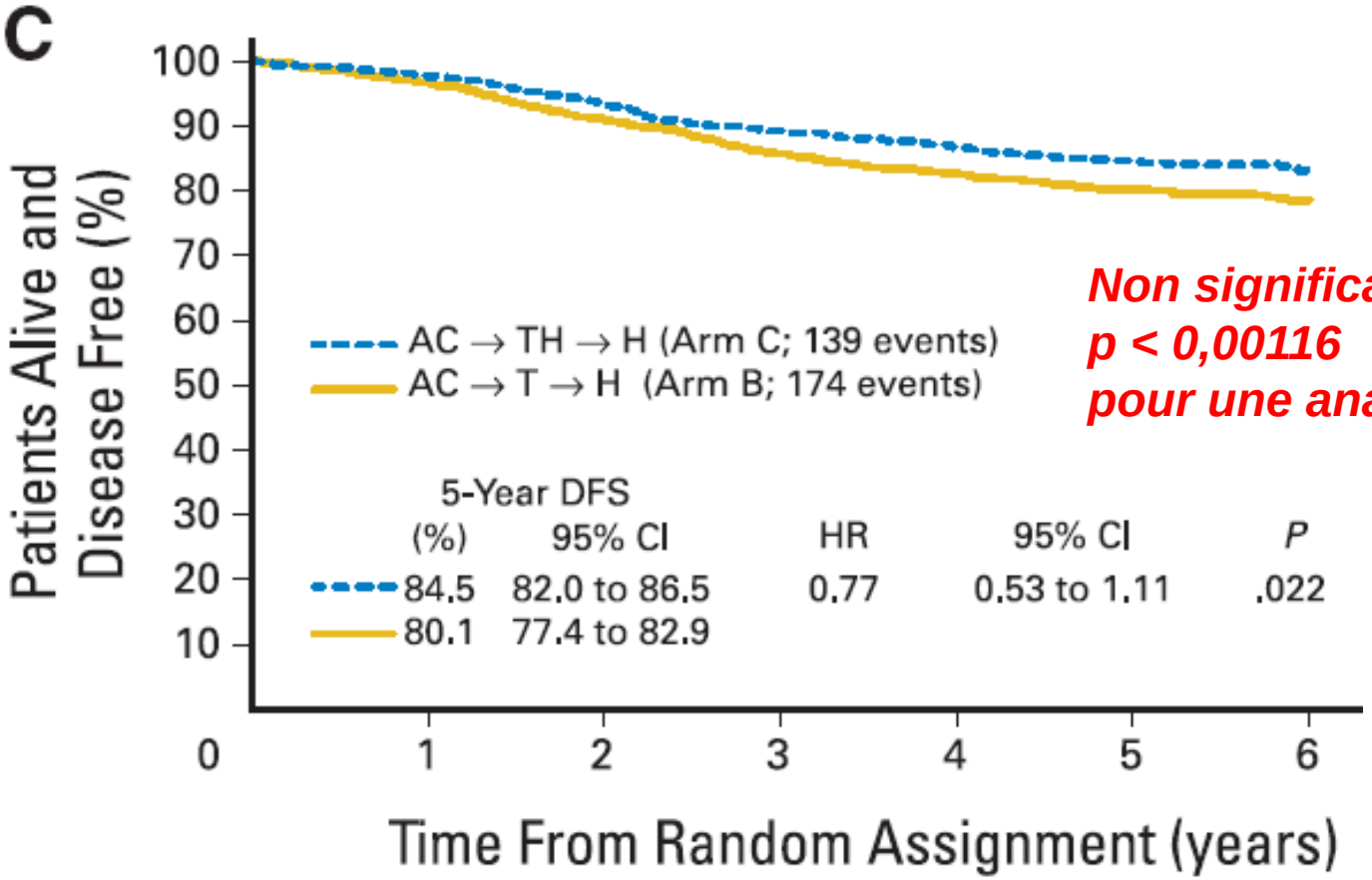


No. at risk

Arm A	1,087	728	643	582	530	470	330
Arm B	1,097	735	675	624	588	539	389

Perez EA et al. JCO 2011

Etude N9831 – Survie sans maladie bras B versus bras C



Non significatif
p < 0,00116
pour une analyse intermédiaire

No. at risk

Arm B	954	830	766	707	654	519	288
Arm C	949	837	790	742	691	576	334

Perez EA et al. JCO 2011

Arrêt du traitement par trastuzumab pour évènements cardiaques

Bras	nombre	Traitement	FEV ↓	IC
A	1087	AC-T	**0**	**0**
B	1097	AC-T-H	**3,6 %**	**1,5 %**
C	949	AC-TH-H	**7 %**	**2,2 %**

⟶ Diminution de 15% de la FEV initiale

⟶ Diminution de 10% sous la valeur inférieure normale

Halyard MY et al. JCO 2009

Altération asymptomatique de la FEV et insufffisance cardiaque congestive

Trials regimens	Severe CHF NYHA Class III/IV (%)	Mild CHF NYHA Class II (%)	Asymptomatic confirmed LVEF drop (%)	Total LVEF systolic toxicity (%)
NSABP B-31, AC → q3wkP	0.9	NR		NR
NSABP B-31, AC → q3wkPH → H	3.8 ←	11.7		15.5
NCCTG N9831, AC → q1wkP	0.3	0.5		0.8
NCCTG N9831, AC → q1wkPH → H	3.3 ←	6.6		9.9
NCCTG N9831, AC → q1wkP → H	2.8	5.0		7.8
BCIRG 006, AC → T	0.7		NR	NR
BCIRG 006, AC → TH → H	2.0		NR	NR
BCIRG 006, TCH → H	0.4		NR	NR
HERA, chemotherapy	0.0	0.1	0.4	0.5
HERA, chemotherapy → H	0.6	1.6	1.4	3.6

Classe NYHA III :
Il existe une limitation évidente de la capacité d'effort : le patient se sent toujours bien au repos mais un effort minime provoque déjà des symptômes.
Classe NYHA IV :
Le patient ne peut plus effectuer aucun effort sans éprouver de symptômes : les symptômes de l'insuffisance cardiaque sont déjà présents au repos et s'aggravent au moindre effort.

Coster RB et al, Ann Oncol 2010

Toxicités lors de l'association RT-Trastuzumab

Belkacémi Y et al	nbre	CMI	Tox cutanée G2	Oesophagite G2	FEV < 50%
	146	71%	51 %	12 %	10 %

Shaffer R et al	nbre	CMI	CHF	Arrêt du trastu
	44	41%	0,7 %	13,6 %

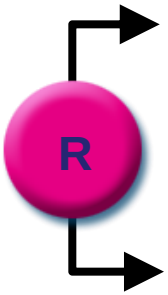
Belkacémi Y et al, Ann Oncol 2008

Shafer R et al, Radioth Oncol 2009

Peut-on prescrire le trastuzumab sans CT ?

