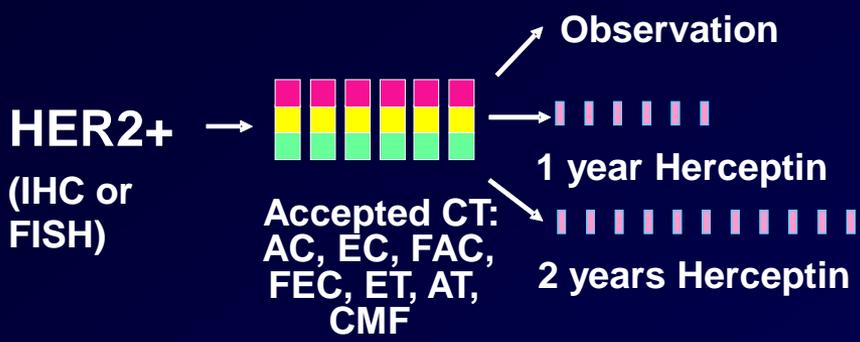


**Existe-t-il un sous groupe à risque qui pourrait bénéficier d'une modification de la durée de traitement par trastuzumab ?**

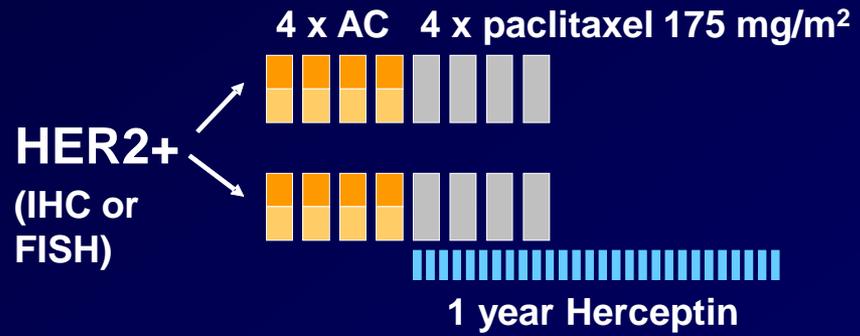
**X. Pivot**  
**CHRU De Besançon**

# In 2005 results of 4 Adjuvant Herceptin trials have definitively changed the standard of care

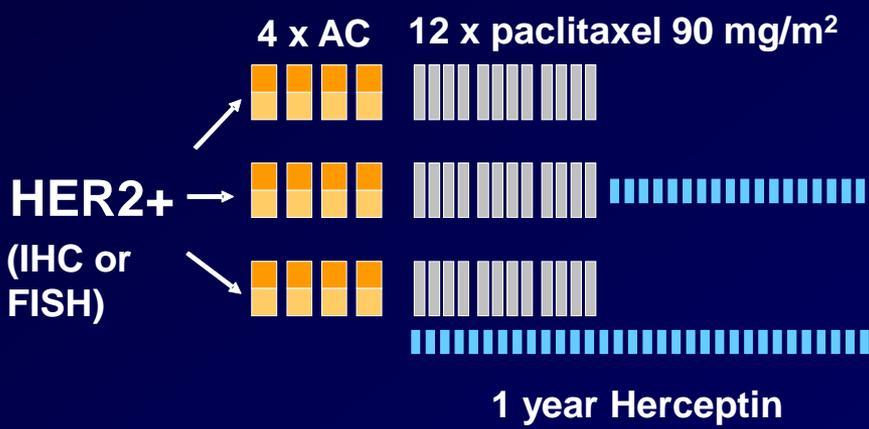
## HERA



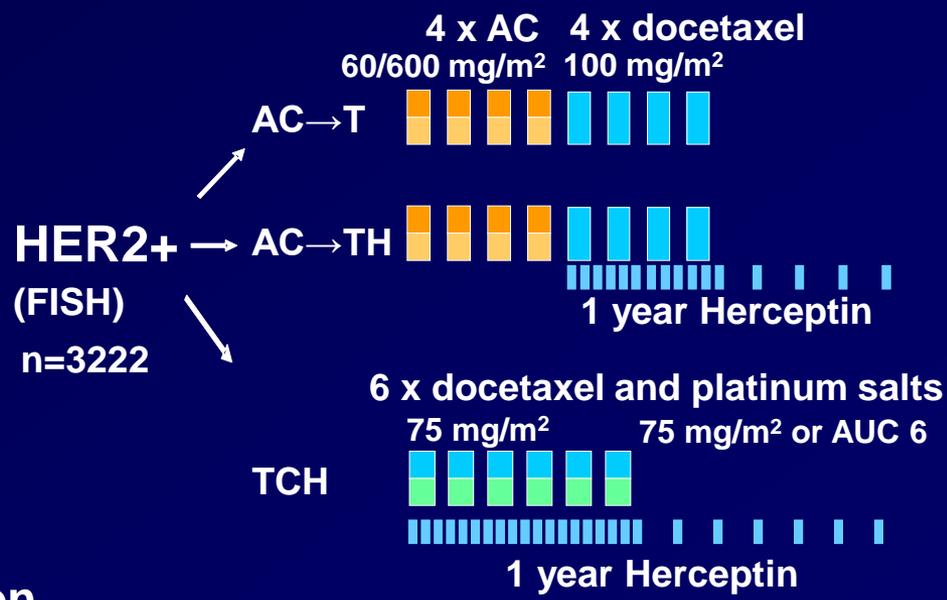
## NSABP B-31



## NCCTG N9831



## BCIRG 006



FISH, fluorescence *in situ* hybridisation

# DFS and OS benefits were demonstrated during long-term follow-up in the four pivotal clinical trials of trastuzumab for 1 year

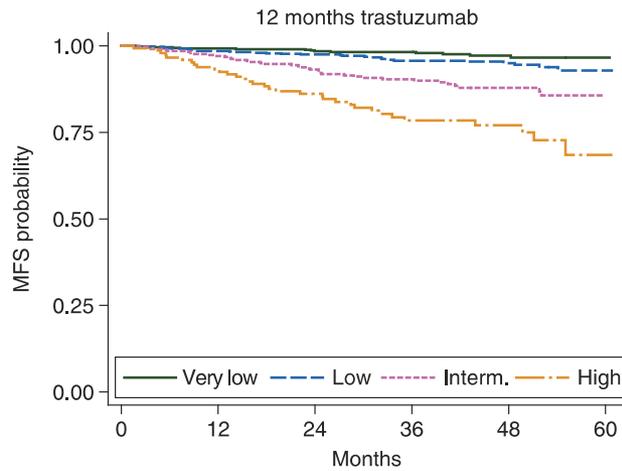
Study	Follow-up (years)	N	DFS		OS	
			HR	p value	HR	p value
<b>HERA<sup>1-4</sup></b> CT±RT→T vs. CT±RT	1	3387	0.54	< 0.0001	0.76	0.26
	2	3401	0.64	< 0.0001	0.66	0.0115
	4	3401	0.76	< 0.0001	0.85	0.1087
	8	3399	0.76	< 0.0001	0.76	0.0005
<b>NCCTG N9831/ NSABP B-31<sup>5-7</sup></b> AC→Tax+T→T vs. AC→Tax	2	3351	0.48	< 0.0001	–	–
	4	4045	0.52	< 0.001	0.61	< 0.001
	8.4	4046	0.60	< 0.0001	0.63	< 0.0001
<b>BCIRG 006<sup>8</sup></b> AC→Tax + T vs. AC→Tax	5.4	3222	0.64	< 0.001	0.63	< 0.001
			Tax+Cb→T vs. AC→Tax	0.75	0.04	0.77

AC, doxorubicin and cyclophosphamide; Cb, carboplatin; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RT, radiotherapy; T, trastuzumab; Tax, taxane.

