

Update of the HERA trial at 4 years' median follow-up

St Gallen, March 2009

HERA trial design

Women with locally determined HER2-positive invasive early breast cancer



Centrally confirmed IHC 3+ or FISH+ and LVEF \geq 55%



Randomisation



Observation



After ASCO 2005,
option of crossover
to trastuzumab

1 year trastuzumab
8 mg/kg \Rightarrow 6 mg/kg
3-weekly schedule

2 years trastuzumab
8 mg/kg \Rightarrow 6 mg/kg
3-weekly schedule

HER2, human epidermal growth factor receptor 2; CT, chemotherapy; RT, radiotherapy;
IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation; LVEF, left ventricular ejection fraction

Interim analysis and IDMC recommendations

- As specified in the protocol, an interim analysis of 1-year vs 2-year trastuzumab was performed in Q3 2008
- The IDMC reviewed the interim analysis on 20 October 2008 and recommended that:
 - no information on the 1-year vs 2-year trastuzumab be released
 - updated information on the 1-year trastuzumab vs observation be presented and published

HERA history

Presentation
ASCO 2005
DFS benefit¹

Presentation
ASCO 2006
OS benefit²

This presentation,
St Gallen 2009
Update of 1-year trastuzumab
vs observation;
effect of crossover

Dec 01

Apr 05

May 05

Jun 05

Mar 06

Jun 06

Oct 08

Mar 09

ASCO 2005
Presentation
St Gallen

IDMC:
update
1-year trastuzumab
vs observation

patient (n=5102)

Crossover to Trastuzumab group

IDMC:
release update
1-year trastuzumab
vs observation
No release for
1-year vs 2-year
trastuzumab

DFS, disease-free survival;
OS, overall survival

¹Piccart-Gebhart et al NEJM 2005;

²Smith et al Lancet 2007

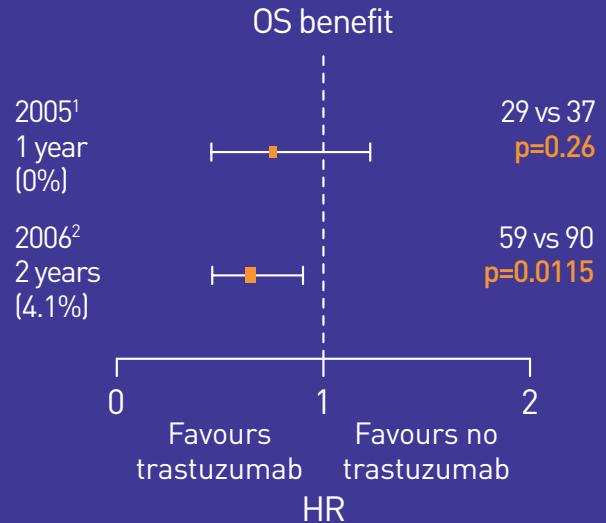
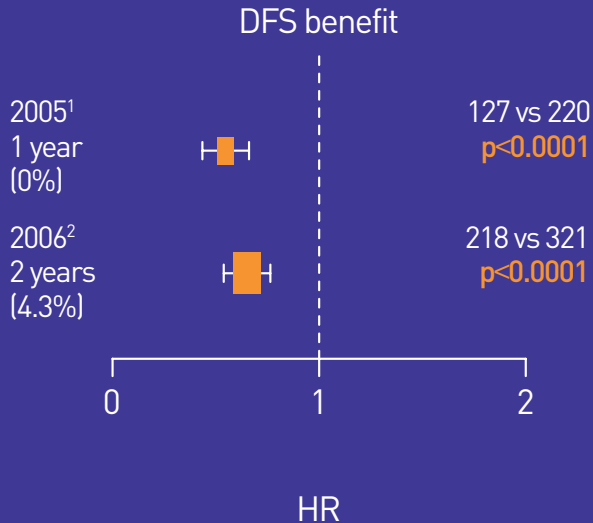
DFS and OS over time: 1 and 2 years' follow-up

Median follow-up
(% follow-up time after
selective crossover)