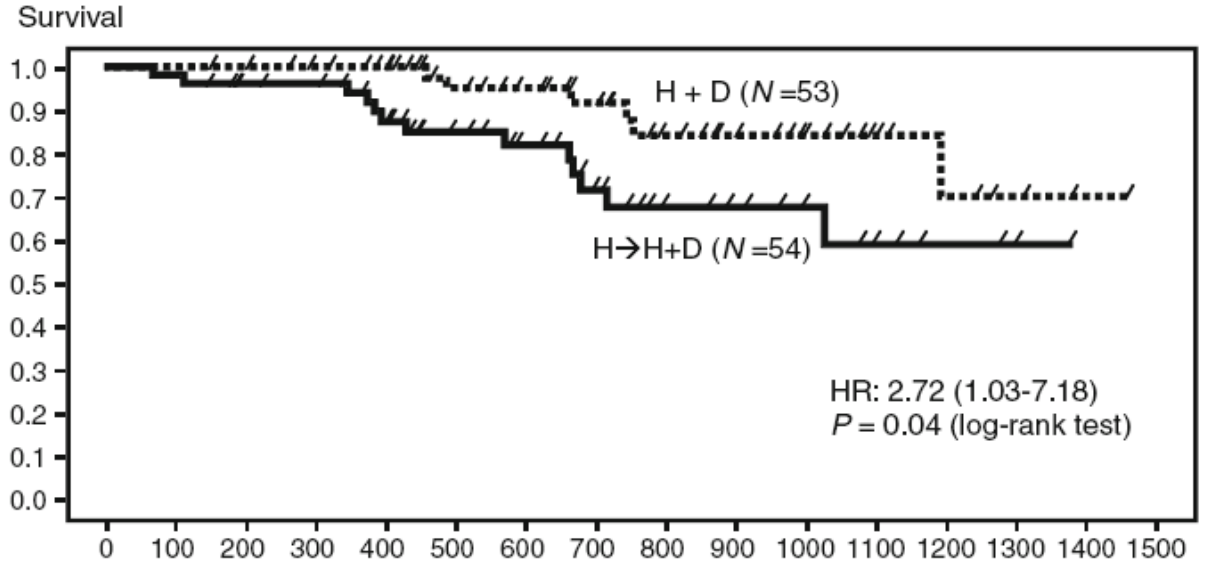
Trastuzumab prescrit en monothérapie

Patientes HER2 +,
1ére ligne M+
Objectif principal : SSP



Trastuzumab
puis docétaxel

Trastuzumab
+ docétaxel

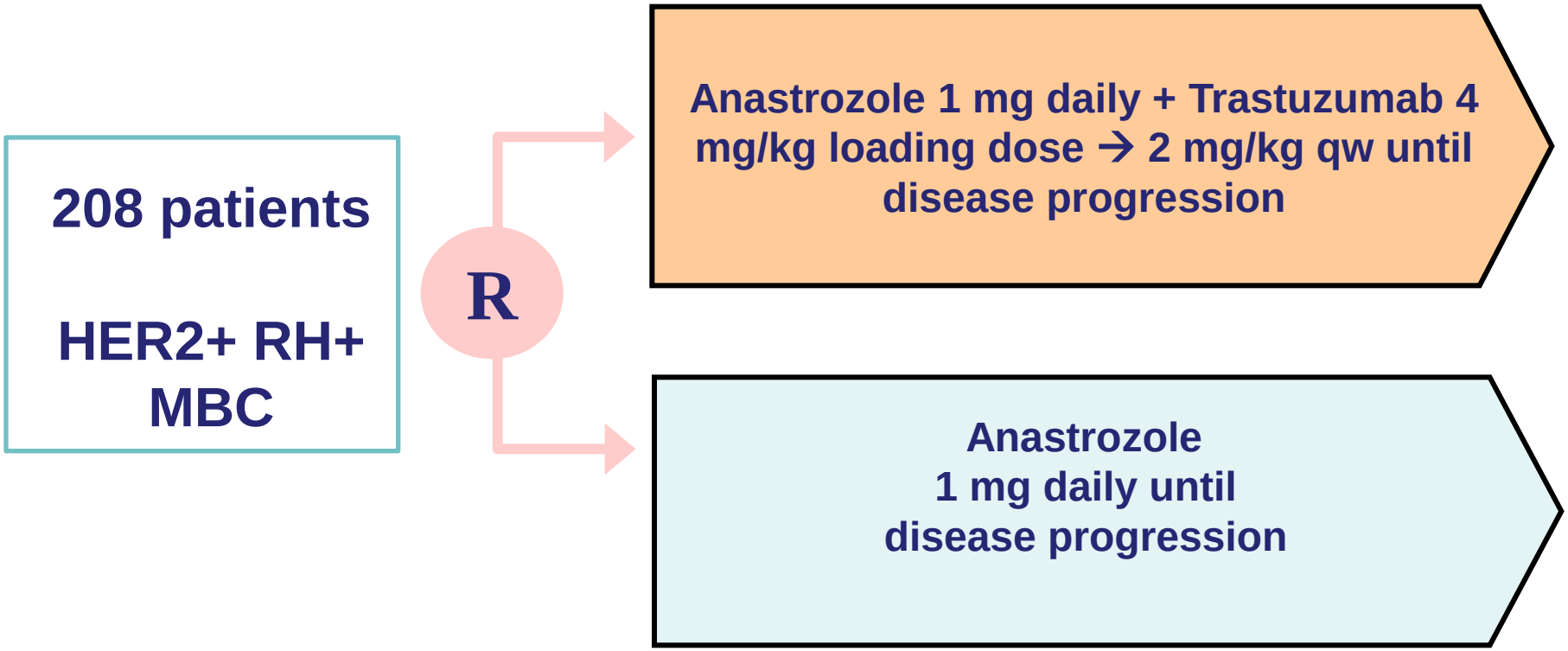


N at risk																
H + D	53	53	51	49	44	37	33	27	21	16	12	7	5	3	1	0
H→H+D (Sequential)	54	53	48	47	38	31	26	19	13	11	8	5	3	1	0	0

Inoue K et al. BCRT 2009, 9

Peut-on prescrire le trastuzumab sans CT pour les tumeurs RH+ ?

Etude TAnDEM



- Objectif principal = SSP
- Objectif secondaire = SG, TBC
- Crossover autorisé à la progression

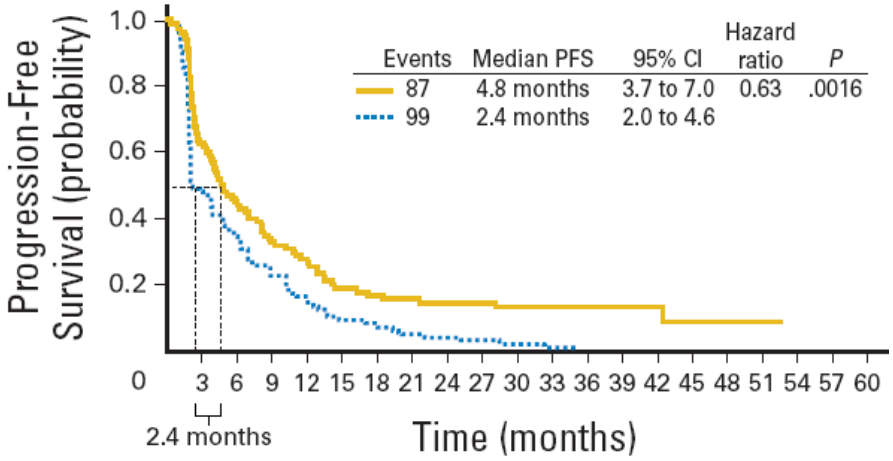
Kaufman B et al. JCO 2009, 27, 5529

SSP et SG - TAnDEM

Survie sans progression

2,4 vs 4,8 mois

p = 0,0016

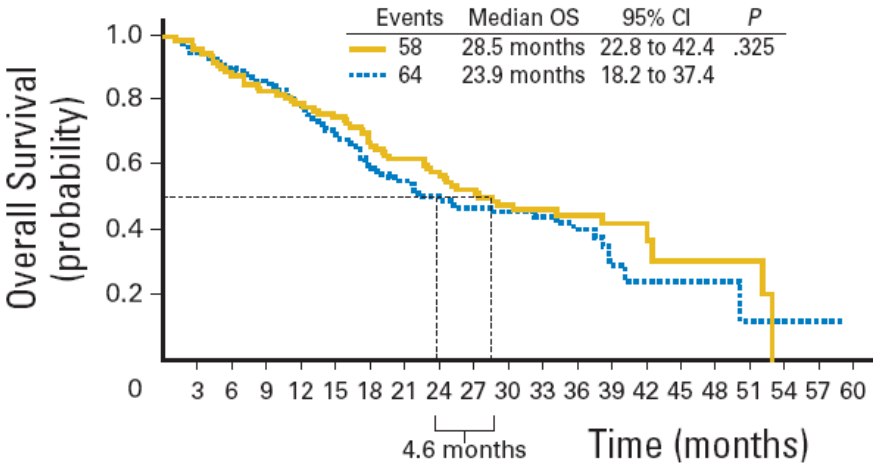


No. at risk													
Trastuzumab + anastrozole	103	48	31	17	14	13	11	9	4	1	1	0	0
Anastrozole alone	104	36	22	9	5	4	2	1	0	0	0	0	0

Survie globale

23,9 vs 28,5 mois

p = 0,325

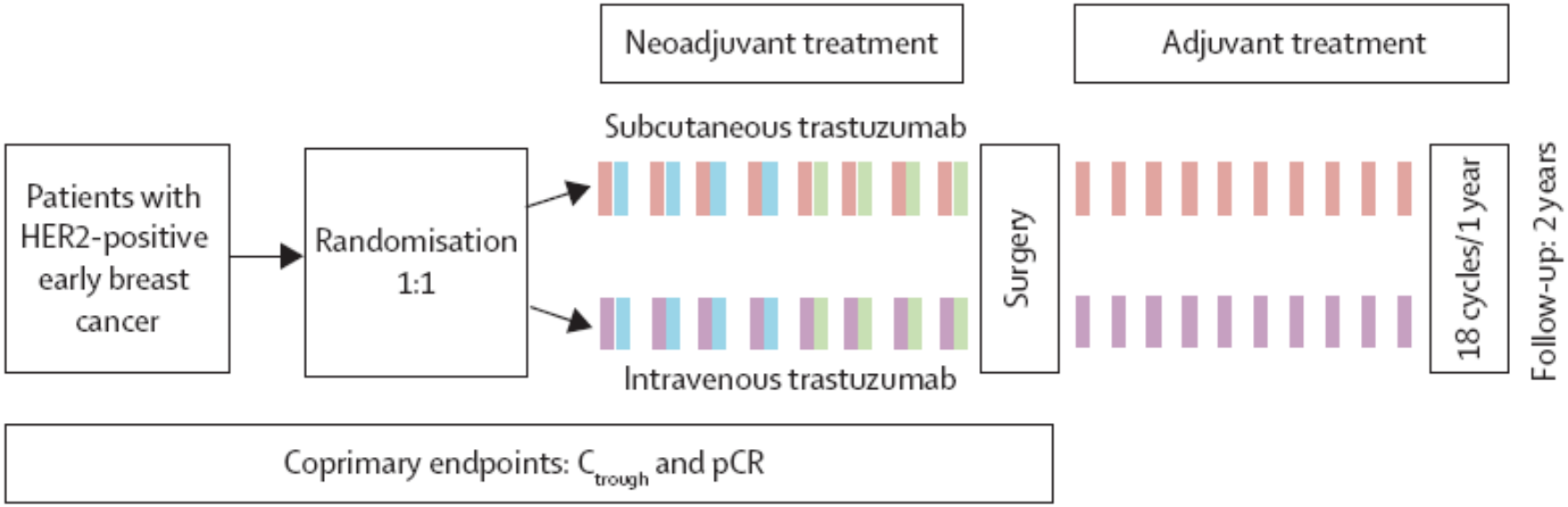


No. at risk													
Trastuzumab + anastrozole	103	91	83	76	63	49	36	24	12	4	3	0	0
Anastrozole alone	104	96	87	73	58	42	34	22	5	2	1	1	0

Kaufman B et al. JCO 2009, 27, 5529

Peut-on prescrire le trastuzumab différemment ?

