National Cancer Institute

Preoperative Therapy in Invasive Breast Cancer

Reviewing the State of the Science and Exploring New Research Directions

Preoperative biologic therapy - anti-HER2 agents

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National Institutes of Health

Data to be Reviewed

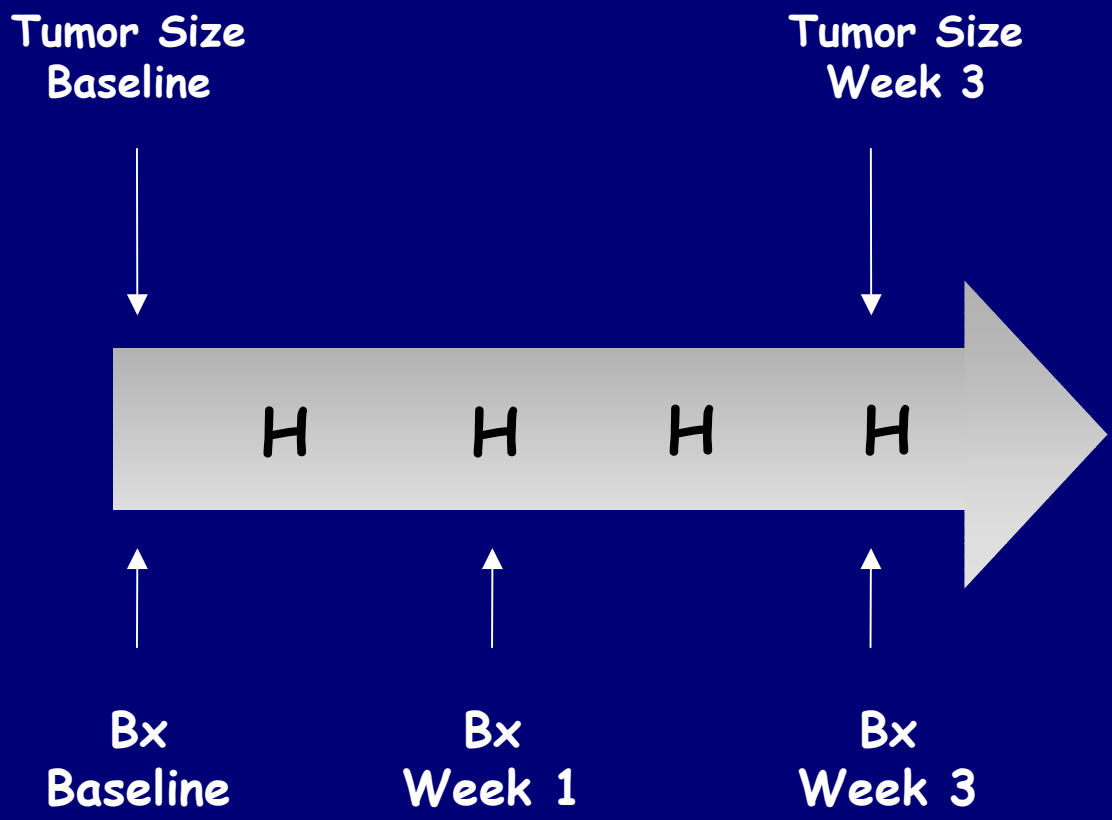
- *Trastuzumab studies*
  Monotherapy
  Combination Therapies – Phase II Trials
  Randomized Phase III Trials

