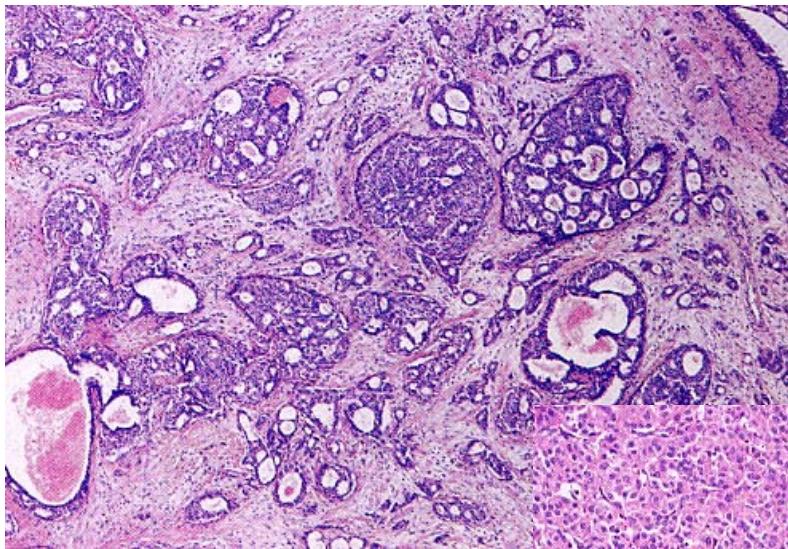


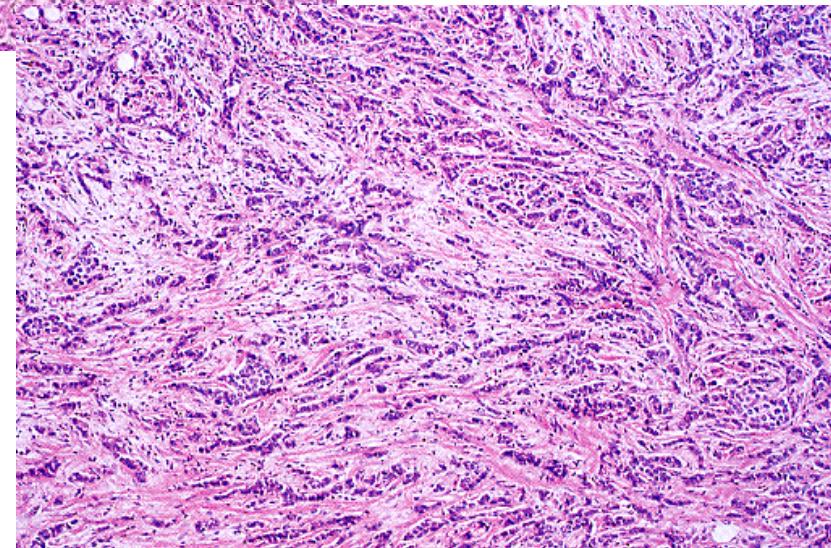
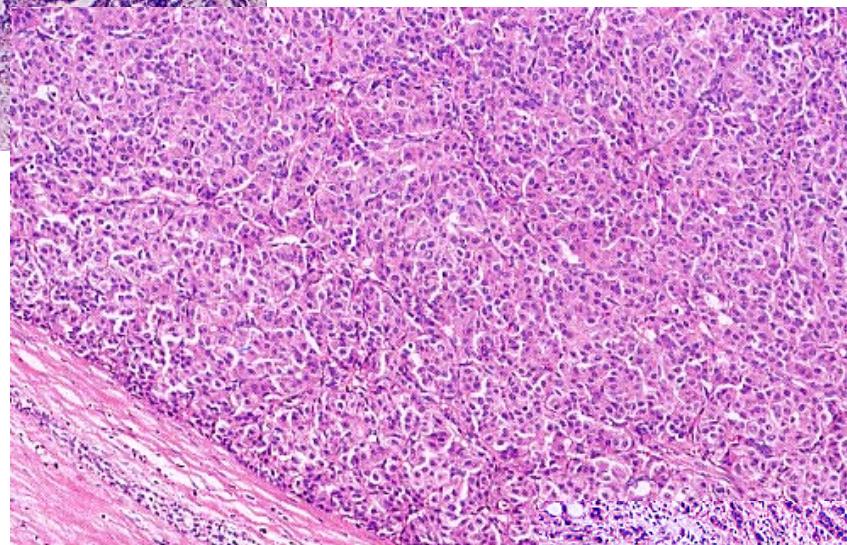
Adjuvant Therapy with Trastuzumab

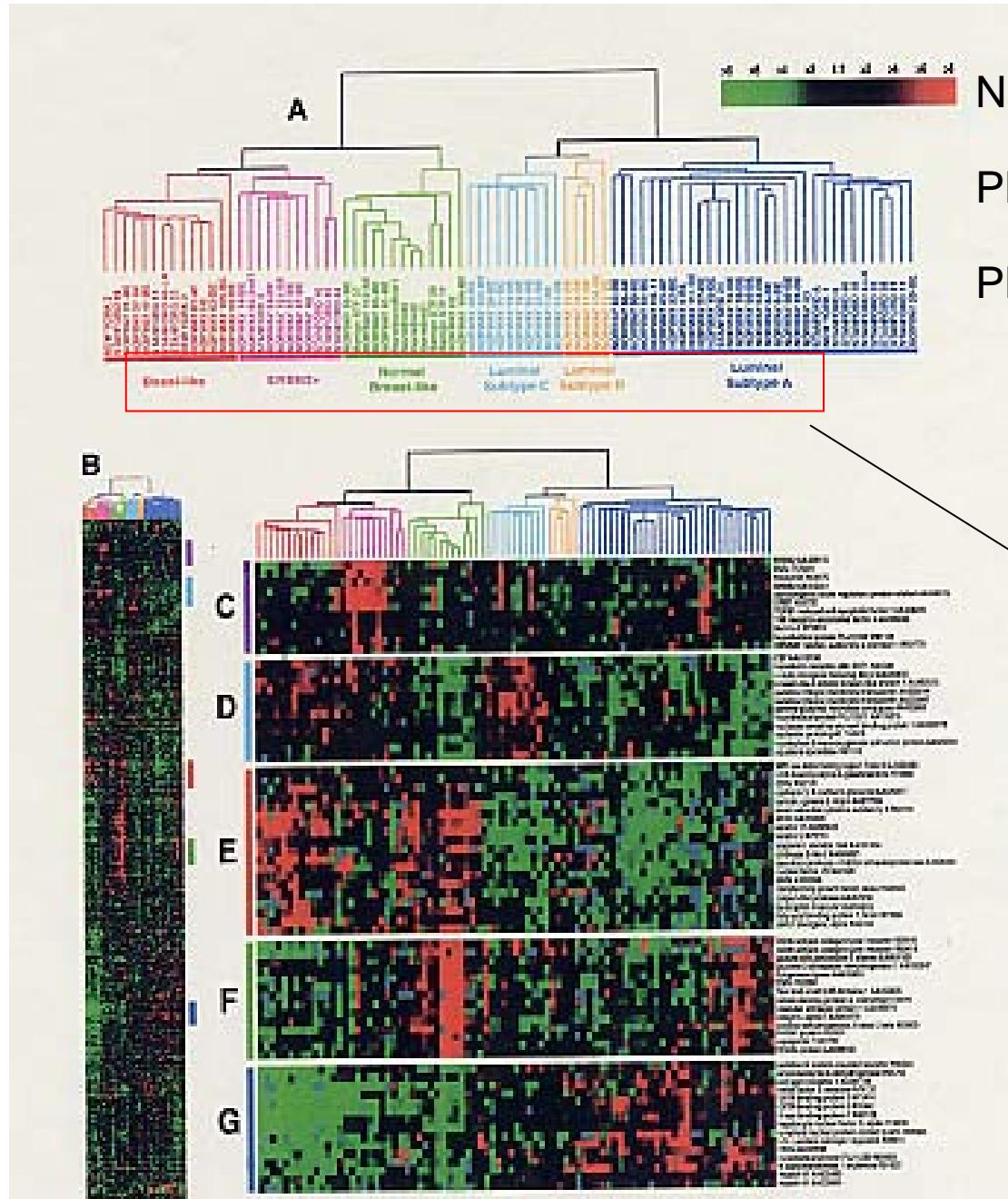
Hiroji Iwata, M.D.
Department of Breast Oncology,
Aichi Cancer Center Hospital

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.



Histopathological Classification





Nature :p747~752,406, 2000

PNAS:p10869~10874,98, 2001

PNAS :p8418~8423,100, 2003

Classification by Gene signature

Luminal subtype A

Luminal subtype B

ERBB2+

Basel-like

Subtype of Breast Cancer by molecular marker

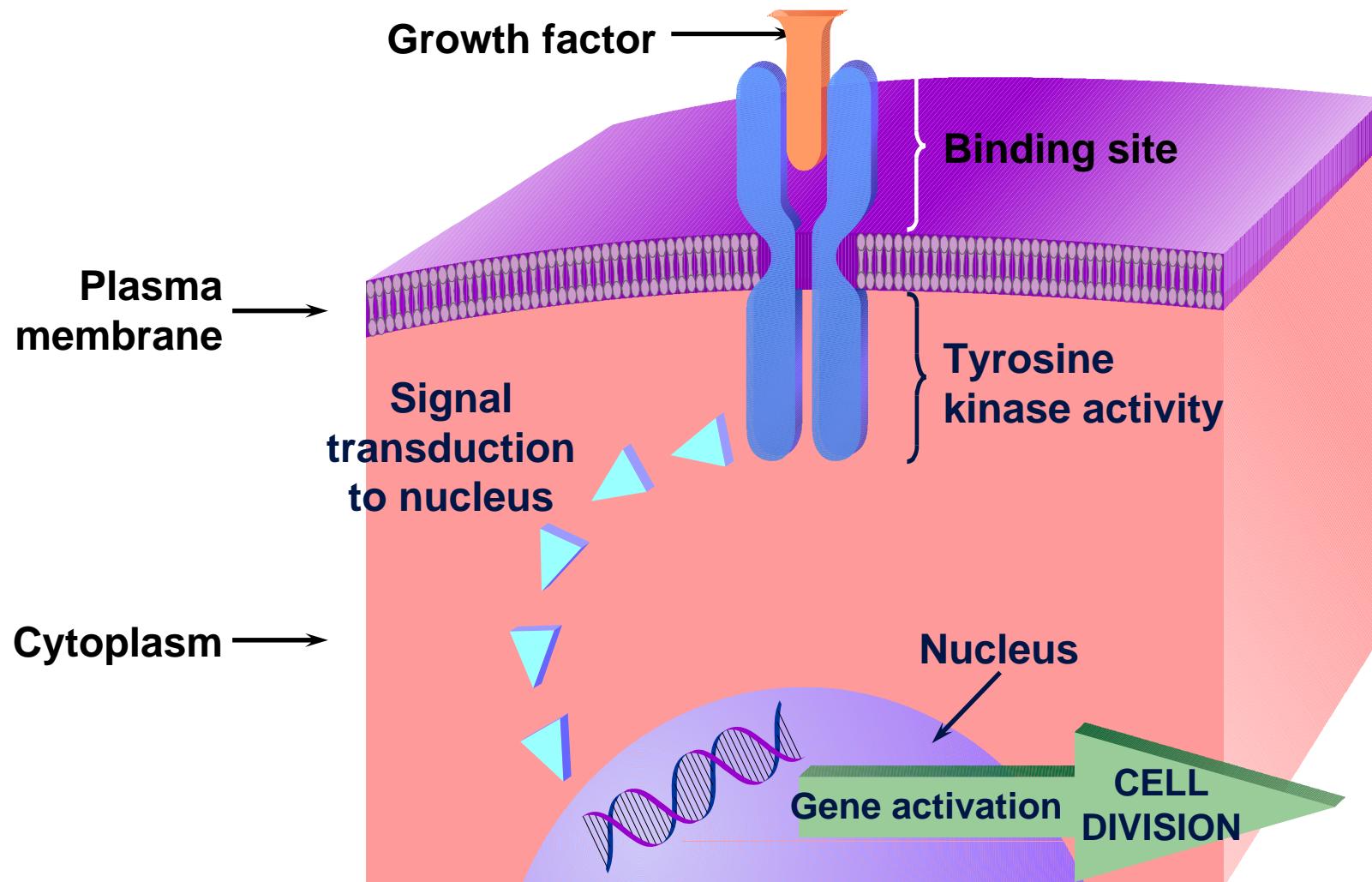
	ER+	ER-
HER2+	Luminal B	HER2 type
HER2-	Luminal A	Basal like

