

Trastuzumab Following Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer (HERA Trial): Disease-Free and Overall Survival after 2 Year Median Follow-Up

The HERA Study Team

Presented by Ian E. Smith



HERA Trial Design

Women with locally determined HER2-positive invasive early breast cancer

Surgery + (neo)adjuvant CT ± RT

Centrally confirmed IHC 3+ or FISH+ and LVEF ≥ 55%

Randomization

Observation

1 year trastuzumab
8 mg/kg → 6 mg/kg
3 weekly schedule

~~2 year trastuzumab
8 mg/kg → 6 mg/kg
3 weekly schedule~~

After ASCO 2005,
option of switch
to trastuzumab

CT, chemotherapy; RT, radiotherapy

End Points and Analyses

- End points

- primary: DFS
- secondary: OS, TTR, TTDR
Safety (3 interim analyses of cardiac end points)

- Interim efficacy analysis

- (n=475 events)
- ASCO 2005
- Piccart-Gebhart et al NEJM Oct 2005

DFS, disease-free survival;

OS, overall survival; TTR, time to recurrence; TTDR, time to distant recurrence

Patient characteristics (1)

	% patients	
	Observation (n=1698)	1 year trastuzumab (n=1703)
Age, years		
<35	7.4	7.5
35-49	44.3	44.4
50-59	32.3	32.2
<u>≥60</u>	16.0	16.0
Prior (neo)adjuvant CT		
No anthracyclines	5.9	5.9
Anthracyclines, no taxanes	68.1	67.8
Anthracyclines + taxanes	26.0	26.3

Patient characteristics (2)

	% patients	
	Observation (n=1698)	1 year trastuzumab (n=1703)
Menopausal status^a		
Premenopausal	45.3	44.9
Uncertain	13.8	15.1
Postmenopausal	40.8	40.0
Hormone receptor status		
Negative	50.4	50.5
Positive	49.6	49.5
Nodal status		
Neoadjuvant CT	10.5	11.4
Negative	32.7	31.9
1-3	28.9	28.5
≥4	27.9	28.1