- *Phase II Lapatinib studies*

- *Summary of Correlative Science Studies*

Preoperative Trastuzumab Single Agent Therapy

Study Schema



Total patients = 35

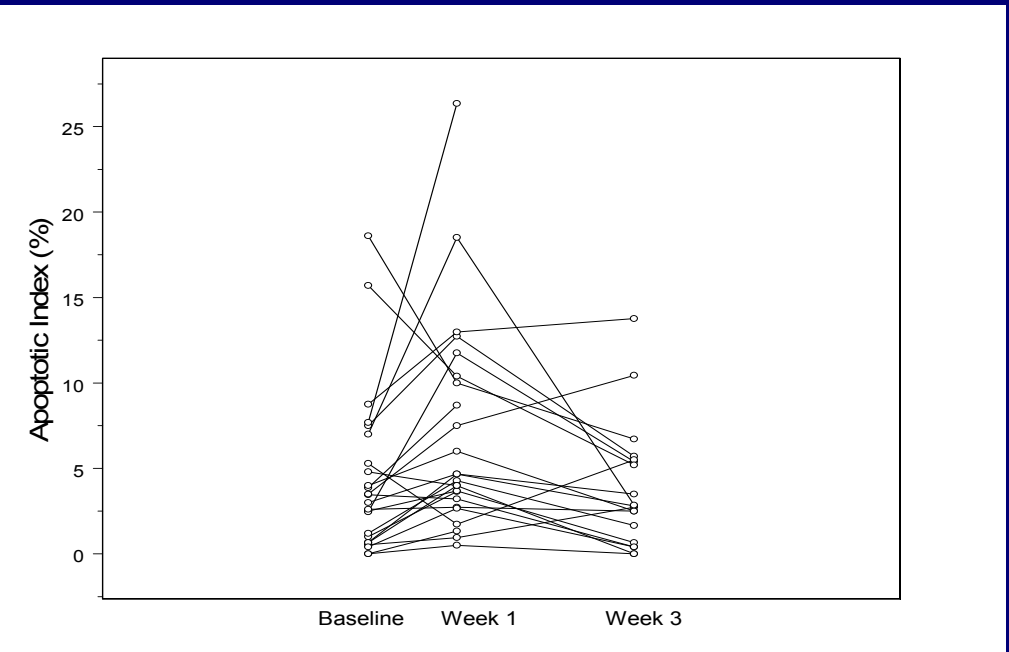
Responses

- *Median Decrease: 20% (0-60)*
- *Partial Response: 23%*
- *Apoptosis: 35-47%*
- *No Change: EGFR and P-HER2*

Mohsin S, et al. *J Clin Oncol* 2005;23:2460-2468

Preoperative Trastuzumab Single Agent Therapy

Induction of Apoptosis



- No significant change in Ki67
- No significant change in p27
- Decrease in cytoplasmic p-MAPK within week 3

Mohsin S, et al. *J Clin Oncol* 2005;23:2460-2468

Preoperative Trastuzumab Single Agent Therapy

Eligibility	HER2+ Disease
Total Patients	11
Duration of Therapy	4 weeks

Efficacy	Percentage
pCR	9
Partial Response	36
Minor Response	54

Gennari R, et al. *Clin Cancer Res* 2004;10:5650–5

Preoperative Trastuzumab* and chemotherapy Phase II Studies

Studies	(N)	Drugs	Percent	
			cCR	pCR
Burstein[1]	(40)	Paclitaxel	30	18
Harris[2]	(42)	Vinorelbine	38	19
Limentani[3]	(45)	Docetaxel+Vinorelbine	59	31**

*Trastuzumab duration = 12 weeks in all trials

****42% of patients had <5 mm residual tumors.**

[1] **Burstein H, et al. *J Clin Oncol.* 2003;21:46-53**

[2] **Harris L, et al. *Proc Am Soc Clin Oncol.* 2003;22:22. Abst. 86**

[3] **Limentani S, et al. *Proc Am Soc Clin Oncol.* 2003;22. Abst. 131.**

Docetaxel and trastuzumab Studies

Studies	(N)	Trastuzumab Duration (wks)	Percent	
			cCR	pCR
Coudert[1]	(29)	18	73	47
Bines[2]	(33)	15	24	12
Schiffhauer[3]	(16)	12	-	25
Van Pelt[4]	(22)	12	40.9	-

[1] Coudert B, et al. *Ann Oncol.* 2006;17:409-414

[2] Bines J, et al. *Breast Cancer Res Treat.* 2003;82:s56. Abst. 243

[3] Schiffhauer LM, et al. *Proc Am Soc Clin Oncol.* 2003;22:242. Abst. 969

[4] Van Pelt A, et al. *Clin Breast Cancer.* 2003;4:348-353.

Docetaxel & platins containing trials

Studies	(N)	Additional Drug	Trastuzumab Duration (wks)	Percent	
				cCR	pCR
Hurley[1]	(48)	Cisplatin	12	-	23
Coudert[2]	(66)	Carboplatin	16	-	36
Chang[3]	(48)	Carboplatin	12	-	36.4
Fenton[4]	(18)	Carboplatin	16	-	45

[1] Hurley J, et al. *J Clin Oncol.* 2006;24:1831-1838

[2] Coudert B, et al. *Breast Cancer Res Treat.* 2005;94:S223. Abst. 5050

[3] Chang HR, et al. *J Clin Oncol.* 2006:24. Abst. 10515

[4] Fenton MA, et al. *Breast Cancer Res Treat.* 2005;94:S224-S225. Abs. 5054

Anthracyclines followed by taxanes and trastuzumab therapy trials

Studies	(N)	Drugs	Trastuzumab Duration (wks)	Percent cCR	Percent pCR
Kelly[1]	(29)	AC→T	12	20	19
Mehta[2]	(31)	AC→T+carb	12-16	-	70*
Untch[3]	(174)	EC→T	12	-	41.4
Sanchez-Rovira[4]	(30)	EC→TG	12	-	28
Wenzel[5]	(14)	ED	6	-	7

*** Some patients had microscopic residual disease**

[1] Kelly H, et al. *Clin Breast Cancer.* 2006;7:237-243
[2] Mehta RS, et al. *Proc Am Soc Clin Oncol.* 2005;23:84s. Abst. 826
[3] Untch M, et al. *Breast Cancer Res Treat.* 2005:94:S60-S61. Abst. 1064
[4] Sanchez-Rovira P, et al. *Proc Am Soc Clin Oncol.* 2004;22:29. Abst. 608
[5] Wenzel C, et al. *J Cancer Res Clin Oncol.* 2004;130:400-404.