Adjuvant Treatment for a 2 x 2 Marker Model of Breast Cancer

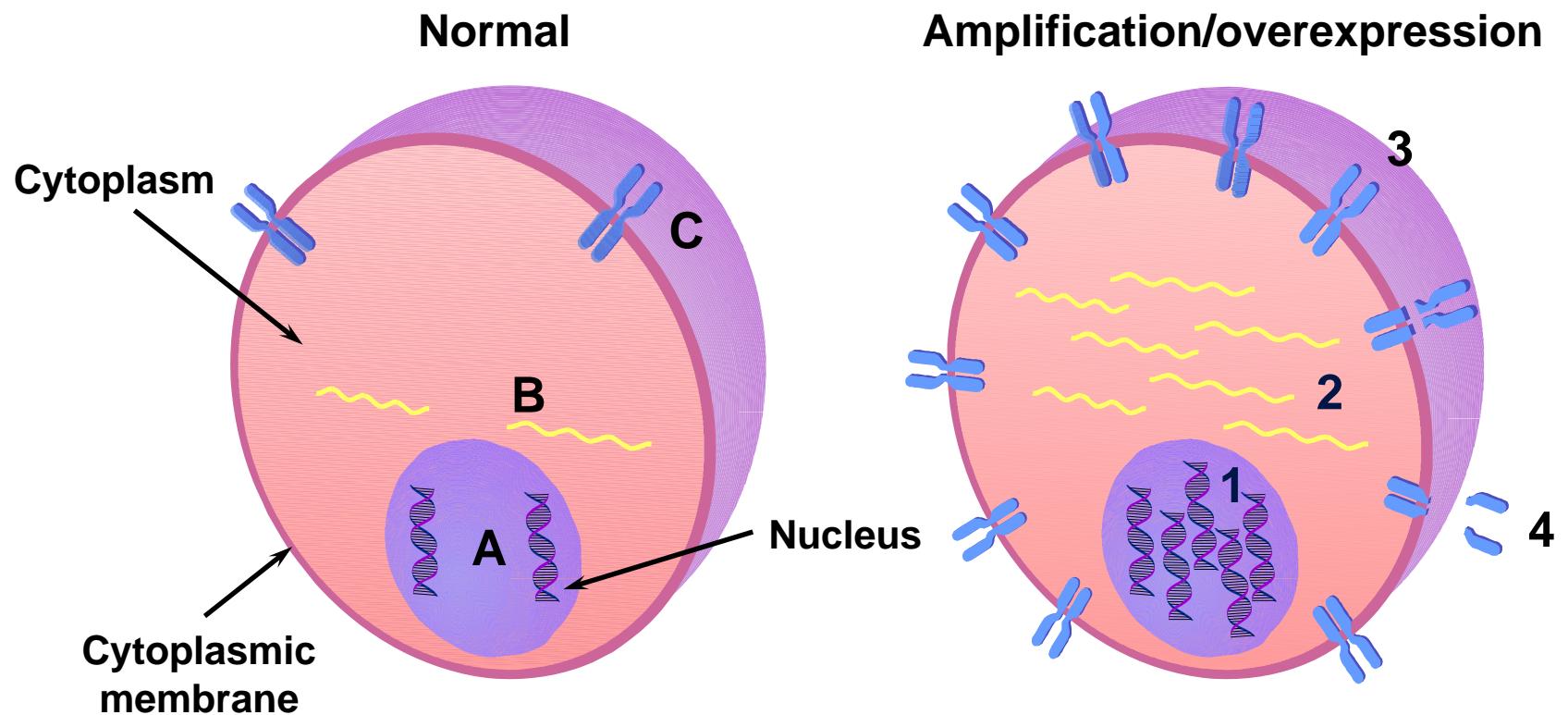
	ER+	ER-
HER2+	trastuzumab chemo endocrine	trastuzumab chemo
HER2-	endocrine \pm chemo	chemo

Selection of patients is the major challenge

HER2 receptor dimer transmembrane signal transduction pathway



Indicators of increased HER2 production



A = HER2 DNA

B = HER2 mRNA

C = HER2 receptor protein

1 = - gene copy number

2 = - mRNA transcription

3 = - cell surface receptor protein expression

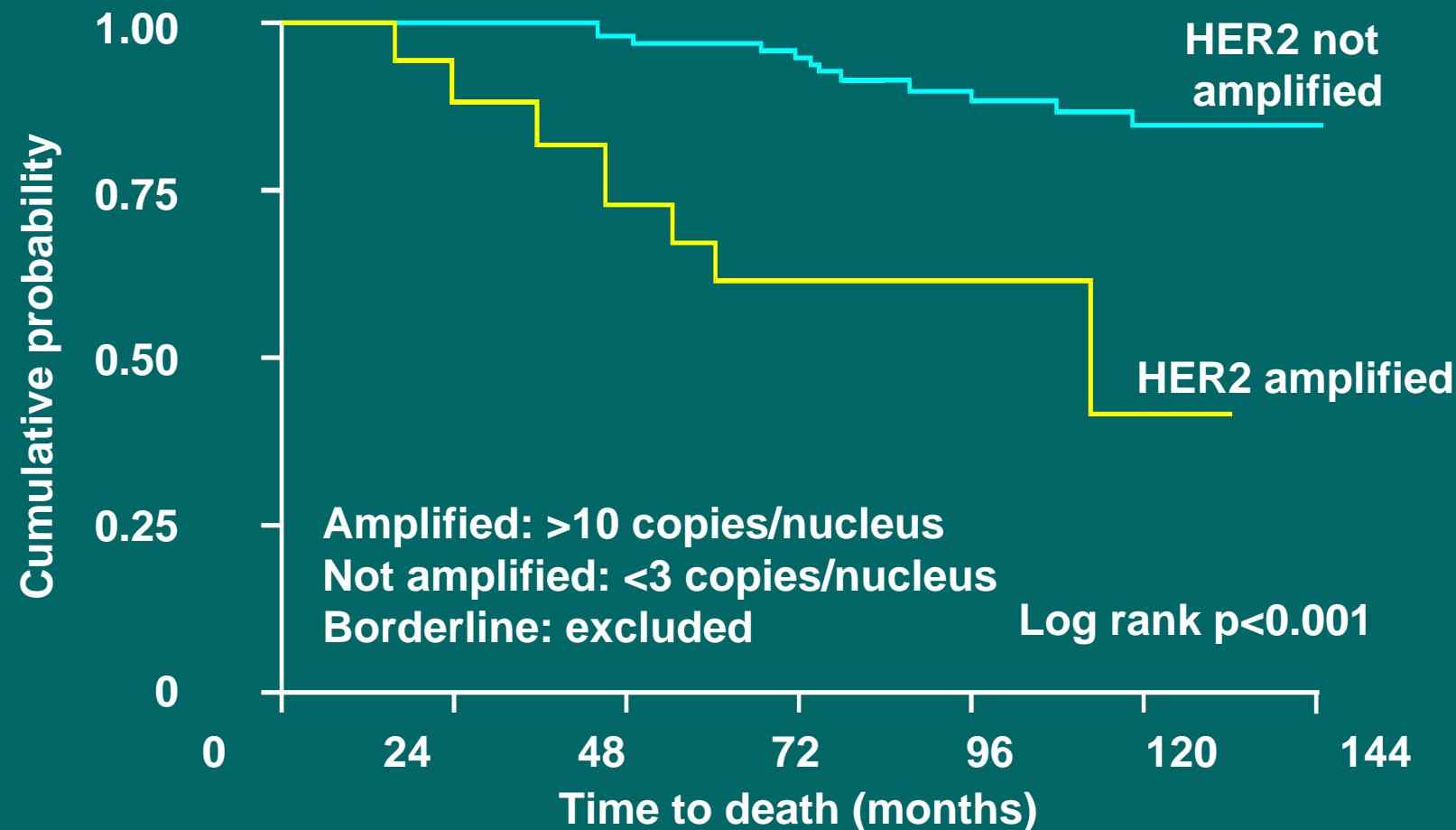
4 = - release of receptor extracellular domain

HER2 overexpression

DNA synthesis is increased;
Cell cycle is rapid;
Metastasis is promoted . . .

It proves to be a more malignant tumor.

Survival of node-negative breast cancer patients related to HER2 status



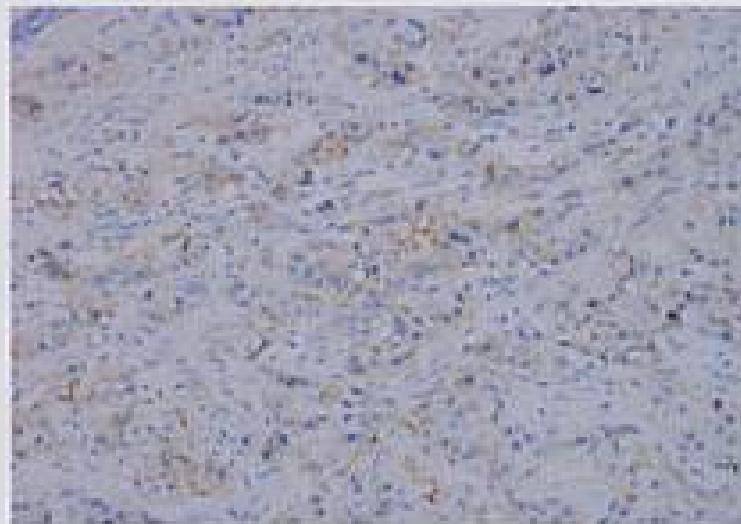
Ross JS, Fletcher JA. Stem Cells 1998;16:413–28