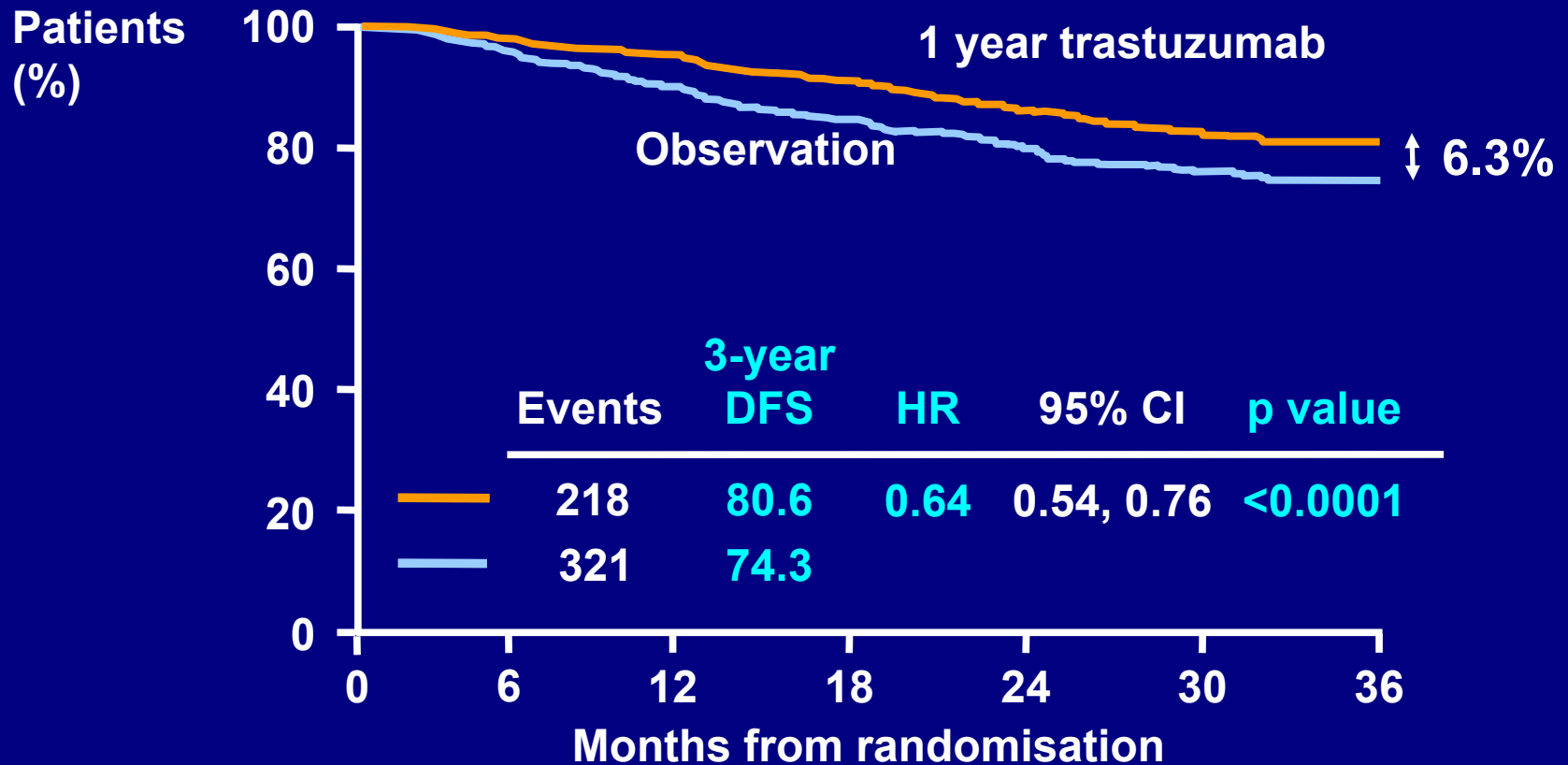
^aStatus at randomisation

Developments in HERA Trial since ASCO 2005

- Median FU now 2 years
(median 1 year at ASCO 2005)
- 539 events observed in the 2 arms
(347 at ASCO 2005)
- As of 15th May 2006, 861 observation patients
are known to have switched to trastuzumab
following ASCO 2005
- Therefore 2 analyses now possible
 1. ITT
 2. Censored at time of switch

Disease-free survival (ITT)