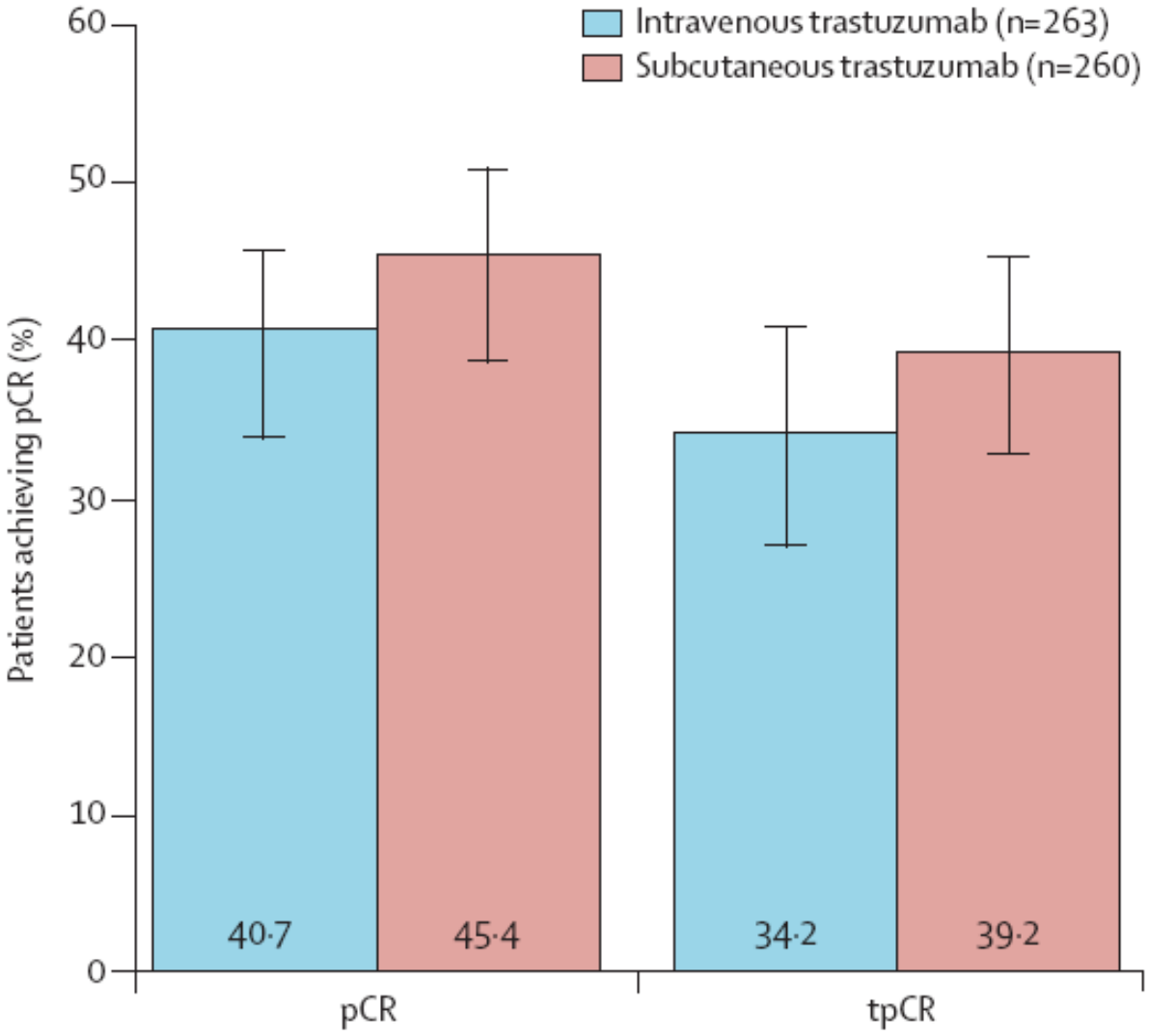
Étude adjuvante HannaH



- Trastuzumab subcutaneous 600 mg (5 mL) given every 3 weeks
- Trastuzumab intravenous 8 mg/kg loading dose; 6 mg/kg given every 3 weeks
- Docetaxel 75 mg/m²
- Fluorouracil (500 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (500 mg/m²) given every 3 weeks

Ismael G. Lancet 2012

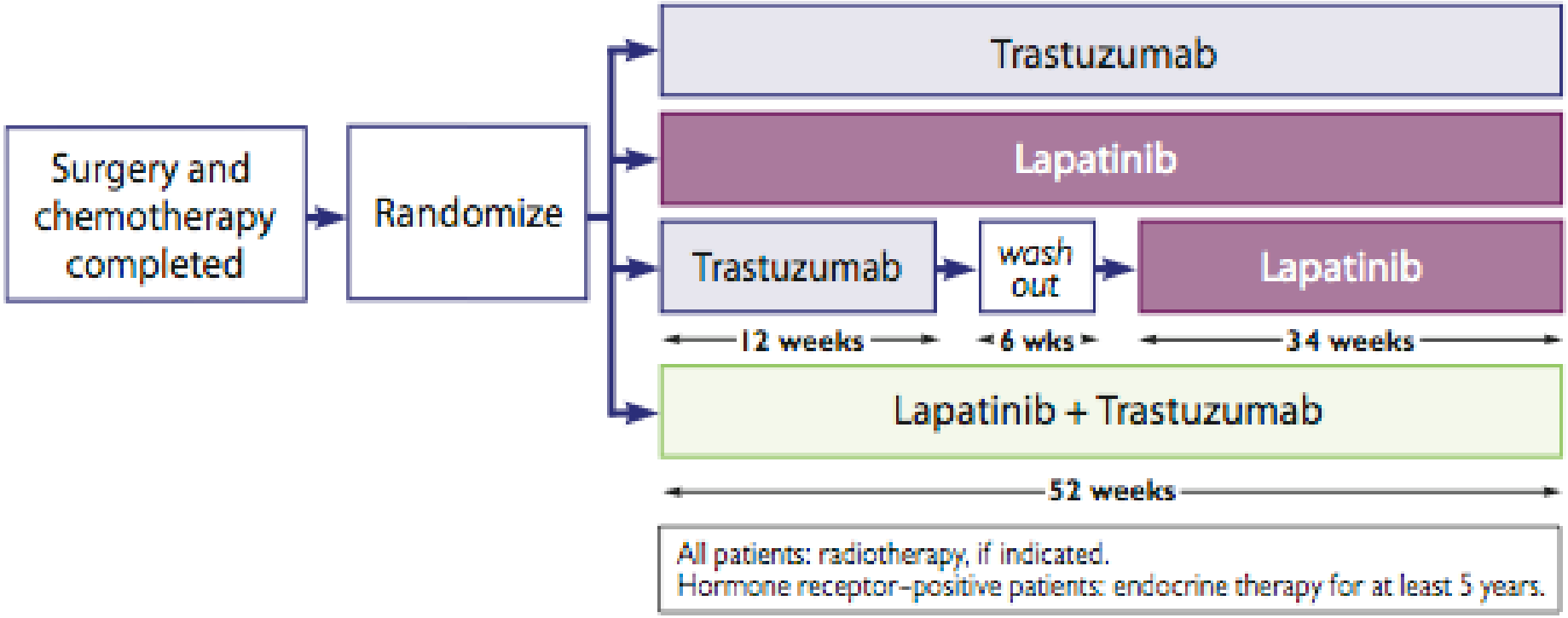
Étude adjuvante HannaH



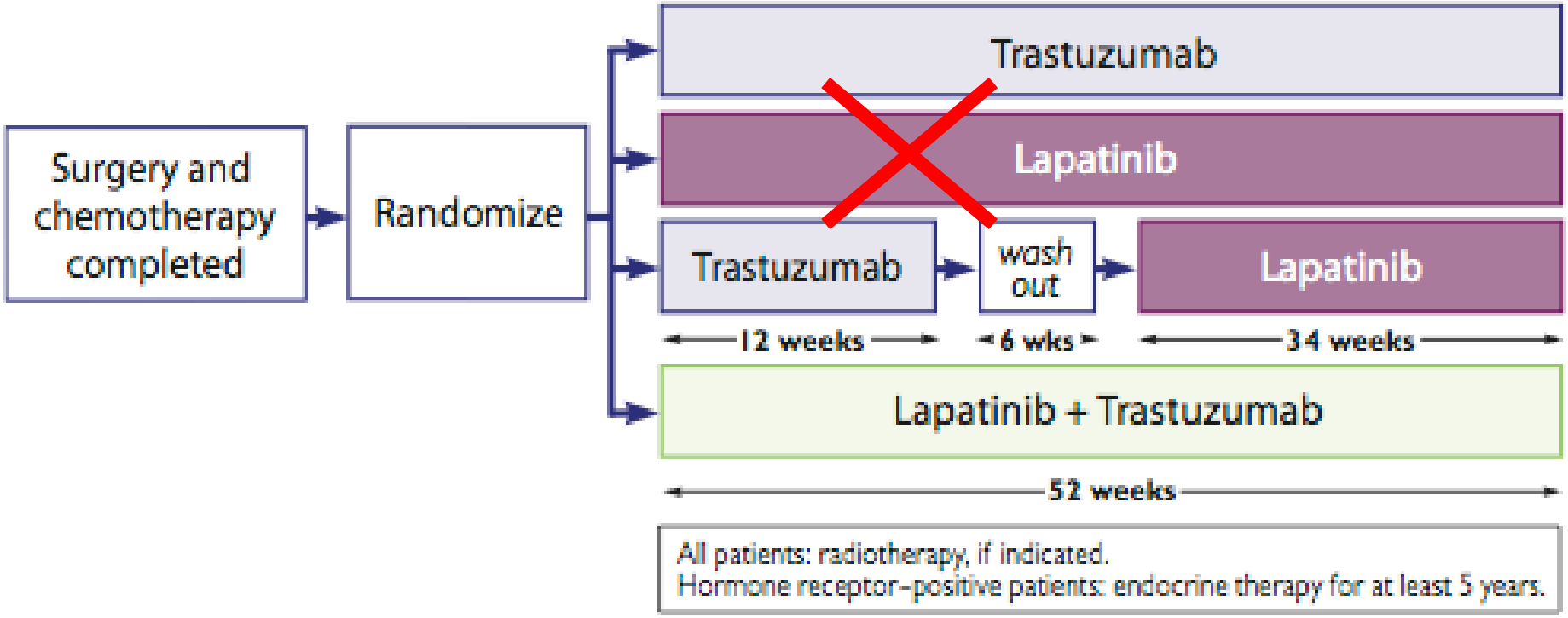
Ismael G. Lancet 2012

Peut-on remplacer le trastuzumab ?