Summary of Correlative Science Studies

-**Genes predictive of PCR – remains to be defined**

-**Non-responder expressed basal markers, IGF-IR positive and large tumors**

-**HER2 mRNA, or copy numbers, or ER mRNA, or Ki67 – no correlation to PCR**

-**Troponin-T - not correlated to changes in cardiac dysfunction.**

- MALDI-TOF protein profiling of pre and post therapy serum showed 89/6972 protein peaks significantly different – need further evaluation.

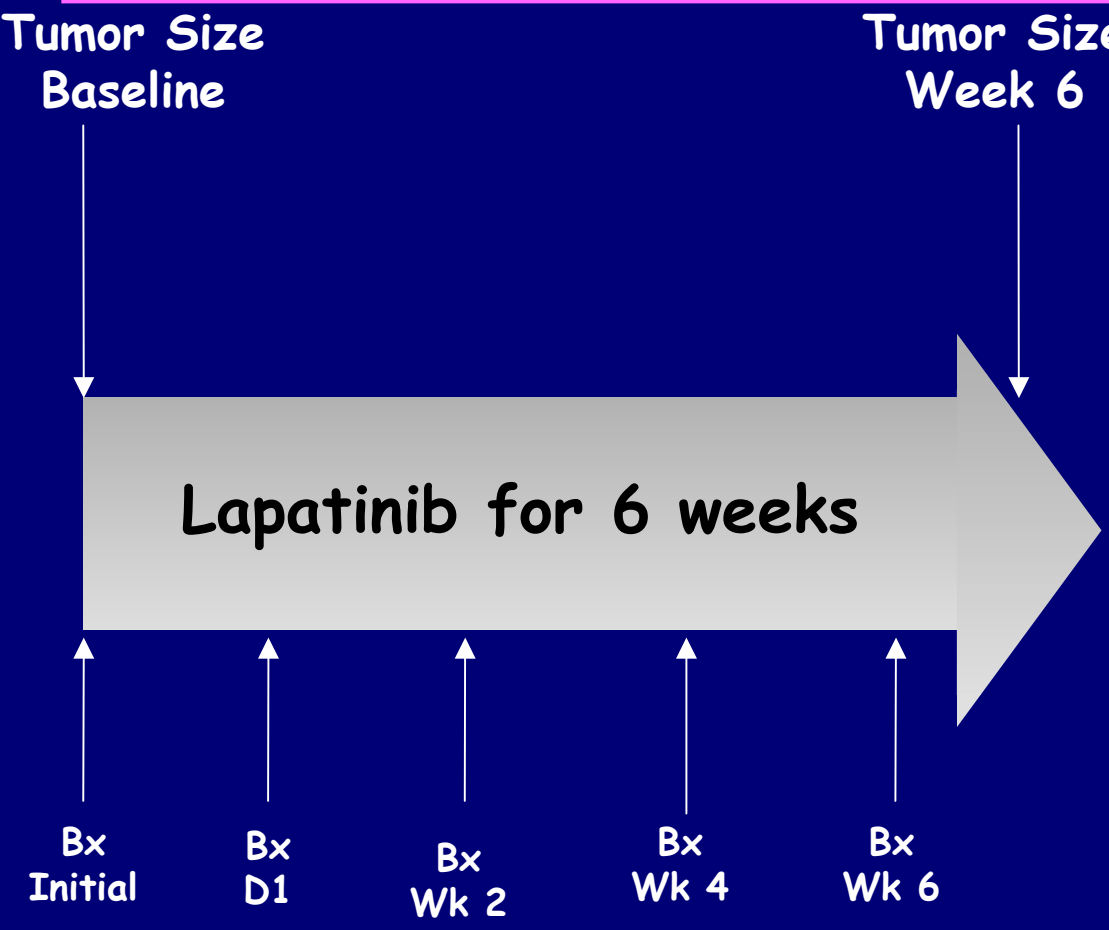
Lapatinib in neoadjuvant therapy Inflammatory breast cancer (HER2)