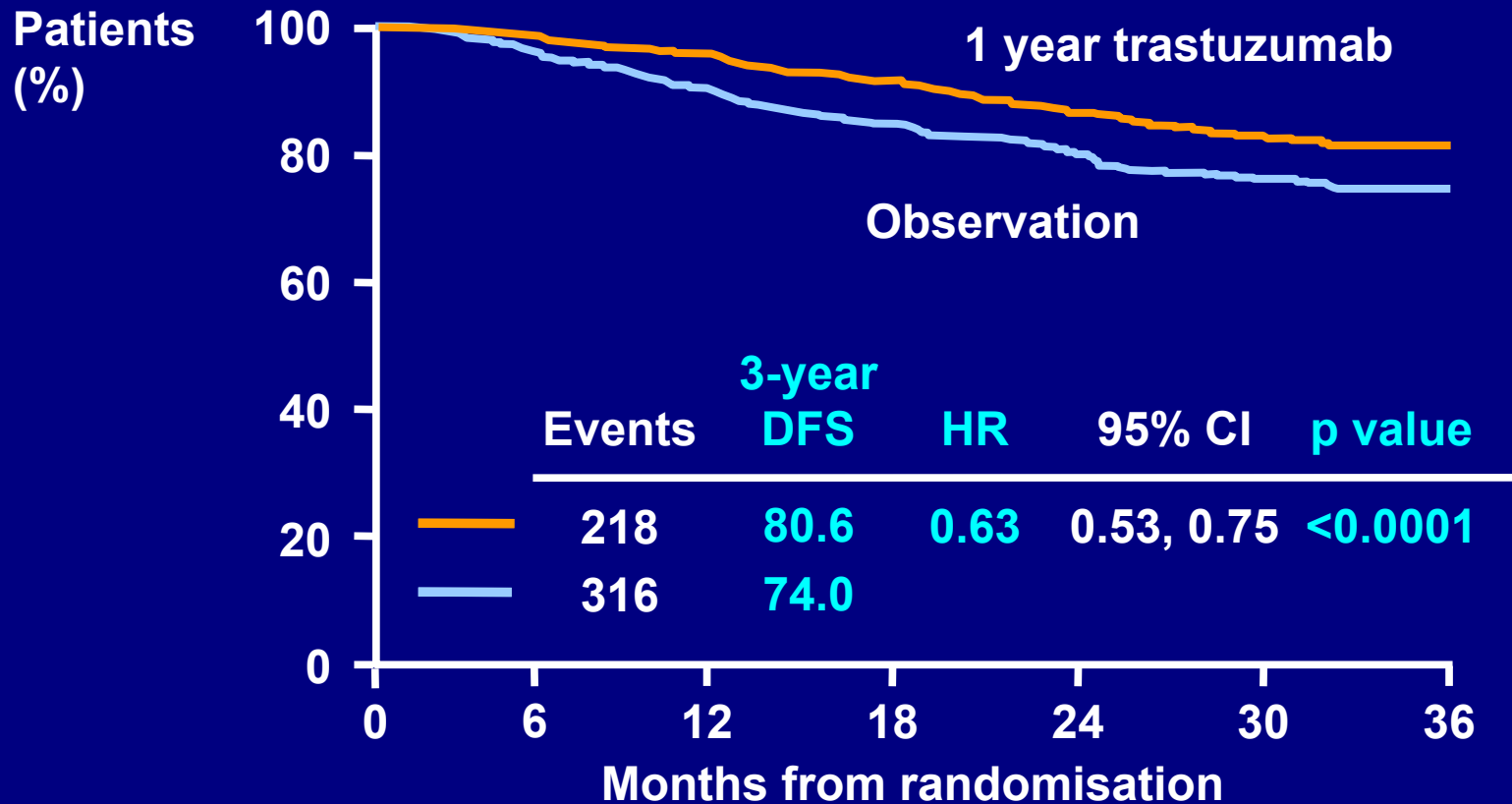
Median FU 2 yrs



No. at risk	0	6	12	18	24	30	36
1 year trastuzumab	1703	1591	1434	1127	742	383	140
Observation	1698	1535	1330	984	639	334	127

Disease-free survival (censored)

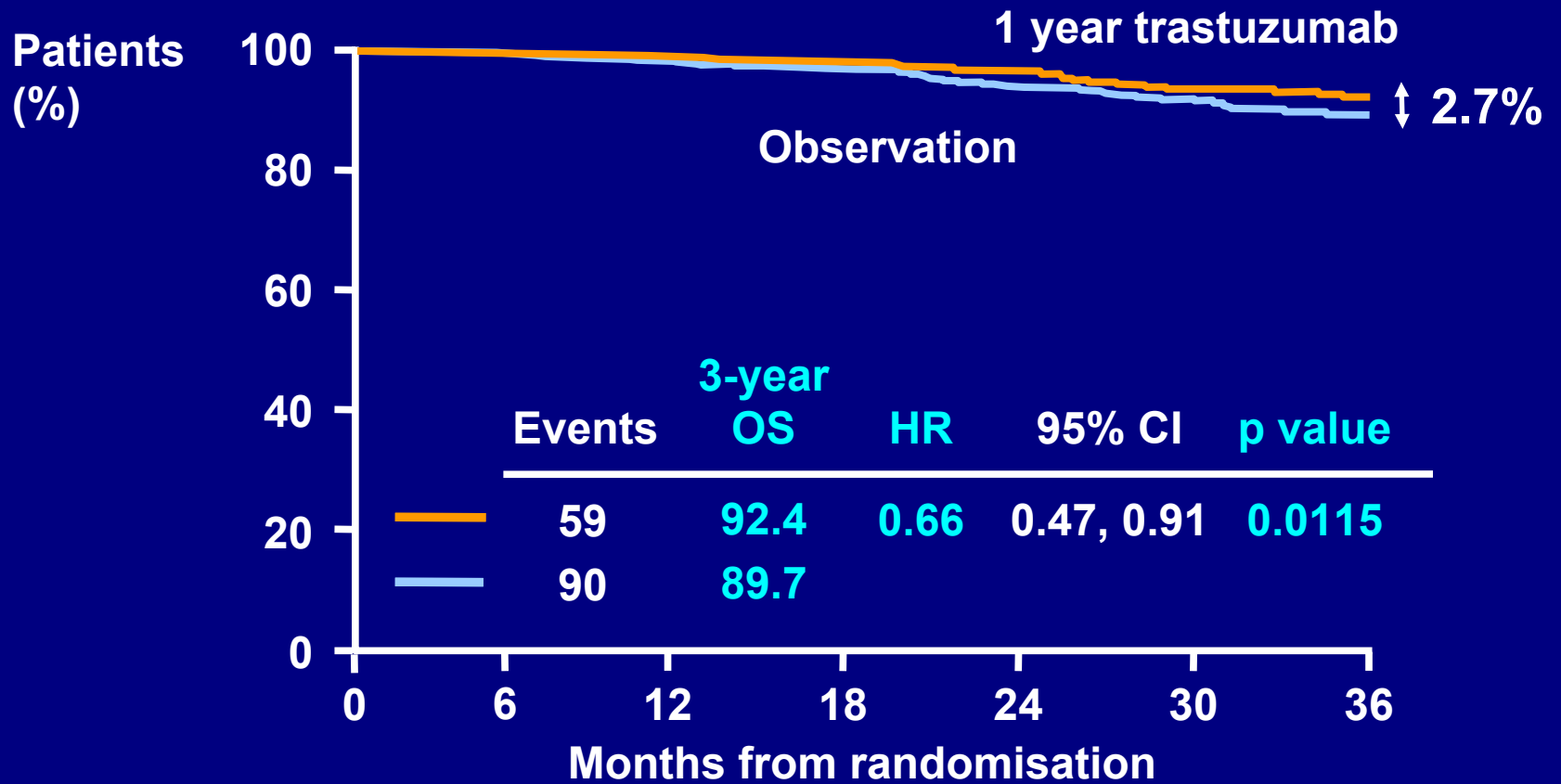
Median FU 2 yrs



No. at risk	0	6	12	18	24	30	36
1 year trastuzumab	1703	1591	1434	1127	742	383	140
Observation	1698	1533	1301	930	606	322	114