Herceptest

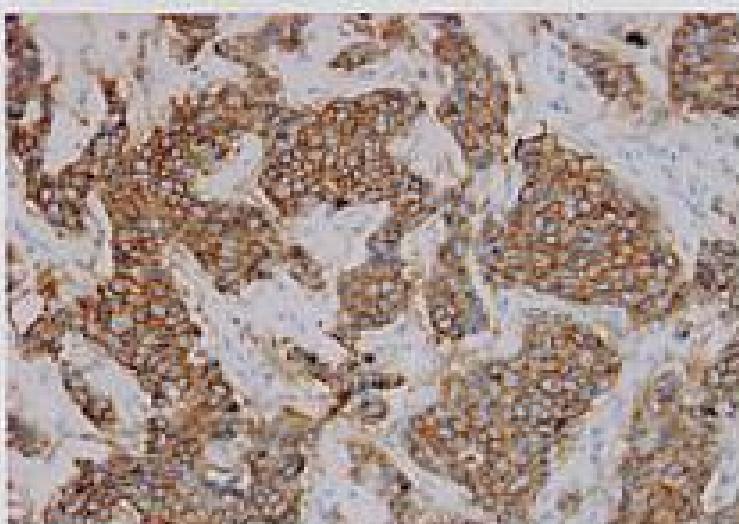
Score 0



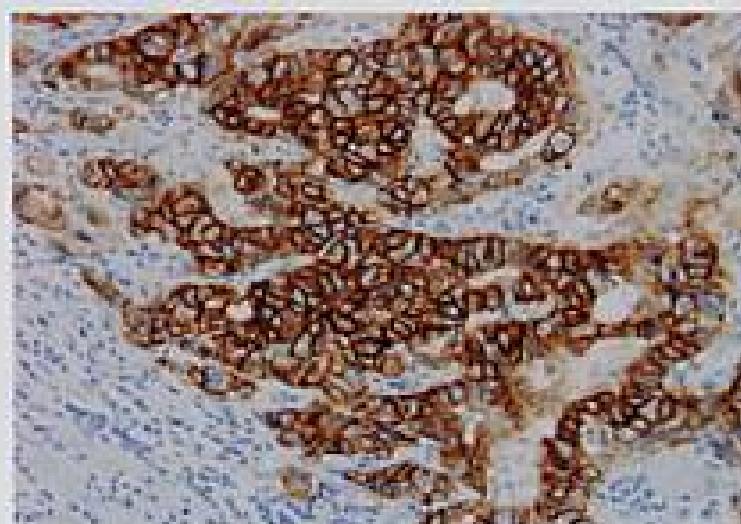
Score 1+



Score 2+

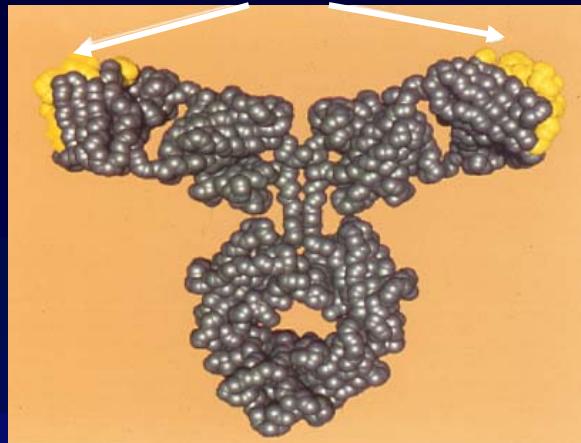


Score 3+



Trastuzumab: Structure and Mechanism of Action

Antigen binding sites: derived from mouse

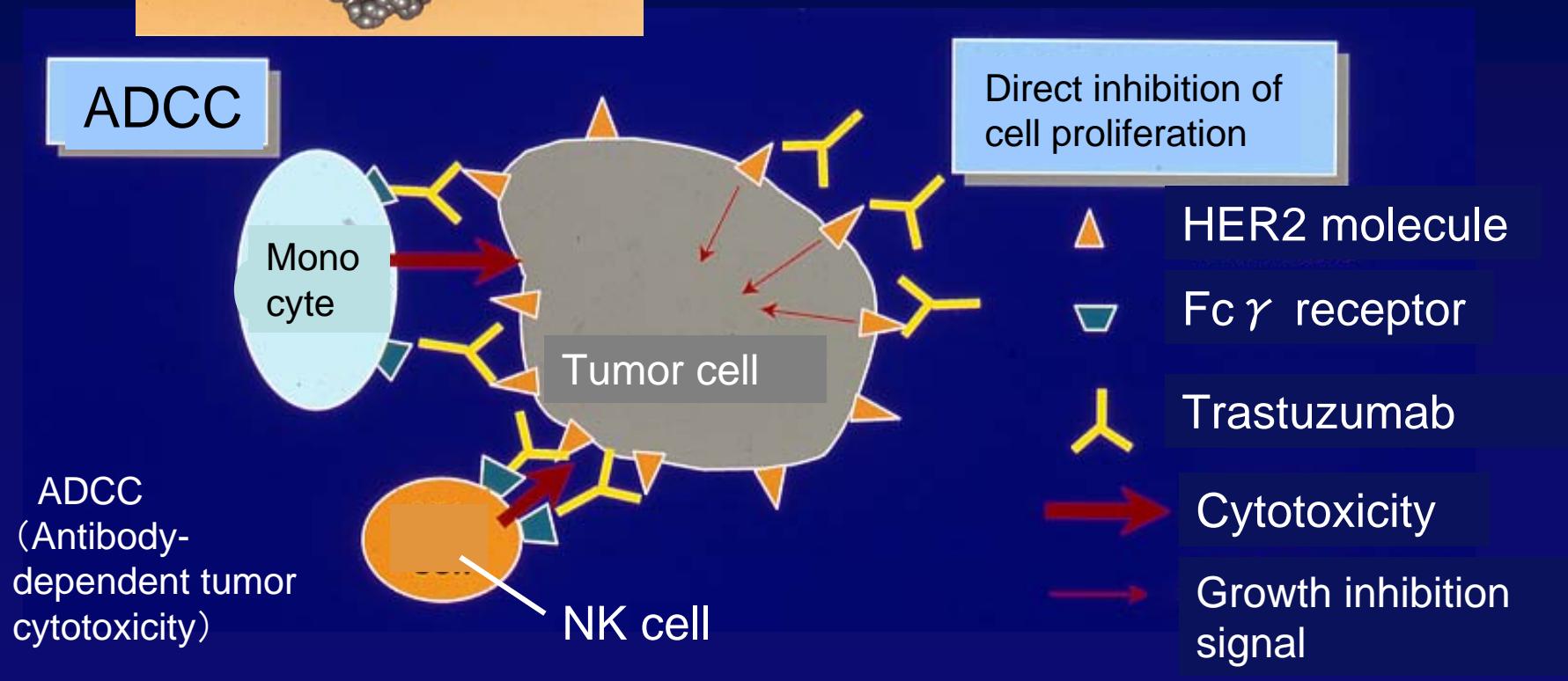


Humanized anti-HER2 monoclonal antibody

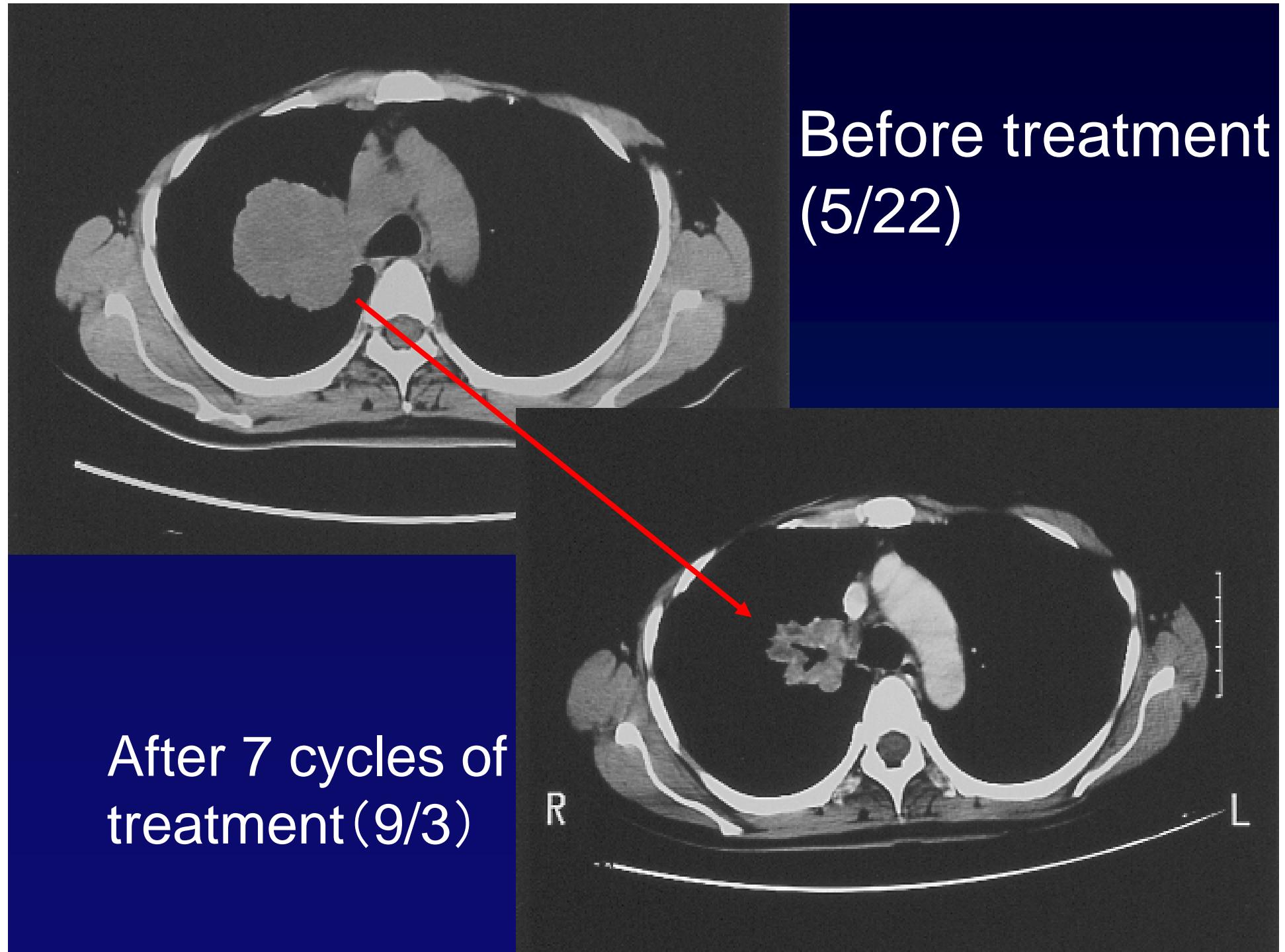
M.W. 148 kDa

Human IgG 95%, Murine IgG 5% (4D5)

ADCC



ADCC
(Antibody-dependent tumor cytotoxicity)





Before treatment(7/10)

PaCO₂ : 33.5mmHg
PaO₂ : 56.9mmHg
(room air)



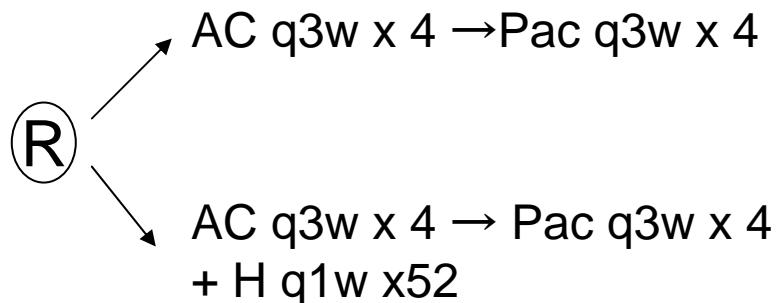
9/19 (After 8 cycles)

