

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Preoperative biologic therapy - anti-HER2 agents

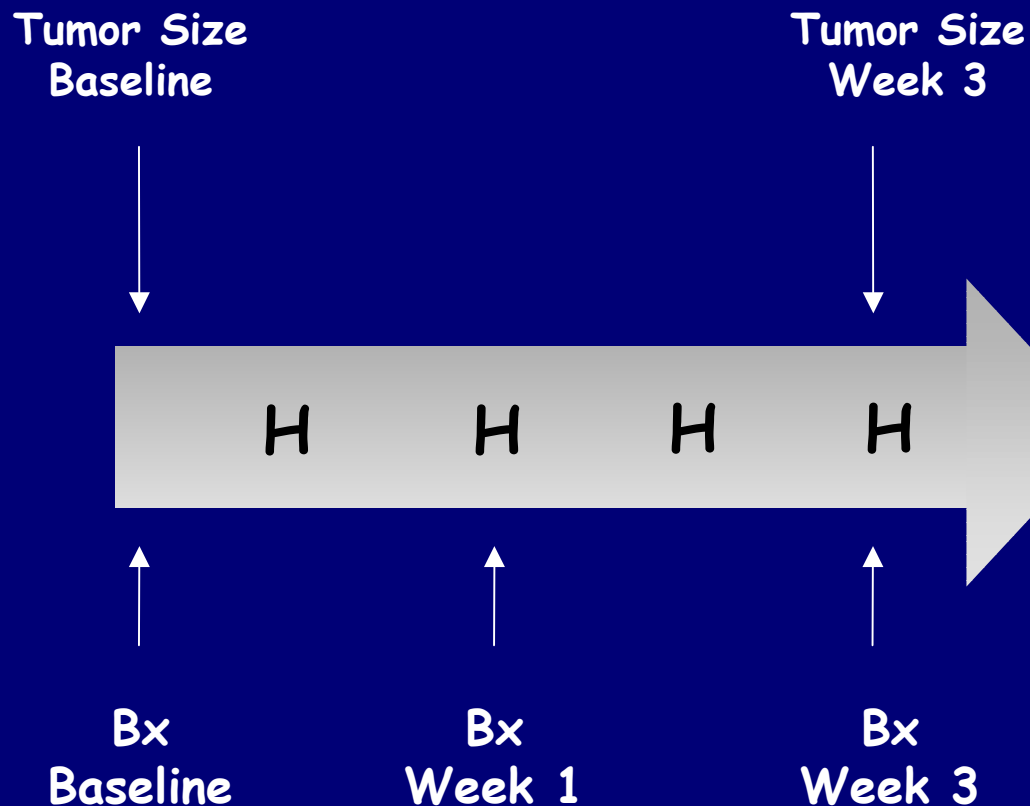
Aman U. Buzdar, M.D.
The University of Texas
M. D. Anderson Cancer Center
Houston, TX. USA

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



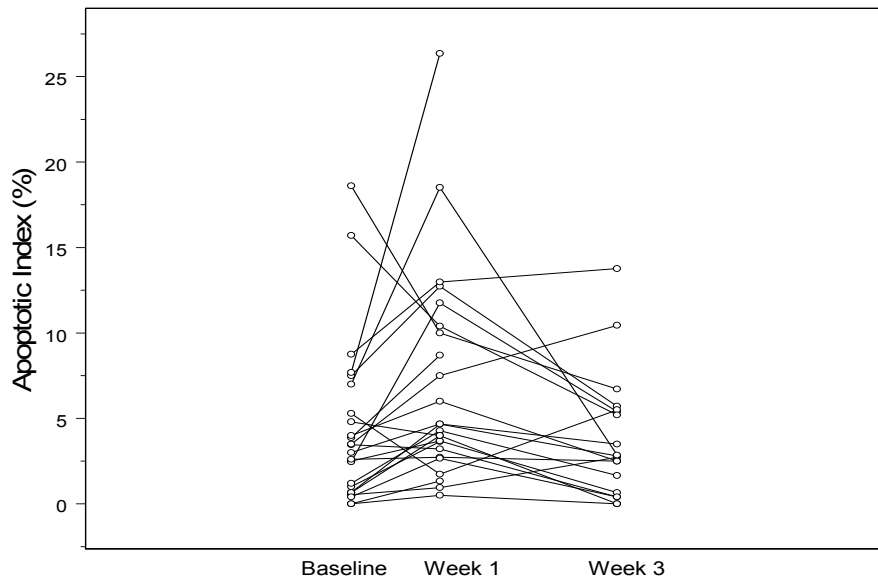
Total patients = 35

Responses

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

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

Preoperative Trastuzumab Single Agent Therapy

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

<u>Efficacy</u>	<u>Percentage</u>
pCR	9
Partial Response	36
Minor Response	54

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	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