Overall survival (ITT)

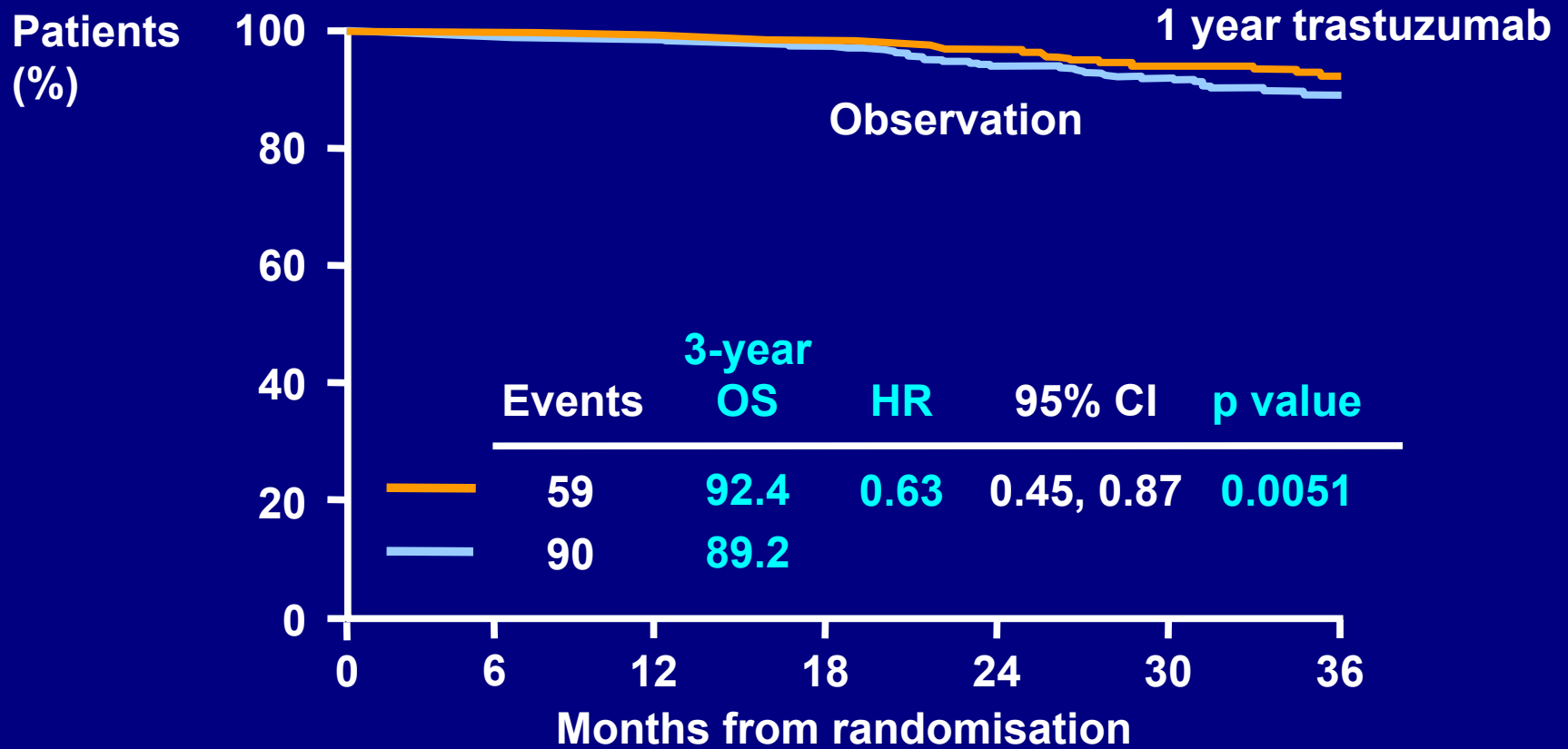
Median FU 2 yrs



No. at risk	0	6	12	18	24	30	36
1 year trastuzumab	1703	1627	1498	1190	794	407	146
Observation	1698	1608	1453	1097	711	366	139

Overall survival (censored)

Median FU 2 yrs



No. at risk	0	6	12	18	24	30	36
1 year trastuzumab	1703	1627	1498	1190	794	407	146
Observation	1698	1606	1424	1042	677	354	126

Site of 1st DFS Event

(ITT Analysis)

