Preoperative Chemotherapy for HER2 Positive Early Breast Cancer

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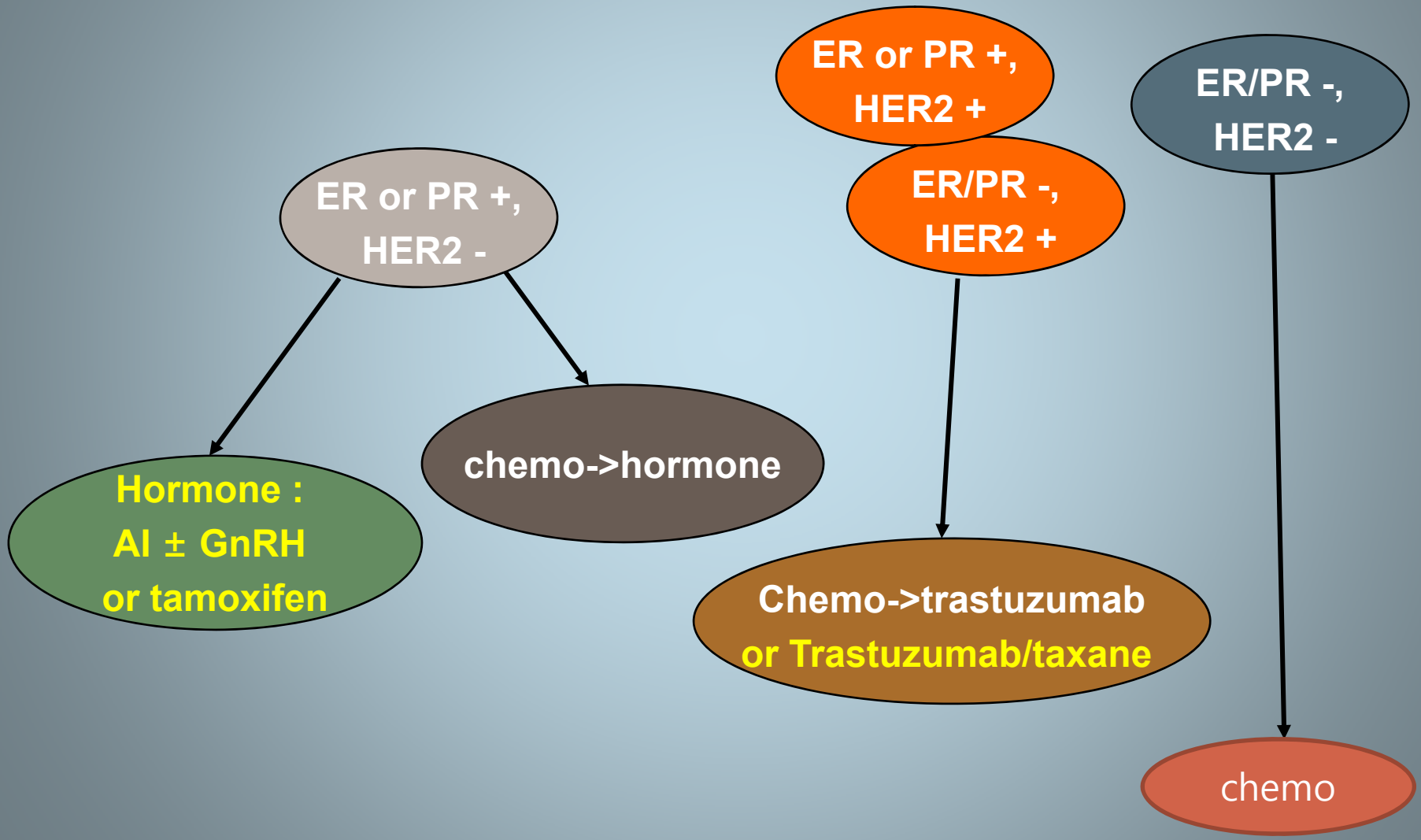
2009 GBCC

Therapeutic options by receptor subtypes (adjuvant/neoadjuvant setting)



Background

Trastuzumab (Herceptin®; H) improves survival in HER2 positive early and metastatic breast cancer

Contents

- Published and presented preoperative clinical trials of trastuzumab combination therapy
- Rationale for non-anthracycline-based regimen
- Paclitaxel and gemcitabine combination

  Paclitaxel/gemcitabine and trastuzumab combination **(PGH)**

Efficacy of trastuzumab plus anthracycline-containing chemotherapy

Trial	Neoadjuvant regimen	*N*	pCR rate
Buzdar 2005	Trastuzumab qwk x 24 + (paclitaxel q3wk x 4+FEC q3wk x 4)	23	65% → 55%
Steger 2002	Trastuzumab qwk x 12 + docetaxel qwk + epirubicin qwk	9	22%
Carey 2002	AC x 4 (trastuzumab + paclitaxel) qwk x 12	22	22%
Mehta 2005	(ddAC + GM-CSF) q2wk x 4 → Trastuzumab qwk x 12 + paclitaxel/carboplatin q3wk x 3-4	8	71%
Untch 2005	EC q3wk x 4 → Trastuzumab q3wk x 4 + paclitaxel q3wk x 4	119	37%
Von Minckwitz (AGO/GBC) 2008	Trastuzumab + various anthracycline-based chemotherapy	671	41%
NOAH 2008	Trastuzumab q3wk x 11 + (doxorubicin/paclitaxel q3wk x 4→ paclitaxel q3wk x 4 CMF q4wk x 3)	115	38%

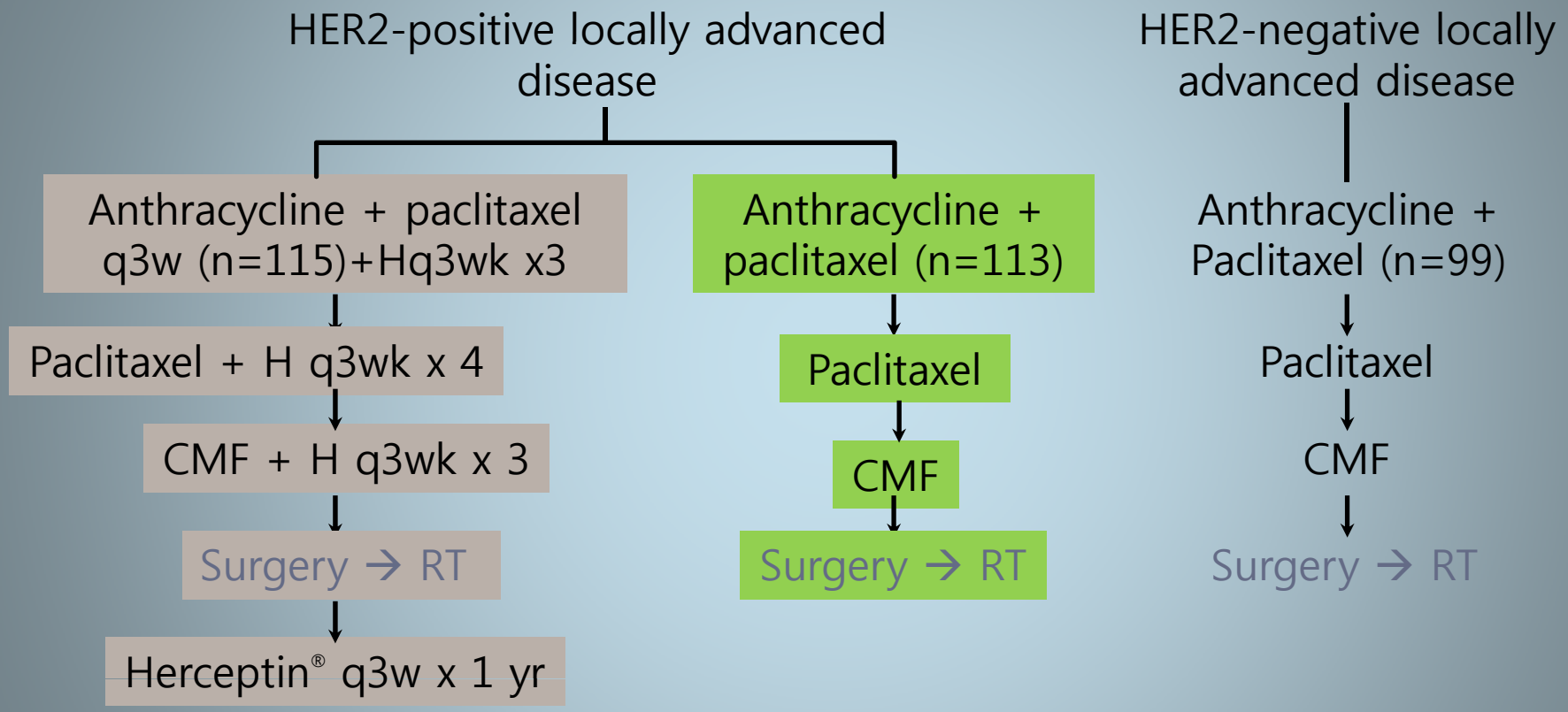
J Clin Oncol 2005;23(16):3676–85
Proc Am Soc Clin Oncol 2002;21 (abstract 1966)
Breast Cancer Res Treat 2002;76(Suppl 1):109;Abstract 424;
SABCS2005 (abstract 1064)

Efficacy rates of trastuzumab plus non-anthracycline-containing chemotherapy

Trial	Neoadjuvant regimen	*N*	pCR rate
PGH	Trastuzumab qwk x 18 + (intermittent weekly paclitaxel+gemcitabine) q3wk x 6	53	59%
Harris 2003	Trastuzumab qwk x 12 + vinorelbine qwk	39	21%
Burstein 2003	Trastuzumab qwk x12 + paclitaxel q3wk x 4	40	IHC 3+ 19% IHC 2+ 13%
Bines 2003	Trastuzumab qwk x 14 + (docetaxel qwk x 6 2 wk off) x 2	33	12%
Schiffhauer 2003	Trastuzumab qwk x 12 + docetaxel q3wk x4	16	25%
Hurley 2006	Trastuzumab qwk x 12 + (cisplatin + docetaxel q3wk x 4 + G-CSF + EPO)	44	17%
Chang 2006	Trastuzumab qwk x 12 + (docetaxel+carboplatin) q3wk x 4	11	36%
Limentani 2007	Trastuzumab qwk x 12 + (docetaxel+vinorelbine) q3wk x 4	31	39%

J Clin Oncol 2003;21(1):46–53 Proc ASCO 2003;Abstract 86 Breast Cancer Res Treat 2003;82(Suppl 1):54;Abstract 238
Breast Cancer Res Treat 2003;82(Suppl 1):56;Abstract 243 Breast Cancer Res Treat 2003;82(Suppl 1):55;Abstract 240
J Clin Oncol 2006;24(12):1831–8.

NeOAdjuvant Herceptin (NOAH) trial



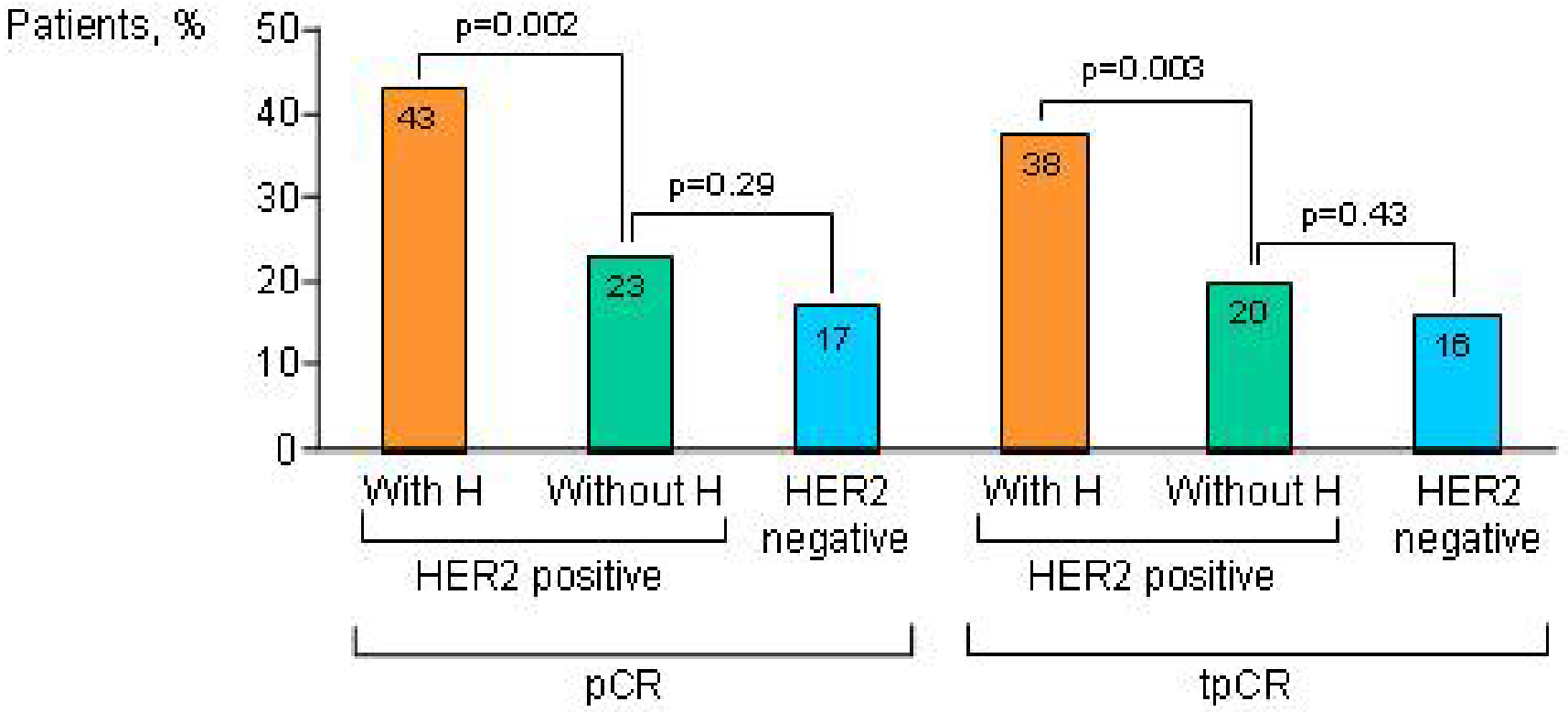
- Primary endpoint : Event-free survival
- Other endpoints:
  - pCR rates
  - Overall survival
  - Safety and tolerability

SABCS 2008

Methods

- Multicenter, randomized, open-label trial,
- women aged ≥18 years with HER2-positive tumor (IHC 3+ or FISH+)
- LABC (T3N1 or T4; any T + N2 or N3)
- The primary endpoint: event-free survival (EFS)
- Secondary endpoints:
  - pathological complete response (pCR),
  - overall response rate (ORR),
  - overall survival (OS)
  - safety

pCR of primary tumour: ITT population



tpCR, total pCR in breast and nodes

Results

- EFS analyzed after 88 events in 228 HER2+ patients
- EFS rate at 3 years: H + CT arm vs CT alone:

  70.1% *vs* 53.3% [HR 0.56; p=0.007]

  (EFS rate in the *HER2-* group: 67.4%)
- Trastuzumab treatment : the only variable significantly associated with EFS outcome in multivariate analysis,
- H + CT arm compared to CT alone:

  ORR 89% *vs* 77% (*p*=0.02);

  pCR 38% *vs* 20% *(p*=0.002*).*

AEs

- Most common serious adverse event:
  febrile neutropenia (8% *vs* 4%)
- Absolute LVEF decreases of 10%:
  11% of pts receiving H
- Cardiac event with an LVEF value of <45%:
  1 pt
- One patient death in HER2-negative disease
  due to pulmonary embolism.