PaCO₂ : 36.9mmHg
PaO₂ : 68.8mmHg
(room air)

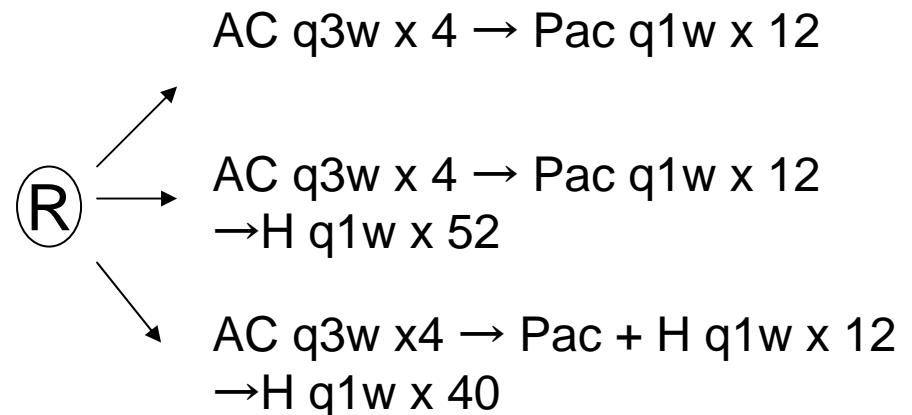
Dramatic Improvement on Treatment Results in HER2+ Recurrent Breast Cancer