No. of DFS events
H 1 year vs
observation

Median follow-up
(% follow-up time after
selective crossover)

No. of deaths
H 1 year vs
observation

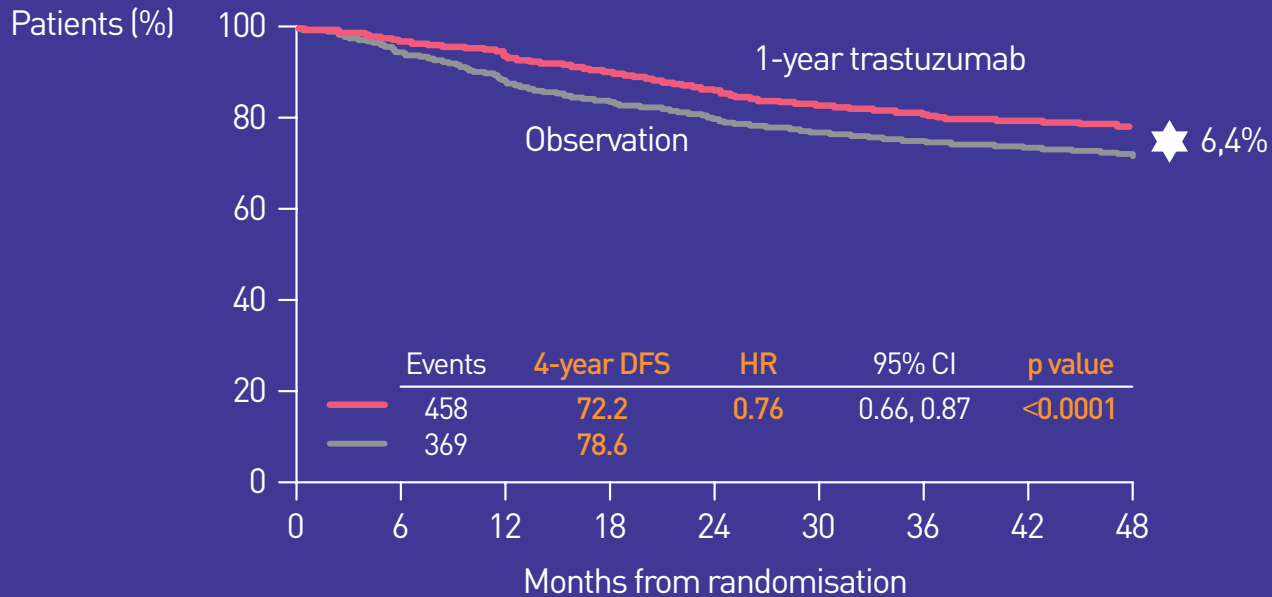


H, trastuzumab; HR, hazard ratio

¹Piccart-Gebhart et al NEJM 2005;