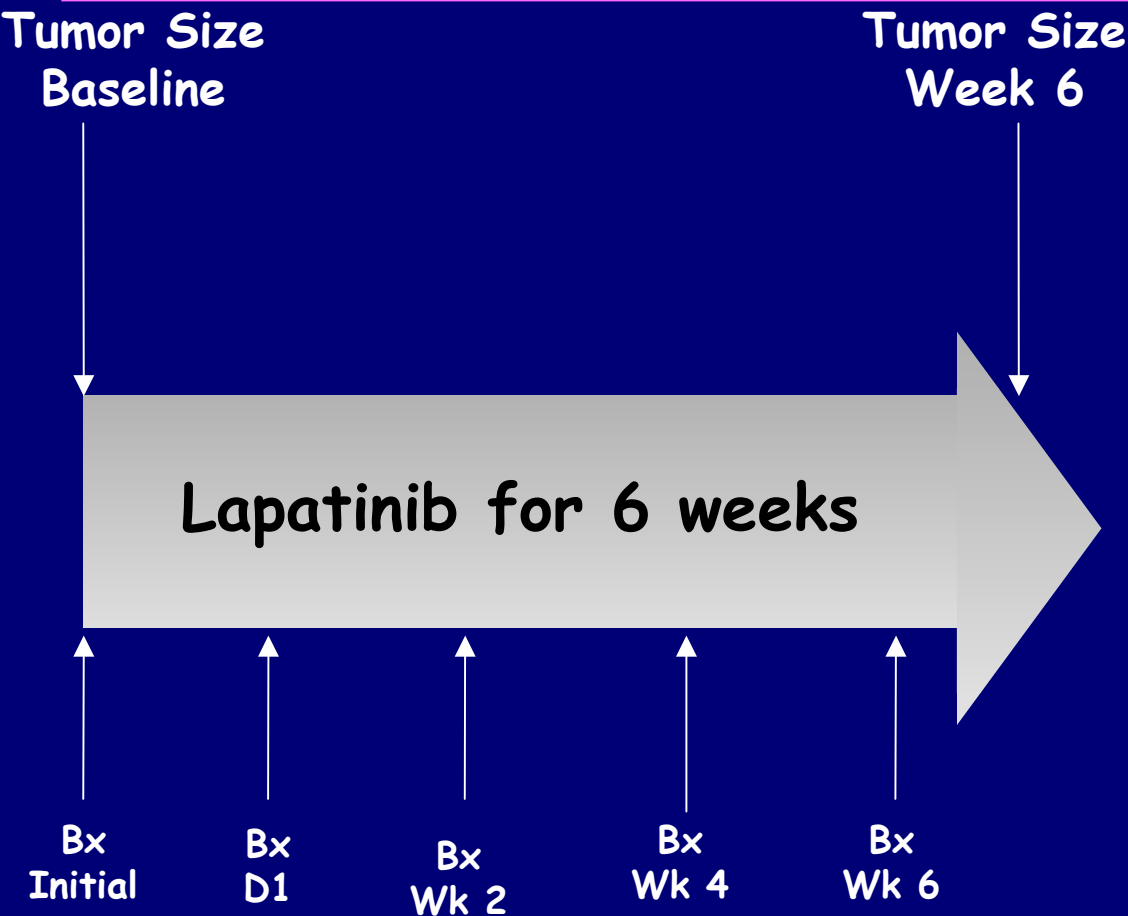
- Genes predictive of PCR – remains to be defined
- Non-responder expressed basal markers, IGF-IR positive and large tumors
- HER2 mRNA, or copy numbers, or ER mRNA, or Ki67 – no correlation to PCR
- Troponin-T - not correlated to changes in cardiac dysfunction.
- MALDI-TOF protein profiling of pre and 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