Trastuzumab adjuvant study design

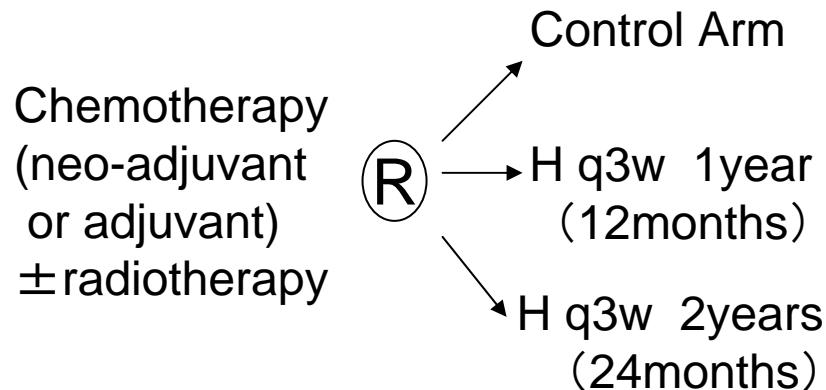
NSABP B-31



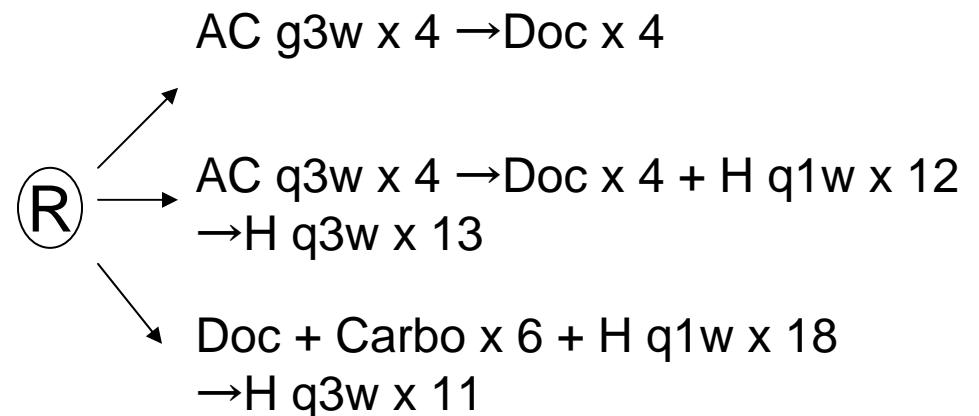
NCCTG N9831



HERA



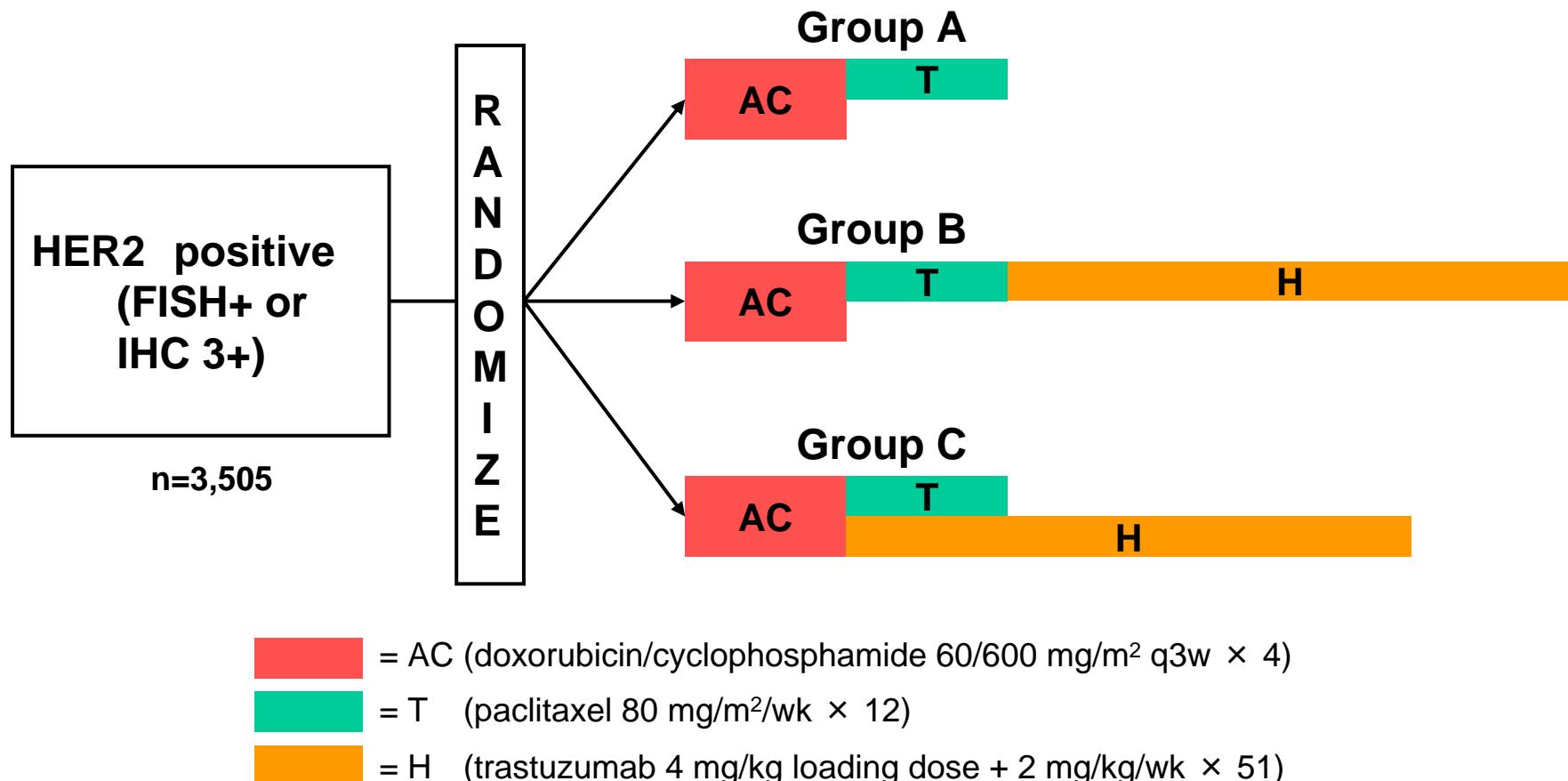
BCIRG006



Pac:Paclitaxel, Doc:Docetaxel, H:Trastuzumab, CT:Chemotherapy, Carbo:Carboplatin

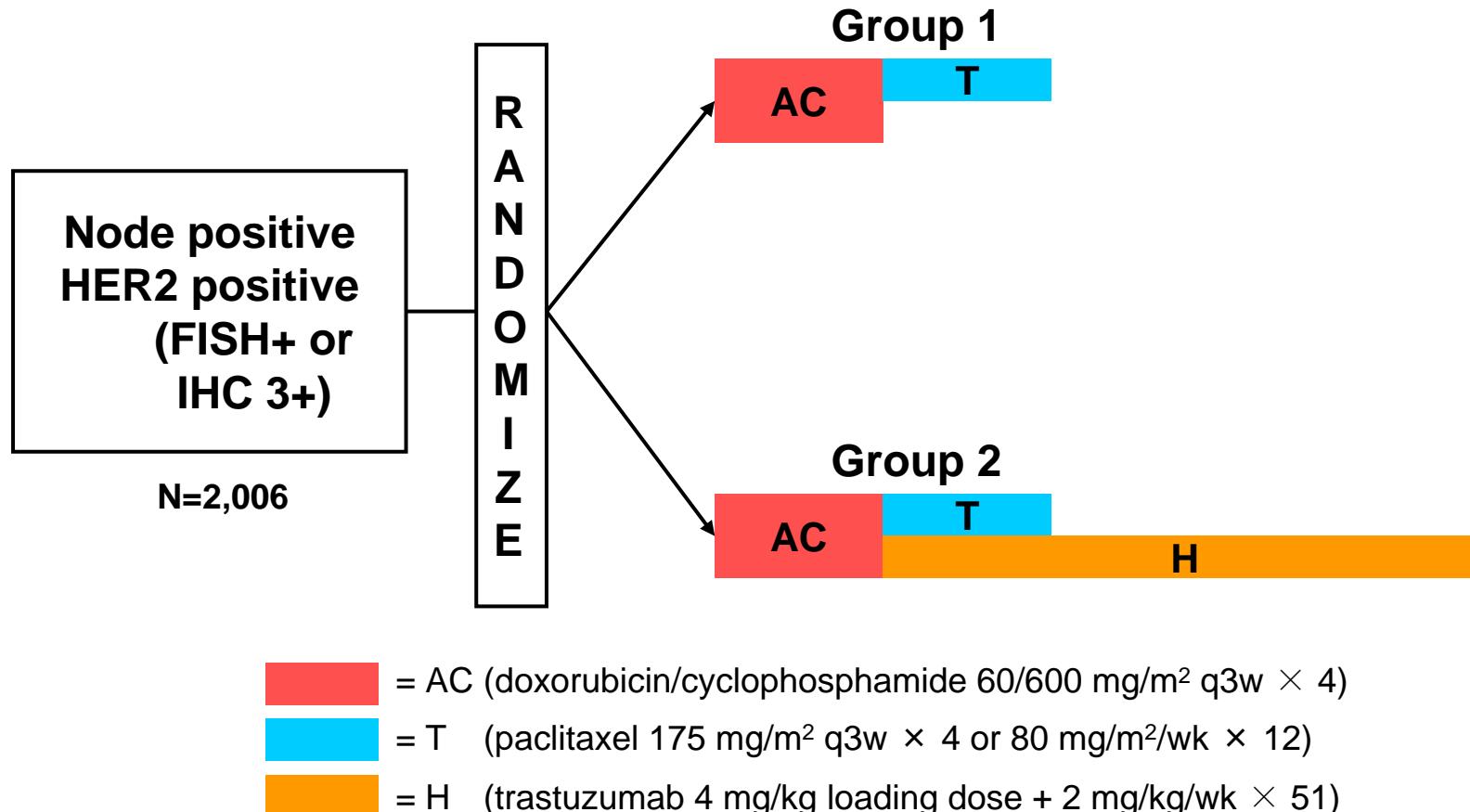
Trastuzumab in Adjuvant Therapy

NCCTG N9831 Trial



Trastuzumab in Adjuvant Therapy

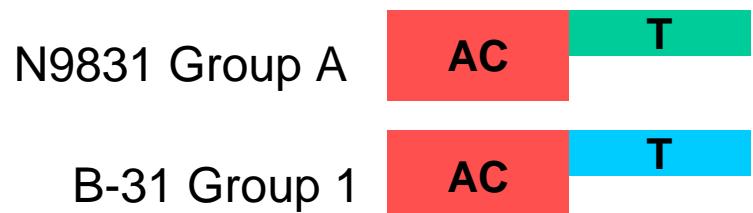
NSABP B-31 Trial



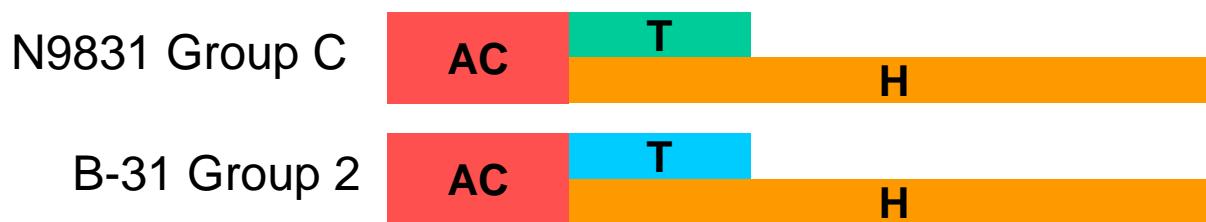
Joint Analysis of HER2+ Adjuvant Trials

2 Arms of N9831 + B-31

Control Group (n=1,979): AC → T

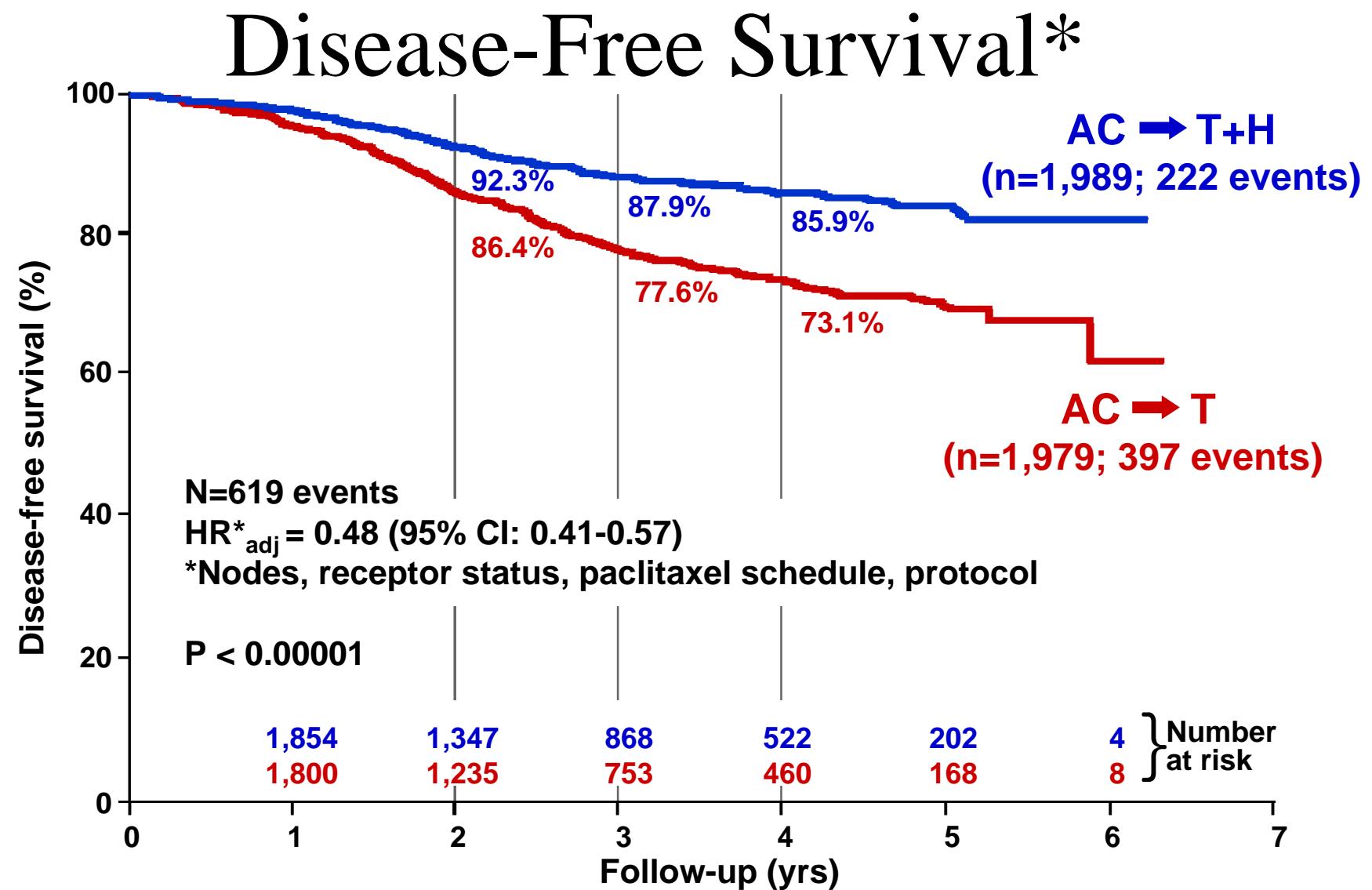


Trastuzumab Group (n=1,989): AC → T+H



- [Red Box] = AC (doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4)
- [Teal Box] = T (paclitaxel 80 mg/m²/wk × 12)
- [Blue Box] = T (paclitaxel 175 mg/m² q3w × 4 or 80 mg/m²/wk × 12)
- [Orange Box] = H (trastuzumab 4 mg/kg loading dose + 2 mg/kg/wk × 51)