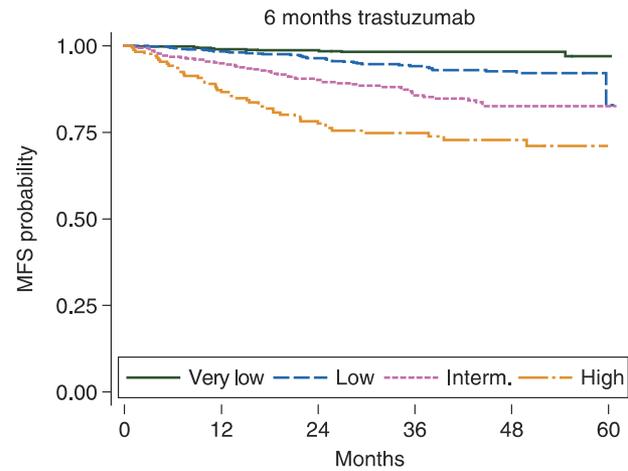
1. Piccart-Gebhart MJ, *et al. N Engl J Med* 2005; **353**:1659–1672; 2. Smith I, *et al. Lancet* 2007; **369**:29–36;
3. Gianni L, *et al. Lancet Oncol* 2011; **12**:236–244; 4. Goldhirsch A, *et al. Lancet* 2013; **382**:1021–1028;
5. Romond EH, *et al. N Engl J Med* 2005; **353**:1673–1684; 6. Perez EA, *et al. J Clin Oncol* 2011; **29**:3366–3373;
7. Perez EA, *J. Clin Oncol* 2014 **32**: 3744 - 3752 ; 8. Slamon D, *et al. N Engl J Med* 2011; **365**:1273–1283.

# Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial

A. Kramar<sup>1</sup>, T. Bachelot<sup>2</sup>, N. Madrange<sup>3</sup>, J.-Y. Pierga<sup>4</sup>, P. Kerbrat<sup>5</sup>, M. Espié<sup>6</sup>, P. Fumoleau<sup>7</sup>, I. Pauporté<sup>8</sup>, D. Khayat<sup>9</sup>, G. Romieu<sup>10</sup> & X. Pivrot<sup>11\*</sup>



Prognosis	0	12	24	36	48	60
Very low	552	539	472	321	171	6
Low	620	600	525	381	214	7
Interm.	347	333	290	215	123	1
High	148	135	113	76	44	4

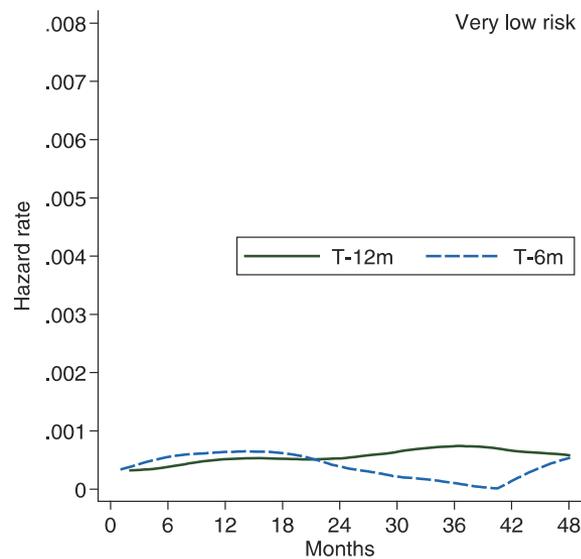
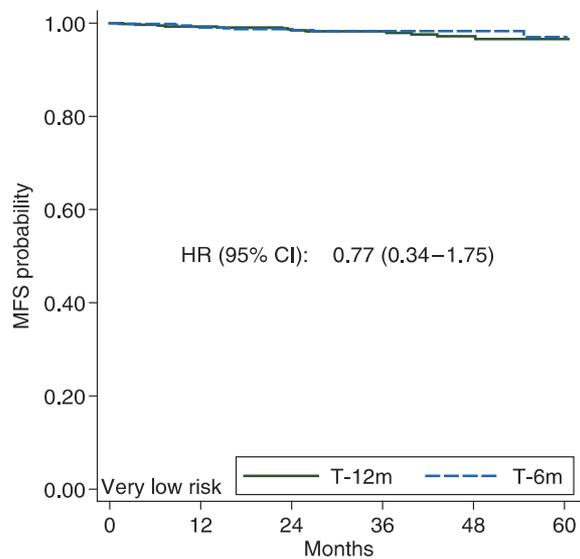


Prognosis	0	12	24	36	48	60
Very low	552	536	472	333	182	4
Low	591	564	489	335	189	9
Interm.	355	334	288	204	117	12
High	174	148	119	83	47	0

# Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial

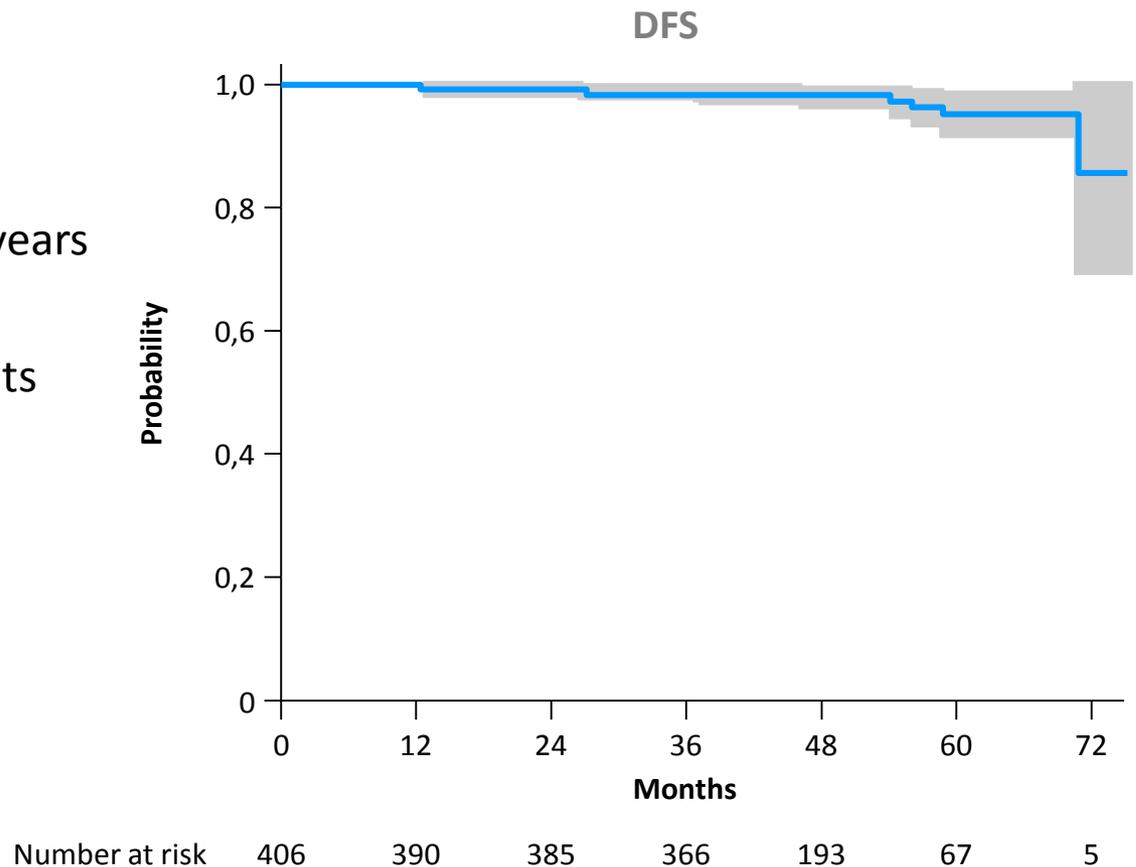
A. Kramar<sup>1</sup>, T. Bachelot<sup>2</sup>, N. Madrange<sup>3</sup>, J.-Y. Pierga<sup>4</sup>, P. Kerbrat<sup>5</sup>, M. Espié<sup>6</sup>, P. Fumoleau<sup>7</sup>, I. Pauporté<sup>8</sup>, D. Khayat<sup>9</sup>, G. Romieu<sup>10</sup> & X. Pivot<sup>11\*</sup>

