Essais de supériorité / d'équivalence / de non-infériorité

Prof. X Pivot

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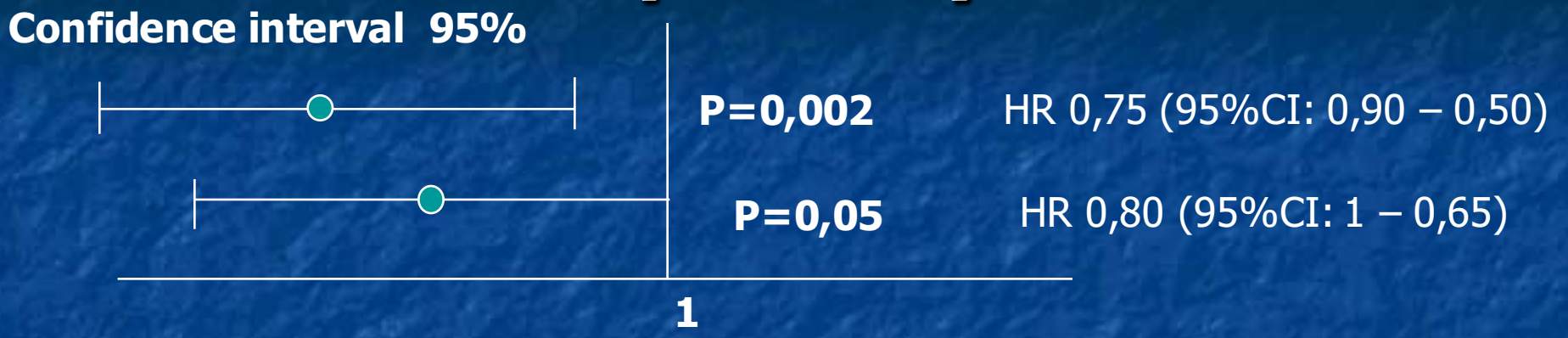
UNICANCER

Superiority



Ratio of events over the time between arm A and B and its 95%CI

Hypothesis

Null:

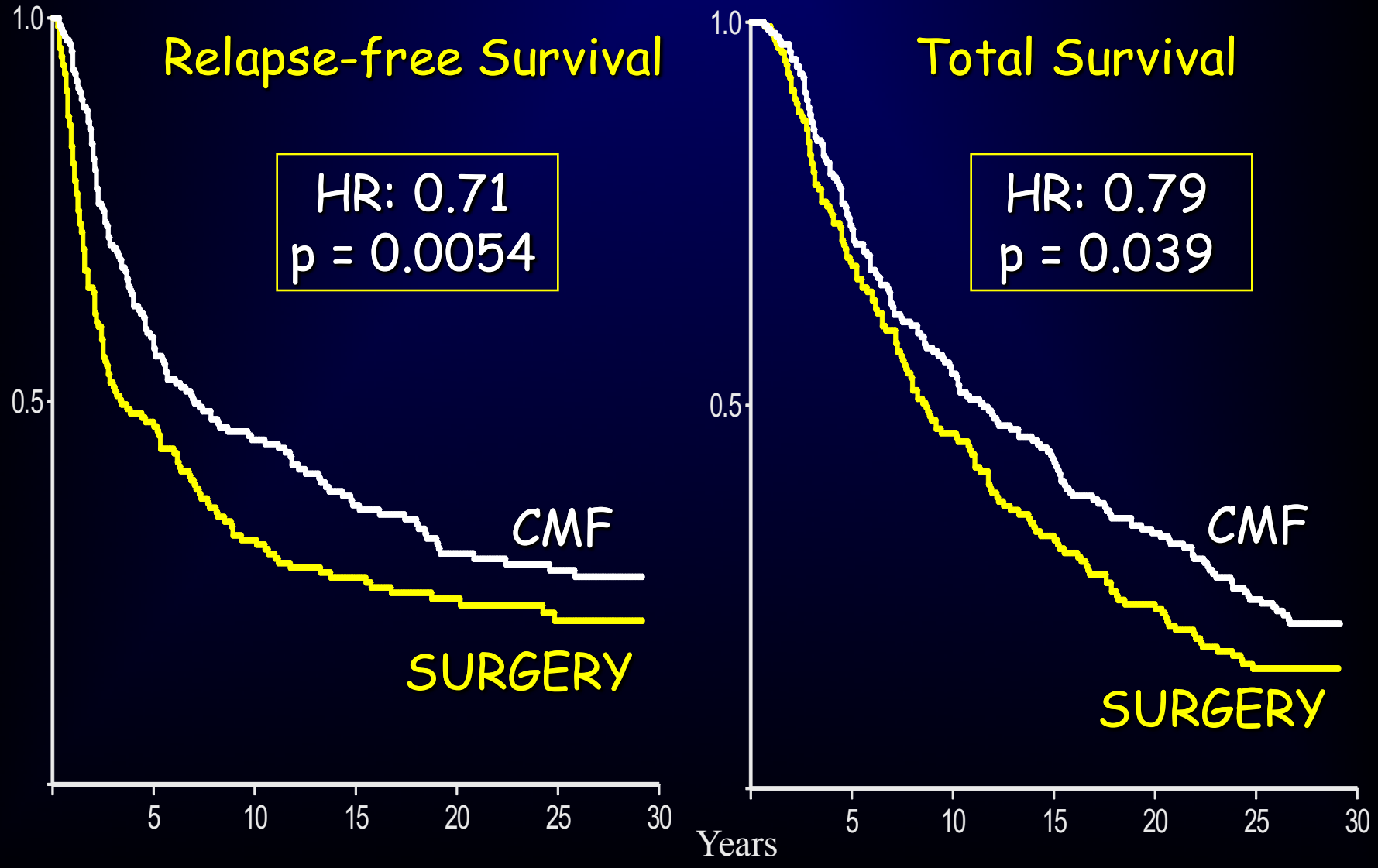
No different between A and B

Alternative:

B different from A (bi sidedl): B ≠ A

B better than A (one sided): B > A

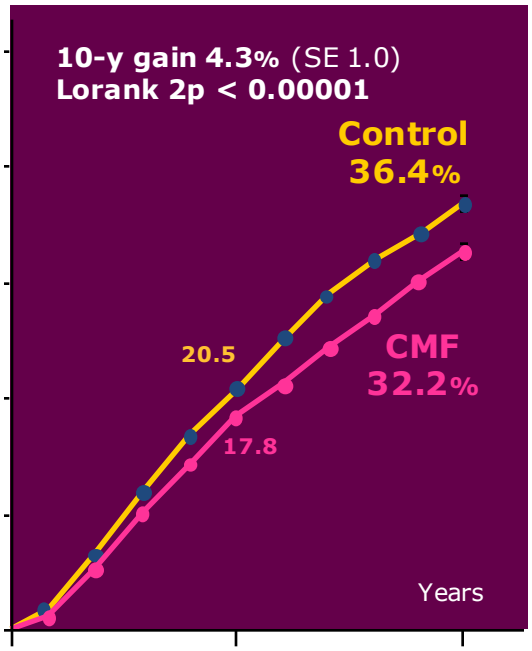
First CMF Program

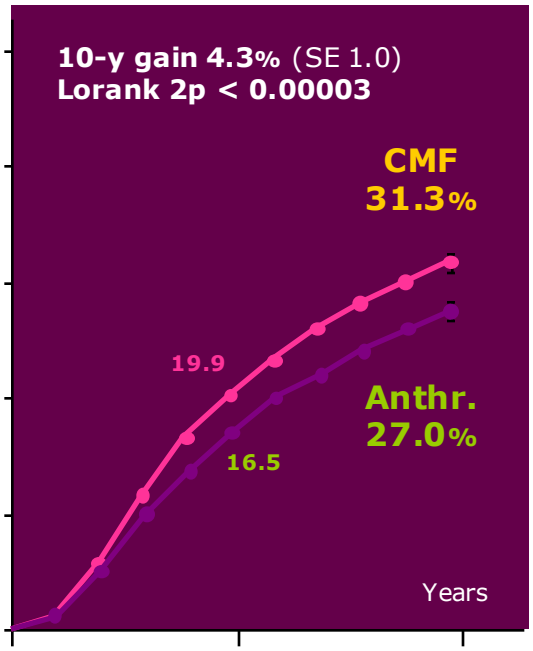


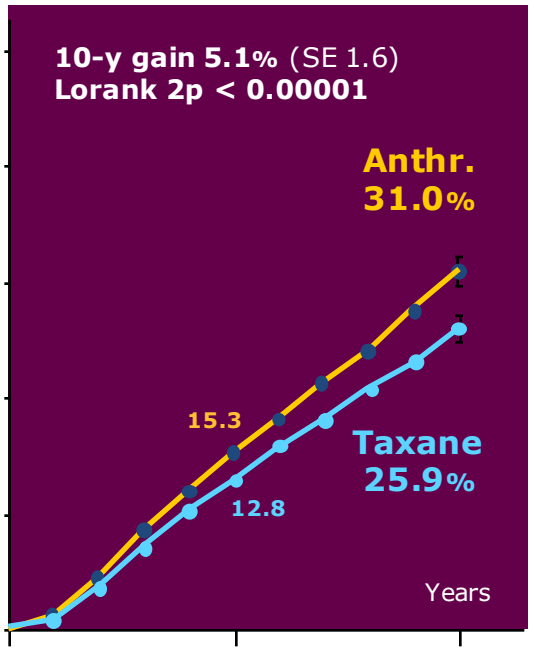
Milan Cancer Institute

EBCTCG Meta-analysis 2005-06
Breast cancer mortality

Taxanes > Anthra. > CMF > No Chemo.







Peto R on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Presented at SABCS 2007, December 13, 2007. San Antonio, TX.

RELATIVE and ABSOLUTE RISK

without adj	N = 100	DCD = 40
With adj	N = 100	DCD = 30

relatif benefit = 25%

absolute benefit= 10%

Without adj	N = 100	DCD = 12
With adj	N = 100	DCD = 9

relatif benefit= 25%

absolute benefit= 3%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2016 VOL. 375 NO. 3

Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar

DFS Outcomes	Letrozole	Placebo	HR (95% CI)	*P* Value
Overall 5-yr DFS, %	95	91	0.66 (0.48-0.91)	.01
Events, n (%)	67 (7.0)	98 (10.2)		
New contralateral breast cancers, n (%)	13 (1.4)	31 (3.2)		.007
Locoregional recurrences, n	19	30		
Distant recurrences, n	42	53		
Bone recurrences, n	28	37		

Goss PE, et al. ASCO 2016. Abstract LBA1.

Hortobagyi G. N Engl J Med 2005;353:173

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Trastuzumab in the Treatment of Breast Cancer

Gabriel N. Hortobagyi, M.D.

October 25th 2005

"Clearly, the results reported in this issue of the Journal are not evolutionary… but revolutionary."