Integrated meta-analysis on 6634 patients with early breast cancer receiving neoadjuvant anthracycline-taxane +/- trastuzumab containing chemotherapy

von Minckwitz G, Kaufmann M, Kümmel S, Fasching P, Eiermann W, Blohmer JU, SD, Loibl S, Mehta

AGO

for the

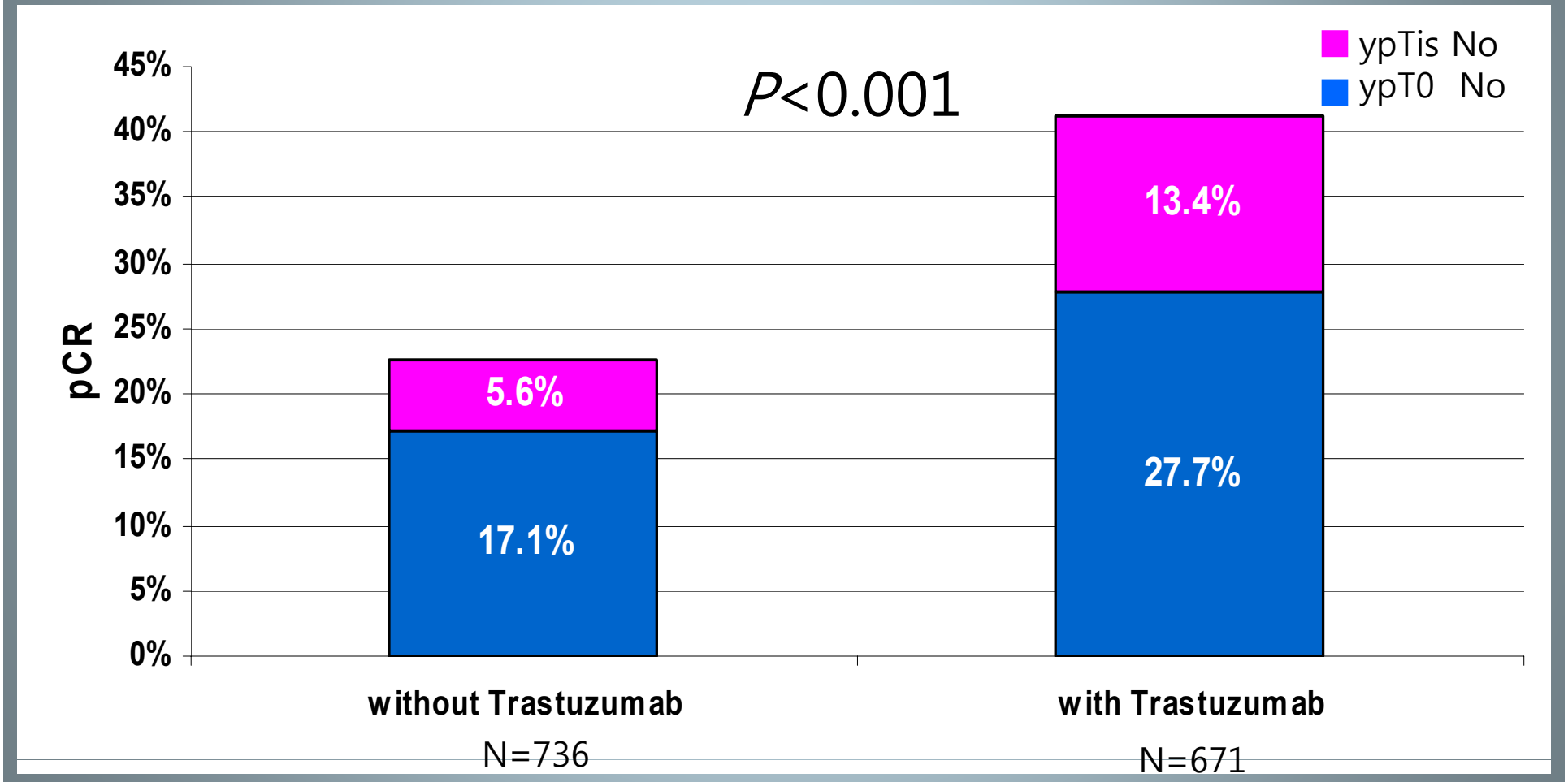
and

GBG

GERMAN BREAST GROUP

SABCS 2008

Treatment group effects*
Use of trastuzumab
in patients with HER2-positive tumors



* excluding patients with HER2 negative or HER2 unknown tumors

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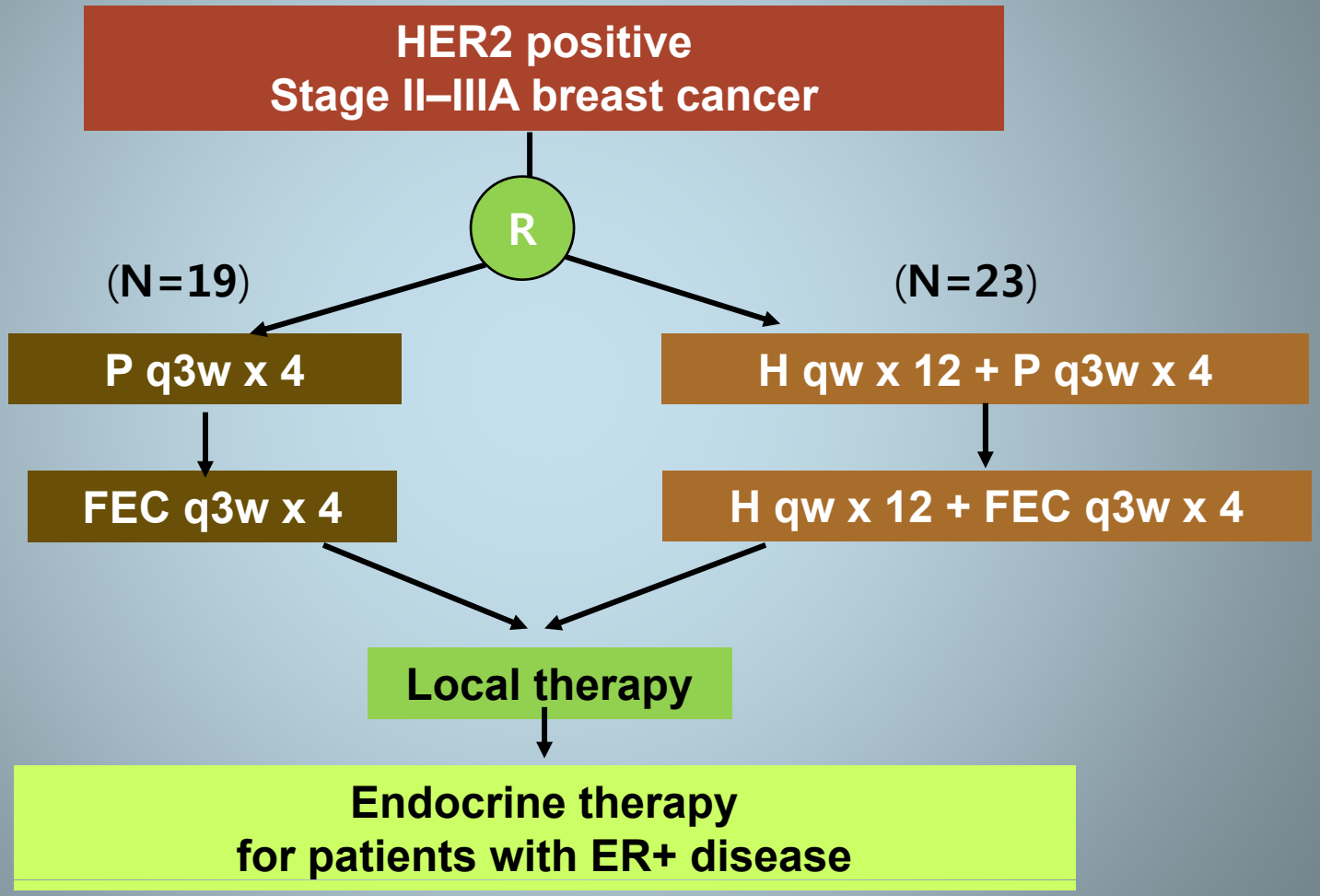
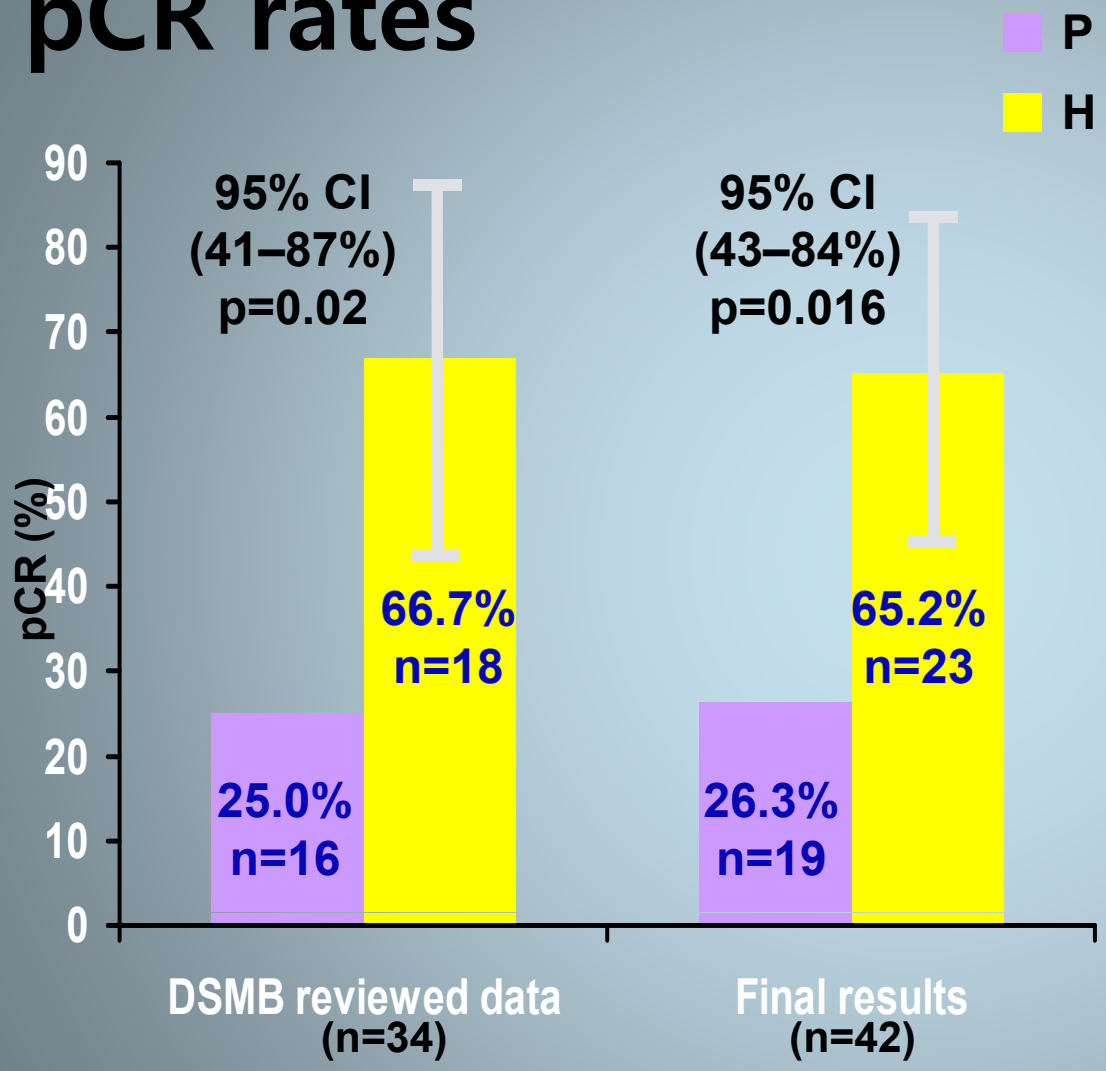
Randomised trial in HER2-positive BC