A. Very low risk



# In low risk cases: Paclitaxel + Trastuzumab seemed to be enough

- Phase II trial
- 406 patients,
- T < 3 cm
- Median follow up 4 years
- Occurrence of only 2 metastatic events



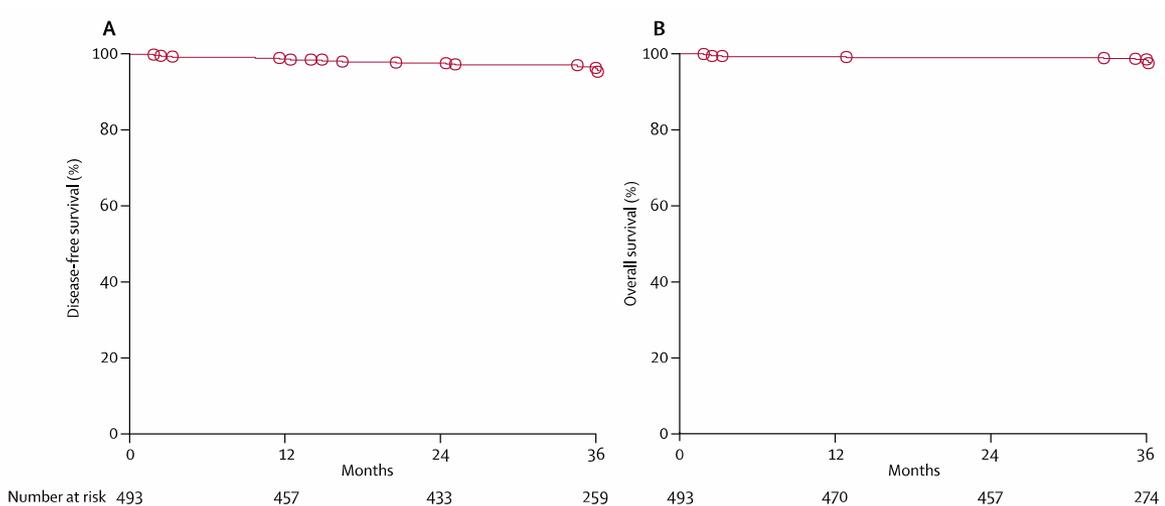
# Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with *HER2*-amplified early stage breast cancer: a single-group, open-label, phase 2 study

Stephen E Jones, Rufus Collea, Devchand Paul, Scot Sedlacek, Anne M Favret, Ira Gore Jr, Deborah L Lindquist, Frankie Ann Holmes, Mary Ann K Allison, Barry D Brooks, Raul M Portillo, Svetislava J Vukelja, Michael S Steinberg, Christopher Stokoe, Maria W Crockett, Yunfei Wang, Lina Asmar, Nicholas J Robert, Joyce O'Shaughnessy

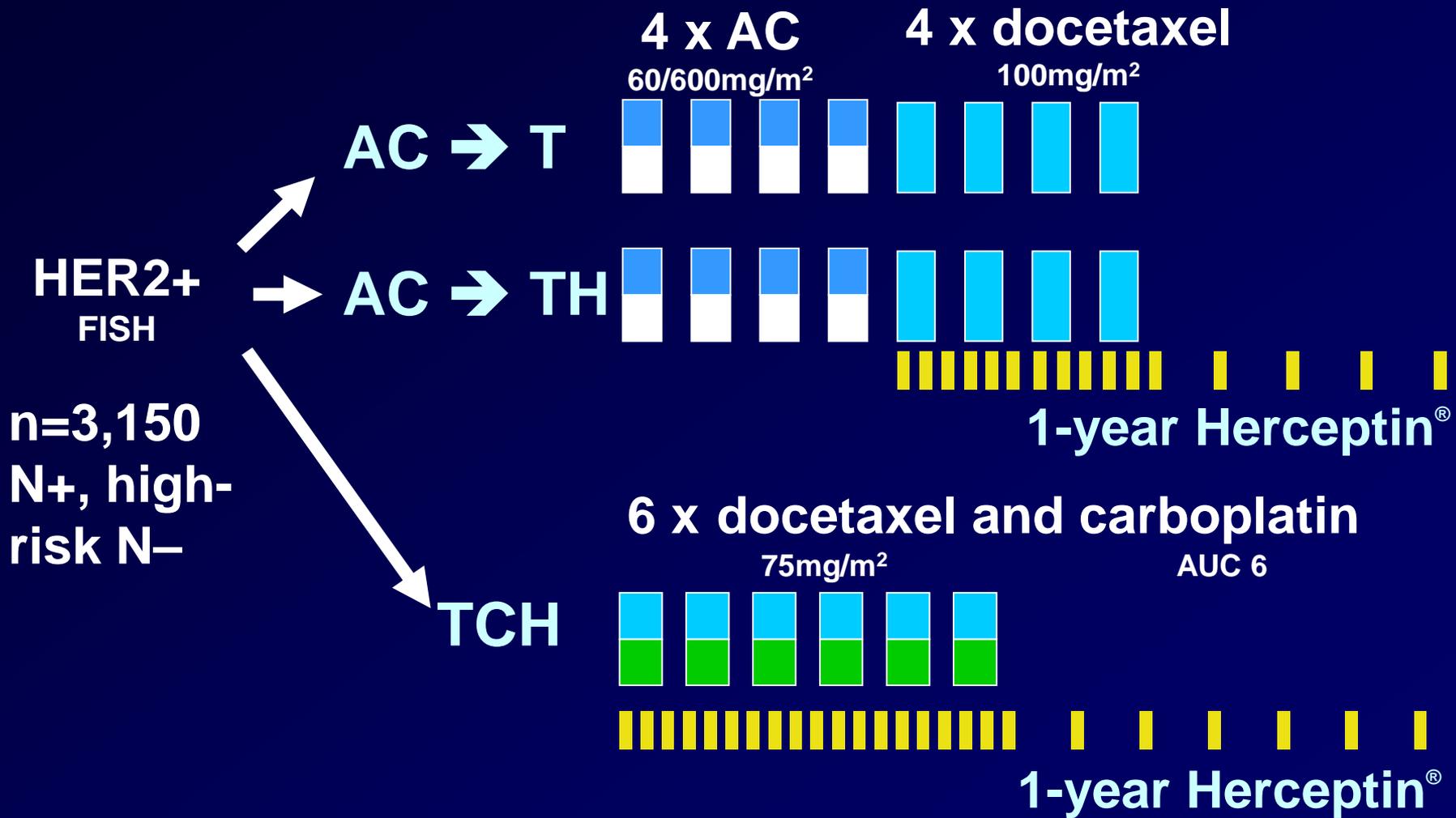
Patients (N=493)	
Age (years)	55 (24-75)
ECOG performance status	
0	431 (87.4%)
1	62 (12.6%)
Stage at diagnosis	
I	284 (57.6%)
II	203 (41.2%)
III	6 (1.2%)
Positive nodes	
None	391 (79.3%)
1-3	96 (19.5%)
≥4	6 (1.2%)
Tumour size (cm)	
<0.5	17 (3.4%)
0.5-1.0	90 (18.3%)
1.1-2.0	224 (45.4%)
2.1-5.0	162 (32.9%)
Oestrogen receptor status	
Negative	173 (35.1%)
Positive	320 (64.9%)
Progesterone receptor status	
Negative	260 (52.7%)
Positive	233 (47.3%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.