Étude ALLTO
en phase adjuvante



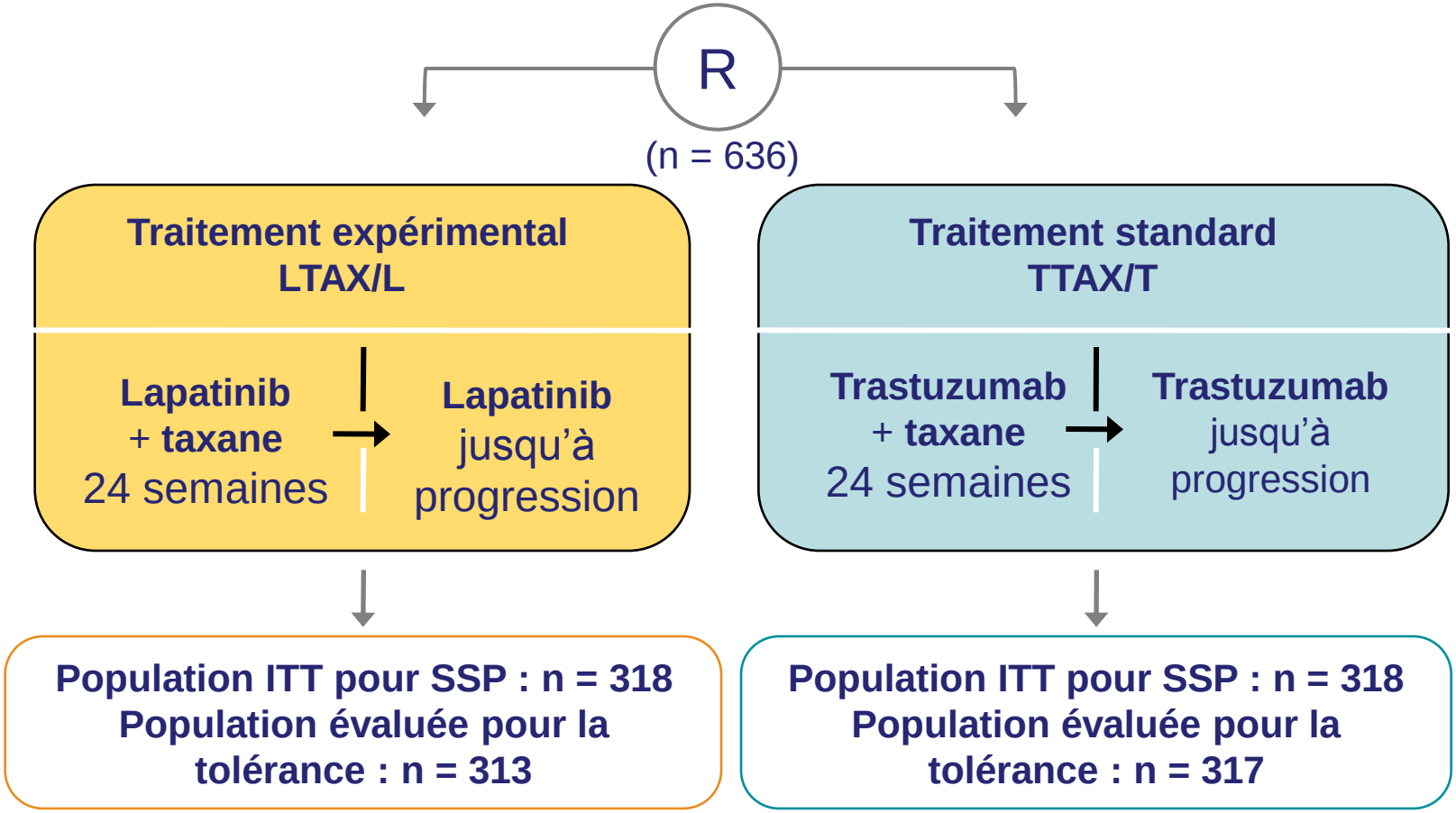
Étude ALLTO
en phase adjuvante



On Sept. 9, 2011, GlaxoSmithKline announced that the arm 2 was closed since an early analysis of the results so far showed that lapatinib wasn't working as well as trastuzumab to lower the risk of recurrence. Other arms of the ALLTO study will continue.

Étude MA.31/EGF108919

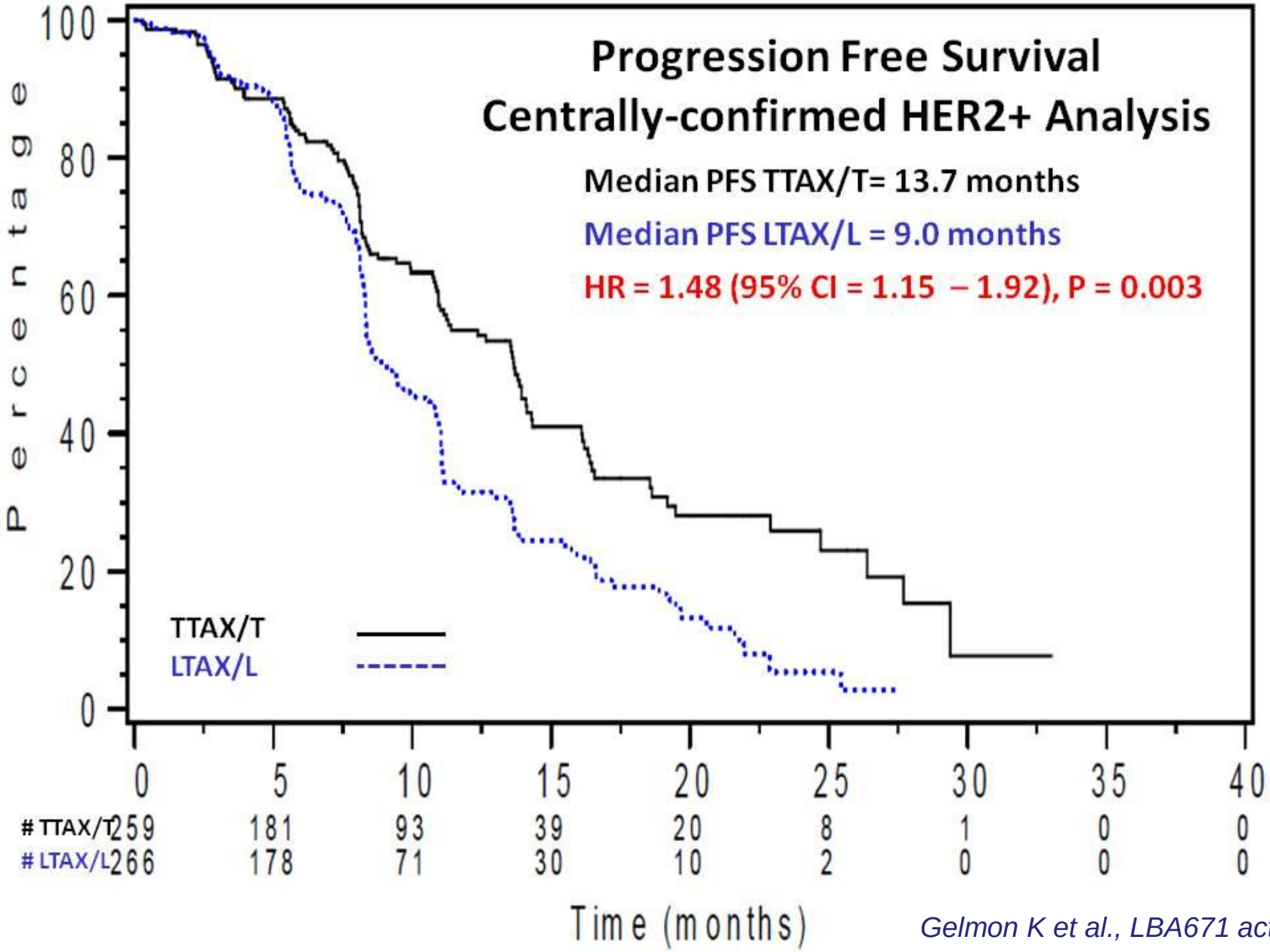
taxane + lapatinib vs taxane + trastuzumab en première ligne du cancer du sein métastatique HER2+



- Objectif principal : survie sans progression

Gelmon K et al., LBA671 actualisé

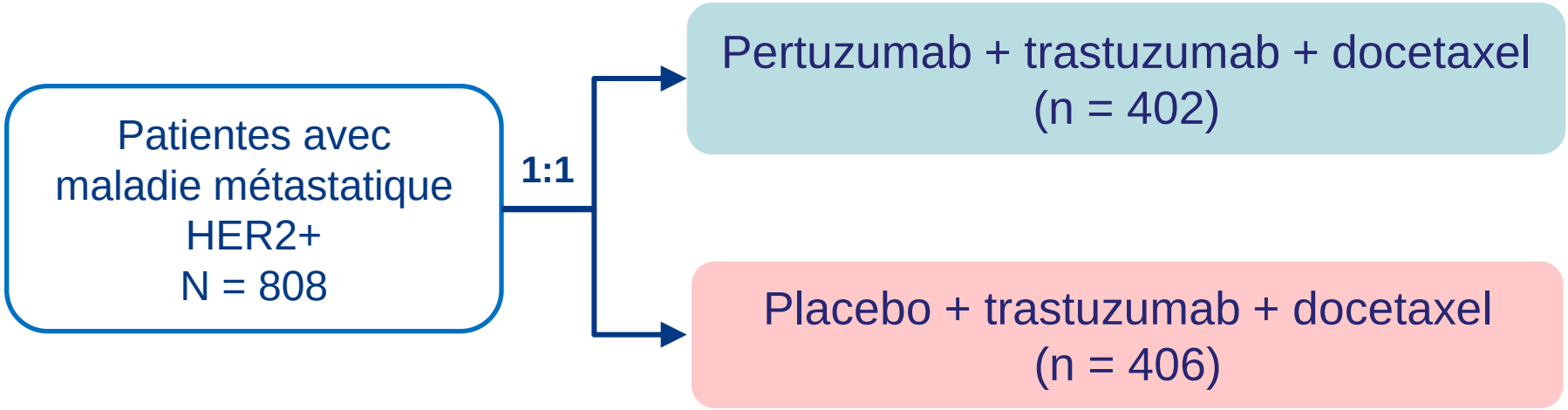
Étude MA.31/EGF108919



Gelmon K et al., LBA671 actualisé

Faut-il associer le trastuzumab avec une autre thérapie anti-HER2 ?