Buzdar A, et al. J Clin Oncol 2005;23:3676-3685

pCR rates



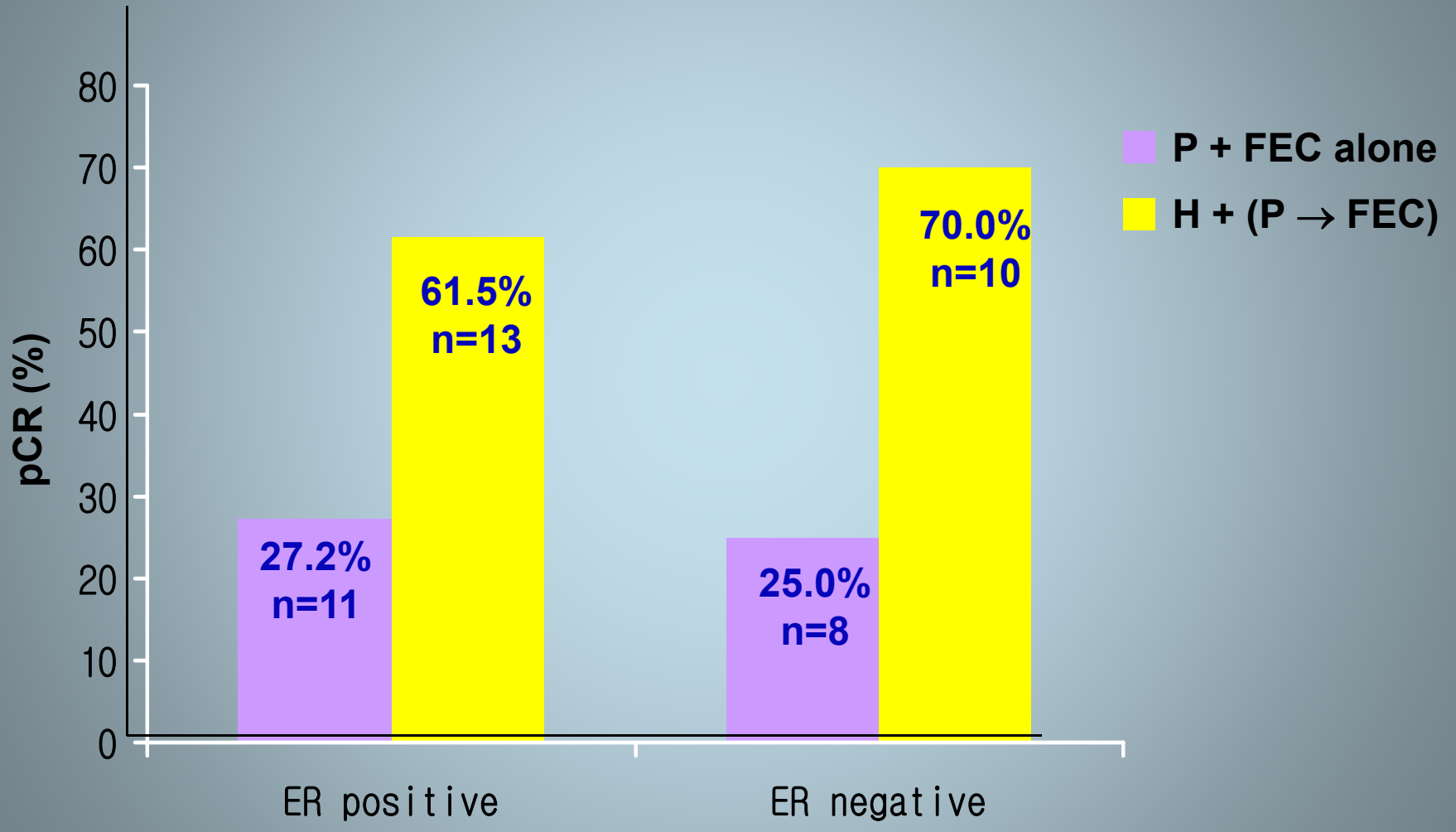
H + (P → FEC)

54.5%
n=22

(n= additional 22)

Buzdar A, et al. J Clin Oncol 2005;23:3676-3685
Buzdar A, et al. BCRT 94:S223, 2005 (abstr 5049)

pCR by ER status



Buzdar A, et al. J Clin Oncol 2005;23:3676-3685

Concerns in anthracycline based chemotherapy

- Cardiotoxicity
  - Clinical CHF is rare (< 1%)
  - In EBCTCG analysis, mortality from heart disease was 0.08% vs 0.06% per year
  - Use of trastuzumab:

    (4~7% with trasuzumab alone)

    27% with concurrently with doxorubicin
- Secondary acute leukemia and myelodysplasia
  - CMF 0.4%, AC 1.3%, CEF 1.7% at a follow-up of 8 years

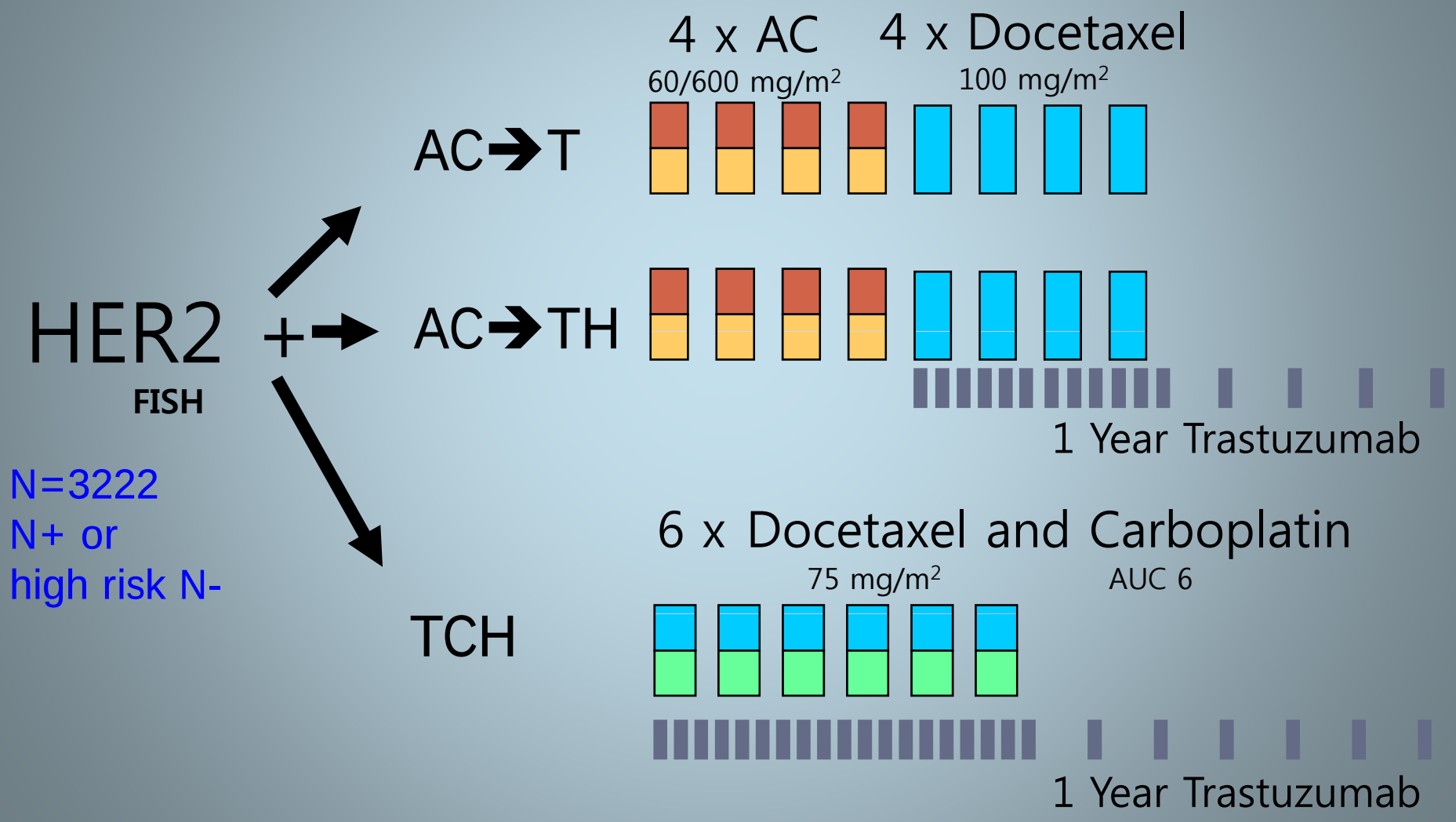
EBCTCG. Lancet. 2005;365:1687-1717

J Clin Oncol 21:3066-3071, 2003

HER2 and *TOP2A* genes

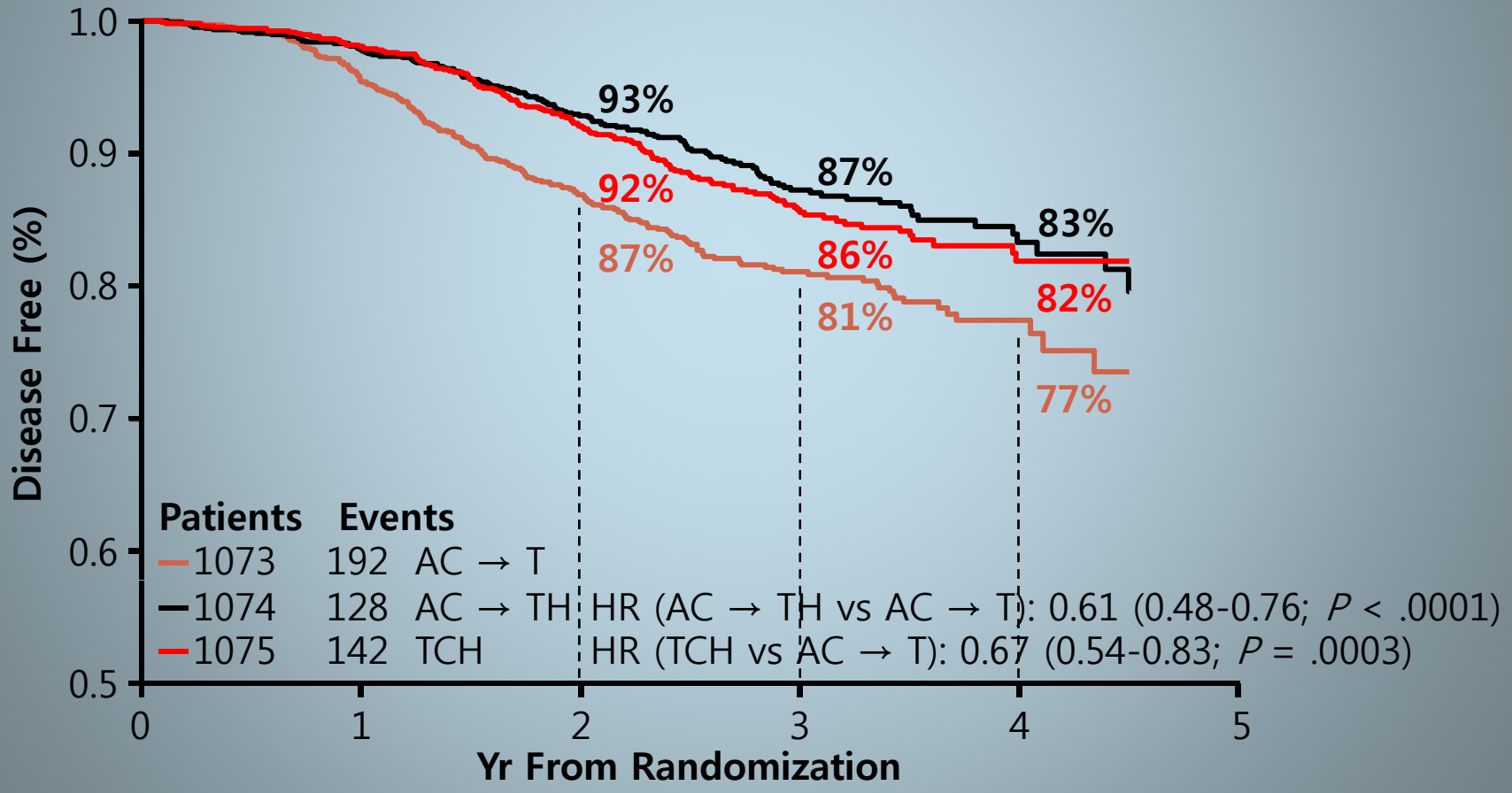
- Both located on long arm of chromosome 17
- TOP2A, often coamplified with HER2
- TOP2A, a possible anthracycline target

BCIRG 006: schema



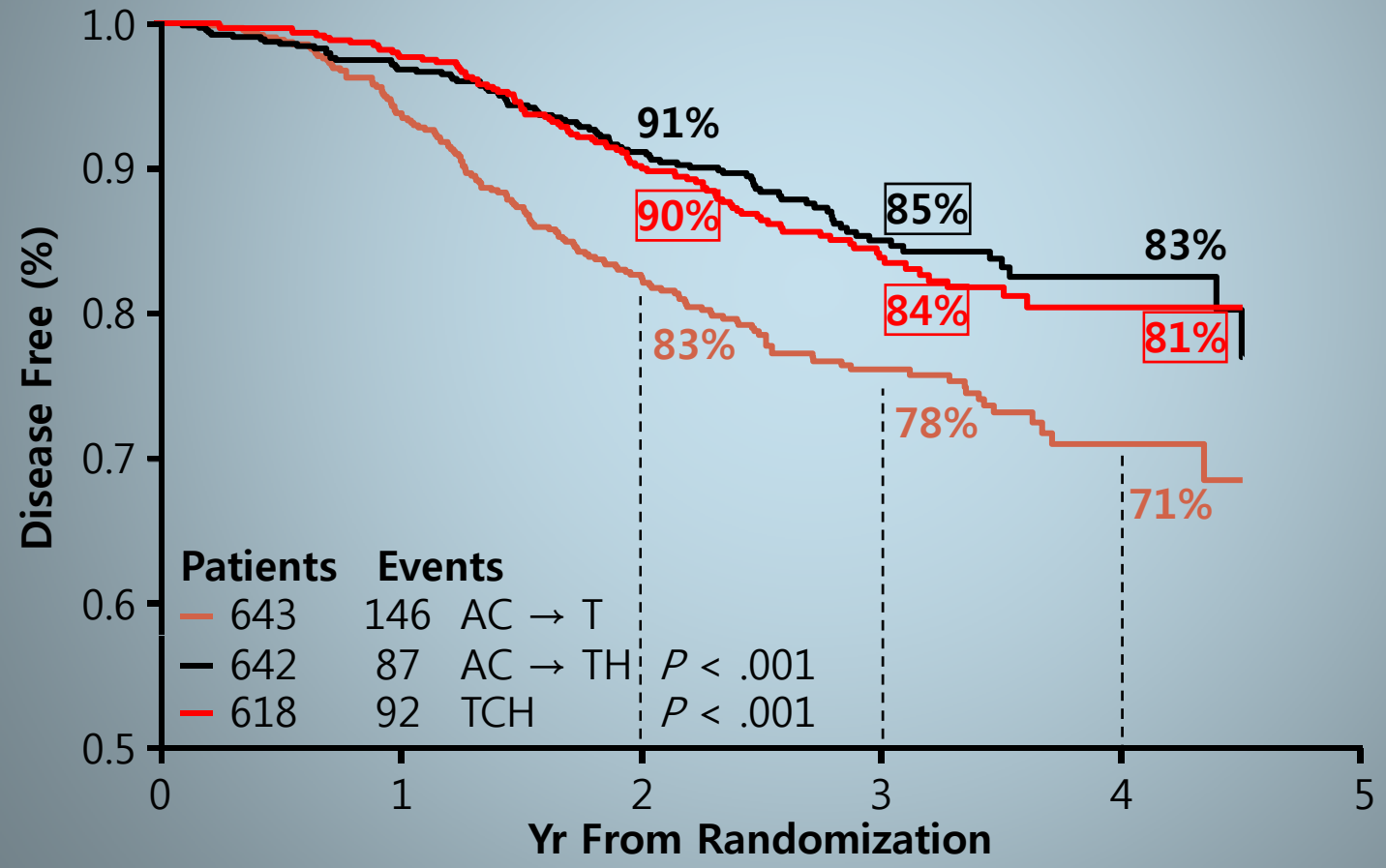
Slamon D, et al. SABCS 2006. Abstract 52.