G Hortobagyi

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

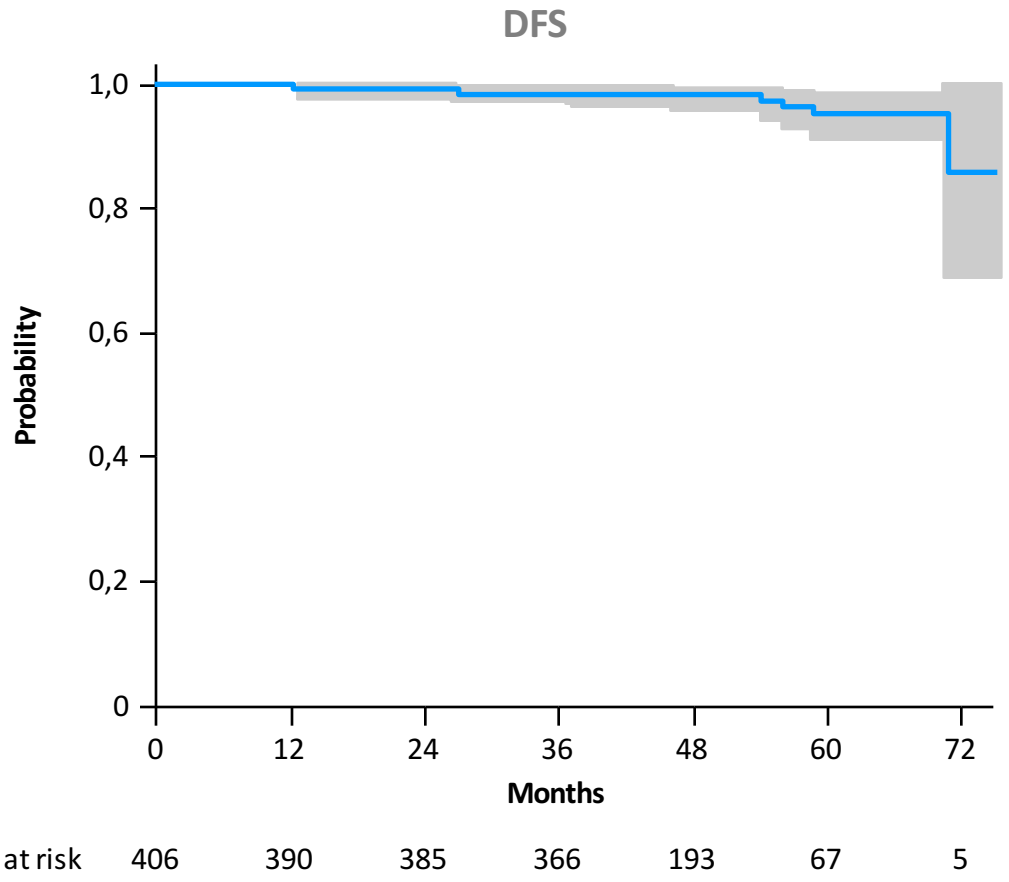
Study	Follow-up (years)	N	DFS HR	DFS p value	OS HR	OS p value
HERA[1–4] CT±RT→T vs. CT±RT	1	3387	0.54	< 0.0001	0.76	0.26
	2	3401	0.64	< 0.0001	0.66	0.0115
	4	3401	0.76	< 0.0001	0.85	0.1087
	8	3399	0.76	< 0.0001	0.76	0.0005
NCCTG N9831/ NSABP B-31[5–7] AC→Tax+T→T vs. AC→Tax	2	3351	0.48	< 0.0001	–	–
	4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

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.

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

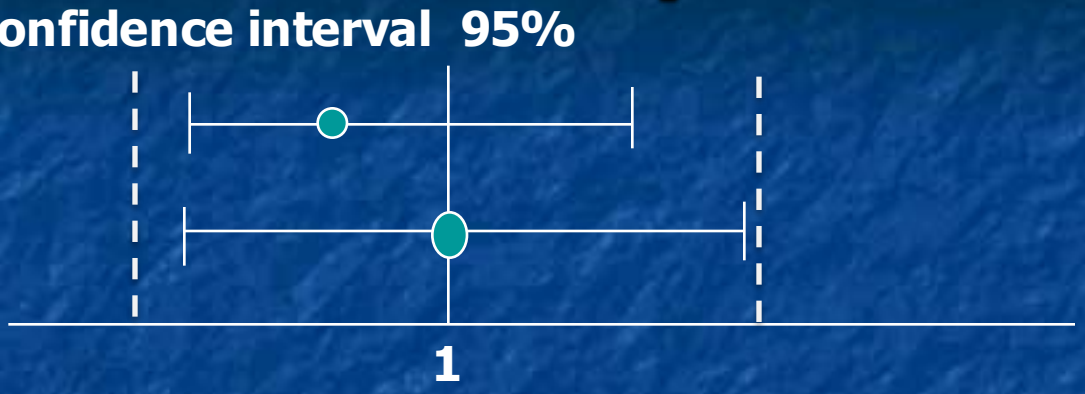
- **Phase II trial**
- **406 patients,**
- **T < 3 cm**
- **Median follow up 4 years**
- **Occurrence of only 2 metastatic events**



Update ASCO 2017
7 years Follow-up
4 metastatic events

Tolaney SM, et al. N Engl J Med. 2015;372(2):134-41.