	No. events (%)	
	Observation (n=1698)	1 year trastuzumab (n=1703)
Total no. events	321 (18.9)	218 (12.8)
Distant event	233 (13.7)	152 (8 .9)
Central Nervous System	22 (1.3)	26 (1 .5)
Locoregional event	68 (4.0)	45 (2.6)
Contralateral breast cancer	9 (0.5)	7 (0.4)
2nd non-breast malignancy	8 (0.5)	6 (0.4)
Death as 1st event	3 (0.2)	8 (0.5)

Exploratory DFS subgroup analysis (ITT): 1 year trastuzumab vs observation (1)

Subgroup (no. patients)

Region of the world

Europe, Canada, SA, Australia, NZ (2438)

Asia Pacific, Japan (405)

Eastern Europe (369)

Central + South America (189)

Age at randomisation

<35 years (253)

35-49 years (1508)

50-59 years (1096)

≥60 years (544)

Menopausal status at randomisation

Premenopausal (491)

Uncertain (1373)

Postmenopausal (1535)

Nodal status

neoadjuvant CT (372)

Negative (1099)

1-3 positive nodes (976)

≥4 positive nodes (953)

All patients (3401)

No. events

T vs obs

161 vs 235

21 vs 37

23 vs 36

13 vs 13

19 vs 31

89 vs 150

71 vs 97

39 vs 43

43 vs 49

70 vs 135

105 vs 137

39 vs 50

34 vs 58

50 vs 80

95 vs 132

218 vs 321

HR (95% CI)

0.66 (0.54, 0.81)

0.53 (0.31, 0.90)

0.54 (0.32, 0.91)

0.98 (0.45, 2.11)

0.57 (0.32, 1.01)

0.54 (0.42, 0.70)

0.71 (0.52, 0.97)

0.91 (0.59, 1.41)

0.80 (0.53, 1.21)

0.48 (0.36, 0.64)

0.75 (0.58, 0.97)

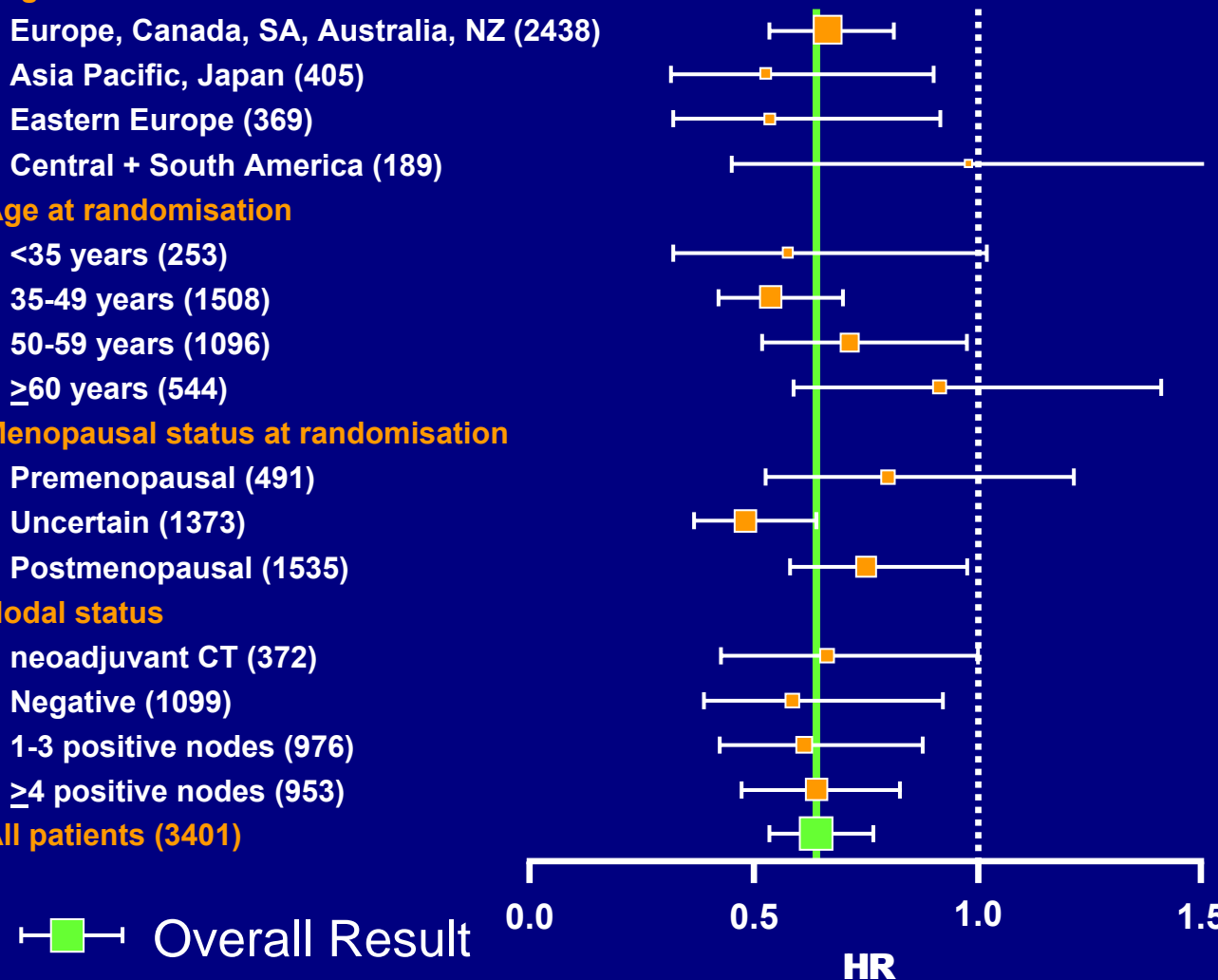
0.66 (0.43, 1.00)