Etude CLEOPATRA

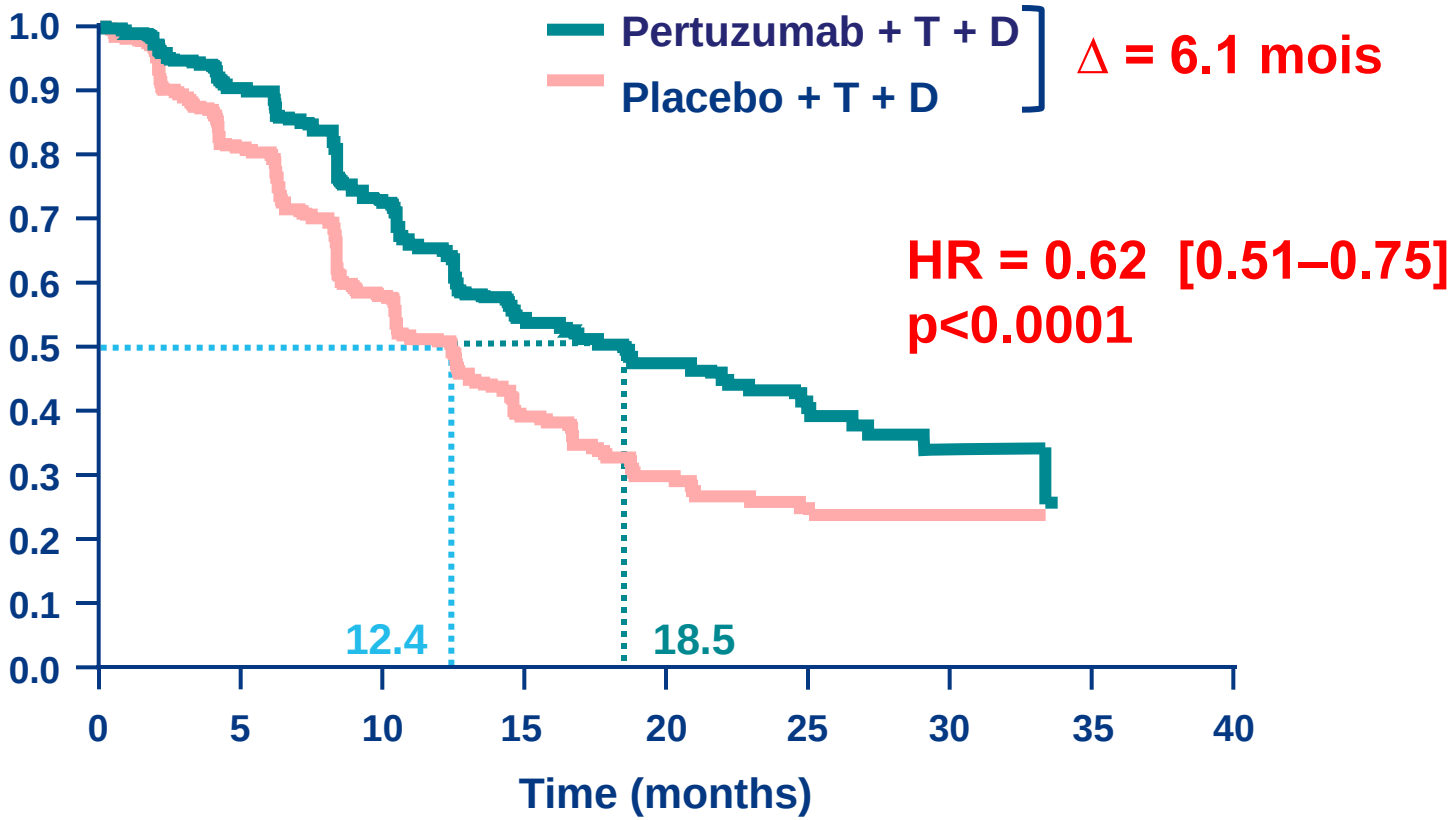


- Pertuzumab : 840 mg dose de charge, 420 mg dose de maintenance
- Trastuzumab : 8 mg/kg dose de charge, 6 mg/kg dose de maintenance
- Docetaxel : 75 mg/m^2 avec escalade à 100 mg/m^2 selon la tolérance
- Avec un nombre minimal recommandé de 6 cures

- **Objectif principal : Survie sans maladie**
- **Objectifs secondaires : Survie globale, Taux de réponse, Tolérance**

Baselga J, NEJM 2012

Etude CLEOPATRA
Survie sans maladie

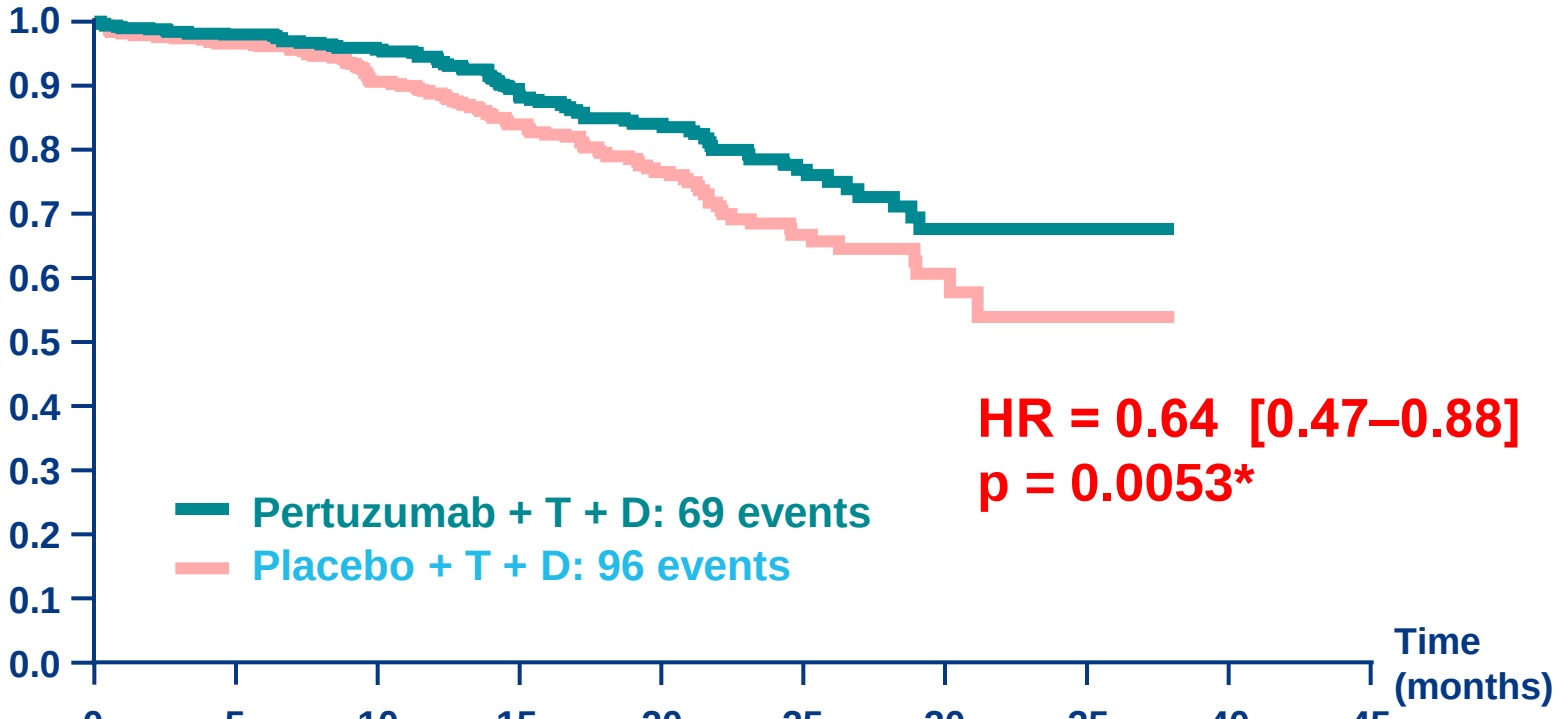


n be à risque									
Pertuzumab + T + D	402	345	267	139	83	32	10	0	0
Placebo + T + D	406	311	209	93	42	17	7	0	0

Baselga J, NEJM 2012

Etude CLEOPATRA
Survie globale

Dans cette analyse intermédiaire avec un recul de 19,3 mois, le seuil de significativité pré-défini (HR ≤0.603; p ≤0.0012) n'a pas été atteint.



n be à risque	0	5	10	15	20	25	30	35	40	45
Pertuzumab + T + D	402	387	367	251	161	87	31	4	0	0
Placebo + T + D	406	383	347	228	143	67	24	2	0	0