Equivalence



HR 0,95 (95%CI: 0,9 – 1,05)

HR 1 (95%CI: 0.9 – 1,1)

Ratio of events over the time between arm A and B and its 95%CI

Hypothesis

Null:

Difference between A and B

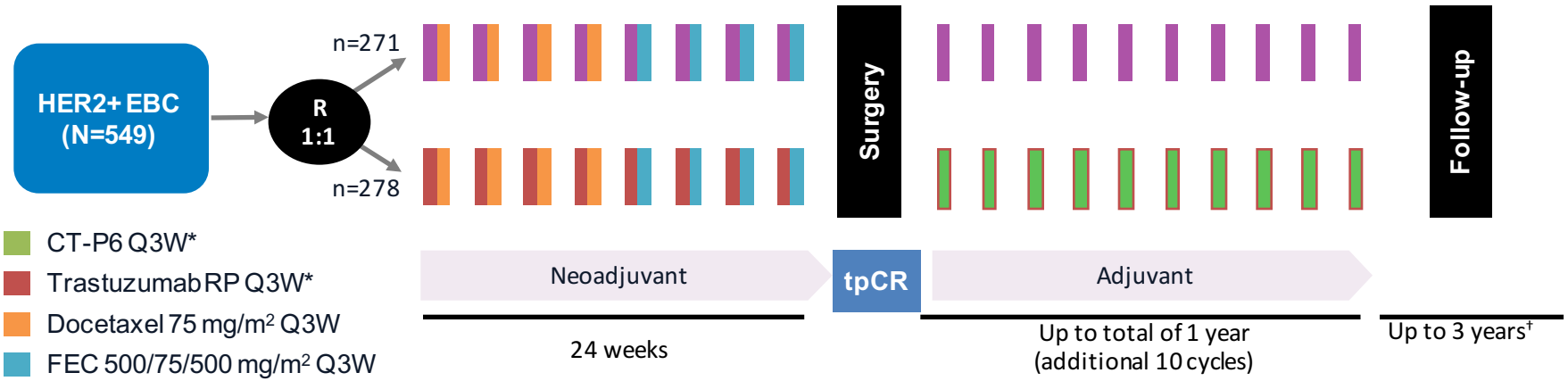
Alternative:

No different between A and B

CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial

Justin Stebbing, Yauheni Baranau, Valeriy Baryash, Alexey Manikhas, Vladimir Moiseyenko, Giorgi Dzagnidze, Edvard Zhavrid, Dmytro Boliukh, Daniil Stroyakovskii, Joanna Pikiel, Alexandru Eniu, Dmitry Komov, Gabriela Morar-Bolba, Rubi K Li, Andriy Rusyn, Sang Joon Lee, Sung Young Lee, Francisco J Esteva

Lancet Oncol 2017; 18: 917–28



Primary endpoint

- tpCR** after neoadjuvant therapy and surgery (up to 30 weeks); per-protocol population
- Pre-defined equivalence margins: 95% CI for RR 0.74–1.35; 95% CI for RD +/-15%

Secondary endpoints

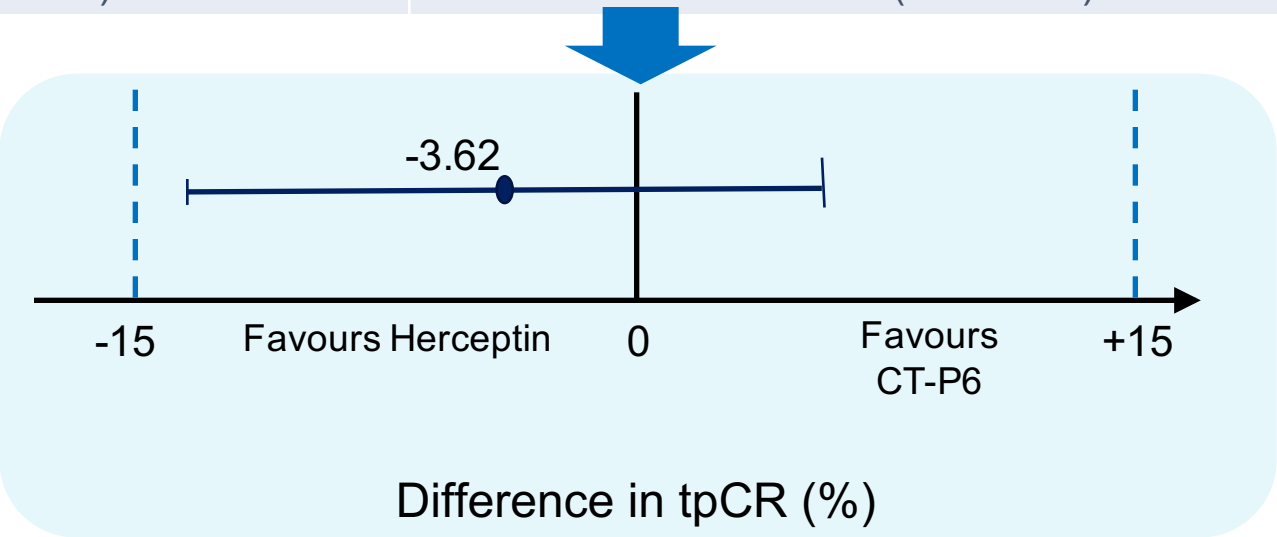
- Efficacy: pCR (breast only), tpCR (without DCIS), ORR, breast conservation rate, DFS, PFS, OS
- Other: PK, PD, biomarkers and safety

itial dose of 8 mg/kg IV, then 6 mg/kg for remaining cycles. **pCR in breast and axillary lymph nodes. †From the date of last patient enrolment. DCIS, ductal carcinoma in situ

Stebbing J, et al. Lancet Oncol 2017;18:917–928; Esteva FJ, et al. ESMO 2017; Poster 152PD

CT-P6 vs trastuzumab reference product in eBC: primary endpoint tpCR in per protocol set

Primary endpoint	CT-P6 + (n=271)	Herceptin (n=278)
tpCR	46.8%	50.4%
Risk difference, (95% CI) Ratio (95%CI)	-3.62% (-12.38, 5.16) 0.93 (0.78-1.11)	