**Table 1: Baseline characteristics**



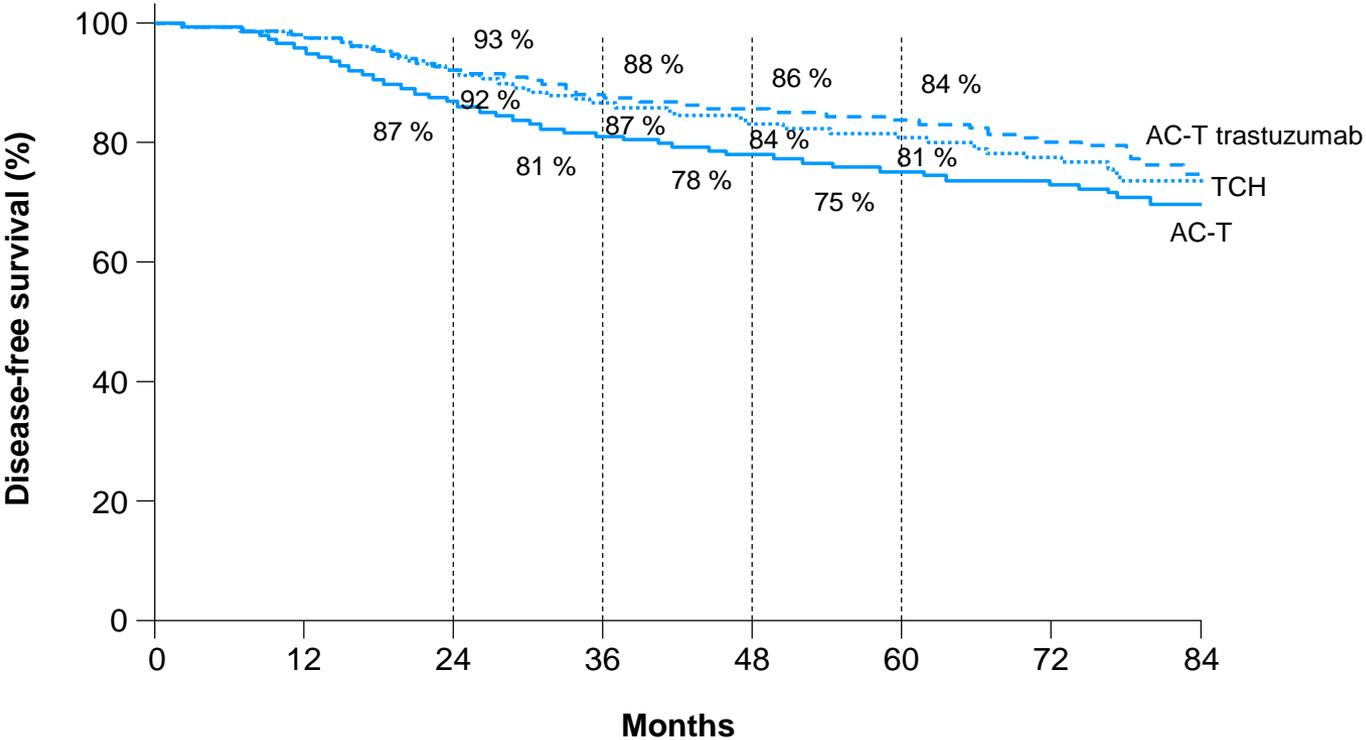
# Is anthracycline containing regimen required in adjuvant HER2 + Breast Cancer?: BCIRG 006



# BCIRG 006 : DFS

	AC-T	TCH	AC-T + trastu
DFS 5 years	75 %	81 %	84 %
HR (vs TC-H)		0,75 ; p = 0,04	0,64 ; p < 0,001