Studies	(N)	Drugs	Percent	
			cCR	pCR
Cristofanilli	(30)	**Paclitaxel**	10	17

***Lapatinib duration = 14 weeks**

Cristofanilli M, Breast Cancer Res.Treat. 2006; 100, S5, abst.1

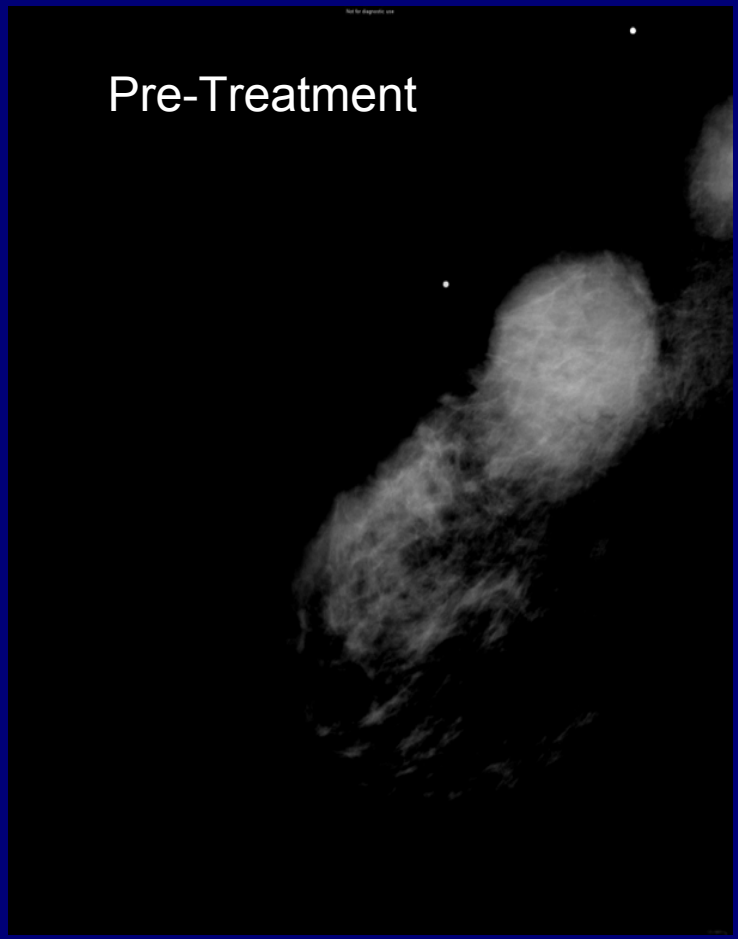
Preoperative Lapatinib Phase II Study

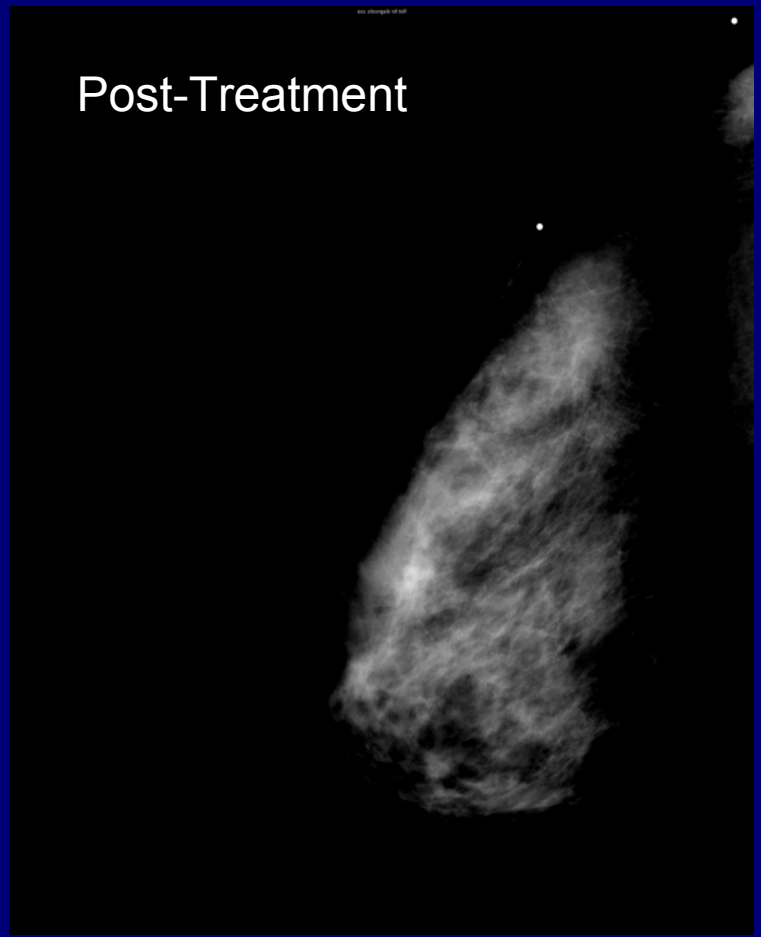


- Clinical efficacy
- Cell survival: apoptosis, p-Akt
- Cell cycle: Ki67, p27, p-MAPK
- HER1 and HER2: total and (p)
- Identify gene array predictive for sensitivity and resistance