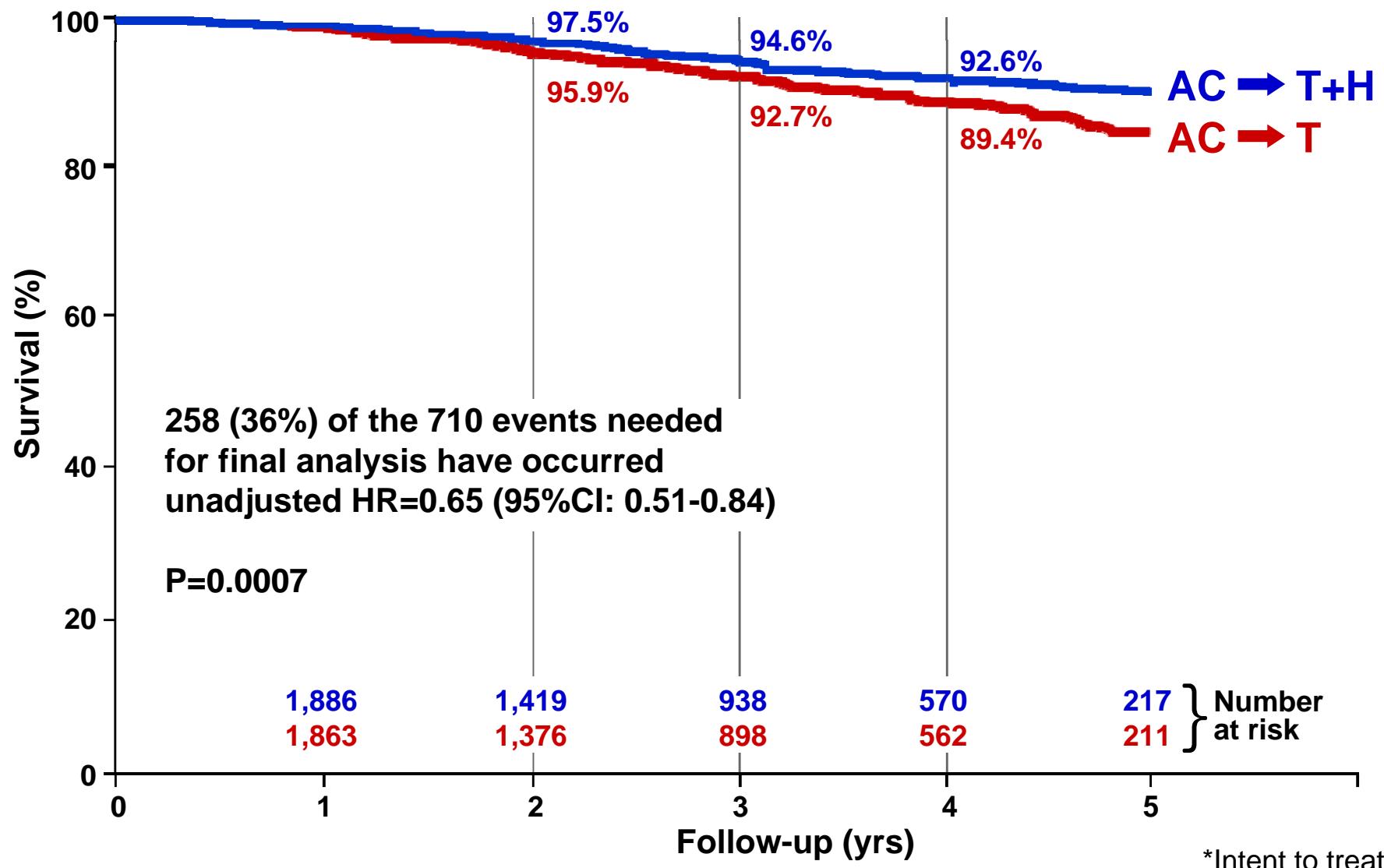
Updated N9831/B-31 Joint Analysis



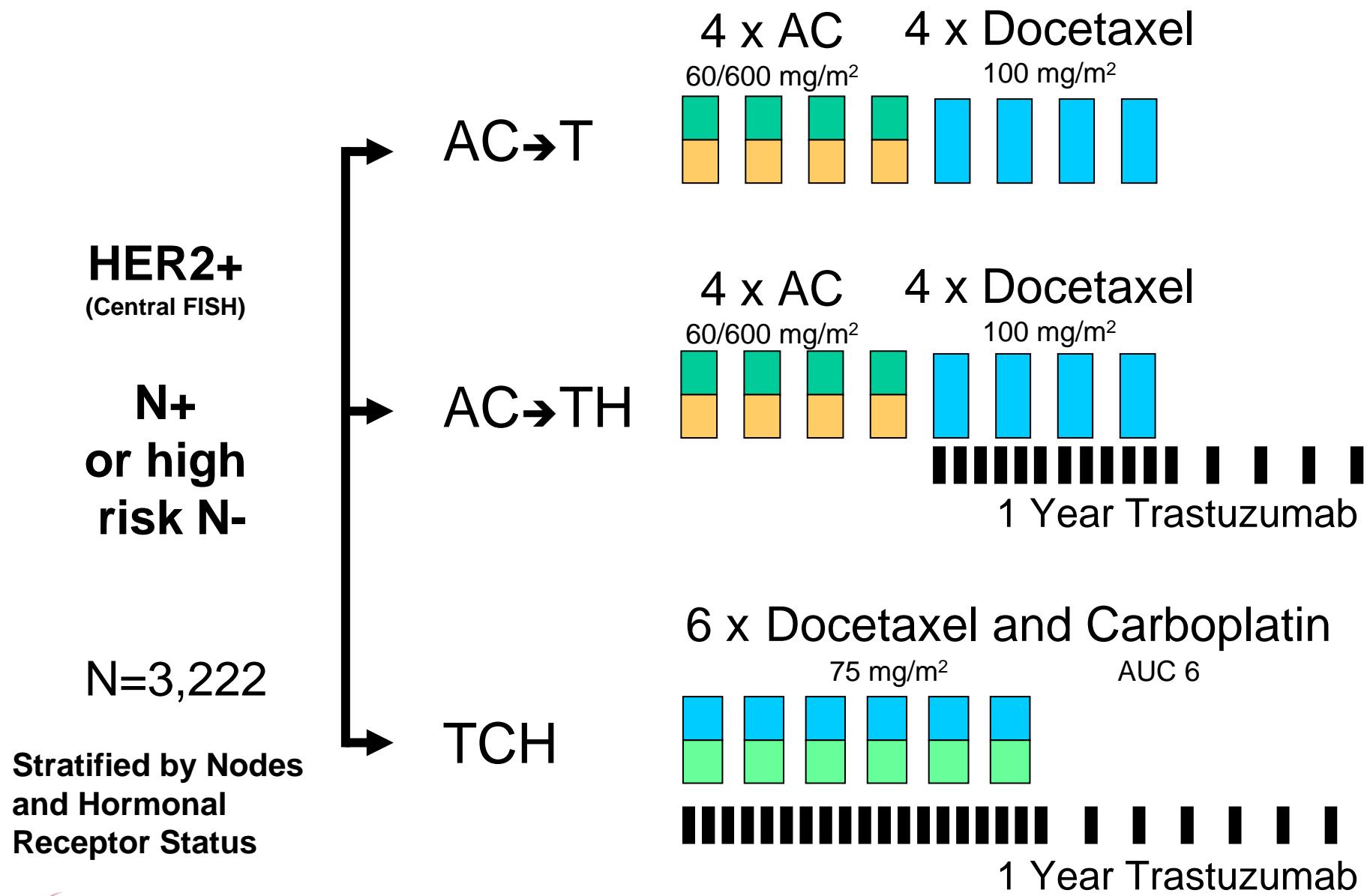
*Intent to treat events: recurrent disease, contralateral bc, 2nd primary, death