0.59 (0.39, 0.91)

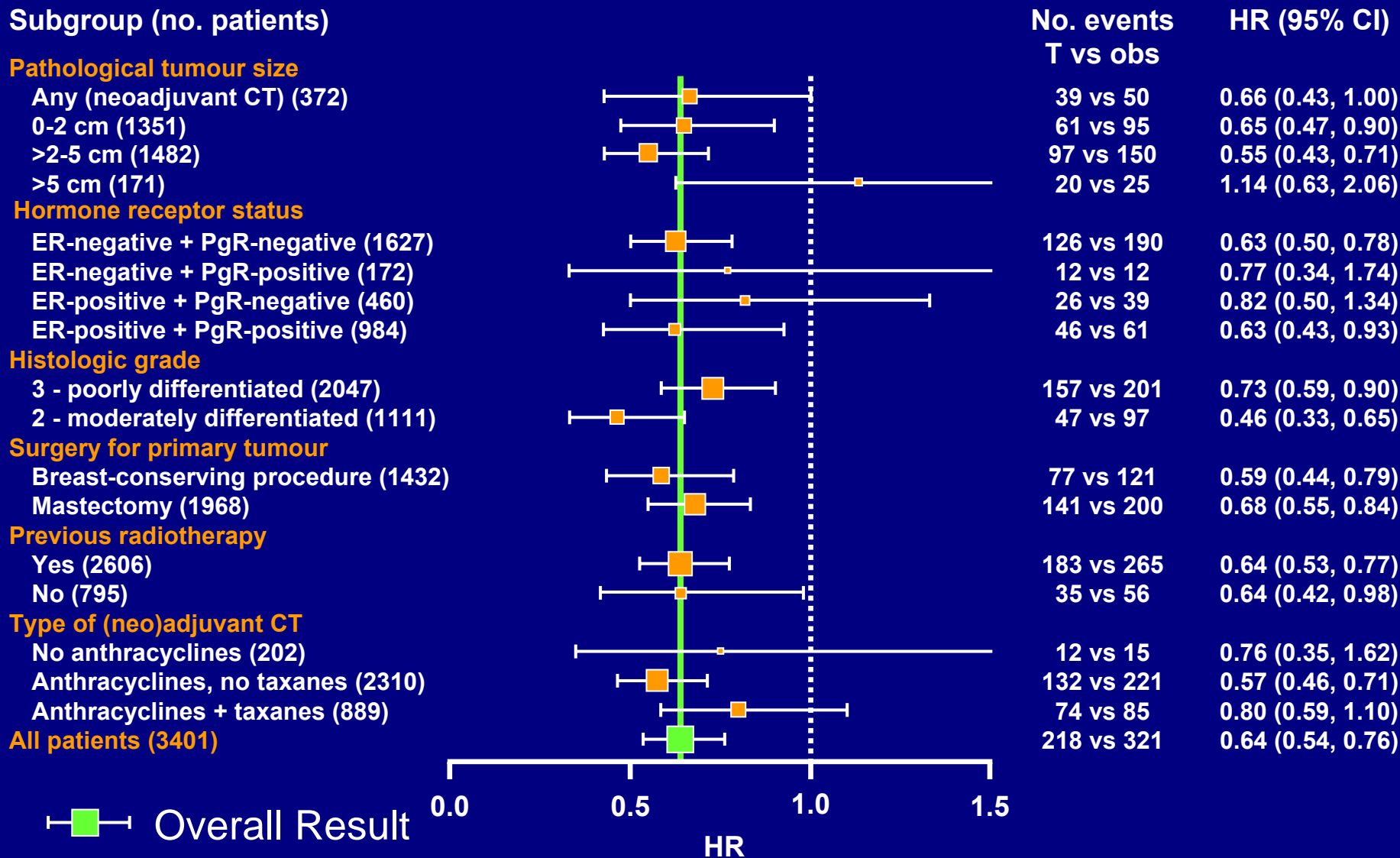
0.61 (0.43, 0.87)