²Smith et al Lancet 2007

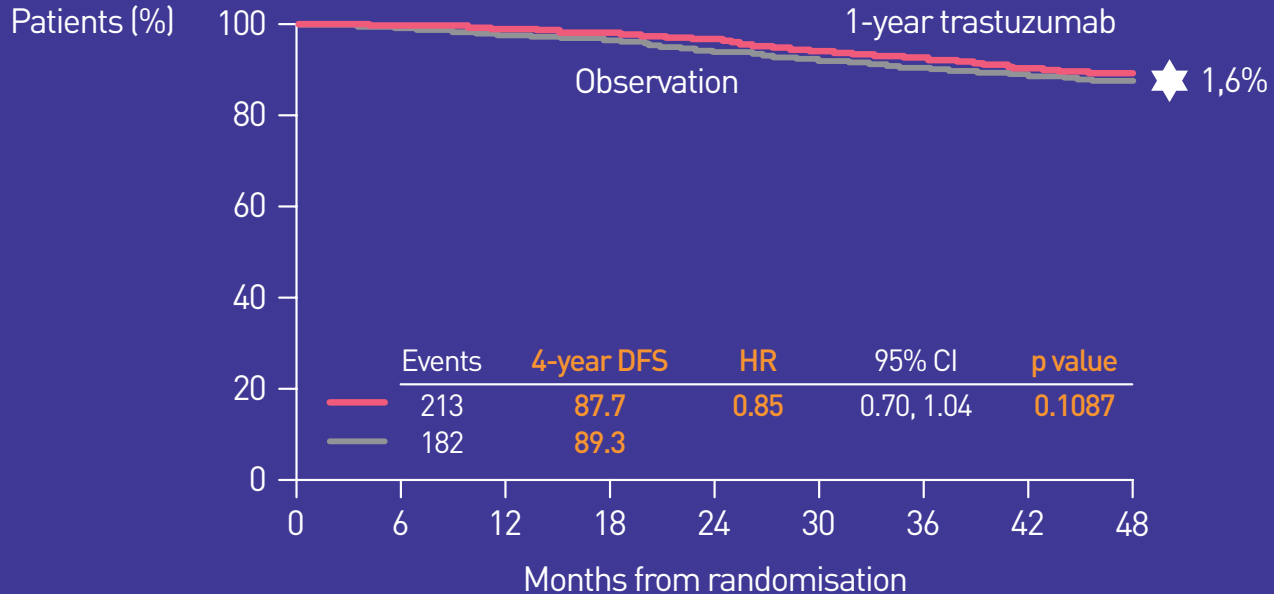
DFS (ITT): median follow-up 4 years (2008)



No. at risk	0	6	12	18	24	30	36	42	48
1-year trastuzumab	1698	1564	1440	1363	1297	1240	1180	992	712
Observation	1703	1619	1552	1485	1414	1352	1280	1020	854

ITT, intent to treat; CI, confidence interval

OS (ITT): median follow-up 4 years (2008)



No. at risk	0	6	12	18	24	30	36	42	48
1-year trastuzumab	1698	1642	1601	1556	1519	1471	1398	1175	828
Observation	1703	1660	1640	1615	1577	1524	1447	1149	953

DFS and OS over time

Median follow-up
(% follow-up time after
selective crossover)

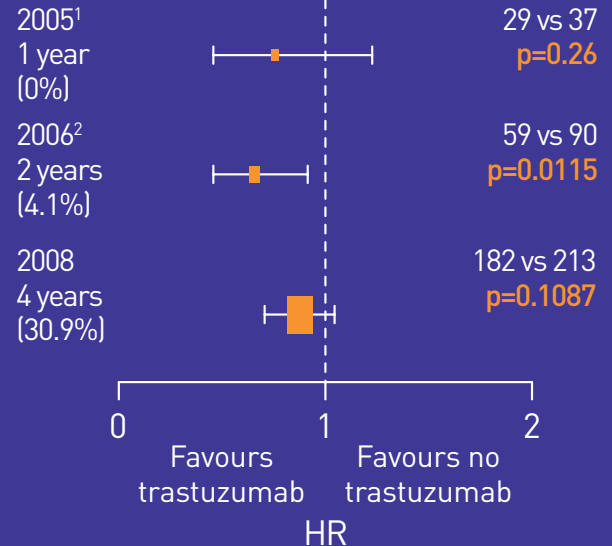
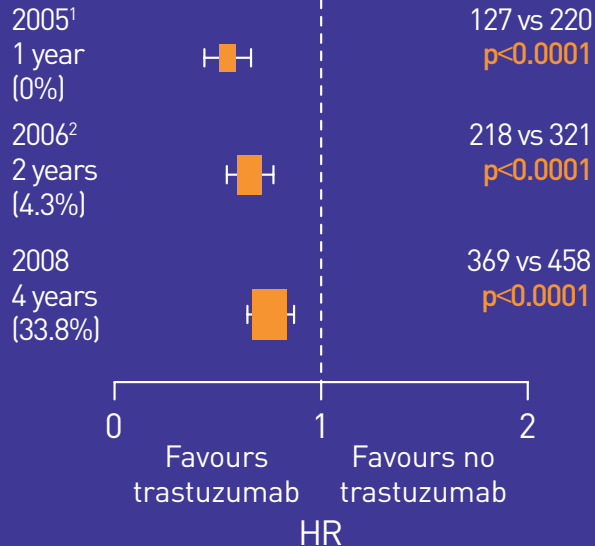
No. of DFS events
H 1 year vs
observation