Baselga J, NEJM 2012

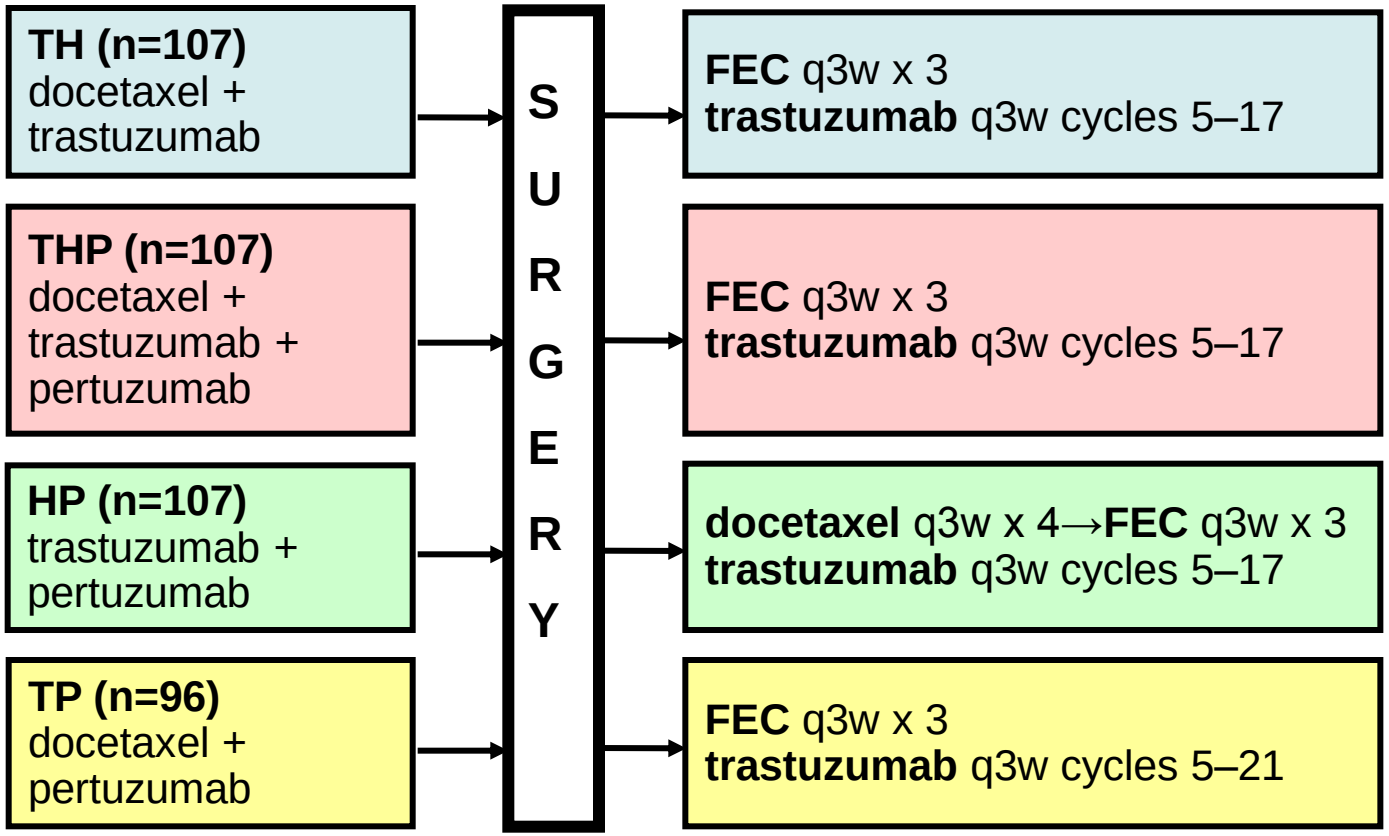
NeoSphere: study design

417 patients

Chemo-naïve & primary tumors >2cm

operable or locally advanced or inflammatory* HER2-positive BC

Primary endpoint: comparison of pCR rates

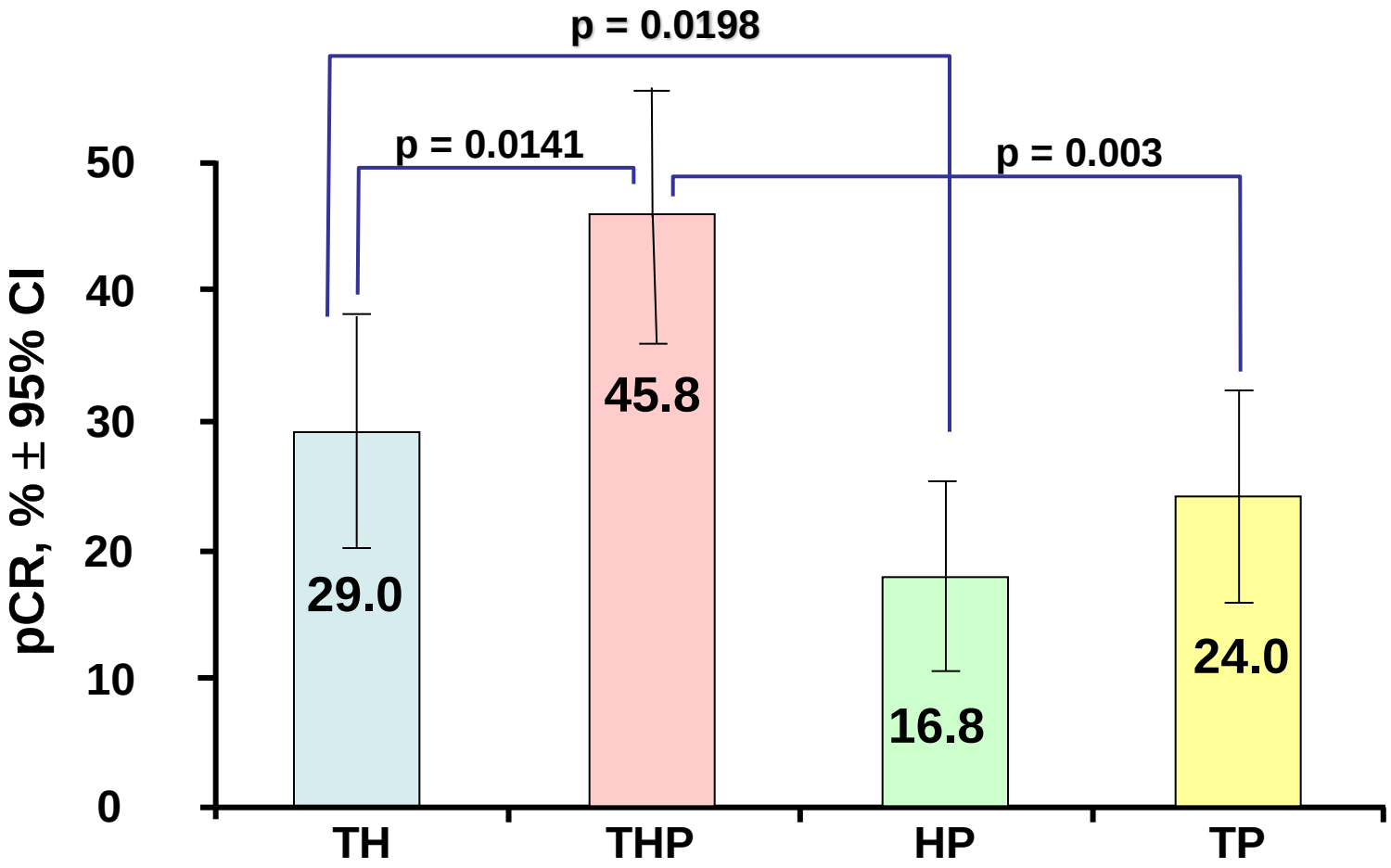


Study dosing: q3w x 4

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L et al. Lancet Oncol 2012

NeoSphere pCR rates: ITT population



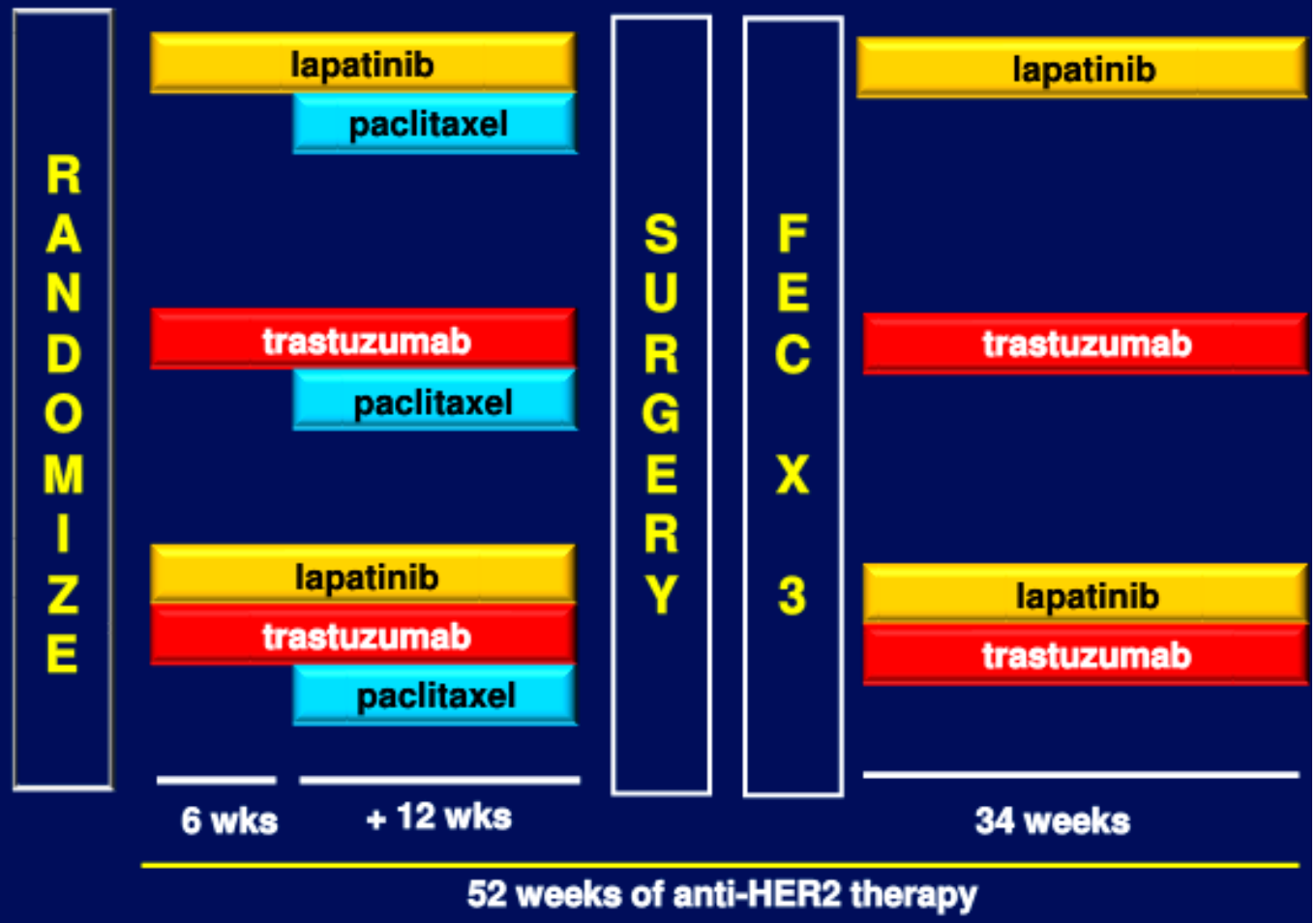
H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L et al. Lancet Oncol 2012