0.64 (0.49, 0.83)

0.64 (0.54, 0.76)



Exploratory DFS subgroup analysis (ITT): 1 year trastuzumab vs observation (2)

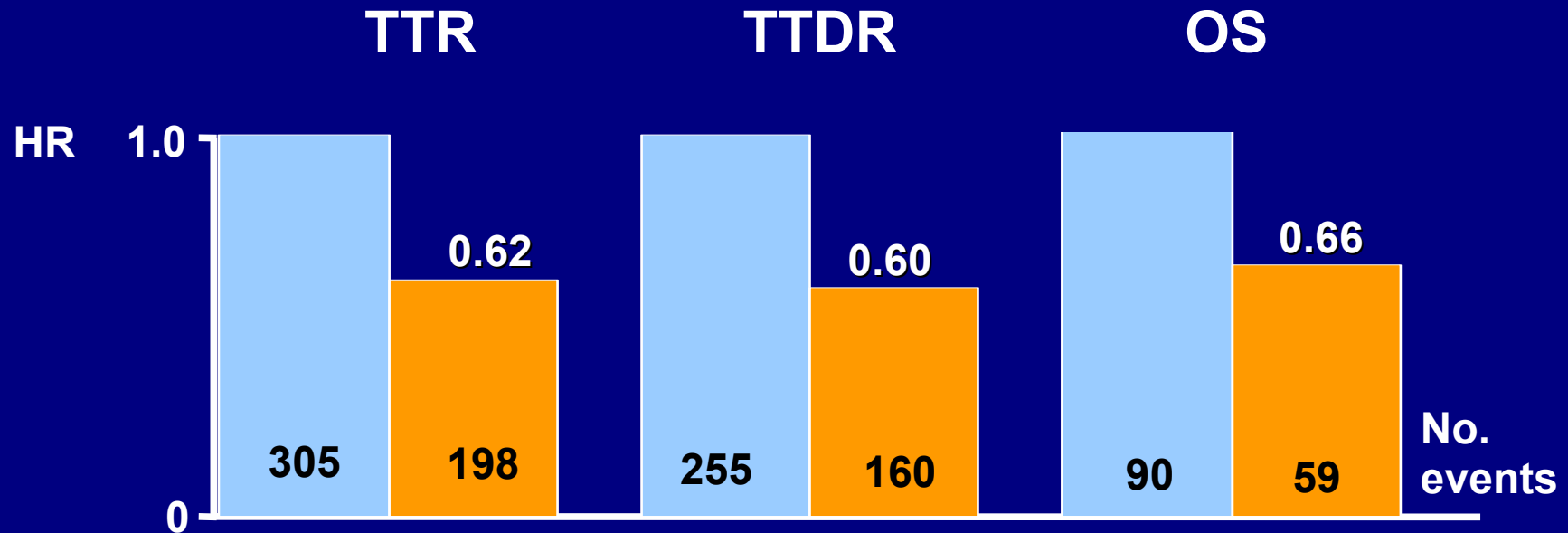


Subgroup Analysis Summary

- No evidence of substantial differences in relative treatment effect between subgroups
- No evidence of any subgroup in which there is less efficacy
(CIs all overlap the overall result)

Secondary efficacy end points (ITT analysis)