Median follow-up
(% follow-up time after
selective crossover)

No. of deaths
H 1 year vs
observation

DFS benefit

OS benefit



¹Piccart-Gebhart et al NEJM 2005;

²Smith et al Lancet 2007

Effects of crossover

- Crossover to trastuzumab of patients originally allocated to the observation arm disrupted the randomised ITT comparison between 1-year trastuzumab and observation
- **Specific question:**
To what extent might crossover have biased the ITT analysis?

Observation patients by status on 16 May 2005

1698 patients originally randomised to observation

1354 patients
alive and disease free

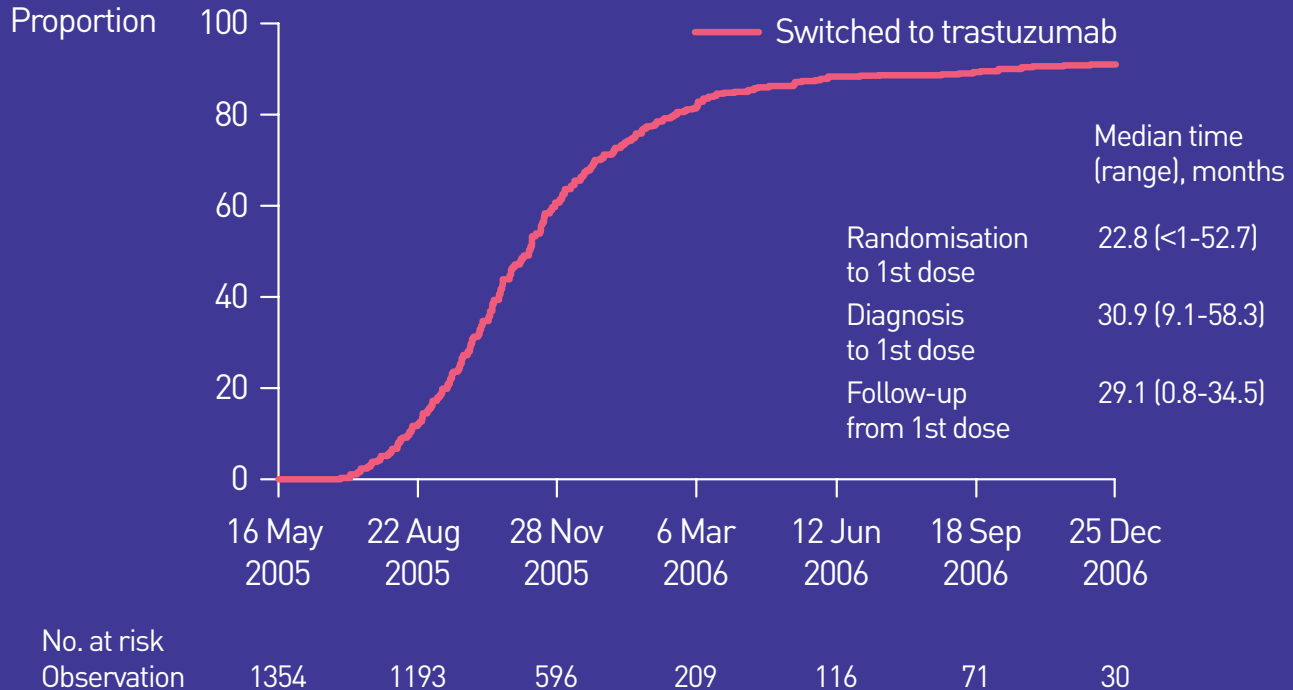
344 patients
DFS event or lost to follow-up
198 alive post DFS event

885 patients
crossed over to
trastuzumab

469 patients
remained
on observation

344 patients
ineligible for
crossover

Time to selective crossover by calendar date (n=885)



Baseline characteristics of observation patients alive and disease free on 16 May 2005