Updated N9831/B-31 Joint Analysis

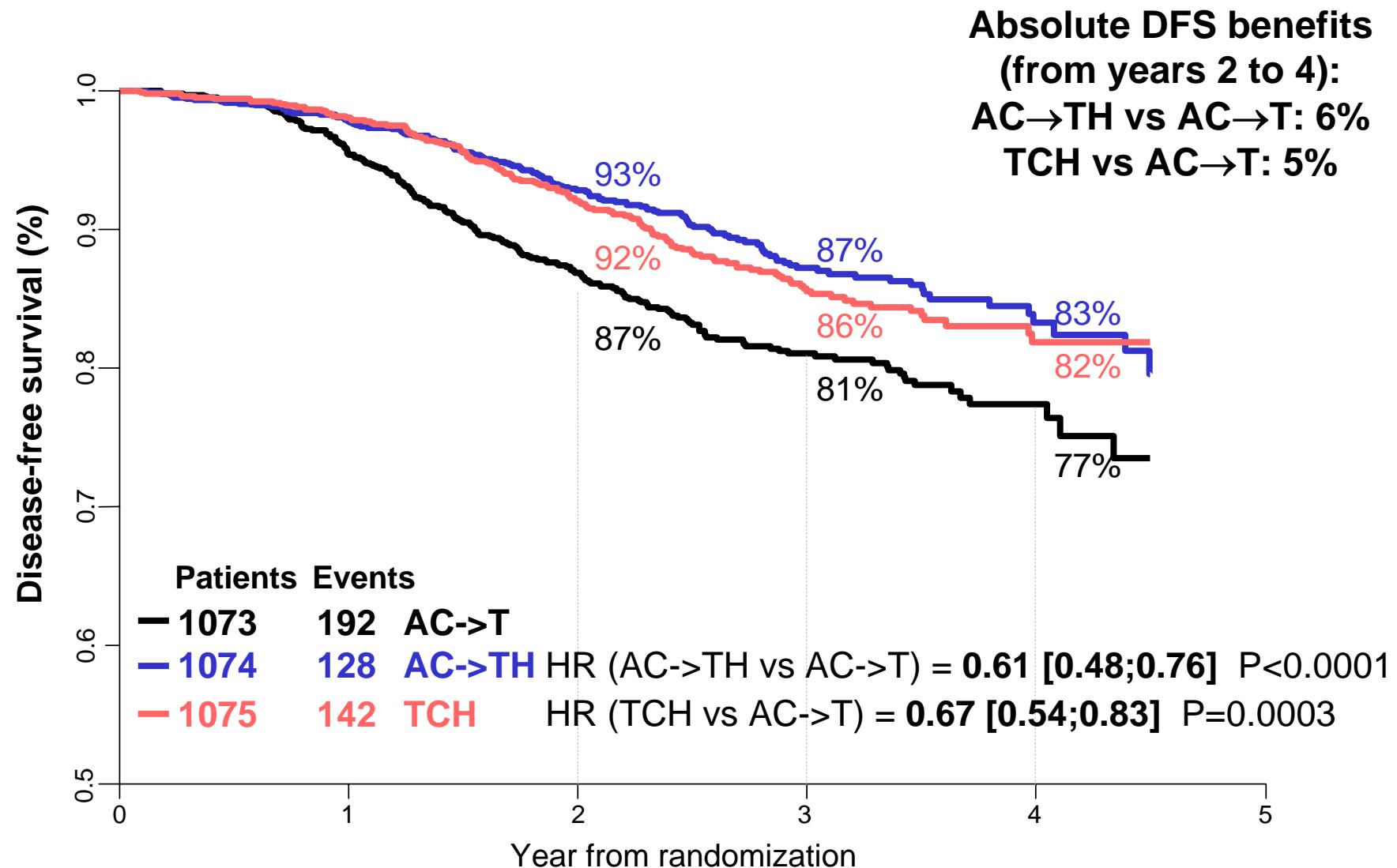
Overall Survival*



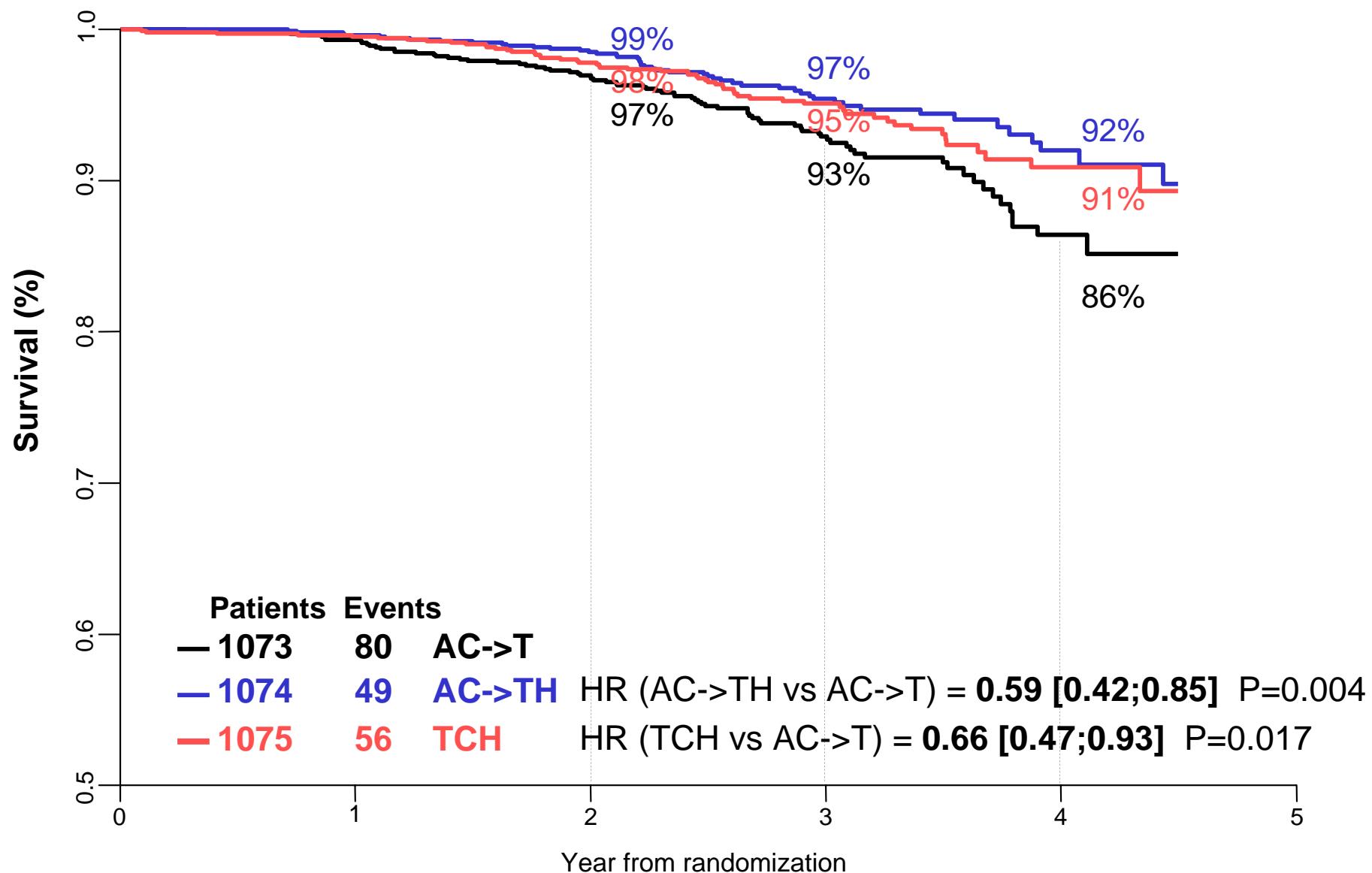
BCIRG 006



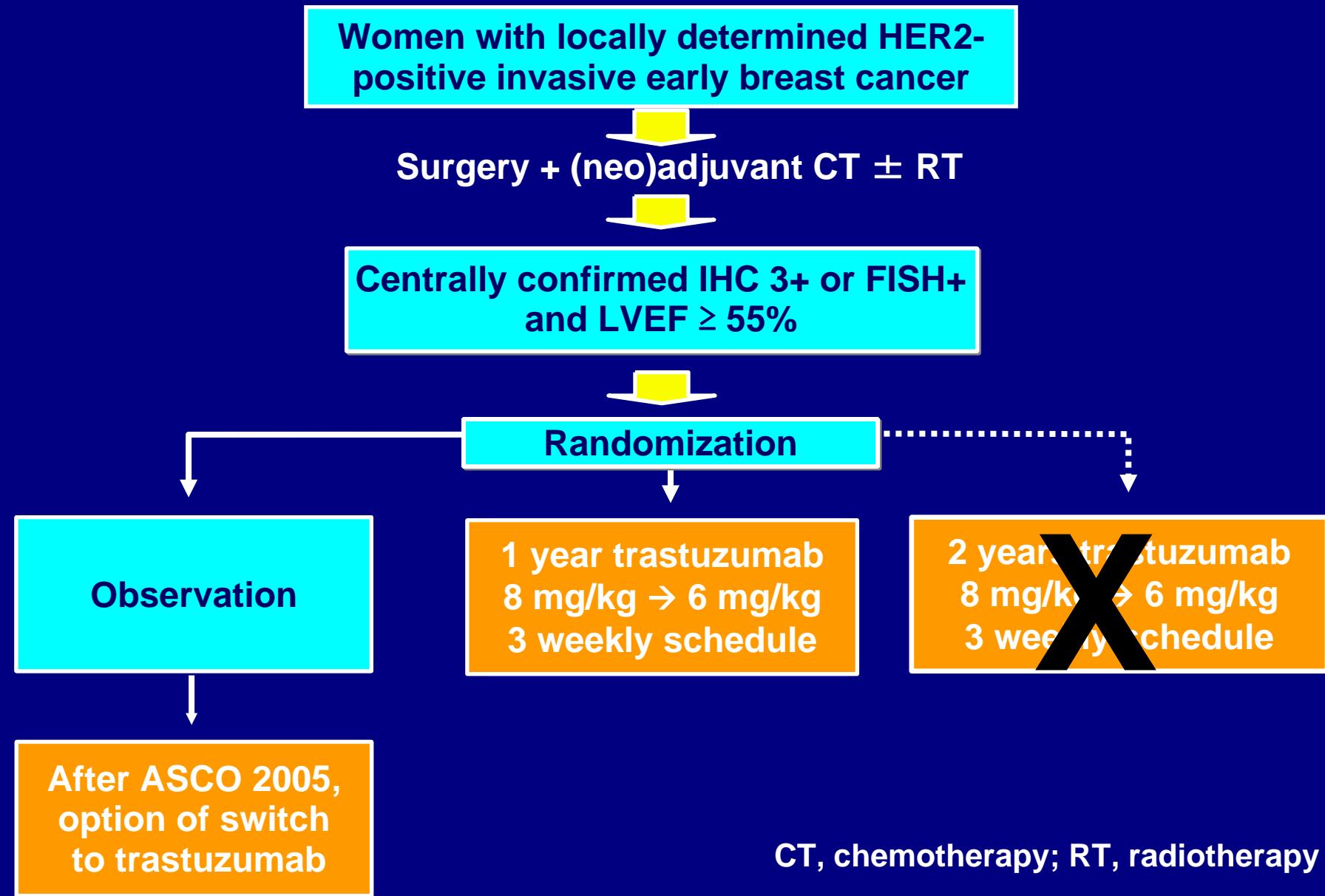
Disease Free Survival - 2nd Interim Analysis



Overall Survival – 2nd Interim Analysis



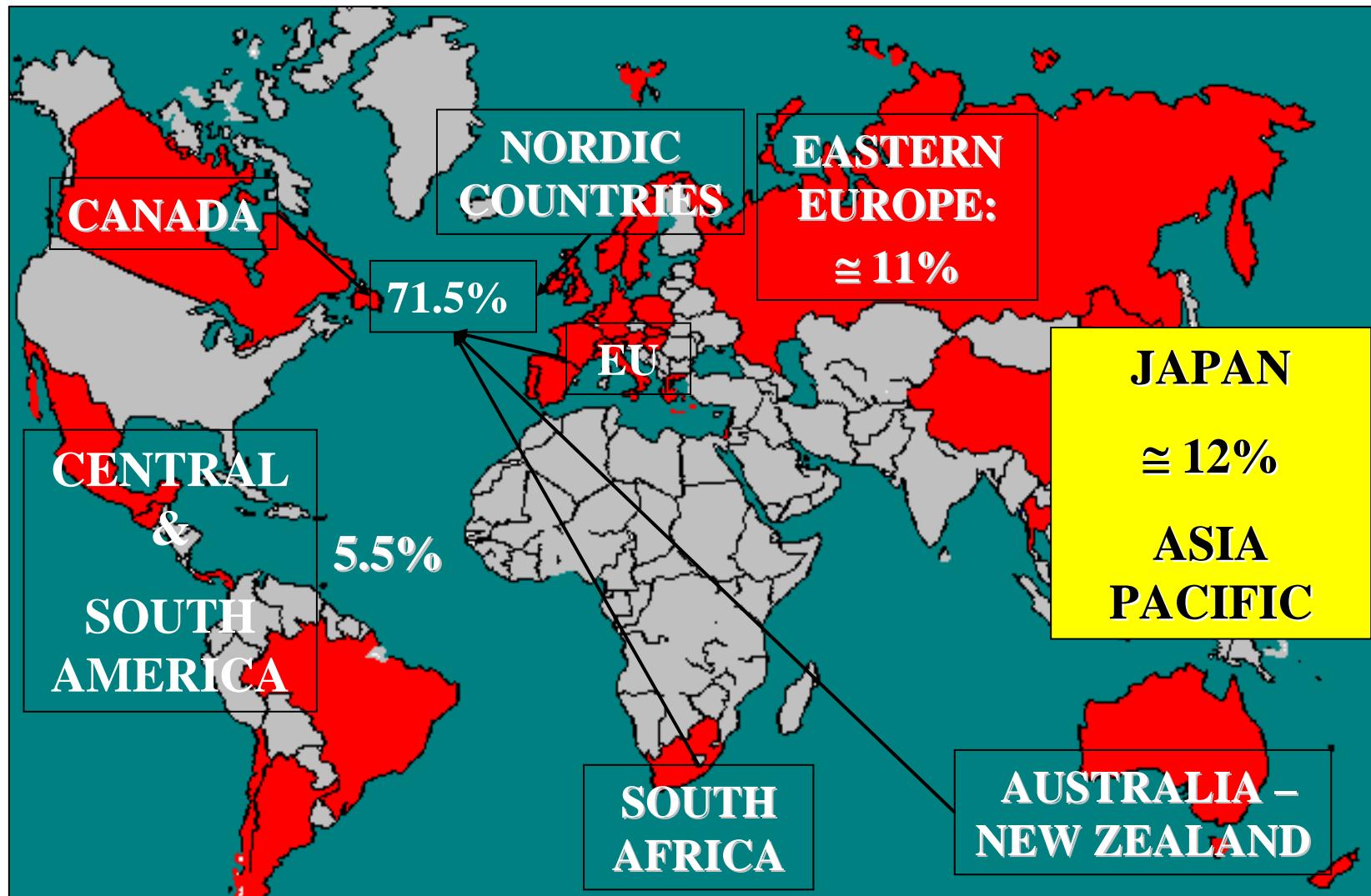
HERA trial design





ACCRUAL: 5090 WOMEN

478 sites in 39 Countries (2002-2005)



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)

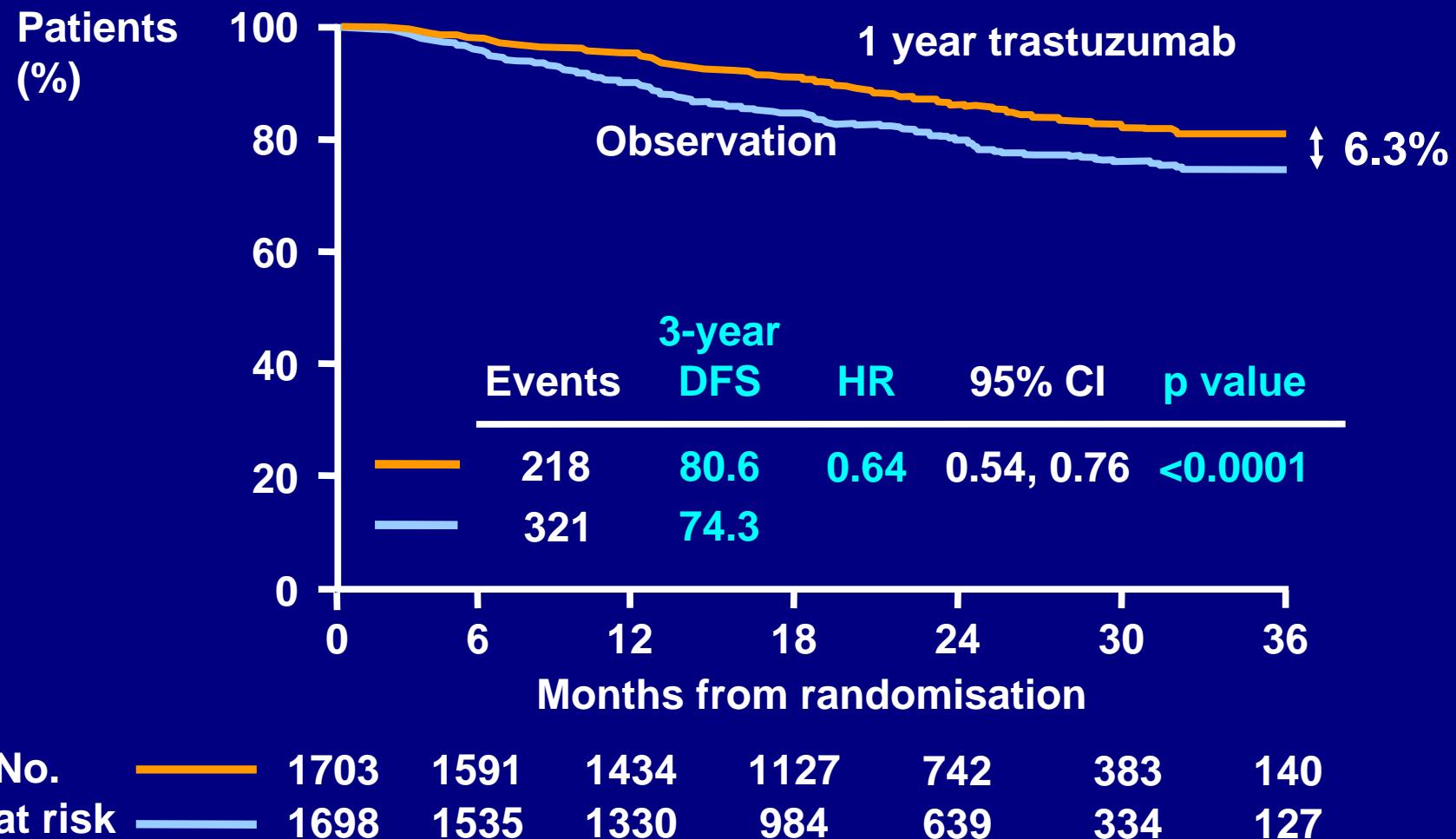
	% patients	
	Observation (n=1698)	1 year trastuzumab (n=1703)
Age, years		
<35	7.4	7.5
35-49	44.3	44.4
50-59	32.3	32.2
<u>≥60</u>	16.0	16.0
Prior (neo)adjuvant CT		
No anthracyclines	5.9	5.9
Anthracyclines, no taxanes	68.1	67.8
Anthracyclines + taxanes	26.0	26.3