All patients



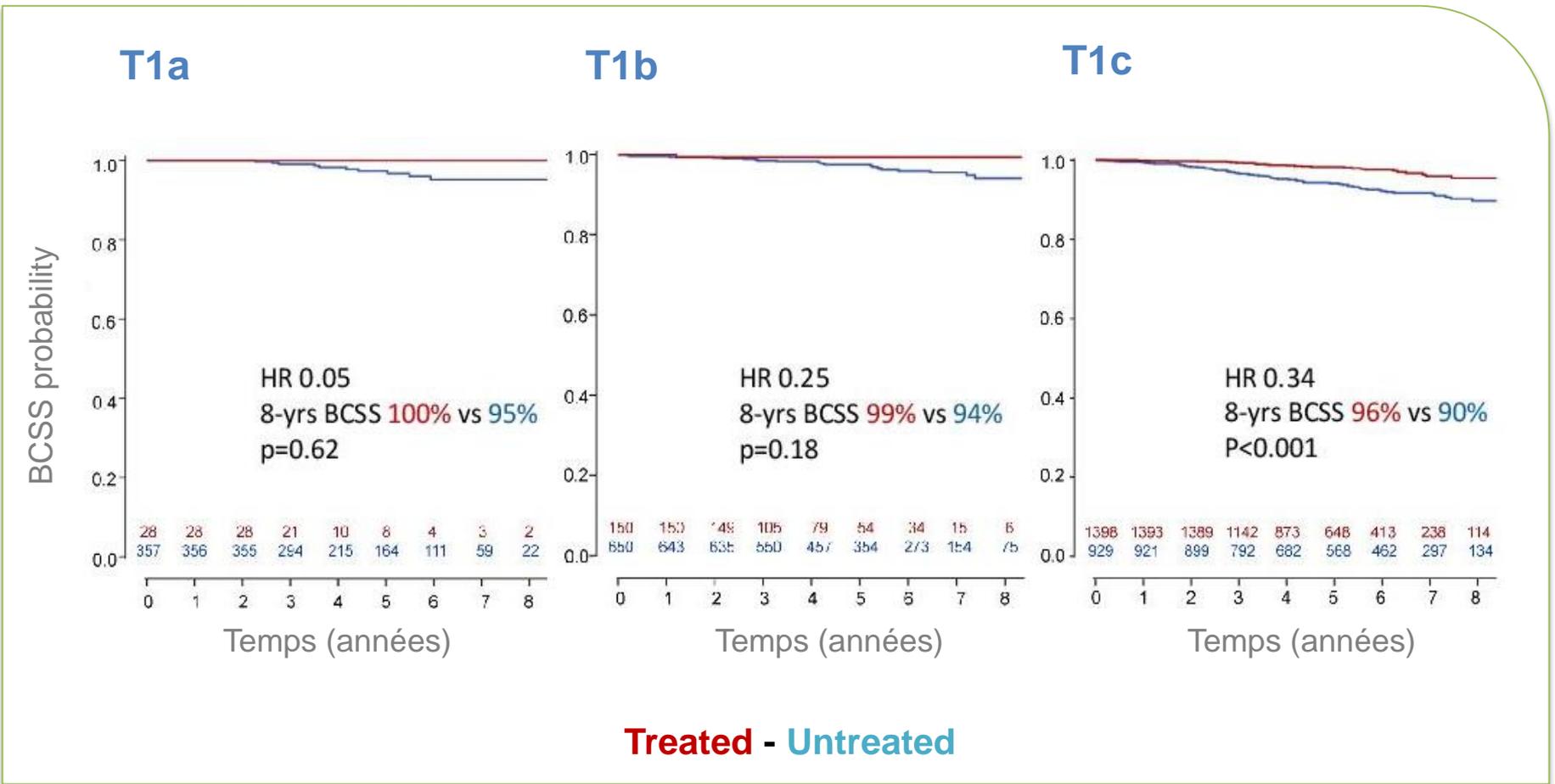
AC-T = Doxorubine – cyclophosphamide followed by docetaxel +/- trastuzumab  
 TCH = Docetaxel – carboplatine – trastuzumab

Slamon. D et al. N Engl J Med. 2011;365(14):1273-83.

# T1 HER2+

## Cohorte néerlandaise de 3512 patientes

### Survie spécifique



# Several ongoing trials are investigating the optimal duration of trastuzumab in HER2-positive eBC



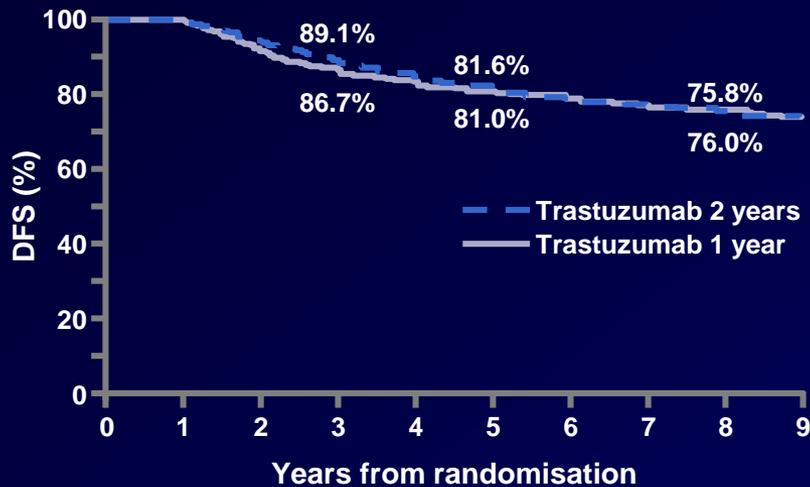
1. Pivot X, *et al. Lancet Oncol* 2013; **14**:741–748; 2. <http://clinicaltrials.gov/ct2/show/NCT00615602>;  
 3. Earl HM, *et al. ASCO* 2013. Abstract TPS667; 4. <http://clinicaltrials.gov/ct2/show/NCT00593697>;  
 5. <http://clinicaltrials.gov/ct2/show/NCT00629278>; 6. Joensuu H, *et al. J Clin Oncol* 2009; **34**:5685–5692;  
 7. Goldhirsch A, *et al. Lancet* 2013; 8. Piccart-Gebhart MJ, *et al. N Engl J Med* 2005; **353**:1659–1672;  
 9. Smith I, *et al. Lancet* 2007; **369**:29–36; 10. Gianni L, *et al. Lancet Oncol* 2011; **12**:236–244;  
 11. Perez EA, *et al. J Clin Oncol* 2011; **29**:3366–3373; 12. Slamon D, *et al. N Engl J Med* 2011; **365**:1273–1283;  
 13. NCCN Clinical Practice Guidelines in Oncology; Breast Cancer v3.2013;  
 14. Senkus E, *et al. Ann Oncol* 2013 [Epub ahead of print]; 15. Goldhirsch A, *et al. Ann Oncol* 2013 [Epub ahead of print].