- Compared to patients who did not selectively cross over, those who did were more likely to:
 - be younger
 - have received anthracyclines and anthracyclines plus taxanes
 - be diagnosed with node-positive disease
 - have hormone receptor-positive tumours

Impact of crossover on results

- 885 of 1354 patients (65%) in the observation group who were alive and disease free on May 16 2005 crossed over and received trastuzumab

- **Specific questions:**

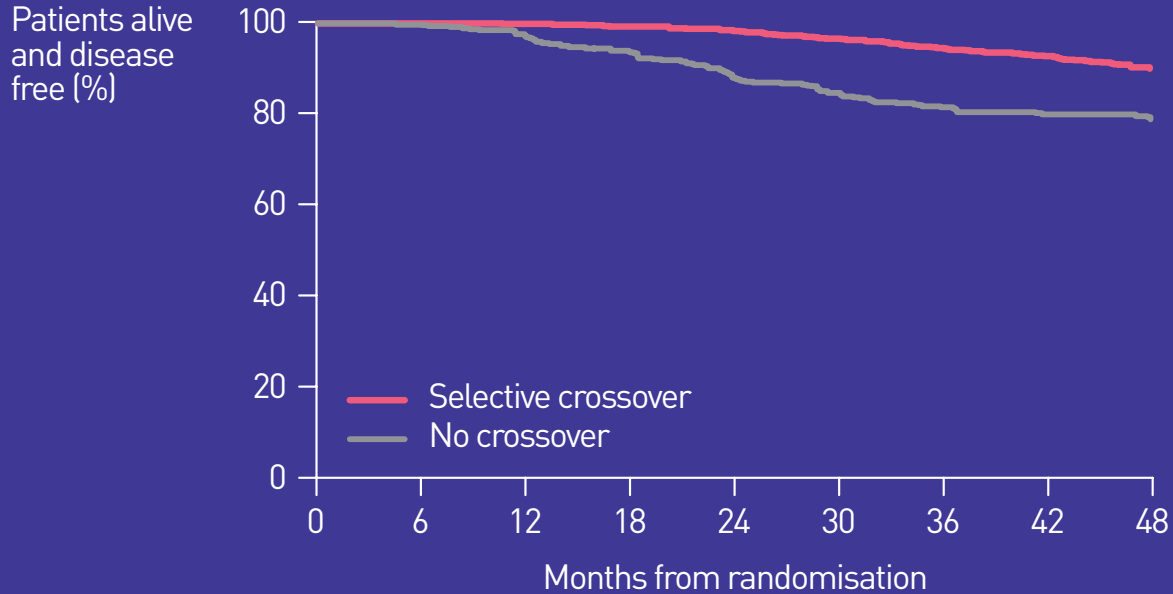
What was the course of disease in the subgroups of observation patients who did or did not cross over to active therapy?

Is there any effect of the late introduction of trastuzumab?

Landmark of 16 May 2005

- The landmark analysis considers only patients who were alive and disease free on 16 May 2005

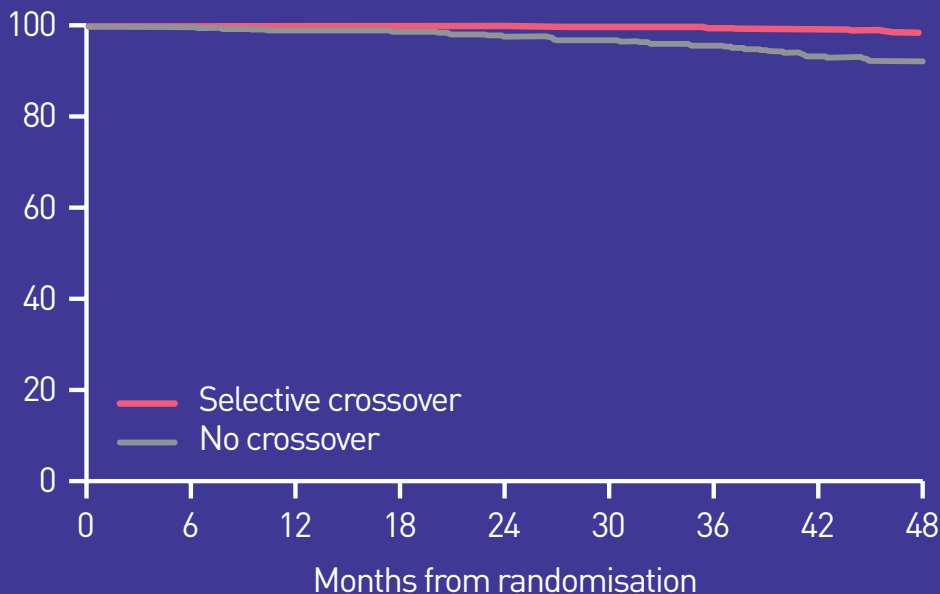
DFS (landmark analysis): selective crossover and no crossover