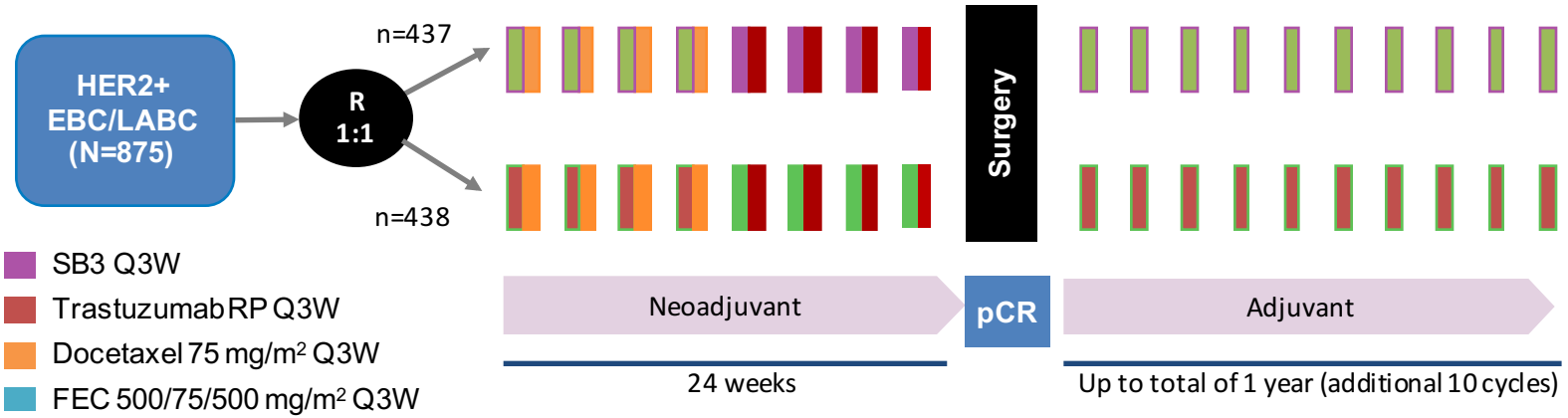
J. Stebbing et al. *Lancet Oncol*. 2017 (18) : 917-28

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

Xavier Pivot, Igor Bondarenko, Zbigniew Nowecki, Mikhail Dvorkin, Ekaterina Trishkina, Jin-Hee Ahn, Yuriy Vinnyk, Seock-Ah Im, Tomasz Sarosiek, Sanjoy Chatterjee, Marek Z. Wojtukiewicz, Vladimir Moiseyenko, Yaroslav Shparyk, Maximino Bello III, Vladimir Semiglazov, Sujeong Song, and Jaeyun Lim

DOI: 10.1200/JCO.2017.74.0126



Primary endpoint

- pCR (breast only) after neoadjuvant therapy and surgery; per-protocol population
- Pre-defined equivalence margins: 90% CI for RR 0.785–1.546; 95% CI for RD +/-13%

Secondary endpoints

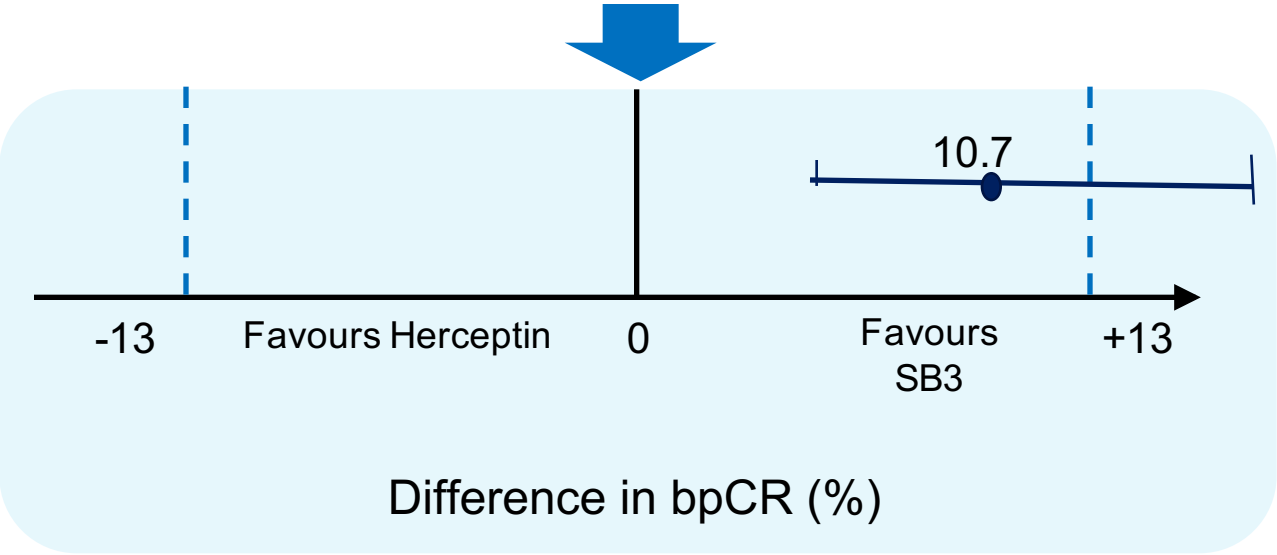
- Efficacy: tpCR, ORR, EFS
- Other: PK, immunogenicity and safety