JC Chang, *unpublished information*

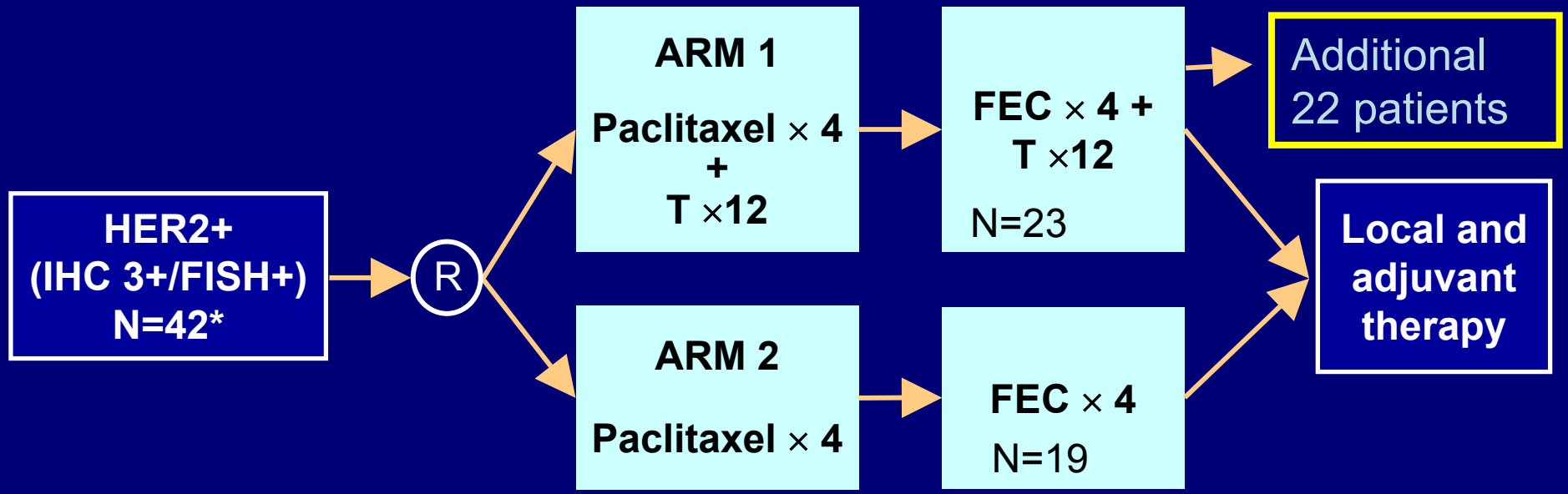
Before and After 6 weeks of Lapatinib





JC Chang, ***unpublished information***

Phase III Trial of Neoadjuvant Trastuzumab + Chemotherapy for Operable Breast Cancer



*Paclitaxel 225 mg/m^2 q3w.

FEC = 5-fluorouracil 500 mg/m^2 d1, 4 + epirubicin 75 mg/m^2 d1 + cyclophosphamide 500 mg/m^2 d1, all q3w.

T = trastuzumab 4 mg/kg d1, then 2 mg/kg qwx24 weeks

Buzdar A, et al. *J Clin Oncol.* 2005;23:3676-85

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Patient Characteristics of 3 subgroups: chemotherapy alone Vs. Chemo + trastuzumab

Age

Race

Stage of disease

Nodal involvement

Hormone receptor status

* Patient characteristics were similar

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Pathological Complete Response Rates

	PCR (%)	(95% CI)
• Chemotherapy Alone (N=19)	26.3	9 - 51
• Chemo + Trastuzumab (N=23) (randomized)	65.2	43 - 84
• Chemo + Trastuzumab (N=22) (assigned)	54.5	32.2 – 75.6

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Pathological Complete Response Rates

	Path CR (%)	
	ER-	ER+
• Chemotherapy Alone (N=19)	25	27.2
• Chemo + Trastuzumab (N=23) (randomized)	70	61.5
• Chemo + Trastuzumab (N=22) (assigned)	60	50

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Extent of Residual Disease by Treatment

	Randomized Groups		Assigned Treatment
	P→FEC alone N=19	P→FEC + H N=23	P→FEC + H N=22
Residual disease in breast			
None	5	15	12
DCIS only in CRs	1	5	4
< 1 cm	3	5	7*
1-3 cm	9	1	3
> 3 cm	2	2	0
Number of + nodes			
0	15	20	20
1-3	2	3	2
4-10	2	0	0
> 10	0	0	0

* Focal cluster of cancer cells in 5 pts

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Summary of left ventricular ejection fraction