DFS: BCIRG 006 2nd Interim Analysis



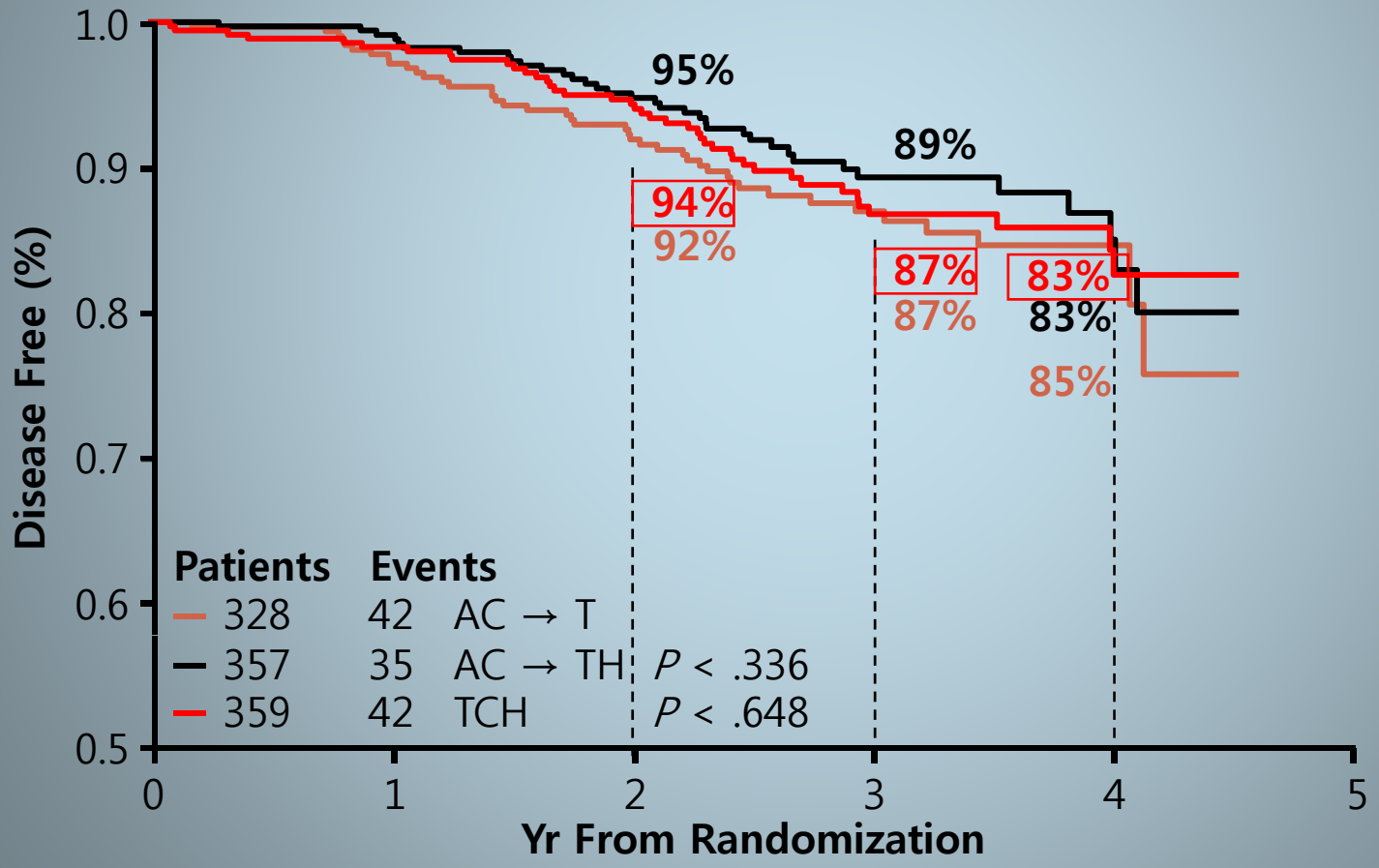
Slamon D, et al. SABCS 2006. Abstract 52.

DFS: Non-coamplified Topo IIα by Arm: BCIRG 006 2nd Interim Analysis



Slamon D, et al. SABCS 2006. Abstract 52.

DFS Coamplified Topo IIα by Arm: BCIRG 006 2nd Interim Analysis



Slamon D, et al. SABCS 2006. Abstract 52.

Characteristics for 438 patients with TOP2A measurements: Canadian NCI Trial, MA.5

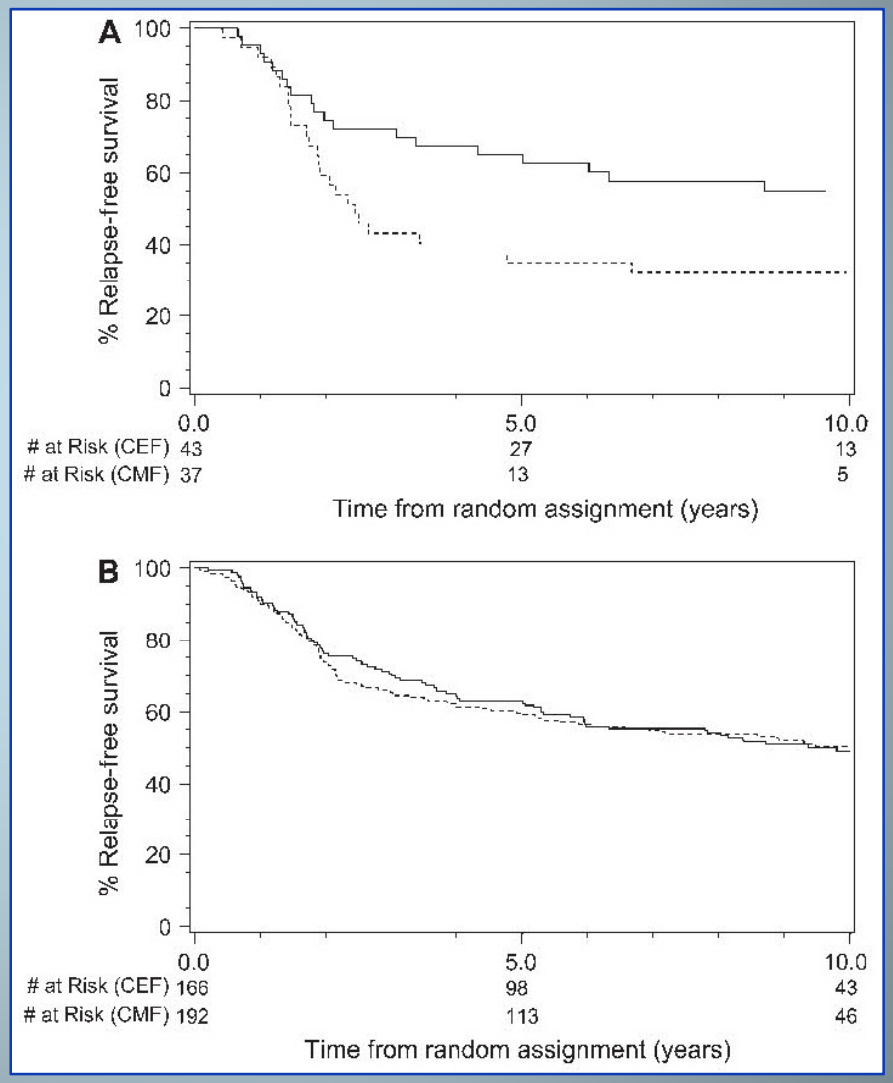
Characteristic	*TOP2A* status: Amplified (n = 54)	Deleted (n = 26)	Normal (n = 358)	*P* value†
Age in y, No. (%)				.23
≤29	0 (0)	1 (4)	6 (2)	
30–39	7 (13)	3 (12)	85 (24)	
40–49	36 (67)	15 (58)	210 (59)	
≥50	11 (20)	7 (27)	57 (16)	
Node positive, No. (%)				.76
1–3	30 (56)	17 (65)	210 (59)	
4–10	20 (37)	6 (23)	121 (34)	
>10	4 (7)	3 (12)	27 (8)	
Grade, No. (%)				.10
1	2 (4)	0 (0)	42 (12)	
2	14 (26)	10 (38)	105 (29)	
3	36 (67)	16 (62)	200 (56)	
Unknown	2 (4)	0 (0)	11 (3)	
HER2 status,‡ No. (%)				<.001
Amplified	33 (62)	17 (65)	66 (19)	
Nonamplified	20 (38)	9 (35)	285 (81)	
ER level,§ No. (%)				.35
<10	18 (33)	11 (42)	107 (30)	
≥10	30 (56)	12 (46)	212 (59)	
Unknown	6 (11)	3 (12)	39 (11)	
Surgery, No. (%)				.21
Lumpectomy	23 (43)	11 (42)	191 (53)	
Mastectomy	31 (57)	15 (58)	167 (47)	
Tumor size, No. (%)				.04
T1	17 (35)	3 (13)	143 (43)	
T2	29 (59)	19 (83)	170 (52)	
T3	3 (6)	1 (4)	18 (5)	
Treatment, No. (%)				.23
CEF	32 (59)	11 (42)	166 (47)	
CMF	22 (41)	15 (58)	192 (53)	