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

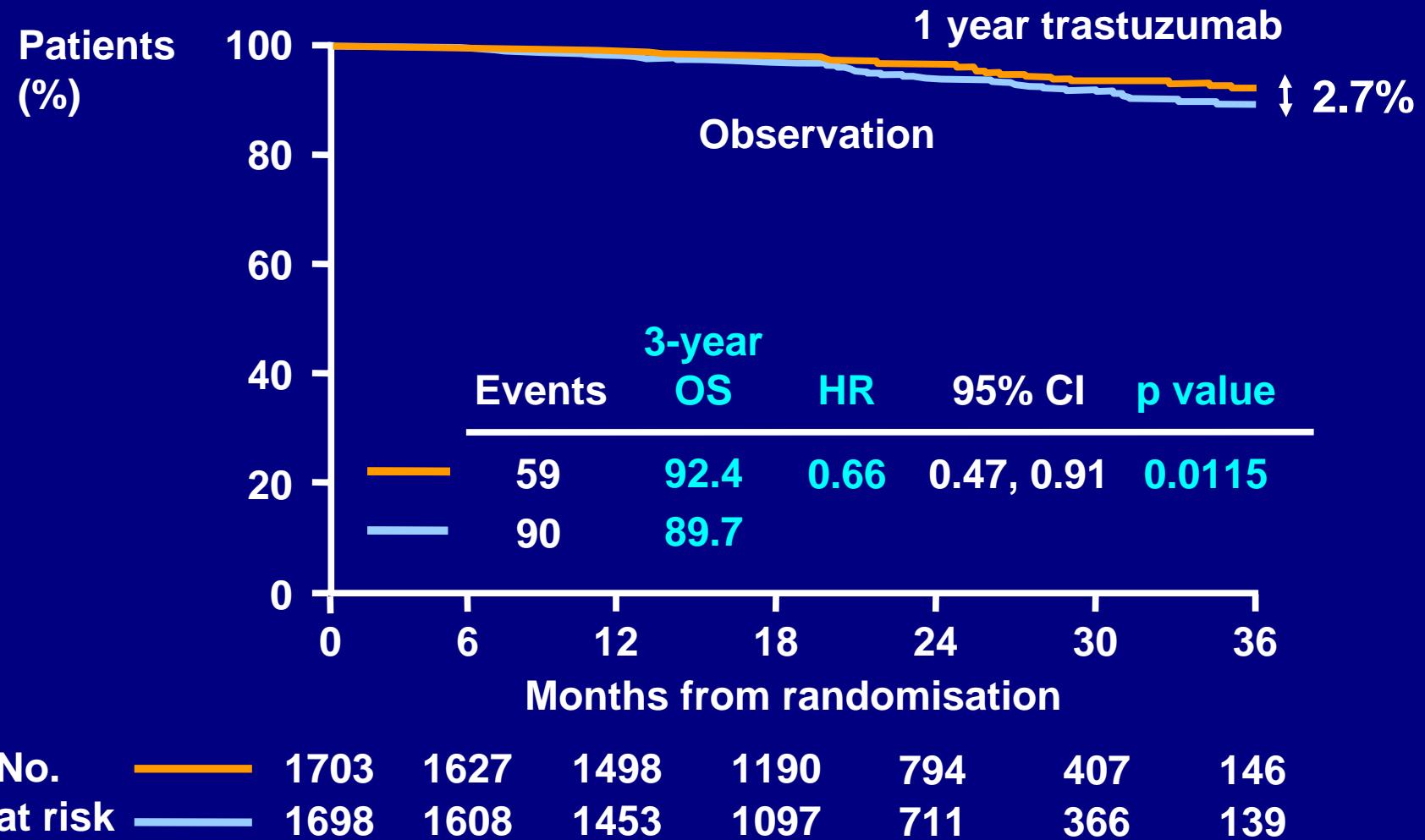
^aStatus at randomisation

Disease-free survival (ITT) Median FU 2 yrs



Overall survival (ITT)

Median FU 2 yrs



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 0.66 (0.54, 0.81)

21 vs 37 0.53 (0.31, 0.90)

23 vs 36 0.54 (0.32, 0.91)

13 vs 13 0.98 (0.45, 2.11)

19 vs 31 0.57 (0.32, 1.01)

89 vs 150 0.54 (0.42, 0.70)

71 vs 97 0.71 (0.52, 0.97)

39 vs 43 0.91 (0.59, 1.41)

43 vs 49 0.80 (0.53, 1.21)

70 vs 135 0.48 (0.36, 0.64)

105 vs 137 0.75 (0.58, 0.97)

39 vs 50 0.66 (0.43, 1.00)

34 vs 58 0.59 (0.39, 0.91)

50 vs 80 0.61 (0.43, 0.87)

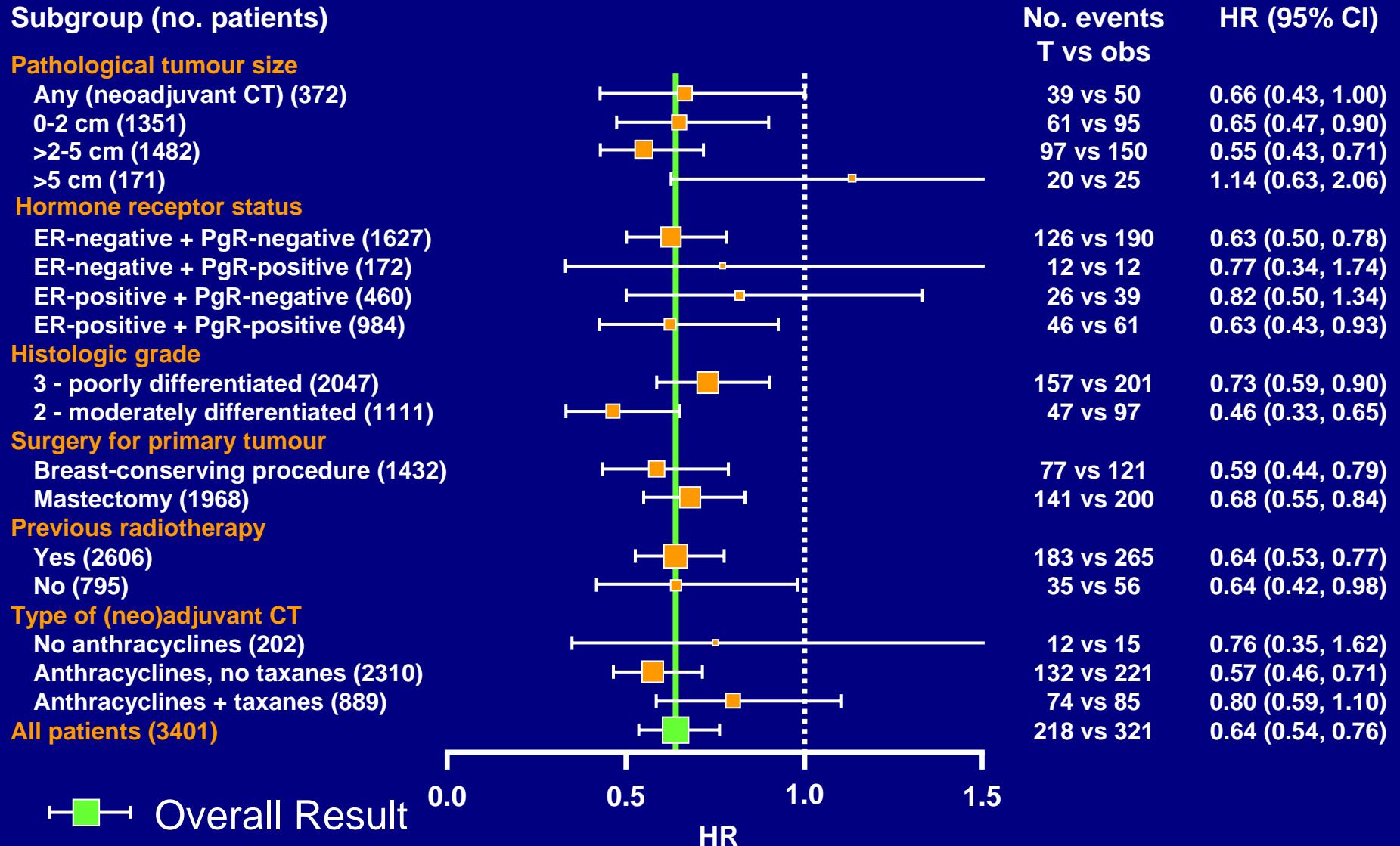
95 vs 132 0.64 (0.49, 0.83)

218 vs 321 0.64 (0.54, 0.76)

Overall Result



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



Adverse Events (AE)

	No. events (%)	
	Observation (n=1466)	1 year trastuzumab (n=1688)
Patients with <u>≥1</u> grade 3/4 AE	88 (6.0)	190 (11.3)
Patients with <u>≥1</u> 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)

St. Gallen update

Risk Assessment of Breast Cancer patients and Selection of optimal Adjuvant Therapy

	sensitive	sensitivity unknown	non-sensitive
Low Risk Node negative AND all of the following features: Pathological tumor diameter $\leq 2\text{cm}$, AND Grade 1, AND Absence of extensive peritumoral vascular invasion ,AND ER and/or PgR expressed, AND HER2/ <i>neu</i> gene neither overexpressed nor amplified, AND Age ≥ 35	Endocrine therapy no treatment	Endocrine therapy no treatment	Controversial
Intermediate Risk Node negative AND at least one of the following features: Pathological tumor diameter $> 2\text{cm}$, OR Grade 2–3, OR Presence of extensive peritumoral vascular invasion ,OR ER and/or PgR absent, OR HER2/ <i>neu</i> gene overexpressed or amplified, OR Age < 35 or Node positive(1–3 involved nodes) AND ER and/or PgR expressed, AND HER2/ <i>neu</i> gene neither overexpressed nor amplified	Endocrine Therapy alone or chemo→ Endocrine Therapy (chemo+ Endocrine therapy) trastuzumab	Chemo→ Endocrine Therapy (Chemo + Endocrine therapy) Trastuzumab	Chemo Trastuzumab
High Risk Node positive(1–3 involved nodes) AND ER and/or PgR absent, OR HER2/ <i>neu</i> gene overexpressed or amplified or Node positive(4 or more involved nodes)	Chemo→ Endocrine Therapy (Chemo + Endocrine therapy) Trastuzumab	Chemo→ Endocrine Therapy (Chemo + Endocrine therapy) Trastuzumab	Chemo Trastuzumab

Trastuzumab Adjuvant Therapy makes changes in HER2+ breast cancer therapy

- The number of recurrence in HER2+ is expected to decrease dramatically in Japan.
- HER2+ breast cancer, which used to be a poor prognostic factor, will turn into a better prognostic factor with proper treatment.
- Trastuzumab treatment for a limited period (1 year) is cost-effectively advantageous.

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