Pivot X, et al. JCO 2018

LABC, locally-advanced breast cancer

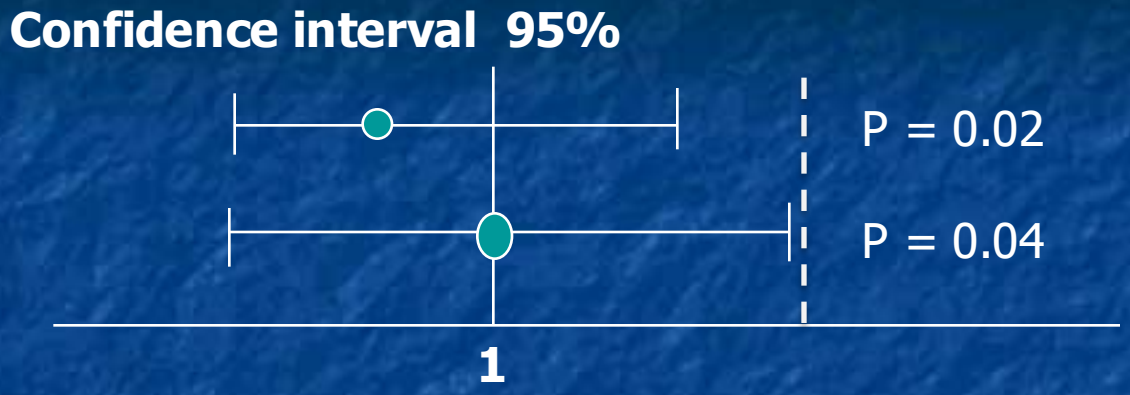
SB3 vs trastuzumab reference product in eBC: primary endpoint tpCR in ITT set

Primary endpoint	SB3 (n=402)	Herceptin (n=398)
bpCR	51.7%	42%
Risk difference, (95% CI) Ratio (95%CI)	10.7% (4.13, 17.26) 1.259 (1.112-1.426)	



X Pivot et al, JCO 2018

Non - Inferiority



Ratio of events over the time between arm A and B and its 95%CI

Hypothesis

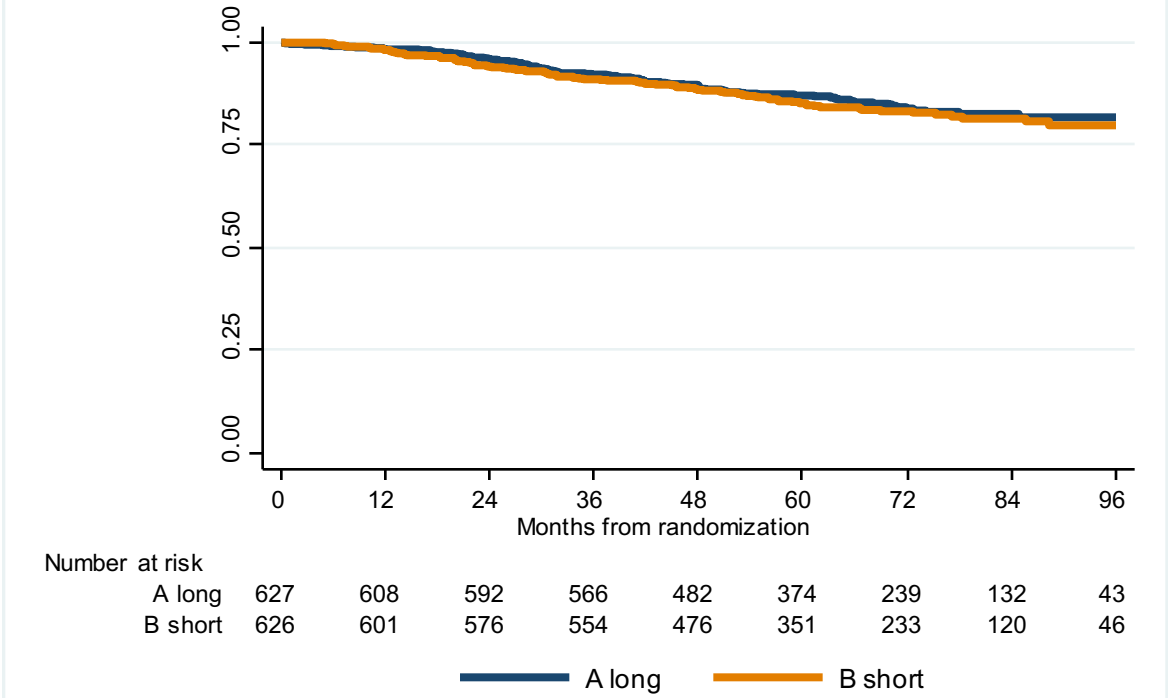
Null:

Difference between A and B

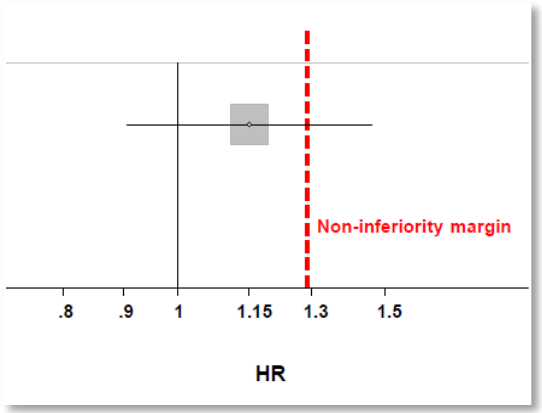
Alternative:

No superiority between A and B

Short-HER: Disease Free Survival



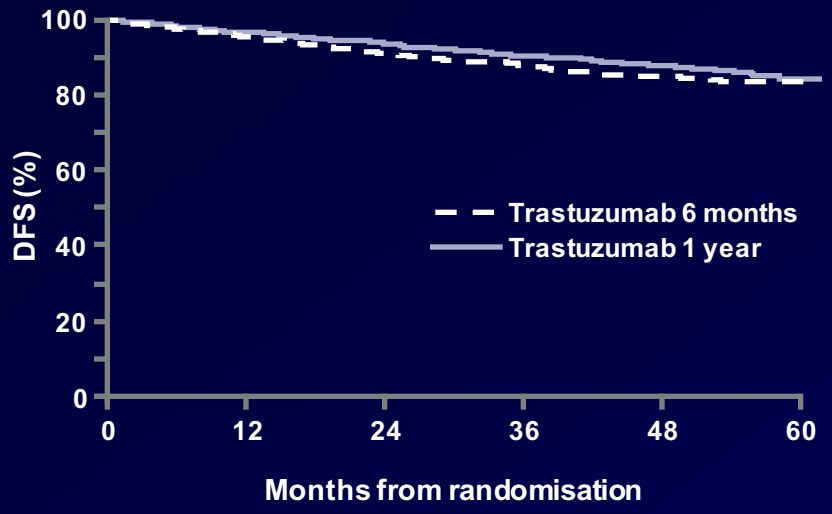
	Long (N=627)	Short (N=626)
DFS events #	89	100
5y DFS %	87.5	85.4
HR (90% CI)	1.15 (0.91-1.46)	



Presented by: PierFranco Conte

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

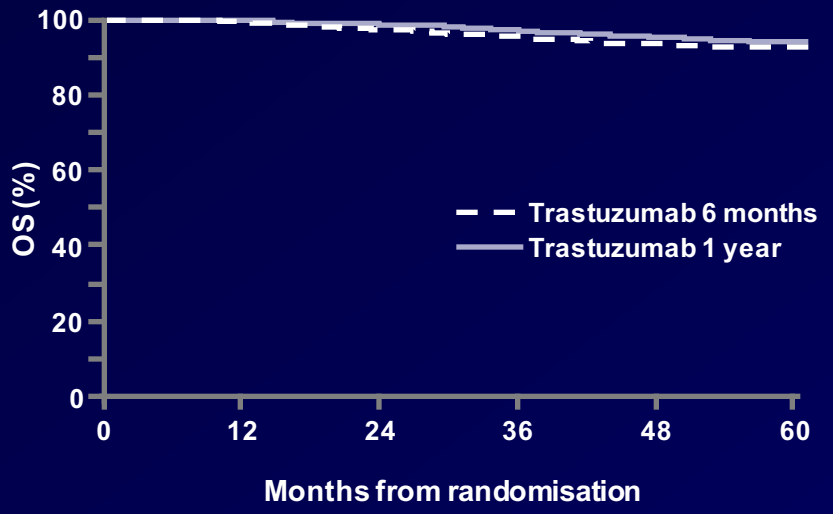
Primary endpoint: DFS



	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)