O ' Malley, FP et al. J Natl Cancer Inst 2009;101: 644 – 650

Recurrence-free survival according to chemotherapy and TOP2A status

Pts with amplified or deleted *TOP2A*

Pts with normal *TOP2A*

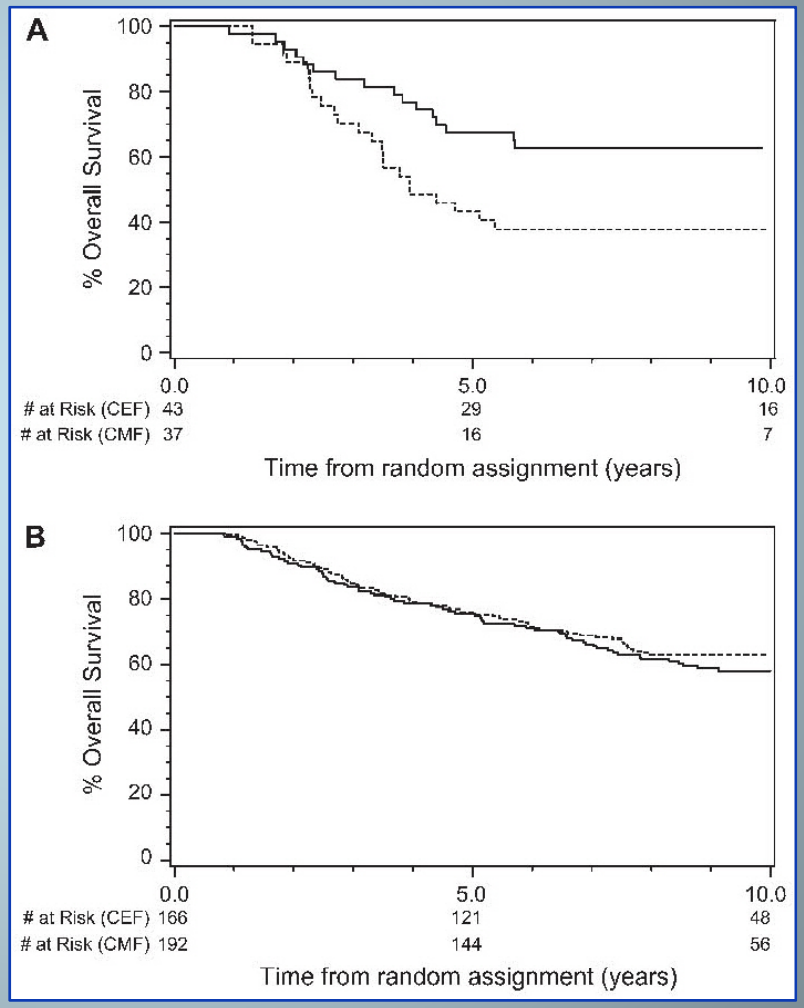


O ' Malley, FP et al. J Natl Cancer Inst 2009;101: 644 – 650

Overall survival according to chemotherapy and TOP2A status

Pts with amplified or deleted *TOP2A*

Pts with normal *TOP2A*



O' Malley, FP et al. J Natl Cancer Inst 2009;101: 644 – 650

Treatment effects for the combination of HER2 status and TOP2A FISH measurements

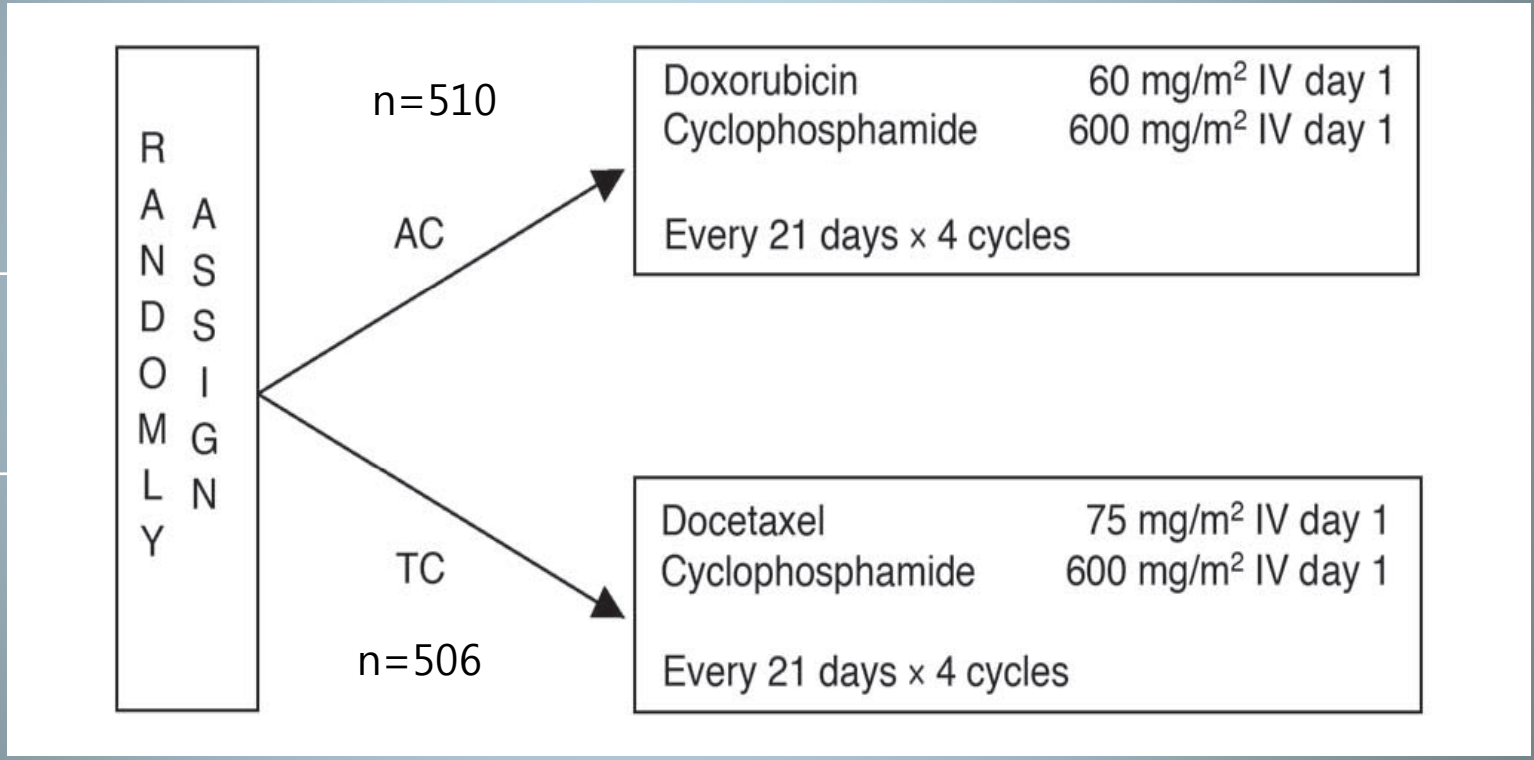
	RFS†		OS†	
	Altered *TOP2A* FISH	Normal *TOP2A* FISH	Altered *TOP2A* FISH	Normal *TOP2A* FISH
HER2				
Amplified	0.35 (0.12 to 0.98) [.05]	0.45 (0.21 to 0.98) [.04]	0.43 (0.15 to 1.20) [.10]	0.59 (0.24 to 1.41) [.23]
Not amplified	0.30 (0.06 to 1.38) [.12]	1.06 (0.74 to 1.51) [.76]	0.12 (0.02 to 0.83) [.03]	1.26 (0.84 to 1.90) [.26]

O ' Malley, FP et al. J Natl Cancer Inst 2009;101: 644 – 650

AC versus TC

US oncology 9735

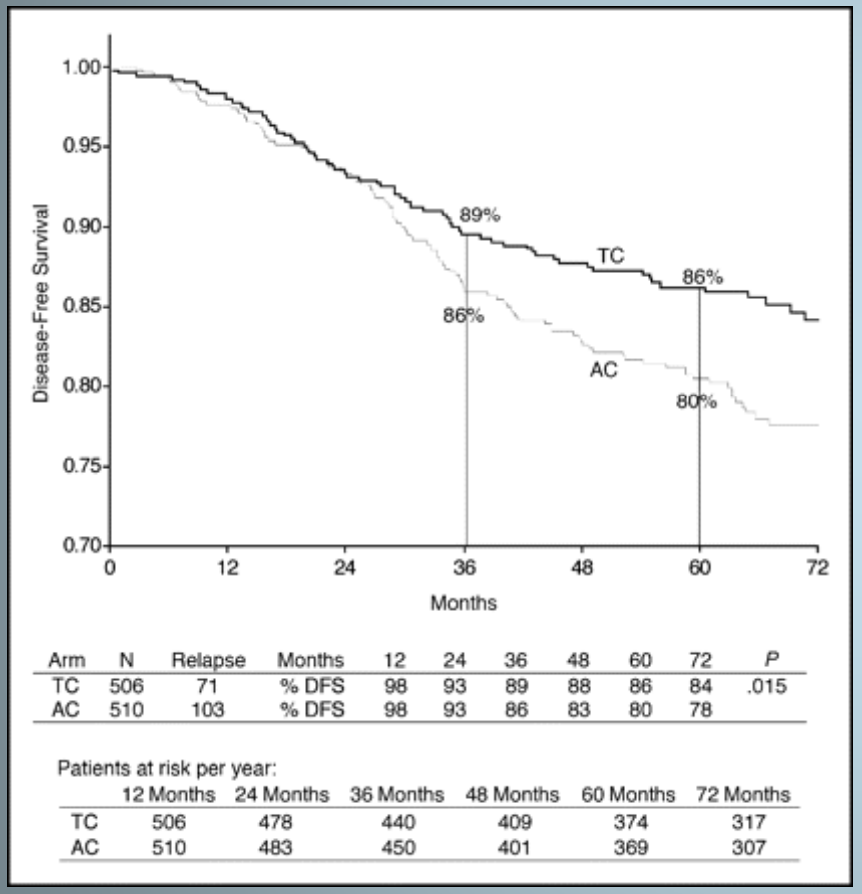
N=1016
71% ER+
48% N–



Between July, 1997 to January, 2000
Eligibility: Stage I, II, or III disease
Tamoxifen was given to all ER+ patients
Median follow up: 5.5 years

Jones et al. J Clin Oncol. 2006;24:5381-87

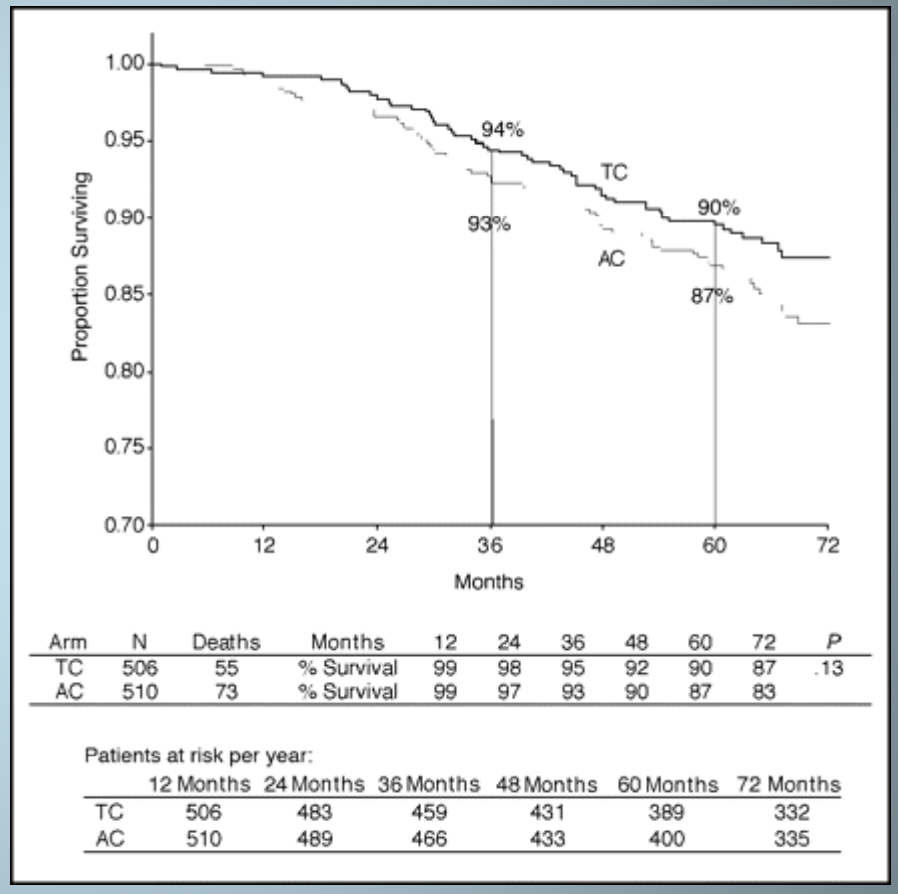
US oncology 9735; AC vs TC



Arm	N	Relapse	Months	12	24	36	48	60	72	*P*
TC	506	71	% DFS	98	93	89	88	86	84	.015
AC	510	103	% DFS	98	93	86	83	80	78	

Patients at risk per year:

	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	478	440	409	374	317
AC	510	483	450	401	369	307



Arm	N	Deaths	Months	12	24	36	48	60	72	*P*
TC	506	55	% Survival	99	98	95	92	90	87	.13
AC	510	73	% Survival	99	97	93	90	87	83	

Patients at risk per year:

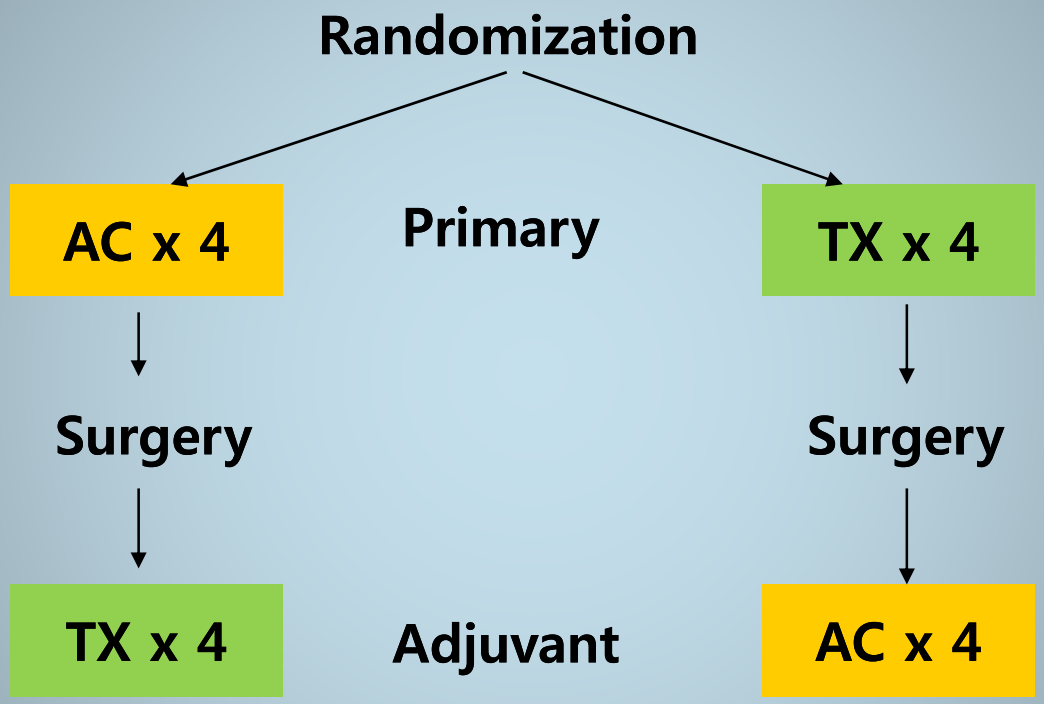
	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	483	459	431	389	332
AC	510	489	466	433	400	335

5 yr DFS: 80% v 86%, p=0.015

5 yr OS: 87% v 90%, p=0.13

Jones et al. J Clin Oncol. 2006;24:5381-87

NCC phase III trial: AC *vs* TX

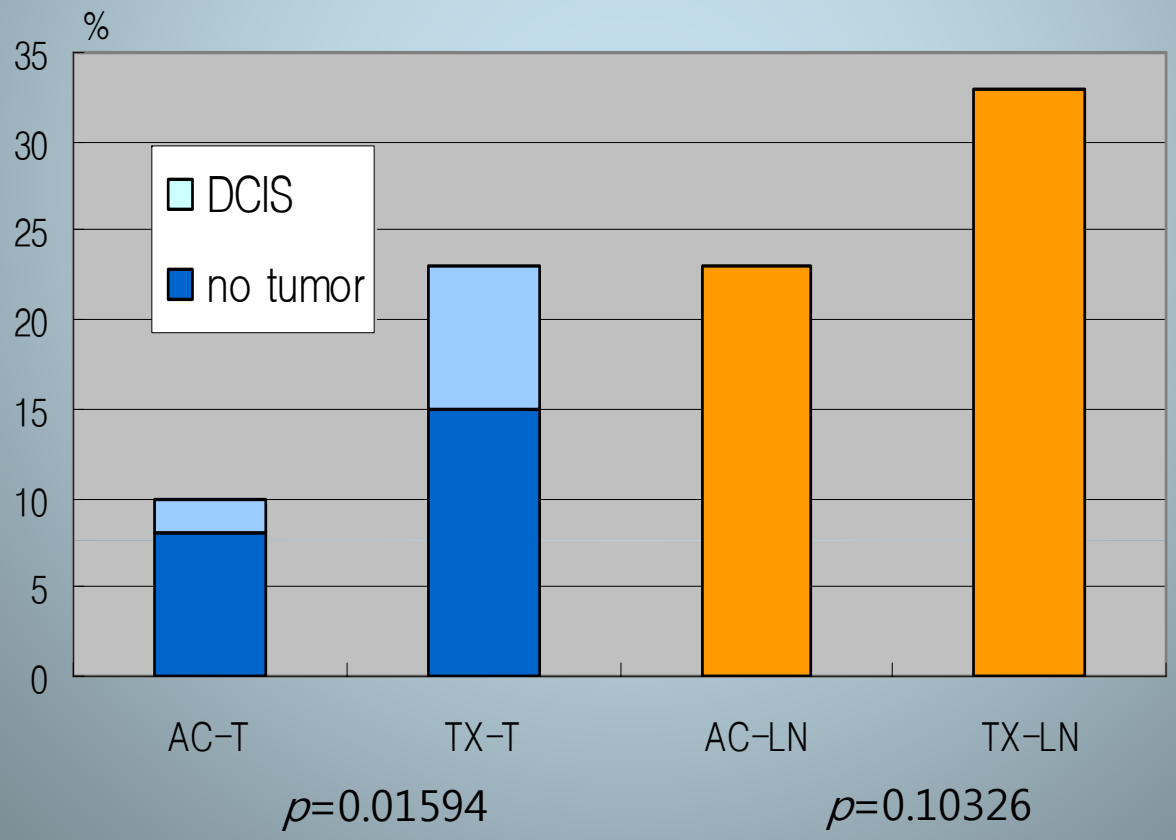


radiotherapy ± tamoxifen following chemotherapy

For unresponsive tumors (SD or PD), surgery or alternative chemotherapy offered at physicians' discretion