**Reported**

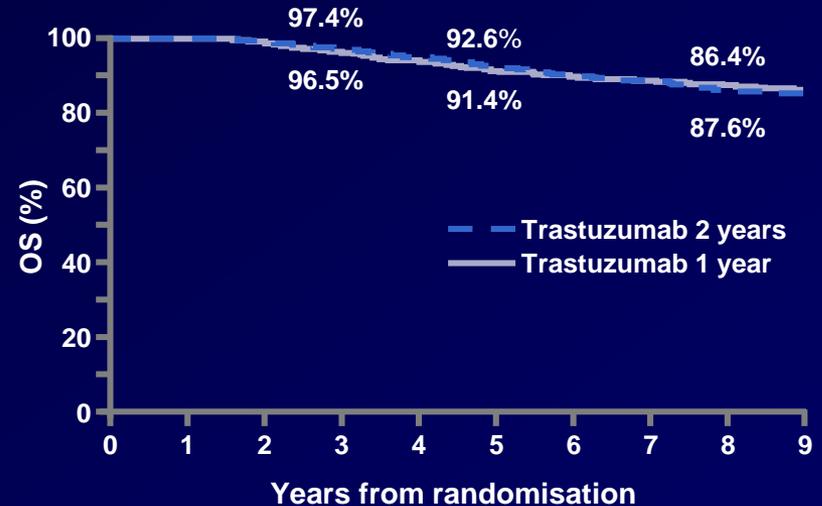
**Ongoing**

# HERA: Trastuzumab for 2 years did not show any additional benefit compared to 1 year of treatment

## DFS<sup>1</sup>



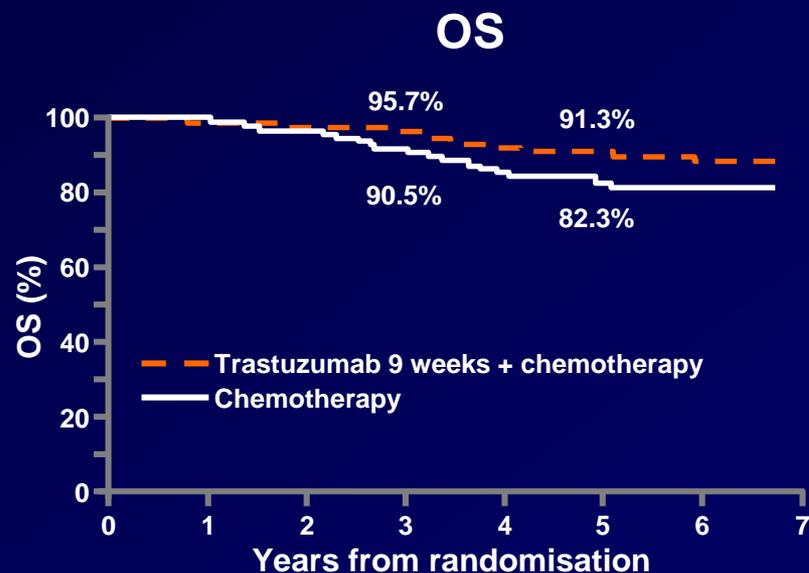
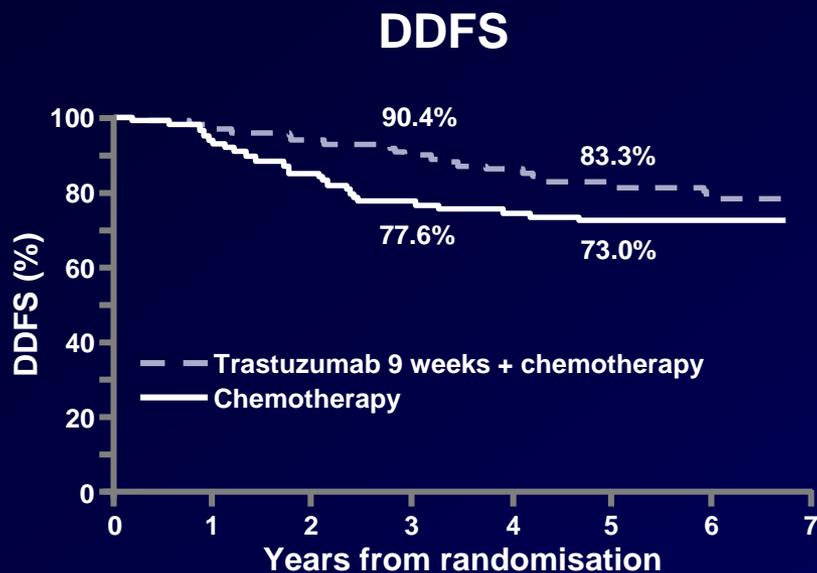
## OS<sup>2</sup>



	Patients	Events	HR (2 vs. 1 year)	95% CI	p value
2 years	1553	367	0.99	(0.84, 1.14)	0.86
1 year	1552	367			

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

# FinHer: No statistically significant improvement in DDFS or OS with 9 weeks of trastuzumab vs. chemotherapy alone



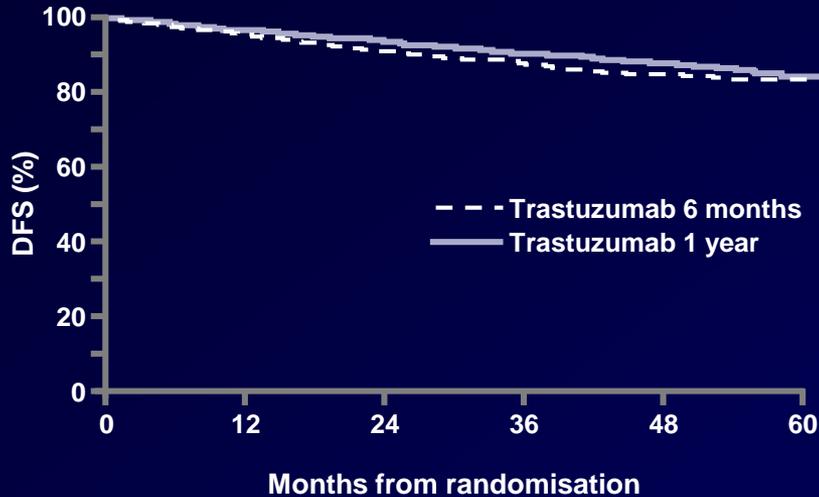
	Patients	Events	HR (9 weeks vs. none)	95% CI	p value		Patients	Events	HR (9 weeks vs. none)	95% CI	p value
9 weeks	115	22	0.65	(0.38, 1.12)	0.12	9 weeks	115	12	0.55	(0.27, 1.11)	0.094
Chemo	116	31				Chemo	116	21			

CI, confidence interval; DDFS, distant disease-free survival.

Joensuu H, et al. *J Clin Oncol* 2009; **27**:5685–5692.

# PHARE: Non-inferiority of 6 months vs. 1 year of trastuzumab was not demonstrated

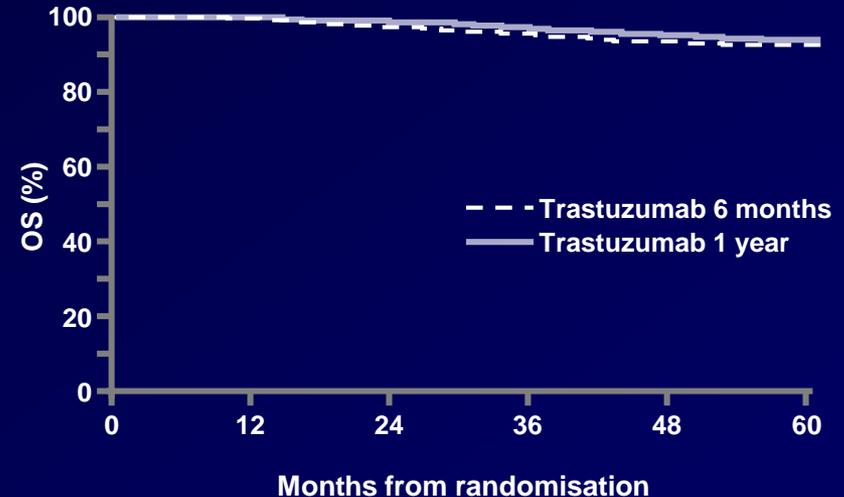
## Primary endpoint: DFS



	Patients	Events	HR (6 months vs. 1 year)	95% CI	p value
6 months	1690	219	1.28*	(1.05, 1.56)	0.29
1 year	1690	175			

HR (95% CI): 1.28 (1.05, 1.56)  
 (above the pre-specified non-inferiority CI of 1.15)  
 Positive heterogeneity test