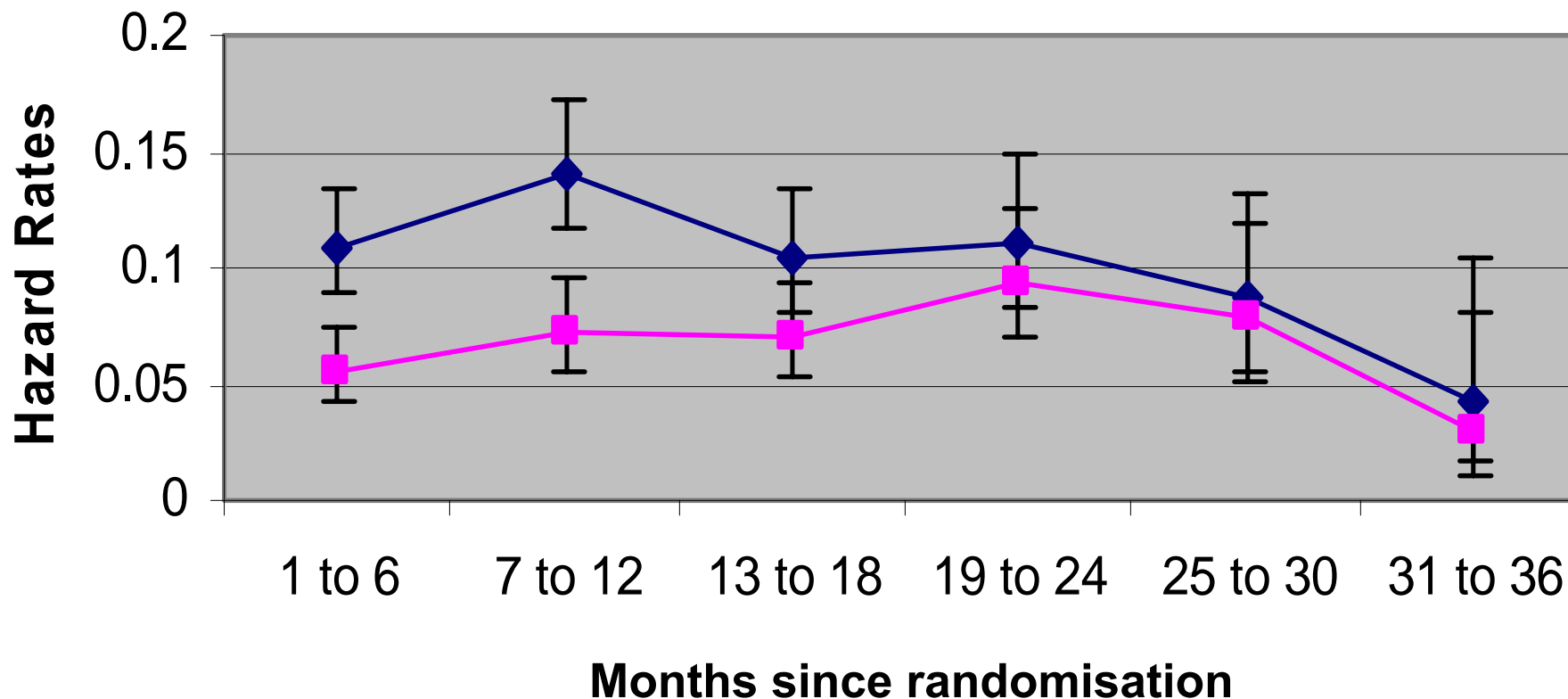
■ Observation
 ■ 1 year trastuzumab



95% CI	0.52, 0.74	0.49, 0.73	0.47, 0.91
p value (log rank)	<0.0001	<0.0001	0.0115
3-year percent, %	75.4 vs 82.1	79.4 vs 85.7	89.7 vs 92.4

TTR, time to recurrence; TTDR, time to distant recurrence; OS, overall survival

Annualized DFS hazards - ITT observation and 1 year trastuzumab groups



—◆— Observation —■— 1 Year Trastuzumab

Adverse Events (AE)

	No. events (%)	
	Observation (n=1466)	1 year trastuzumab (n=1688)
Patients with ≥ 1 grade 3/4 AE	88 (6.0)	190 (11.3)
Patients with ≥ 1 serious AE	97 (6.6)	156 (9.2)
Fatal AE	3 ^b (0.2)	9 ^c (0.5)
Treatment withdrawals		172 (10.2 ^d)

^bCardiac failure, suicide, unknown

^cCerebral haemorrhage, cerebrovascular accident, sudden death, appendicitis, intestinal obstruction, unknown following a road accident, carcinomatous lymphangitis, 2 unknown
The intestinal obstruction occurred after a second non-breast malignancy

^dSafety in 6.8%, refusal in 2.5%, other in 0.8%

Cardiac Safety

	No. patients (%)	
	Observation n=1708	1 yr trastuzumab n=1678
Cardiac death	1 (0.1)	0 (0.0)
Severe CHF (NYHA III and IV)	0 (0.0)	10 (0.6)
Symptomatic CHF (II, III and IV)	3 (0.2)	36 (2.1)
Confirmed significant LVEF drop	9 (0.5)	51 (3.0)
Trastuzumab discontinued due to cardiac problems		72 (4.3)

Conclusions

- Trastuzumab following adjuvant CT significantly improves overall survival (HR 0.66) in women with HER2 +ve breast cancer
- The DFS gain after 1 year median FU is maintained after 2 years median FU
- The risk of cardiac toxicity remains low

Next Steps

- Long-term follow-up will provide
 - Continuing safety data
 - Information on trastuzumab treatment duration (1 vs 2 years)
 - Information on delayed switching to trastuzumab

And finally....

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BIG groups

ABCSG GOCCHI
ACCOG GOIRC
ANZ BCTG GONO
BOOG IBCSG
BREAST ICCG
CEEEOG NCIC-CTG
DBCG NCRI
EORTC SAKK
GABG SBCG
GEICAM YBCRG

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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

Others

3 year	Combined USA	HERA
DFS T	87.1	80.6
DFS O	75.4	74.3
OS T	94.3	92.4
OS O	91.7	89.7