Lee, KS et al. Breast Cancer Res Treat 2008 Jun;109(3):481-9

Pathological complete response in primary tumors and lymph nodes



Summary

- Non-anthracycline-based (trastuzumab) containing regimens have superior or at least comparable efficacy to anthracycline-based regimens in early breast cancer

Docetaxel, Cisplatin, and Trastuzumab As PST for HER2 Positive LABC

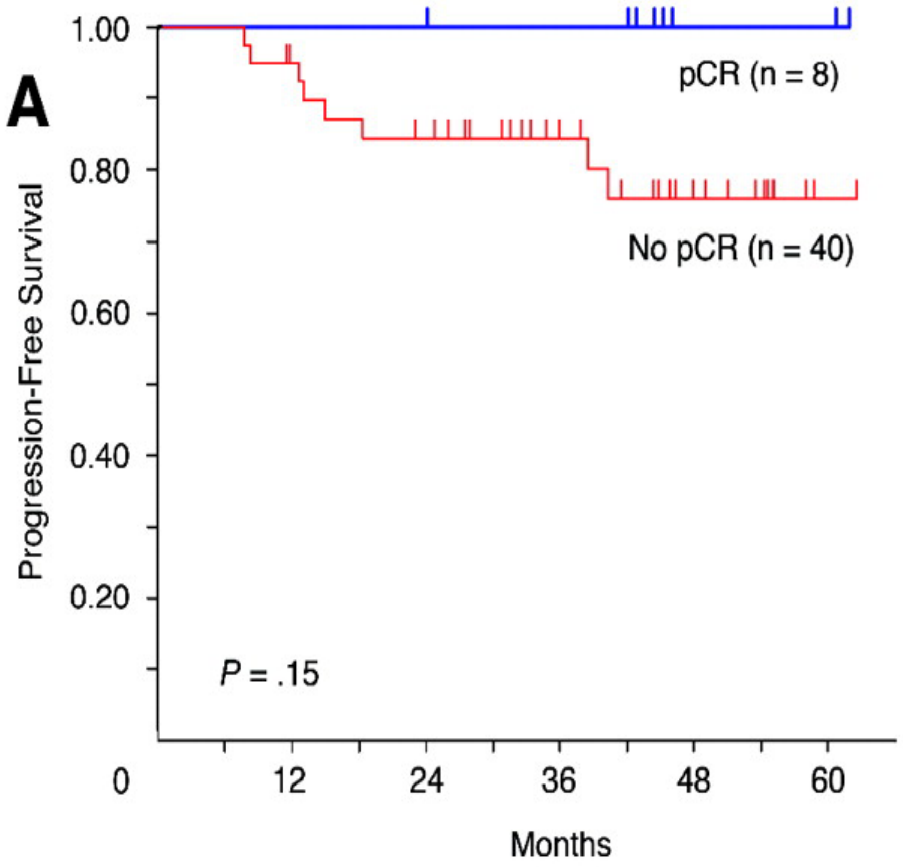
- Between 2000 and 2003
- To evaluate the efficacy and safety of docetaxel, cisplatin, and trastuzumab
- 48 patients with immunohistochemistry-confirmed HER2 positive LABC or inflammatory breast cancer
- Treatment:
  docetaxel, 70 mg/m^2
  cisplatin, 70 mg/m^2 } every 3 weeks x 4 with filgrastim
  trastuzumab 12 weeks
  →surgery → **adjuvant AC**→XRT with or without tamoxifen
- primary end point : pathologic complete response (pCR) in breast

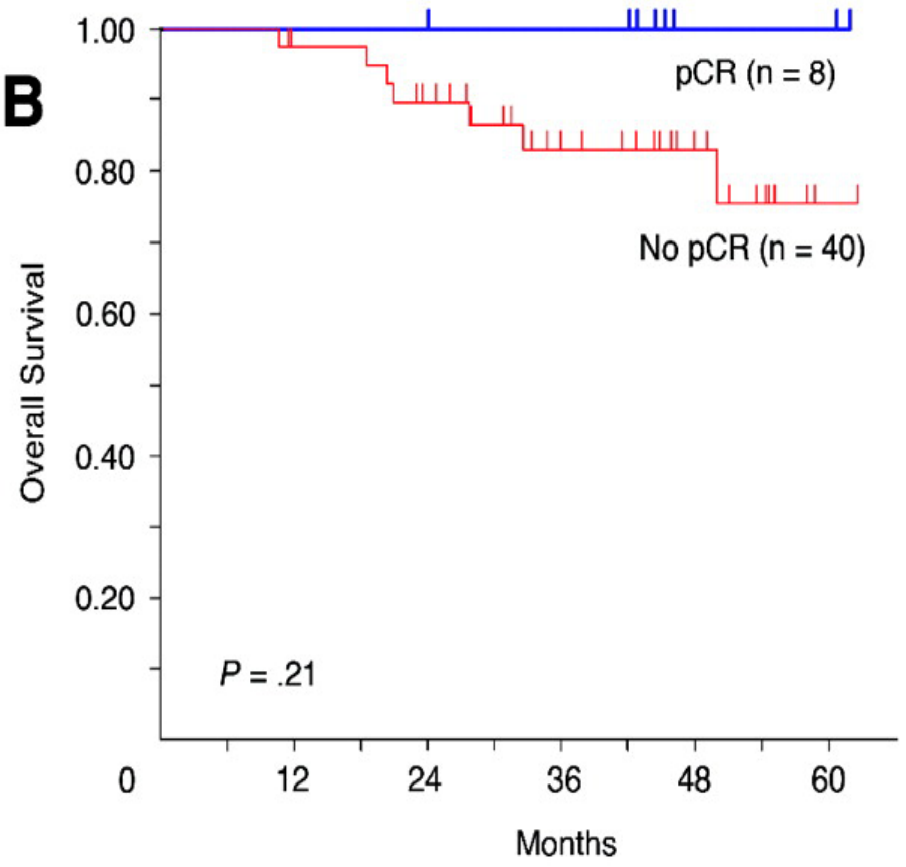
Hurley J et al. J Clin Oncol 2006;24(12):1831–8.

RESULTS

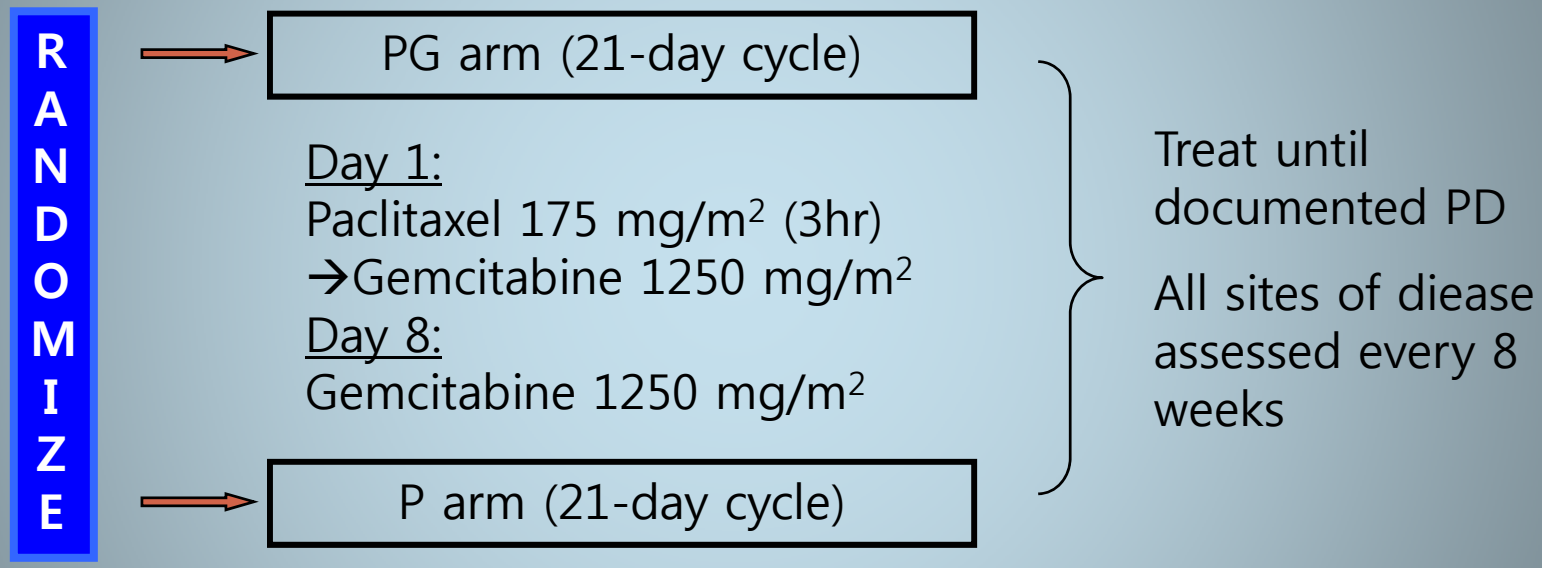
- Baseline mean tumor size, 9.2 cm (range, 4 to 32 cm).
- 11 pCR in breast (23%; 95% CI, 12-37)
  8 pCR in breast and axilla (**17%**; 95% CI, 8-30).
- pCR rates, similar regardless of HER2 status by FISH
- At a median follow-up time of 43 months,
  4-year PFS rate: 81% (95% CI, 64-90);
  OS rate: 86% (95% CI, 71-94).
- In patients with pCR in breast and axilla,
  PFS and OS rates :100% (95% CI, inestimable).
- In patients without pCR,
  PFS rate: 76% (95% CI, 57-88; *P* = .15, log-rank test),
  OS rate: 83% (95% CI, 66-92; *P* = .21).

PFS and OS by pCR in breast and LN





Paclitaxel ± gemcitabine: Randomized phase III trial for MBC

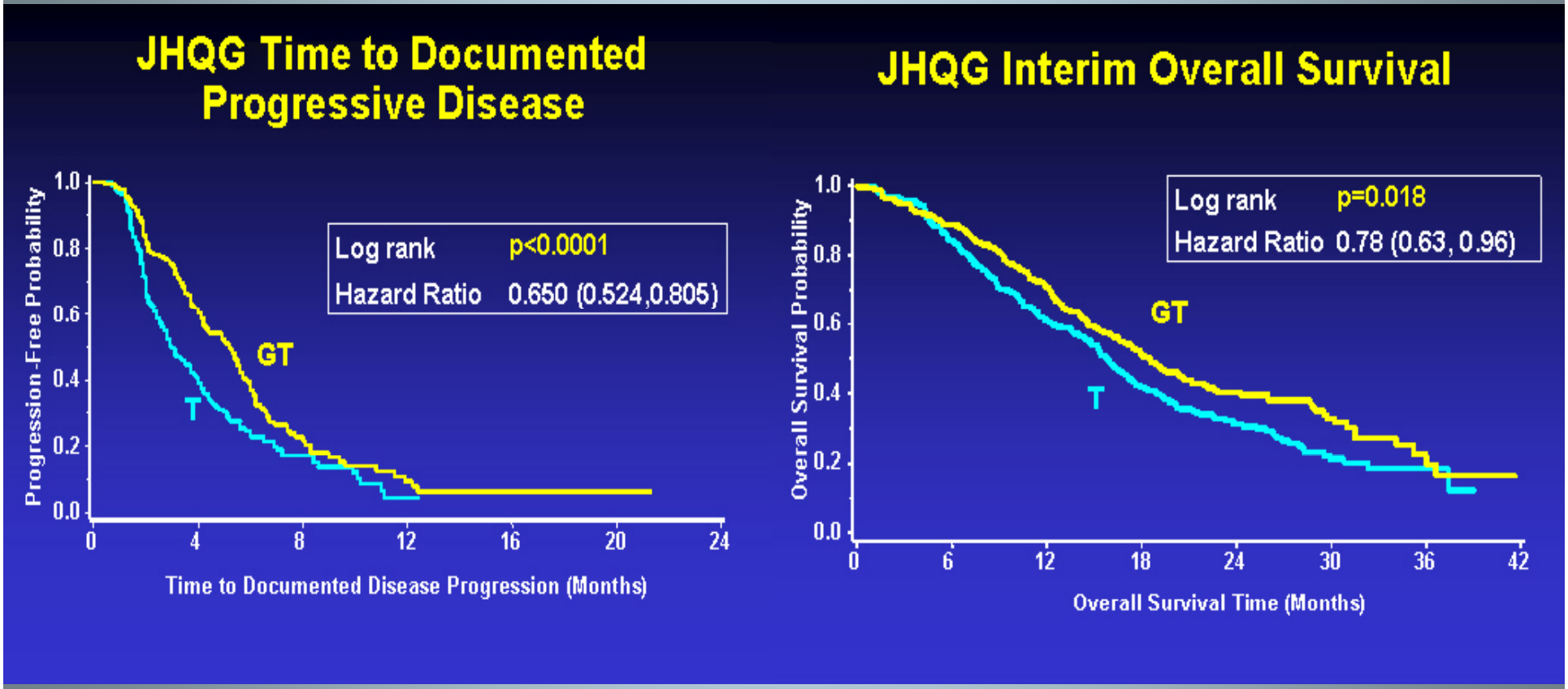


Albain KS, et al. Proc Am Soc Clin Oncol 2004

PG *vs* P for MBC: Efficacy

Efficacy	PG	P	P-value
RR	40.8%	22.1%	<0.0001
Median TTP	5.2 mo	2.9 mo	<0.0001
6-month PFS	37%	23%	0.0027
Median OS	18.5 mo	15.8 mo	0.018