	FEC	FEC + Herceptin	Assigned
Baseline			
Number of patients	19	23	22
Median LVEF (range)	65 (55-76)	65 (50-71)	65 (55-70)
Post Treatment			
Months from Baseline	27 (12.4-44.2)	30.4 (24.4 - 49)	12.6 (6-17.7)
Median LVEF (range)	65 (35-70)	60 (52-71)	65 (45-70)

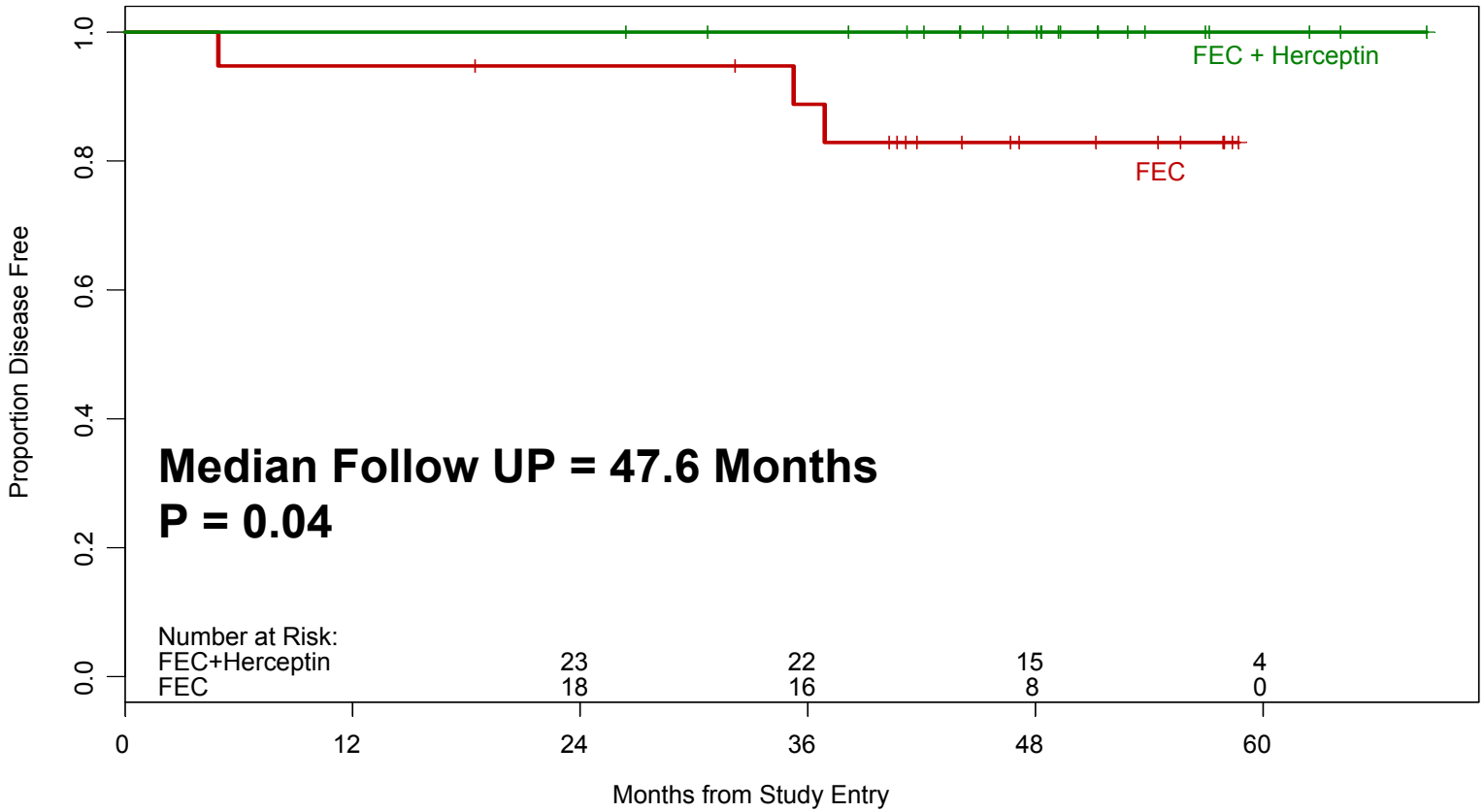
Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Pre-existing Cardiac Risk Factors by Treatment Group

	Randomized Groups		Assigned Treatment
Risk Factors	P→FEC alone N=19	P→FEC + H N=23	P→FEC + H N=22
Hypertension	6	5	4
Diabetes	2	1	0
EKG Abnormalities	1	6	8
H/O arrhythmias	0	1	1
Valvular Dysfunction	3	3	3
H/O Cerebrovascular accident	1	0	0