OS

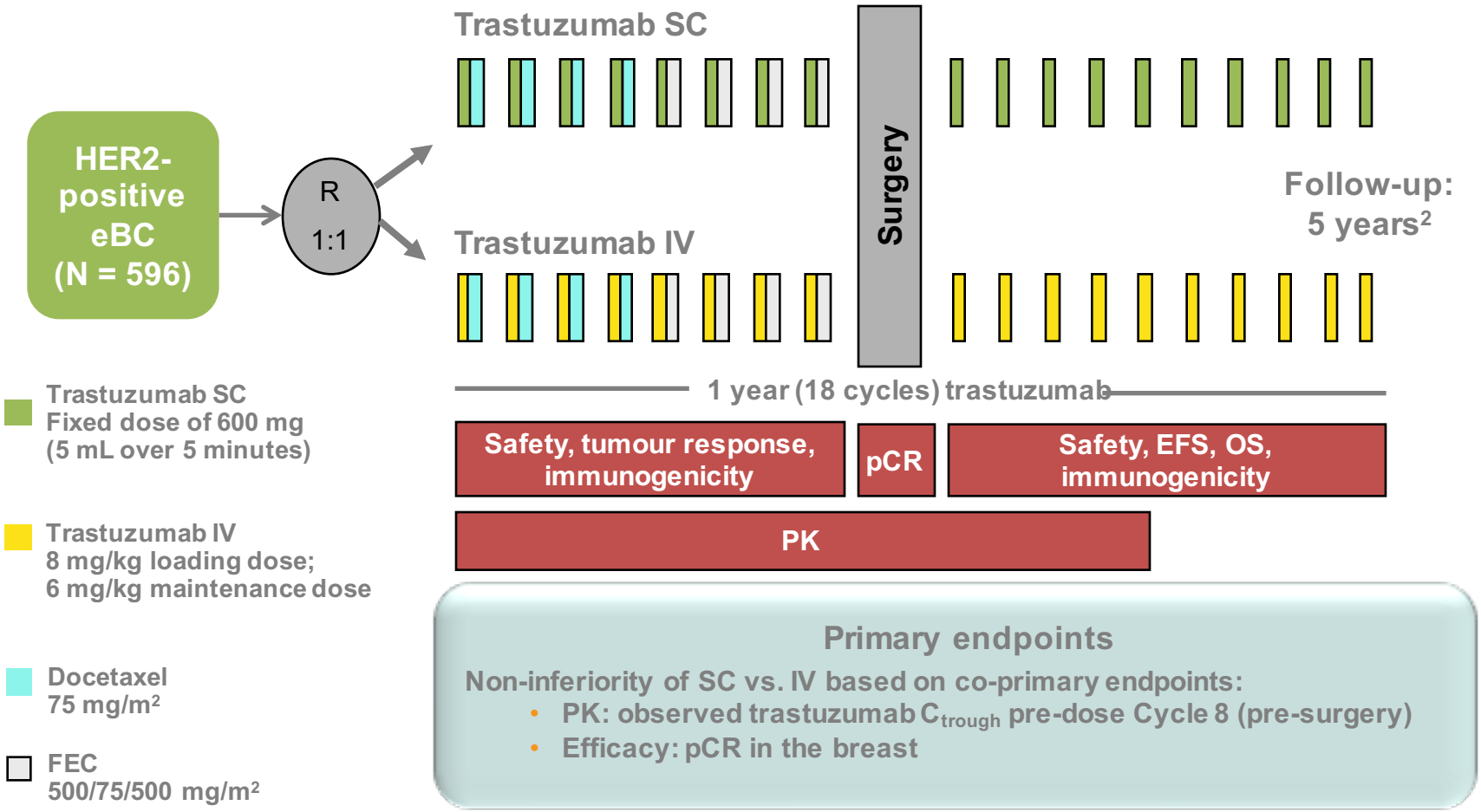


	Patients	Events	HR (6 months vs. 1 year)	95% CI	p value
6 months	1690	93	1.46	(1.06, 2.01)	0.03
1 year	1690	66			

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

Pivot X, *et al*. *Lancet Oncol* 2013;**14**:741–748.

HannaH: A pivotal Phase III trial to demonstrate the non-inferiority of trastuzumab SC vs. IV in terms of PK and efficacy[1]



EFS, event-free survival; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; OS, overall survival; R, randomisation;

Ismael G, *et al*. *Lancet Oncol* 2012; **13**:869–878;
www.clincialtrials.gov NCT00950300 (HannaH).

HannaH: Non-inferiority margins for co-primary endpoints

Pharmacokinetic co-primary endpoint:

- Observed C_{trough} at pre-dose Cycle 8
  - Prespecified non-inferiority margin for geometric mean ratio SC *vs.* IV: 0.8

Efficacy co-primary endpoint:

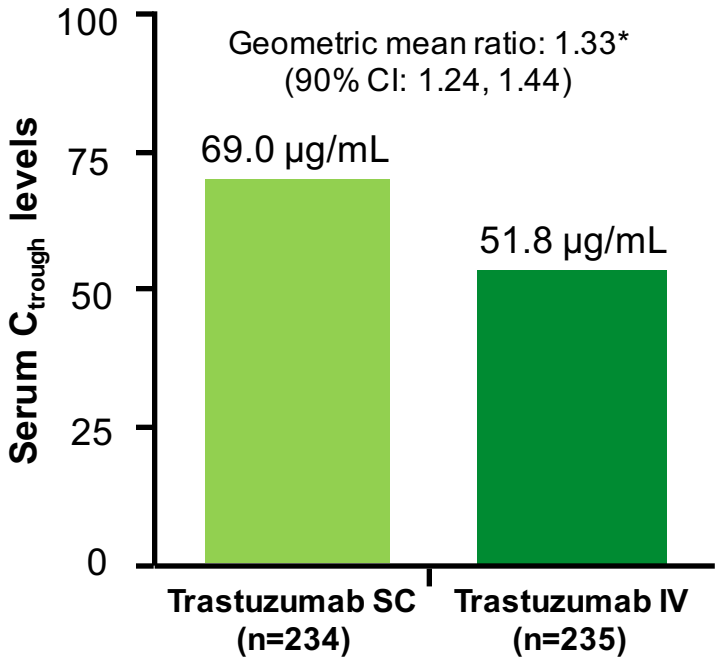
- pCR in the breast
  - Pre-specified non-inferiority margin for pCR rate difference SC–IV: –12.5%

C_{trough}, serum trough concentration; IV, intravenous; pCR, pathological complete response; SC, subcutaneous

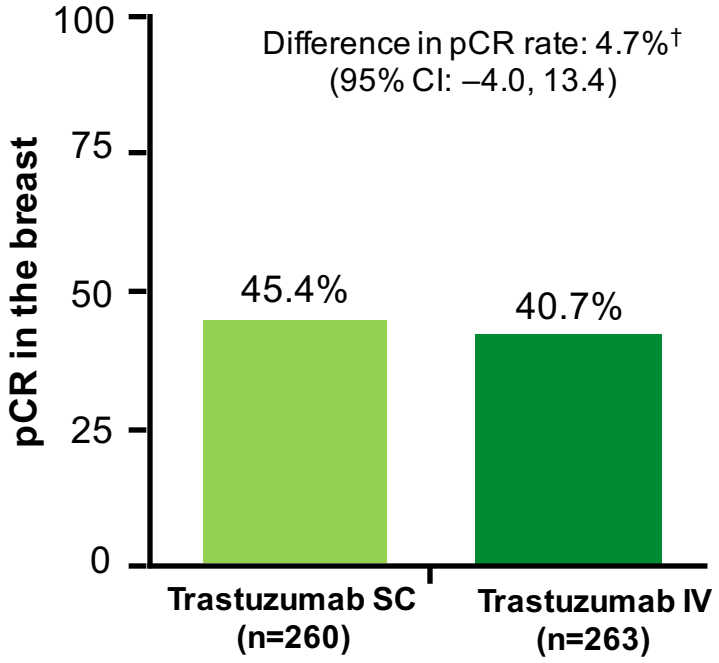
Ismael G, *et al. Lancet Oncol* 2012

HannaH: both co-primary endpoints were met

PK



Efficacy



Trastuzumab SC demonstrated a comparable efficacy and PK profile to the IV formulation

*Non-inferiority margin for the ratio between groups of 0.80;
†Non-inferiority margin for the difference between groups of -12.5%;
CI, confidence interval.
Ismael G, et al. Lancet Oncol 2012;13:869–78