PG *vs* P for MBC

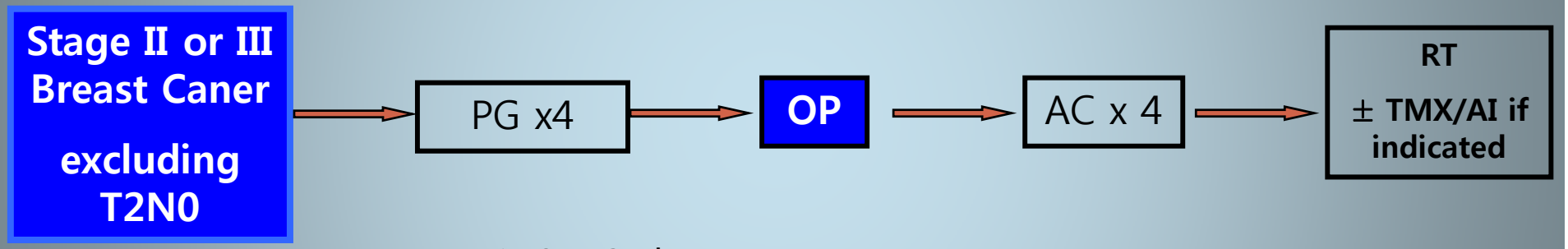


Phase II preoperative paclitaxel and gemcitabine in EBC

- Sequence-dependent synergism
- Weekly paclitaxel > 3-weekly paclitaxel
- "Intermittent" weekly paclitaxel
  - Reduce adverse events, especially neuropathy, while maintaining efficacy

Lee,KS et al. New Drugs 2009 DOI: 10.1007/s10637-009-9229-5(Online)

Study Scheme



Day 1, 8: q3wk
Paclitaxel 80 mg/m^2 (1hr)
→Gemcitabine 1200 mg/m^2(30 min)

Baseline characteristics (1)

	No.	%
No. of patients		
Enrolled	44	100
Evaluable for toxicity	44	100
Evaluable for response	43	97.7
Clinical tumor status		
T1	2	4.5
T2	36	68.2
T3	6	13.6
T4	6	13.6
Clinical nodal status		
N1	15	34.1
N2	26	59.1
N3	3	6.8
Age		
< 50 years	34	77.3
≥ 50 years	10	22.7
Median, years	43	
Range, years	(30-72)	

Baseline characteristics (2)

	No.	%
ECOG PS		
0	27	61.4
1	17	38.6
Stage		
IIA	1	2.3
IIB	11	25.0
IIIA	24	54.5
IIIB	5	11.4
IIIC	3	6.8
Tumor multiplicity		
Multiple	33	75.0
Single	11	25.0

Tumor receptor status

	No.	%
Hormone receptor (ER or PR)		
Positive	30	68
Negative	14	32
HER2		
Positive	18	41
Negative	26	59
Intrinsic subtypes		
Luminal A (ER+ or PR+/HER2–)	21	48
Luminal B (ER+ or PR+/HER2+)	9	21
HER2+/ER– (ER–/PR–/HER2+)	9	21
Triple-negative (ER–/PR–/HER2–)	5	11

Clinical and pathologic response

(n=44)

	No.	%	95% CI
Clinical Response			
Complete response	1	2	0~13
Partial response	34	77	63~87
Stable disease	7	16	8~30
Progressive disease	1	2	0~13
N/A	1	2	0~13
CR + PR	35	80	65~89
Pathologic Response			
pCR in breast	8	18	9~32
pCR in axilla	11	25	14~40
pCR in breast and axilla	5	11	5~24

Hematologic toxicity

Toxicity	CTCAE Grade (N=44)							
	1		2		3		4	
	N	(%)	N	(%)	N	(%)	N	(%)
Leukocytopenia	10	23	21	48	5	11	1	2
Neutropenia	7	16	11	25	16	36	9	21
Anemia	31	71	9	21	0	0	0	0
Thrombocytopenia	15	34	0	0	0	0	0	0
Neutropenic fever	-	-	-	-	1	2	0	0

*CTCAE: Common Terminology Criteria for Adverse Events Version 3.0

Non-hematologic toxicity (1)

Toxicity	CTCAE Grade (N=44)							
	1		2		3		4	
	N	(%)	N	(%)	N	(%)	N	(%)
Dysgeusia	5	11	1	2	0	0	0	0
Anorexia	9	21	0	0	0	0	0	0
Nausea	16	36	2	5	0	0	0	0
Vomiting	8	18	1	2	0	0	0	0
Dyspepsia	12	27	0	0	0	0	0	0
Myalgia	22	50	4	9	0	0	0	0
Arthralgia	8	18	1	2	0	0	0	0
Stomatitis	6	14	0	0	0	0	0	0
Gastritis	5	11	1	2	0	0	0	0
Diarrhea	8	18	0	0	0	0	0	0
Constipation	7	16	1	2	0	0	0	0

*CTCAE: Common Terminology Criteria for Adverse Events Version 3.0

Non-hematologic toxicity (2)

Toxicity	CTCAE Grade (N=44)							
	1		2		3		4	
	N	(%)	N	(%)	N	(%)	N	(%)
Rash	26	59	4	9	0	0	0	0
Pruritus	24	55	4	9	0	0	0	0
Fatigue	17	39	3	7	0	0	0	0
Insomnia	2	5	0	0	0	0	0	0
Headache	16	36	1	2	1	2	0	0
Dizziness	22	50	0	0	0	0	0	0
Neuropathy, Sensory	25	57	1	2	0	0	0	0
Hot flushes	15	34	1	2	0	0	0	0
Fever	1	2	0	0	0	0	0	0

*CTCAE: Common Terminology Criteria for Adverse Events Version 3.0

Summary

- "Intermittent" weekly paclitaxel plus gemcitabine combination PST :

  effective, with 18% pCR rate in the breast
- Adverse events: mild and tolerable,

  myelosuppression and neuropathy
- Paclitaxel and gemcitabine doublet:

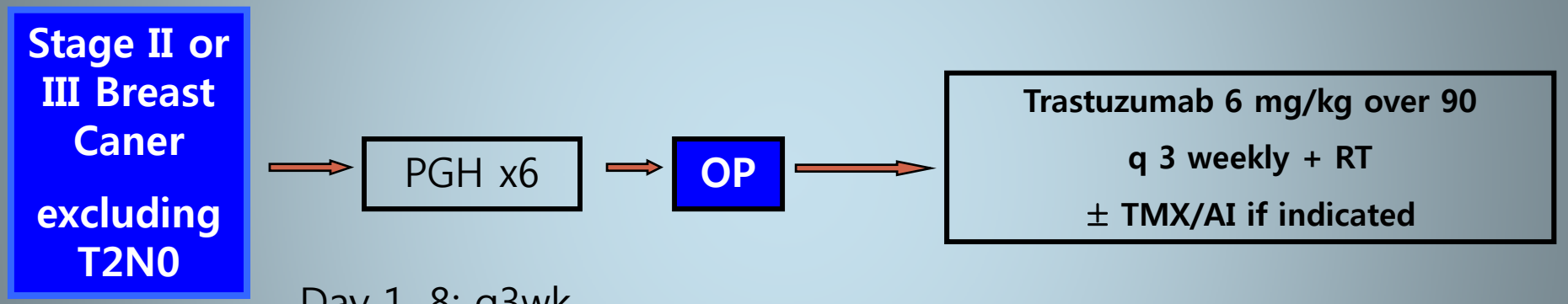
  an excellent candidate for combination with targeted agents

Primary Chemotherapy with Paclitaxel , Gemcitabine and Trastuzumab (PGH): Multicenter phase II trial

NCC, SNU, AMC, SMC, B-SNU

2008 SABCS abstract #550265

Study Scheme



Day 1, 8: q3wk
Paclitaxel 80 mg/m^2 (1hr)
→Gemcitabine 1200 mg/m^2
(30 min)
Every week x 18
Trastuzumab 4 mg/kg over 90 min loading
→ 2 mg/kg over 30 min weekly

Postop within 1-3 week:
Trastuzumab 6 mg/kg every 3 weeks x 11 and TMX/AI for 5 years as indicated
Postop in 4-6 weeks:
Radiation therapy

Objectives

Primary objective

- To evaluate pathologic response rate

Secondary objectives

- To evaluate clinical response rate and toxicities
- To investigate event free survival and overall survival

Inclusion criteria

- Histologic diagnosis of breast cancer node positive stage IIA or all stage IIB, III
- **HER2 positive (IHC 3+ or FISH +** in case of IHC 2+)
- **Pathologically axillary node positive** or internal mammary node positive (cytologically or pathologically determined node) or supraclavicular node positive (cytologically or pathologically determined node) and/or tumor size > 5 cm
- No prior hormonal , chemotherapy or radiotherapy
- No breast operation other than biopsy to make diagnosis
- ECOG PS of ≤ 1
- Bidimensionally measurable primary tumor
- Age ≥ 18 years and older, not pregnant pre- and postmenopausal women
- Adequate hematologic (WBC ≥ 3,000 and ANC ≥ 1,000/mm^3, PLT ≥ 100,000/mm^3), hepatic (AST, ALT, ALP ≤ 2.0XUNL), and renal (creatinine ≤ 1.5 mg/dl, T.bilirubin ≤ 1.5mg/dl) function
- **Adequate cardiac function**: normal or nonspecific EKG and LVEF ≥ 50% by MUGA or echocardiogram taken within 1 month of enrollment
- Adequate mental function to understand and sign the consent

Exclusion criteria

- Patients with a history of uncompensated congestive heart failure
- Patients with **node-negative stage IIA (T2N0)** breast cancer
- Patients with **inflammatory breast cancer (T4d)**
- Patients without primary tumor (T0)
- Patients who have history of cancer other than in situ uterine cervix cancer or nonmelanotic skin cancer

Sample size

- Single-stage design by A'Hern
- pCR rate of 40% as the target activity level and chose 20% as the lowest pCR rate of interest
- α=0.05, β=0.1
- If there are fewer than 15 pCRs out of the 47 patients, the study will conclude that the anticipated pCR rate is less than 20% and the combination is not worthy of moving to a phase III trial
- Allowing for an inevaluable rate up to 10%, a total of 53 patients are required

Dose level

Level	Dose level on D1		Dose level on D8	
	Paclitaxel	Gemcitabine	Paclitaxel	Gemcitabine
0	80mg/m^2	1200 mg/m^2	80mg/m^2	1200 mg/m^2
-1	70mg/m^2	1000 mg/m^2	70mg/m^2	1000 mg/m^2
- 2*	60mg/m^2	800 mg/m^2	60mg/m^2	800 mg/m^2
-3* or lower*	60mg/m^2	800 mg/m^2	Daily CBC → chemo at –2 level as soon as level goes up	

* For levels –2, –3 ,or lower, G-CSF use is encouraged.

Evaluation during Treatment

- **Repeat ultrasound and/or mammogram** of affected breast **prior to 4th preoperative cycle** of chemotherapy and prior to the operation
- LVEF measurement by **MUGA or echocardiogram** is performed upon completion of chemotherapy prior to surgery or if indicated during therapy
- All patients undergo either mastectomy or lumpectomy with axillary dissection after sentinel LN sampling
- Radiation therapy starts within 4-6 weeks after operation.

Characteristics		No. of Pt (%)
Median age	All (range)	43 (range 26-61)
	Age <50	40 (75.5)
	Age ≥50	13 (24.5)
Performance status	ECOG 0	35 (66.0)
	ECOG 1	18 (34.0)
Initial clinical stage	IIA	1 (1.9)
	IIB	5 (9.4)
	IIIA	29 (54.7)
	IIIB	3 (5.7)
	IIIC	15 (28.3)
Baseline median tumor size (range)	5.3 cm (range, 2.0 to > 12 cm)	
Multiple vs single	Single primary tumor	29 (54.7)
	Multiple primary tumors	24 (45.3)
ER	Positive	20 (37.7)
	Negative	33 (62.3)
PR	Positive	20 (37.7)
	Negative	33 (62.3)
HER2	IHC 2 + /HER2 FISH +	20 (37.7)
	IHC 3 +	33 (62.3)
Type of surgery	Conserving surgery	42 (79.2)
	Mastectomy	11 (20.8)
Adjuvant hormonal therapy	Yes	25 (47.2)
	No	28 (52.8)

Clinical and pathologic response

Response	No. of Pts (%)
Radiologic response	
Overall response (CR+PR)	50 (94.3)
Complete response	17 (32.1)
Partial response	33 (62.2)
Stable disease	3 (5.7)
Pathologic complete response	
Both primary tumor and LN	31 (58.5)
Primary tumor only	6 (11.3)
LN only	8 (15.1)
Residual disease in primary tumor and LN	8 (15.1)

Adverse events

Toxicity	NCI-CTC Grade (n=53)							
	1		2		3		4	
	n	(%)	n	(%)	n	(%)	n	(%)
Leukopenia	13	(24.5)	21	(39.6)	12	(22.7)	0	(0)
Neutropenia	7	(13.2)	12	(22.7)	23	(43.4)	5	(9.4)
Anemia	39	(73.6)	3	(5.6)	0	(0)	0	(0)
Thrombocytopenia	19	(35.8)	0	(0)	1	(1.9)	0	(0)
AST elevation	17	(32.1)	4	(7.5)	1	(1.9)	0	(0)
ALT elevation	17	(32.1)	11	(20.8)	4	(7.5)	0	(0)
ALP	9	(17.0)	1	(1.9)	0	(0)	0	(0)
fatigue	28	(52.8)	0	(0)	1	(1.9)	0	(0)
myalgia	32	(60.4)	5	(9.4)	0	(0)	0	(0)
neuropathy	27	(50.9)	1	(1.9)	0	(0)	0	(0)
arthralgia	7	(13.2)	0	(0)	0	(0)	0	(0)
constipation	14	(26.4)	1	(1.9)	0	(0)	0	(0)
diarrhea	12	(22.6)	5	(9.4)	0	(0)	0	(0)