Buzdar A, et al. *Clin Cancer Res.* 2007;13:228-33

Disease-Free Survival of Randomized Study Population



Preoperative Trastuzumab therapy concomitantly with Nab-paclitaxel and FEC

Studies	(N)	Drugs	Percent	
			cCR	pCR
Robidoux	(18)	Nab-T- FEC	-	59

***Chemotherapy duration = 24 weeks**

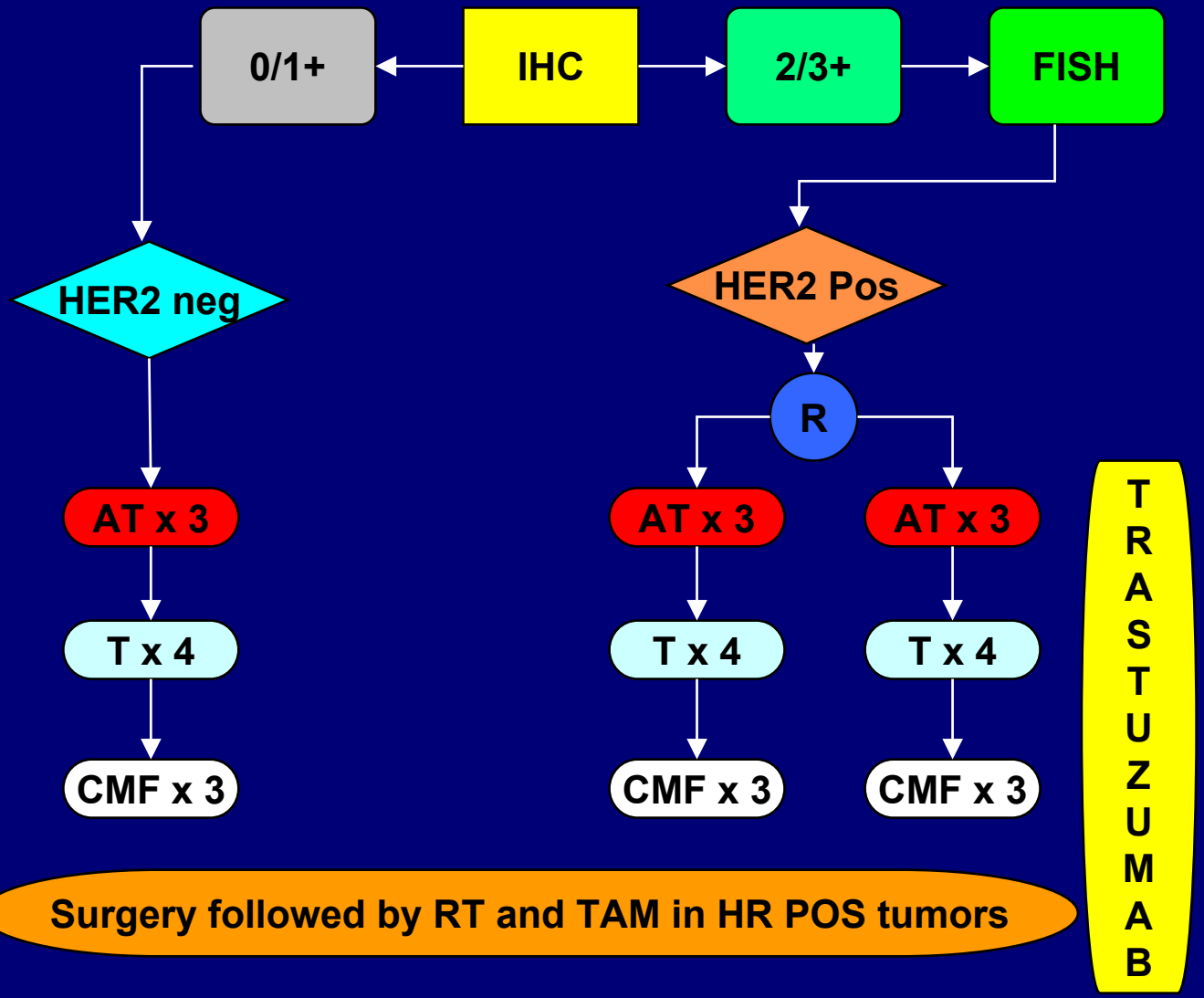
Robidoux A, Breast Cancer Res.Treat. 2006; 100, S147, abst. 3068

Other randomized trials

- NCI – Milan randomized trial.