No. at risk	885	885	884	878	870	851	822	690	480
	469	468	455	438	408	388	358	302	232

DFS (landmark analysis): selective crossover and no crossover

Patients alive
and disease
free (%)



No.	885	885	885	883	881	875	852	718	499
at risk	469	469	465	461	451	441	418	647	260

Cardiac safety: safety analysis population*

	No. patients (%)	
	Observation ^a n=1719	1-year trastuzumab n=1682
Cardiac death	1 (0.1)	0 (0.0)
Severe CHF (NYHA III and IV)	0 (0.0)	13 (0.8)
Symptomatic CHF (II, III and IV)	3 (0.2)	33 (2.0)
Confirmed significant LVEF drop	13 (0.8)	62 (3.7)
Trastuzumab discontinued due to cardiac problems		87 (5.2)

*Patients who crossed over are censored from the date of starting trastuzumab treatment

CHF, congestive heart failure; NYHA, New York Heart Association

Cardiac safety: observation group

	No crossover after 16 May 2005 n=469	Crossover n=885
Cardiac death	0 (0.0)	0 (0.0)
Severe CHF (NYHA III and IV)	0 (0.0)	0 (0.0)
Symptomatic CHF (II, III and IV)	1 (0.2)	9 (1.0)
Confirmed significant LVEF drop	5 ^a (1.1)	26 (2.9)
Trastuzumab discontinued due to cardiac problems		43 (4.9)

*For 3 of the patients, the LVEF drop occurred after 16 May 05 and may have influenced the patient decision

Summary

- The updated analysis at 4 years was limited to 1-year trastuzumab vs observation as recommended by IDMC
- Extensive selective crossover of observation patients to active therapy biased the ITT comparison
- Landmark analysis of observation patients who were disease free on 16 May 2005 explored the effects of later introduction of trastuzumab
- Lack of randomisation limits the interpretation of the landmark analysis
 - different outcome due to drug effect or patient characteristics?

Conclusions

- Trastuzumab for 1 year following chemotherapy is effective (ITT analysis) without excessive cardiac risk
- Crossover patients (landmark analysis) had better DFS and OS, mostly without cardiac events
- The findings are consistent with benefit from trastuzumab even when introduced late

Hypothesis

- These data support the hypothesis that the risk of relapse in HER2-positive early breast cancer persists over time
- Prolonged exposure to the trastuzumab antibody may improve efficacy
- This is being tested in the comparison of the 1-year and 2-year groups in the HERA study

Acknowledgements

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■ BIG groups

ABCSG	GOCCHI
ACCOG	GOIRC
ANZ BCTG	GONO
BOOG	IBCSG
BrEAST	ICCG
CEE0G	NCIC-CTG
DBCg	NCRI
EORTC	SAKK
GABG	SBCG
GEICAM	YBCRG

Cardiac advisory board: T Suter

IDMC members

Protocol: C Lohrish

Central HER2 testing: J Rueschoff, O Stoss

BIG coordination: C Straehle

Monitoring coordination: S Guillaume, P Wermuth

Trial design / day-to-day supervision:

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■ Non-BIG groups

AGO
ASG & WSG
BIOMED NO
GIM
IBCg
MICHELANGELO
NBCG
SOLTI
TCOG

■ 91
independent
centres

All 5102 women who enrolled in the HERA trial