Cardiac toxicities

	No. (%)
Baseline LVEF*	
50 % ≤ LVEF <60%	**13/53 (24.5)**
LVEF ≥ 60%	**40/53 (75.5)**
LVEF changes after neoadjuvant therapy	
> 10% decrease in LVEF**	**5/53 (9.4)**
Symptomatic CHF	**0 (0)**
Improvement in LVEF on follow-up evaluation	**4/5 (80)**

* LVEF : left ventricular ejection fraction
** LVEF of all patients were > 50%

Summary

- A remarkably high pCR was obtained by non-anthracyline based **PGH** combination therapy for HER2 positive stage II/III breast cancer
- This combination was well tolerated with mild degree of AEs
- All patients could maintain normal cardiac function

Representaive neoadjuvant clinical trials of trastuzumab combination therapy

Patients characteristics	PGH	P/FEC+H	TCH	NOAH
	(n=53)	(n=89)	(n=48)	(n=115)
pCR of breast and LN	**58.5 %**	**54 %**	**17 %**	**38 %**
Median age, (range)	43 (26-61)	50 (21-81)	51	50
	No (%)	No (%)	(%)	No. of Pt (%)
Primary tumor size (median) T1/T2 (T<5cm) T3/T4 (≥ 5 cm)	5.3cm 30 (56.6) 23 (43.4)	NA 62 (69.8) 26 (29.2)	9.2 cm 0 48 (100)	5.5 cm 30(28.3) Inflammatory(38.7)
LN involvement , N0 N1 N2 or N3	0 (0) 13 (24.5) 40 (75.4)	27 (30.3) 48 (53.9) 14 (15.7)	13 (27) 19 (40) 16 (33)	13 (12.3) 44 (41.5) 49(46.2)

Representaive neoadjuvant clinical trials of trastuzumab combination therapy

Patients characteristics	PGH	P/FEC+H	TCH	NOAH
	(n=53)	(n=89)	(n=48)	(n=115)
	No. of Pt (%)	No. of Pt (%)	No. of Pt (%)	No. of Pt (%)
Initial clinical stage, I	0 (0)	2 (2)	0	NA
IIA	1 (1.9)	24 (27)	0	
IIB	5 (9.4)	33 (37)	9 (19)	
IIIA	29 (54.7)	15 (17)	23 (48)	
IIIB	3 (5.7)	3 (3)	16 (33)	
IIIC	15 (28.3)	12 (14)		
Hormone receptor status				
Postitive (ER + or PR +)	24 (47.2)	43 (48.3)	26 (54)	35 (35%)
Negative (ER - and PR -)	28 (52.8)	46 (51.7)	22 (46)	65 (65%)
Grade 4 neutropenia	12 (22.6)	21 (91.3)	1 (2)*	NA
Neutropenic fever	**2 (3.8)**	**8 (34.8)**	**1 (2)***	**9 (7.8)**
LVEF decrease > 10%	**5 (9.4)**	**7 (30.4)**	**10(21)+**	**11(10)**
CHF	0	0	1 (2)	2(1.8)

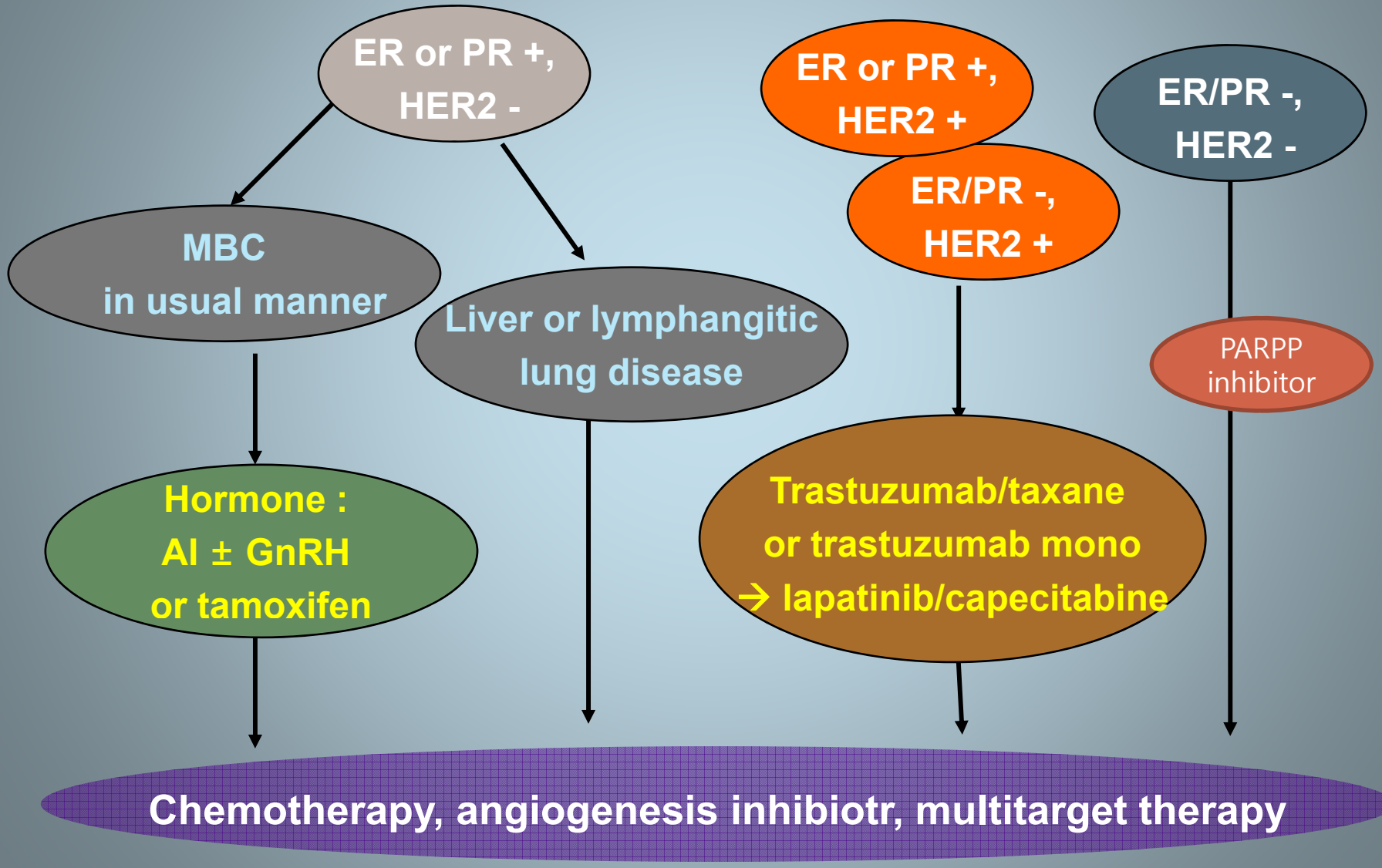
Conclusion

- PGH regimen: very promising new generation non-anthracycline-based regimens
- Alternative therapy in case of unfit candiate due to cardiac condition or other comorbidity
- Need further follow-up for event free survival
- Worthy to pursuit a randomized phase III trial

Acknowledgement

- All participating patients
- All multidisciplinary team investigators including research coordinators at 5-participating centers
- CJ, Lilly, and Roche for providing Genexol, Gemzar and Herceptin
- Special thanks to MY Lee, RN, a lead coordinator at NCC

Therapeutic options by receptor subtypes in MBC



NeOAdjuvant Herceptin (NOAH) trial

Baseline characteristics

	HER2 positive		HER2 negative
	With H (n=115)	Without H (n=112[a])	(n=99)
Stage group, %			
T4, non-inflammatory	42	43	44
Inflammatory disease	27	27	14
N2 or ipsilateral nodes	31	30	41
Hormone receptor status, %			
ER and / or PgR positive	35	35	64
Both negative	65	65	36
Age group, %			
<50 years	46	41	51
≥50 years	54	59	49

[a]1/113 did not receive ethics approval for the last protocol amendment at the moment of the analysis

ER, oestrogen receptor; PgR, progesterone receptor

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Baseline characteristics (%)

	HER2 positive		HER2 negative
	With H (n=115)	Without H (n=113)	(n=99)
Stage group			
T4, non-inflammatory	30	30	44
Inflammatory disease	41	40	14
N2 or ipsilateral nodes	30	30	41
Hormone receptor status			
ER and / or PgR positive	35	35	64
Both negative	65	65	36
Age group			
<50 years	46	42	51
≥50 years	54	58	49
Axillary nodes			
N0	13	16	17
N1	44	47	38
N2	40	37	44
Ipsilateral supraclavicular nodes			
No	94	96	96
Yes	6	4	4
Baseline LVEF, median	63	63	63

ER, oestrogen receptor; LVEF, left ventricular ejection fraction; PgR, progesterone receptor

Serious adverse events (SAEs)

	HER2 positive		HER2 negative
	With H (n=115)	Without H (n=113)	(n=99)
Total patients with ≥1 SAE	17	9	10
Sudden post-surgery death[a]	0	0	1
Cardiac toxicity	1	0	0
Febrile neutropenia	9	4	3
Neutropenia G4, hospitalised	0	3	0
Fever with pneumonitis	0	0	1
Fever and pharyngitis	2	0	0
Infection	2	0	3
Stomatitis	0	1	2
Diarrhoea	0	2	0
Vomiting	1	1	0

[a]Lung artery embolism <24 h from surgery

Conclusion

- Neoadjuvant H significantly increased EFS in patients with HER2-positive LABC.
- Neoadjuvant H with CT could be a standard treatment option in HER2-positive LABC.

Background & methods

- All co-operative neoadjuvant trials including anthracycline and taxane conducted in Germany between 1998 and 2006
- Integrated meta-analysis based on individual data
- Definition of pCR:

  No invasive residuals in the breast and axillary lymph nodes (ypT0/is, ypN0)

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Paclitaxel and gemcitabine in MBC

- Phase II studies of paclitaxel plus gemcitabine (PG) in MBC showed good tolerance and encouraging response rates (35%-71%)
- A global phase III trial (JHQG) showed that PG results in prolonged overall survival compared to P alone, when both are given on a q3 week schedule

Preoperative study treatment

- **Trastuzumab** 4 mg/kg IV over 90 min on day 1 →
  2 mg/kg IV over 30 min weekly
- **Paclitaxel** 80 mg/m^2 IV over 1 hr on days 1 and 8,
  q 3-week
- **Gemcitabine** 1,200 mg/m^2 IV over 30 min on days
  1 and 8, q 3-week
- Premedication:
  dexamethasone, serotonine antagonist, pheniramine,
  H2 blocker

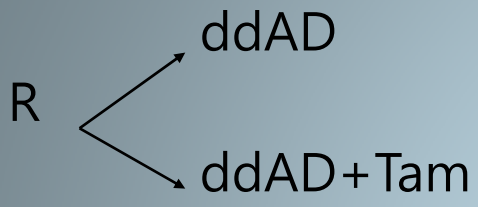
Day 8 dose modification scheme

ANC (/uL)*		Platelet count (/uL)*	Dose level on D8
≥1,000	AND	>75,000	Dose level on D1 –0
≥1,000	AND	50,000-75,000	Dose level on D1 –1
700-999	AND	≥50,000	Dose level on D1 –2
<700	OR	<50,000	Dose level on D1 –3

* ; according to the result of blood counts Day 8

Five Gepardo Trials

GeparDo (N=248)



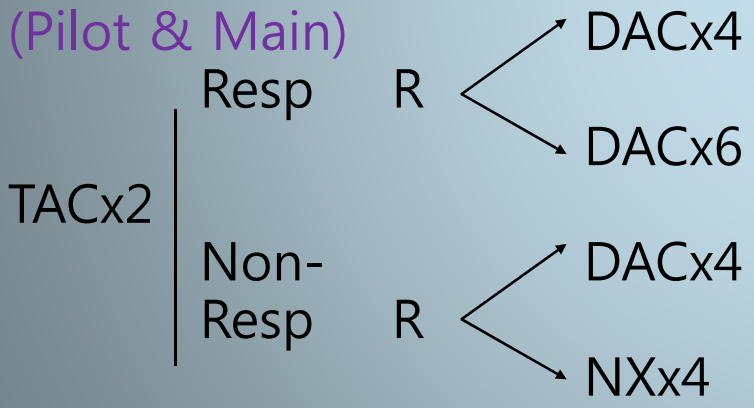
von Minckwitz G et al, JCO 2001

GeparDuo (N=907)

von Minckwitz G et al, JCO 2005

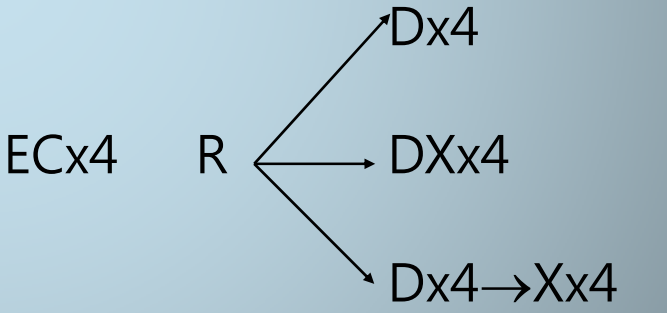
GeparTrio (N=2357)

(Pilot & Main)



von Minckwitz G, Ann Oncol 2005, JNCI 2008, JNCI 2008

GeparQuattro (N=1495)



HER2 pos: + H in all cycles

von Minckwitz G, SABCS 2007, Untch M EBCC 2008

A=Doxorubicin; C=Cyclophosphamide; D=Docetaxel; dd=dose-dense/bi-weekly; E=Epirubicin;
H=Trastuzumab; N=Vinorelbin; Resp=patients with midcourse CR/PR; Tam=Tamoxifen; X=Capecitabine

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Three AGO Trials

AGO 1 (N=668)

R → EPx4

R → $ddE_{160}x3 \rightarrow ddP_{260}x3$

Untch M et al, SABCS 2007

TECHNO (N=226)
HER2 pos:

ECx4 → PHx4

Untch M et al, SABCS 2005

Prepare (N=733)

R → ECx4→Px4

R → $ddE_{150}x3 \rightarrow ddP_{225}x3 \rightarrow CMFx3$

Untch M et al, ASCO 2008

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C=Cyclophosphamide; dd=dose-dense/bi-weekly; E=Epirubicin;
H=Trastuzumab; M=Methotrexate; P=Paclitaxel; R=randomization