NeO Adjuvant Herceptin - NOAH

NOAH Study Design in LABC including Inflammatory Breast Cancer



NOAH Systemic therapy

AT: Doxorubicin (60 mg/m^2) and Paclitaxel (150 mg/m^2 over 3 h) q 3 weeks

T: Paclitaxel (200 mg/m^2 over 3 h) q 3 weeks

CMF: Intravenous on days 1 and 8 q 4 weeks

Herceptin:

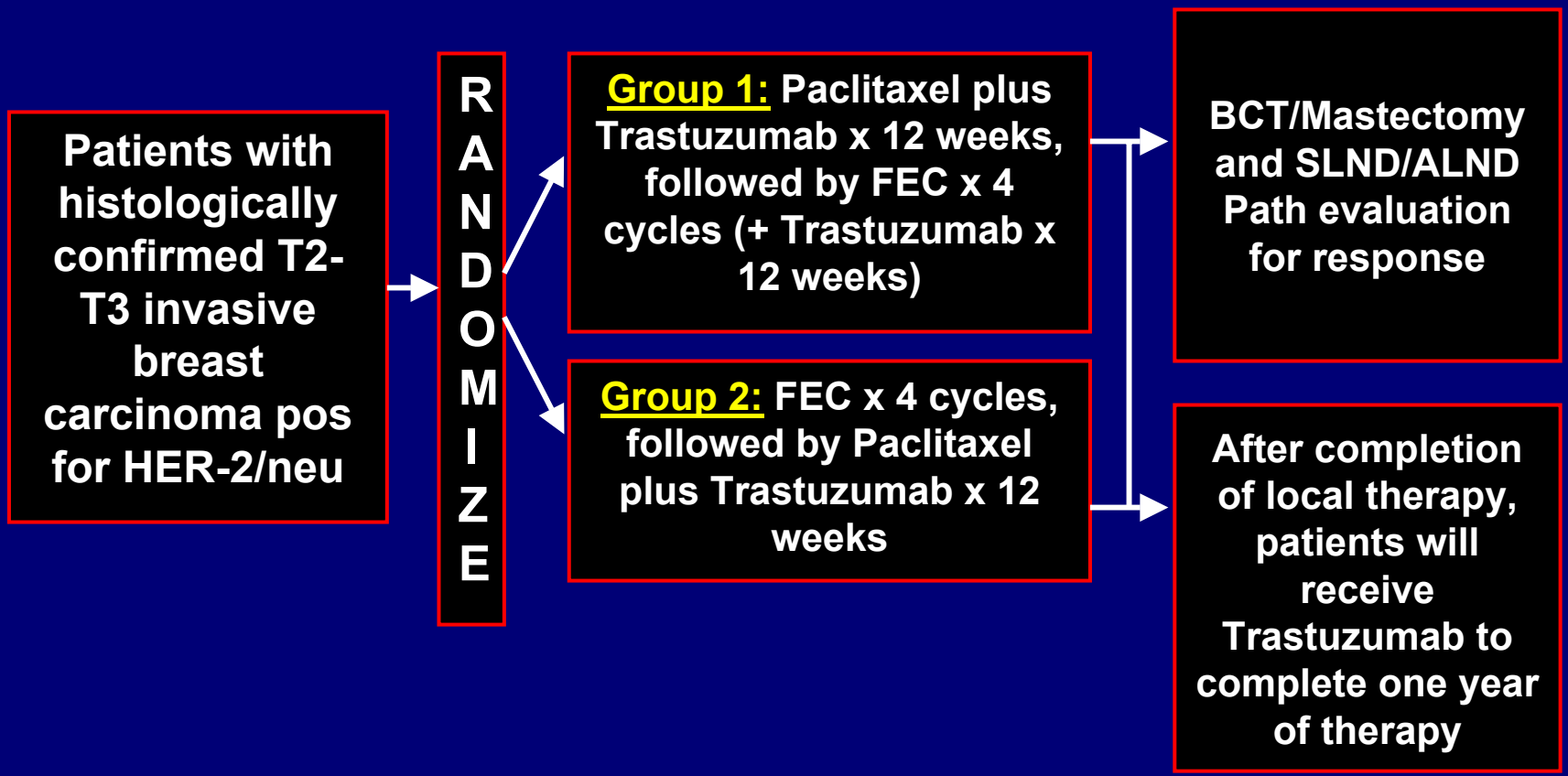
8 mg/kg loading dose followed by 6 mg/kg q3 weeks for 1 year

Patients Population

Enrollment completed on December 2005

Total enrolled patients	334
HER2-neg	99
HER2-pos NO trastuzumab	117
HER2-pos & trastuzumab	118

ACOSOG Z1041



Summary

- Preoperative trastuzumab as single agent
  - significant antitumoral activity
- Trastuzumab and single agent chemotherapy studies
  - Enhanced pCR
  - Addition of platins didn't further enhance pCR
- Concurrent trastuzumab with taxane and anthracycline therapy
  - Higher pCR rate
  - Favorable efficacy data (small studies)
  - Favorable cardiac safety data (with attenuated doses of anthracycline)

Conclusion

- Preoperative study model
  - Accurately predicted outcome of adjuvant trastuzumab studies

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Thank You !