Study Design

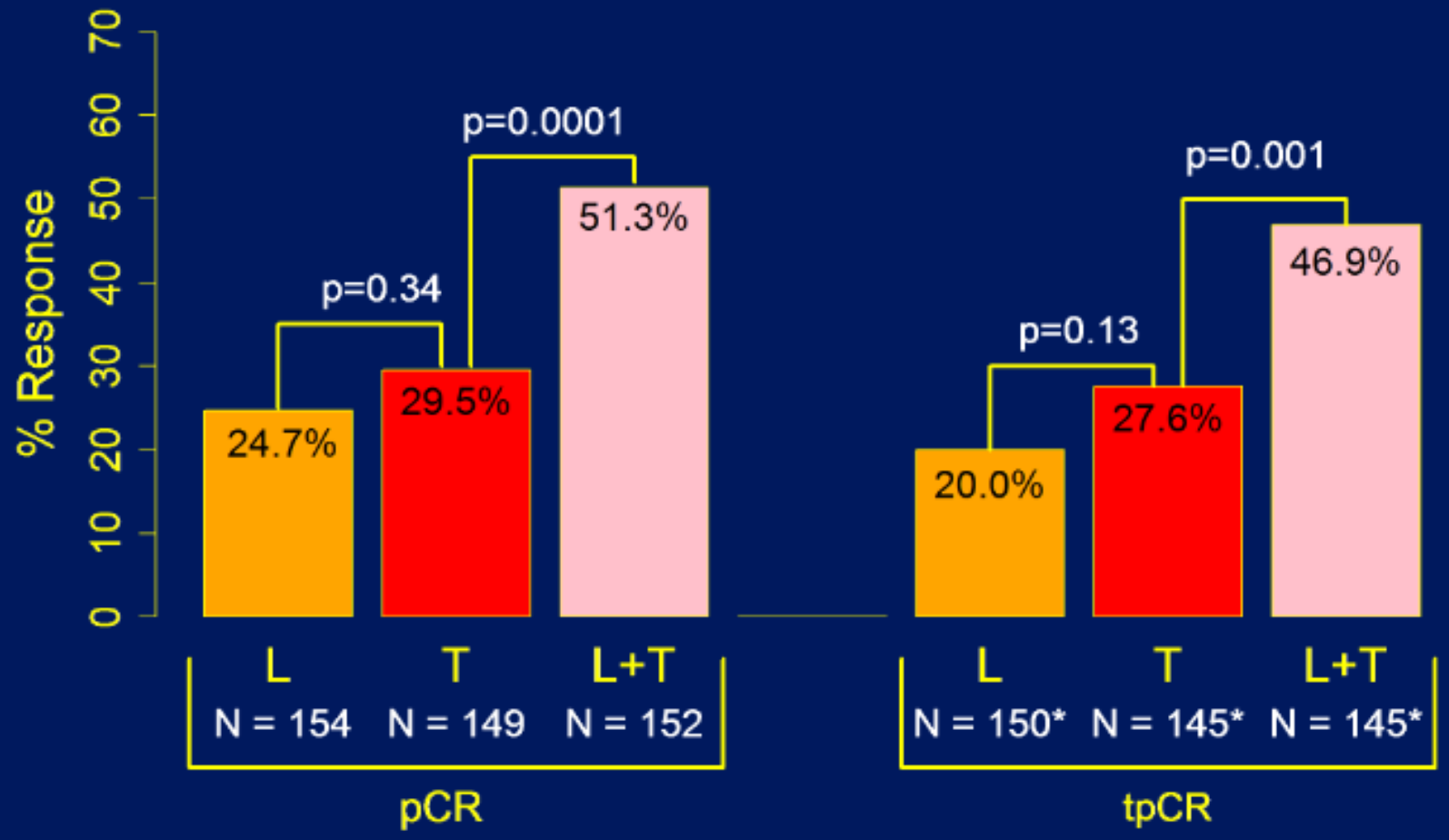
Invasive operable HER2+ BC
T > 2 cm
(inflammatory BC excluded)
LVEF ≥ 50%
N=450

Stratification:
- T ≤ 5 cm vs. T > 5 cm
- ER or PgR + vs. ER & PgR –
- N 0-1 vs. N ≥ 2
- Conservative surgery or not



Baselga J et al. Lancet 2012

Efficacy – pCR and tpCR



Pathological Complete Response

Locoregional (total) pCR

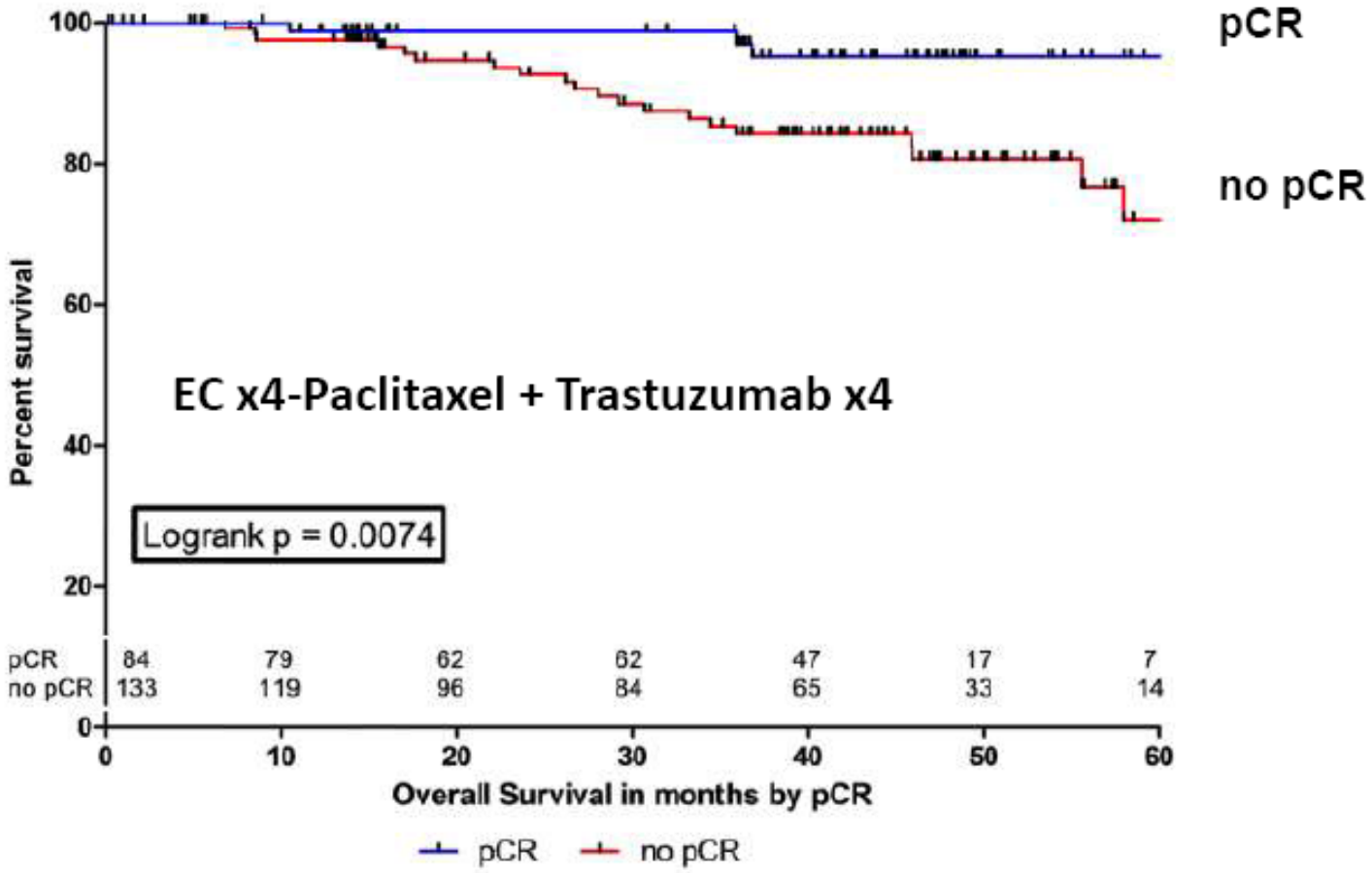
* Excludes 15 patients with non-evaluable nodal status