## OS



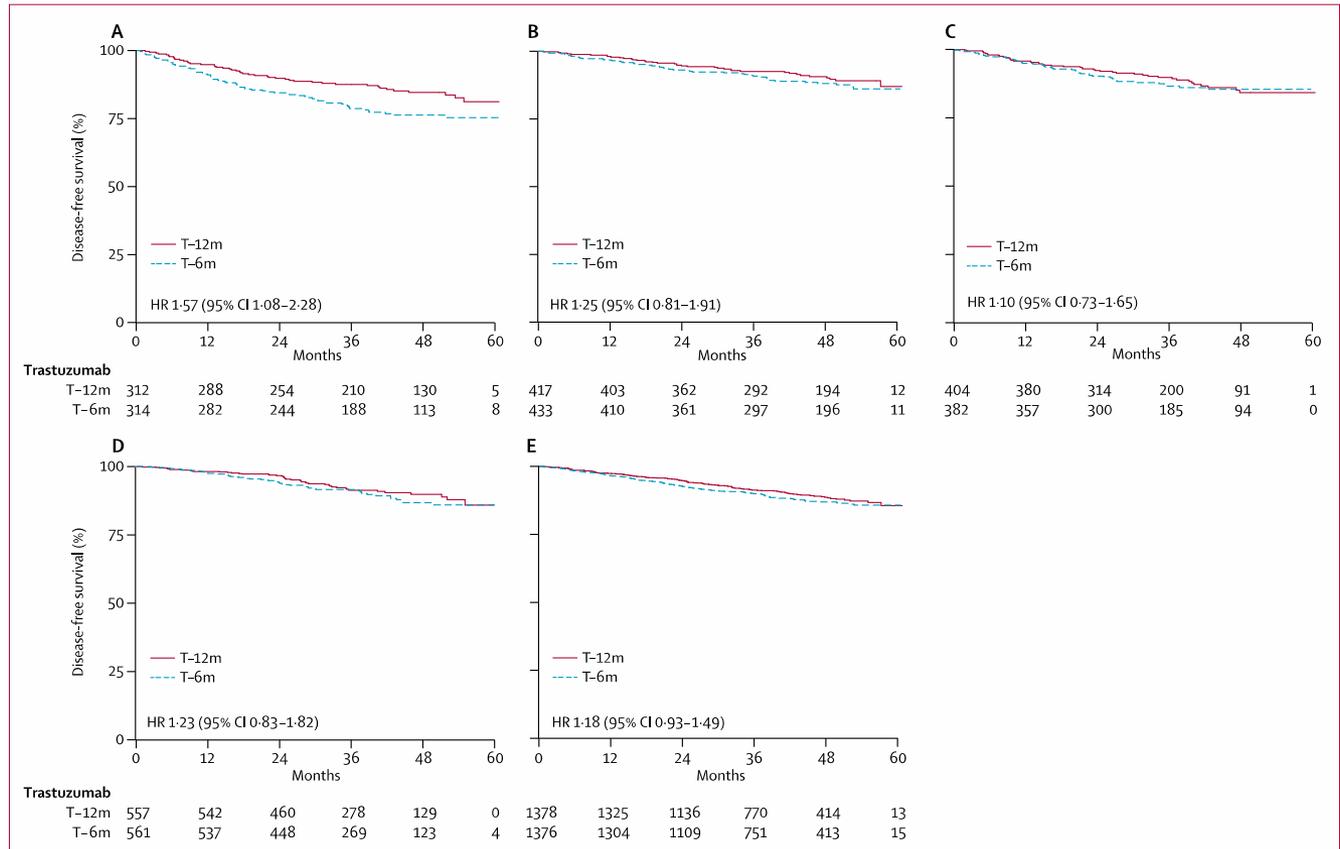
	Patients	Events	HR (6 months vs. 1 year)	95% CI	p value
6 months	1690	93	1.46	(1.06, 2.01)	0.03
1 year	1690	66			

HR (95% CI): 1.46 (1.06, 2.01)

# 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial

Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar, and the PHARE trial investigators\*

Lancet Oncol 2013; 14: 741-48

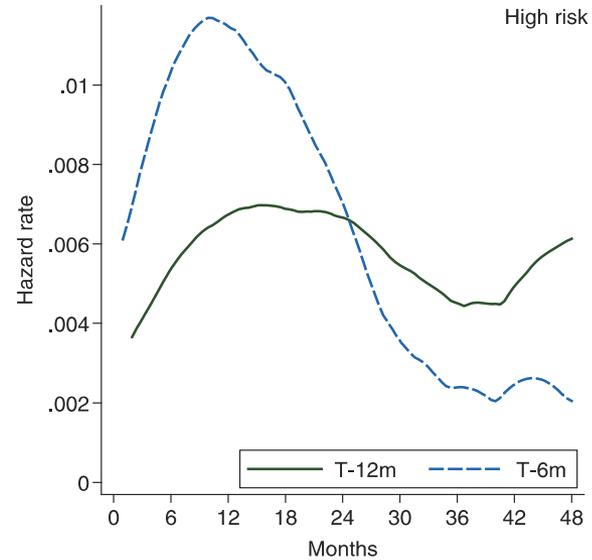
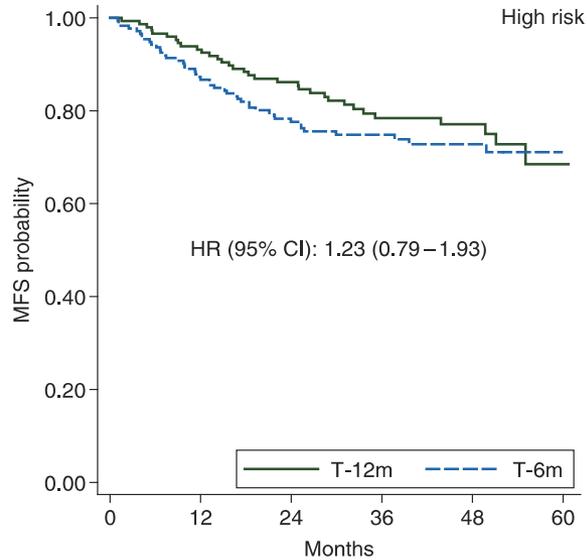


**Figure 4:** Effect of trastuzumab duration in subgroups defined according to oestrogen-receptor status and timing of trastuzumab administration relative to chemotherapy. Oestrogen-receptor negative, sequential chemotherapy and trastuzumab (A). Oestrogen-receptor positive, sequential chemotherapy and trastuzumab (B). Oestrogen-receptor negative, concomitant chemotherapy and trastuzumab (C). Oestrogen-receptor positive, concomitant chemotherapy and trastuzumab (D). Oestrogen-receptor positive or treated with concomitant chemotherapy and trastuzumab (E). T-12m=12 months of trastuzumab. T-6m=6 months of trastuzumab. HR=hazard ratio.

# Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial

A. Kramar<sup>1</sup>, T. Bachelot<sup>2</sup>, N. Madrange<sup>3</sup>, J.-Y. Pierga<sup>4</sup>, P. Kerbrat<sup>5</sup>, M. Espié<sup>6</sup>, P. Fumoleau<sup>7</sup>, I. Pauporté<sup>8</sup>, D. Khayat<sup>9</sup>, G. Romieu<sup>10</sup> & X. Pivot<sup>11\*</sup>

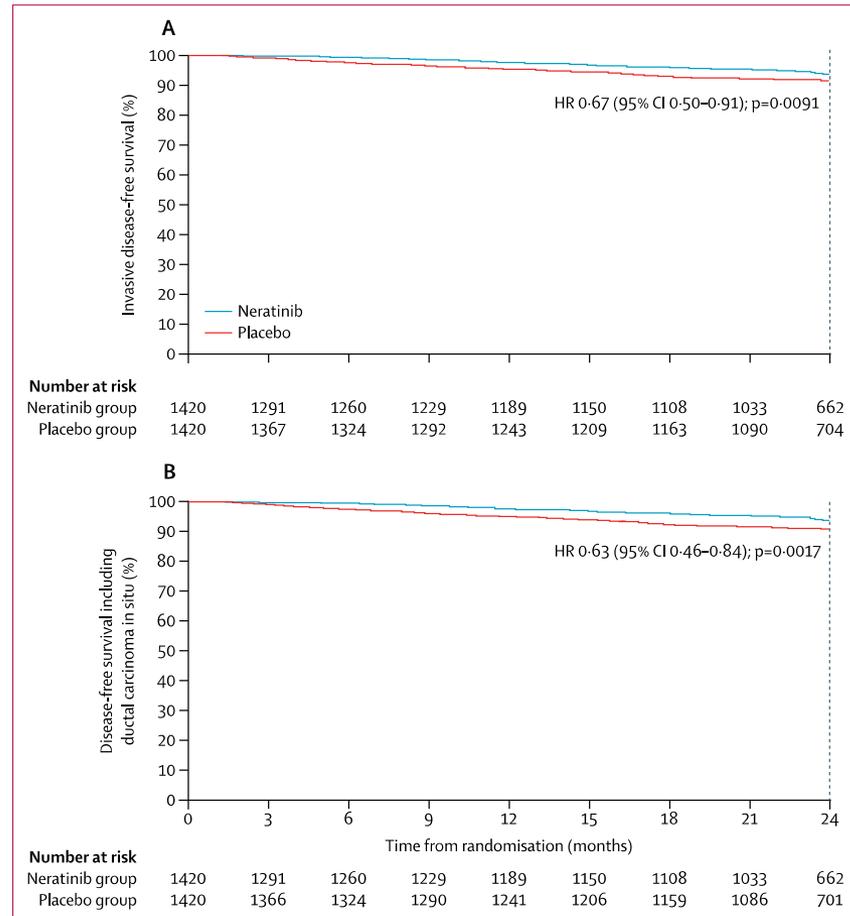
D. High risk



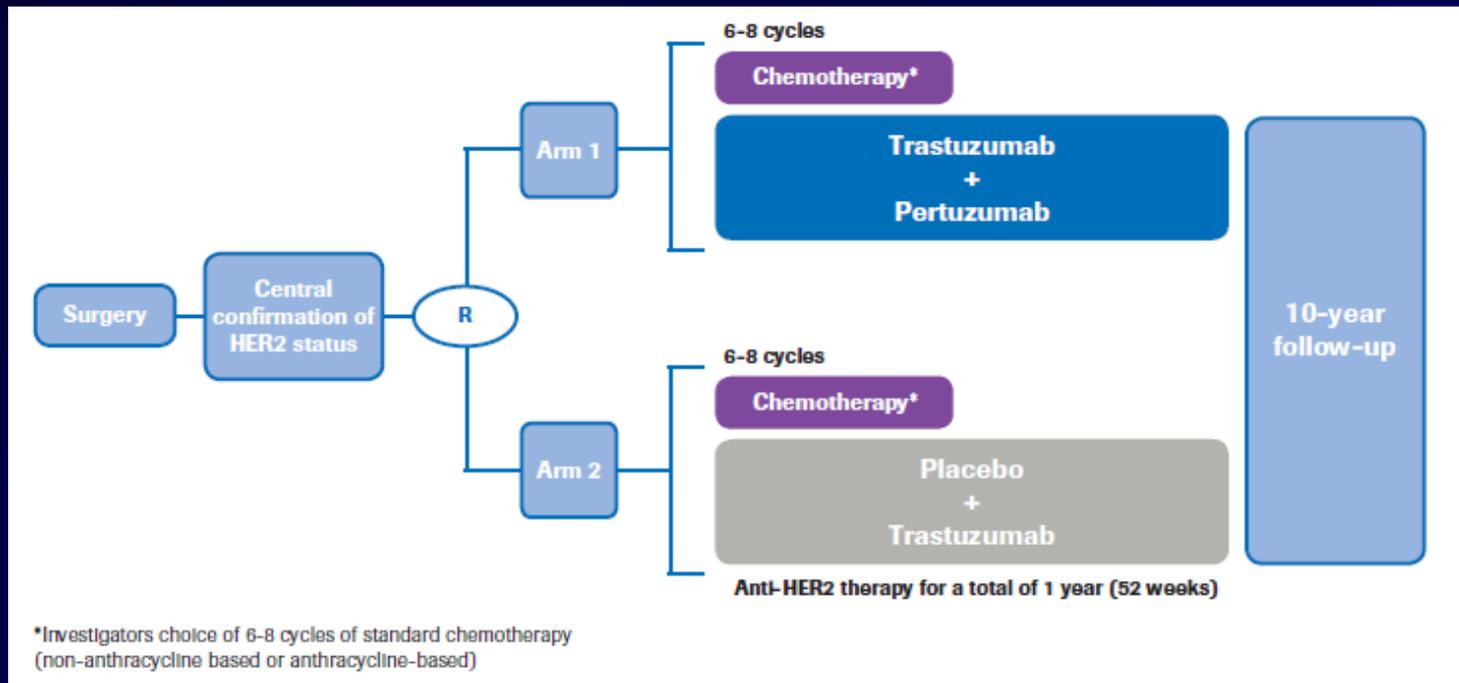
# Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Arlene Chan, Suzette Delalogue, Frankie A Holmes, Beverly Moy, Hiroji Iwata, Vernon J Harvey, Nicholas J Robert, Tajana Silovski, Erhan Gokmen, Gunter von Minckwitz, Bent Ejlertsen, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Marc Buyse, Ira Gore, John Smith II, Graydon Harker, Norikazu Masuda, Katarina Petrakova, Angel Guerrero Zotano, Nicholas Iannotti, Gladys Rodriguez, Pierfrancesco Tassone, Alvin Wong, Richard Bryce, Yining Ye, Bin Yao, Miguel Martin, for the ExteNET Study Group

Lancet Oncol 2016; 17: 367-77



# APHINITY



- **Primary Objectif**

- Invasive Disease-Free Survival (IDFS)

Expected results in 2017

	Trastuzumab	Chimio	Pop cible	Niveau de preuve
Standard	1 an	A + T	N+	I
Alternative	1 an	TC	N+	II
Alternative	1 an	T	N- / < 3cm	II
Avenir ?	+ Pertuzumab			APHINITY
Sans bénéfice	2 ans			I
?	9 semaines			Shorter
?	6 mois		?	PHARE / PERSEPHONE