L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response

Baselga J et al. Lancet 2012

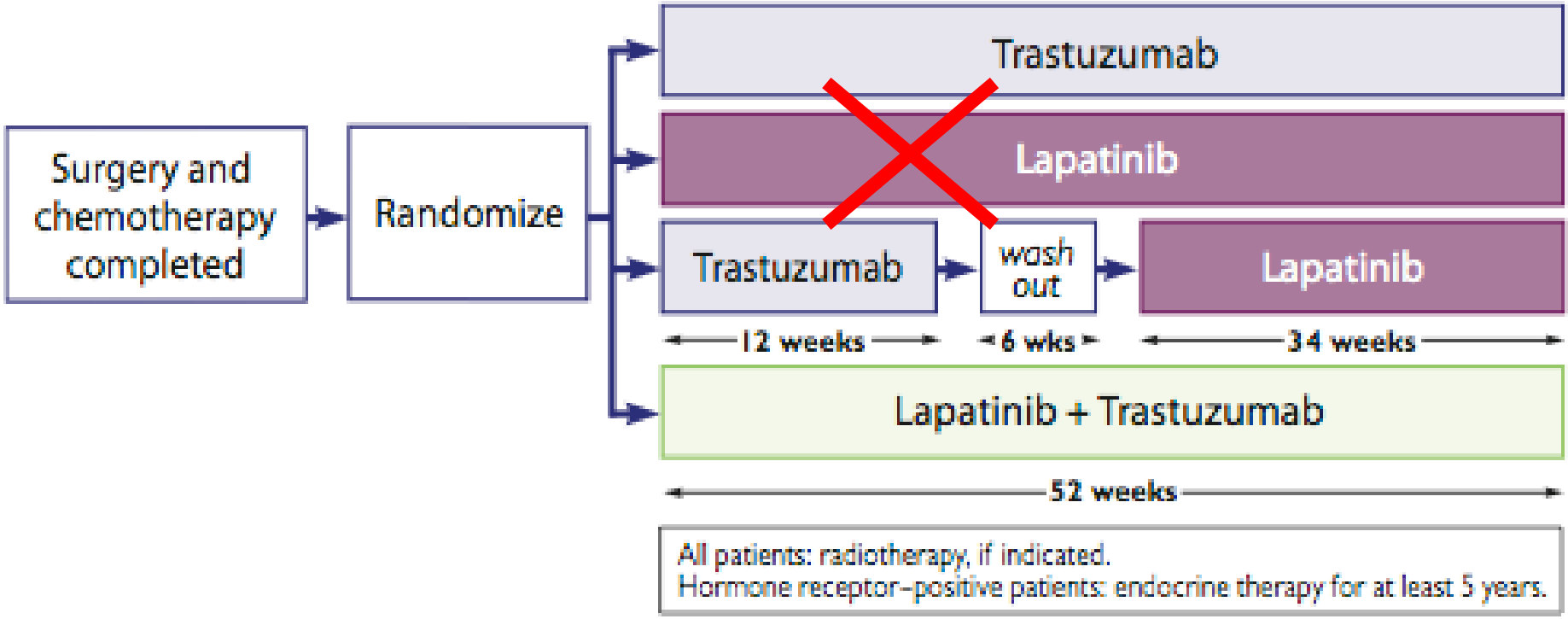
Valeur pronostique de la RCh pour les tumeurs HER2+

TECHNO Study - Overall Survival

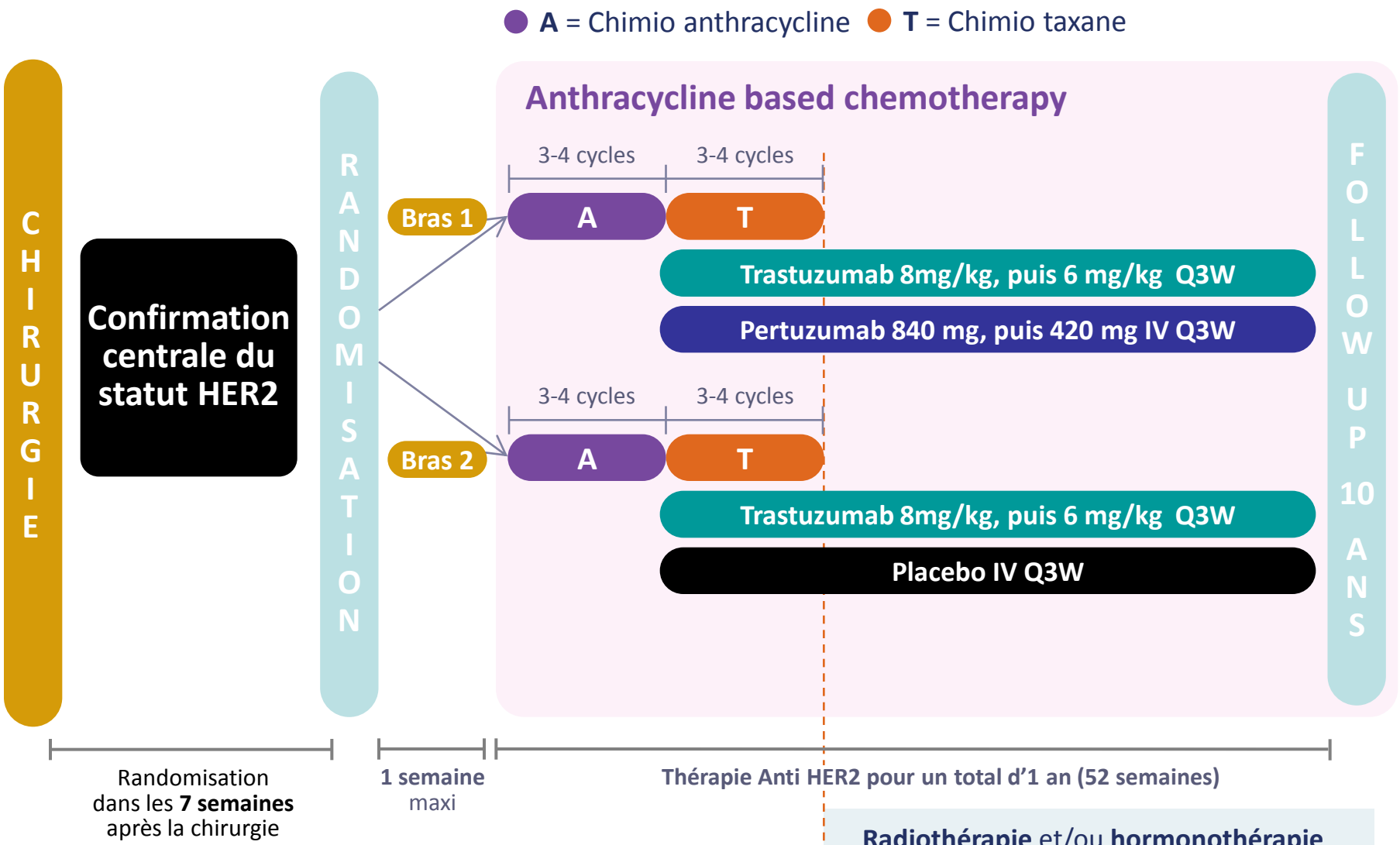


Untch M et al. JCO 2011

Étude ALLTO
en phase adjuvante

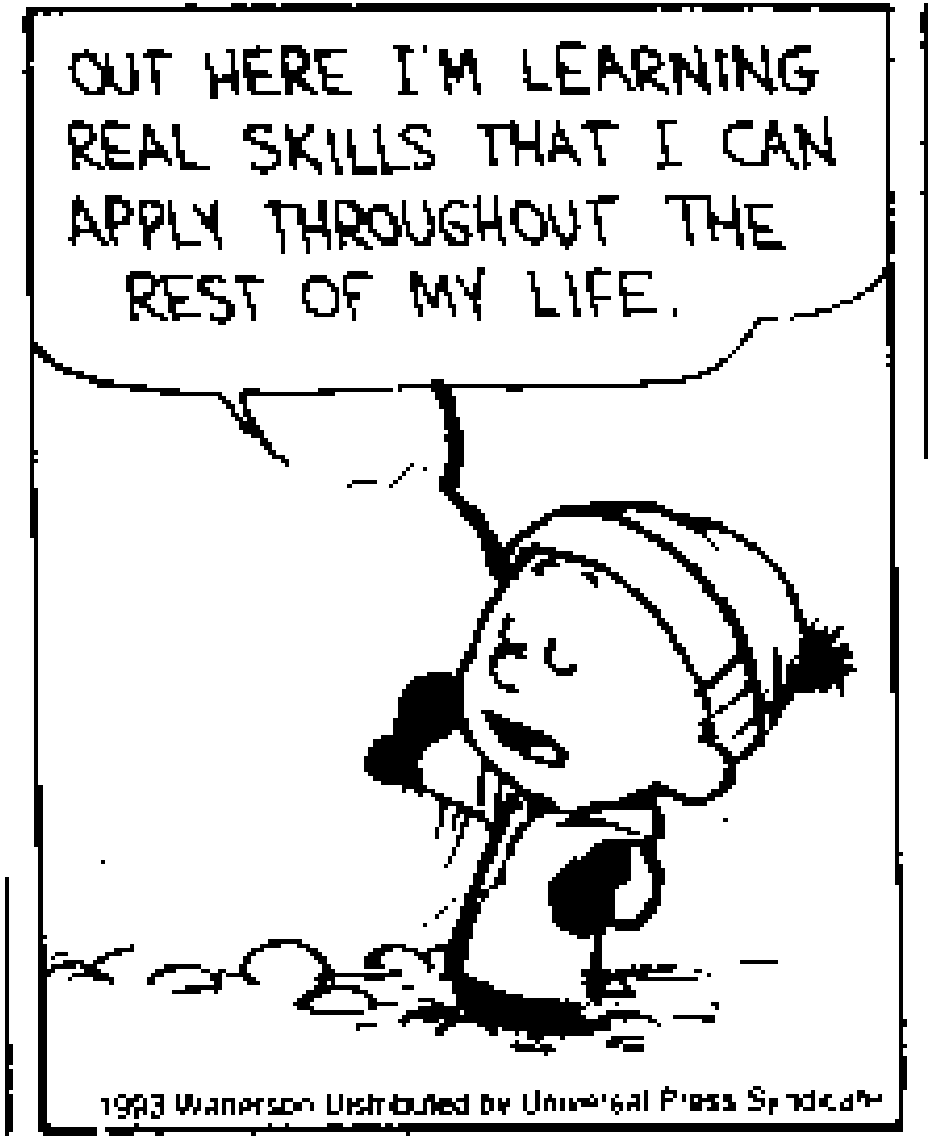


APHINITY: Chimiothérapie avec Anthracycline



Radiothérapie et/ou **hormonothérapie** peuvent être débutées à la fin de la chimiothérapie adjuvante

Chimio Anthracycline :
FEC (ou FAC) → T
AC (or EC) → T

Dose maxi autorisée :
Doxorubicine = 360 mg/m²
Epirubicine = 720 mg/m²

Je vous remercie