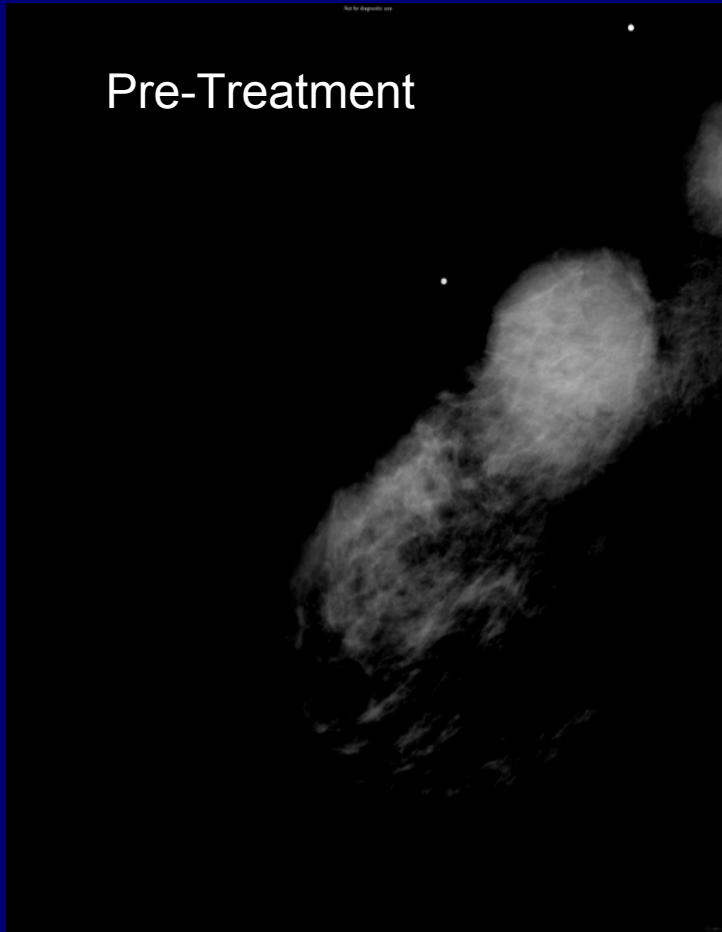
Preoperative Lapatinib Phase II Study



- **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**

Before and After 6 weeks of Lapatinib

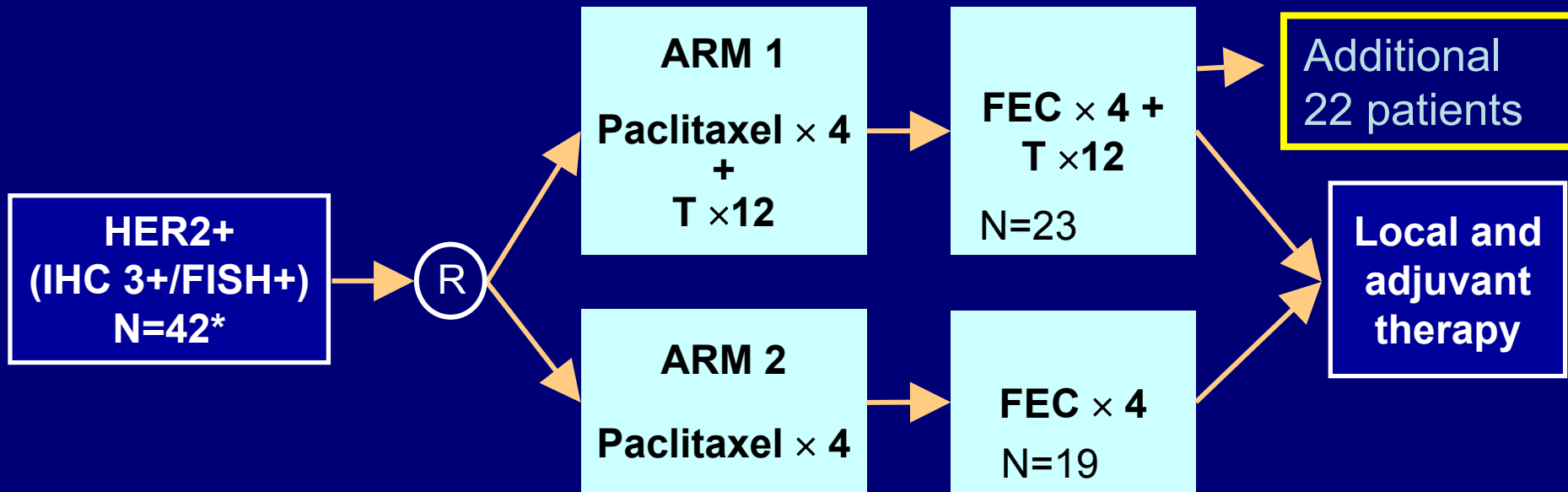
Pre-Treatment



Post-Treatment



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



*Paclitaxel 225 mg/m² q3w.

FEC = 5-fluorouracil 500 mg/m² d1, 4 + epirubicin 75 mg/m² d1 + cyclophosphamide 500 mg/m² d1, all q3w.

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

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

Age

Race

Stage of disease

Nodal involvement

Hormone receptor status

* Patient characteristics were similar

Pathological Complete Response Rates

	<u>PCR (%)</u>	<u>(95% CI)</u>
• 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

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

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

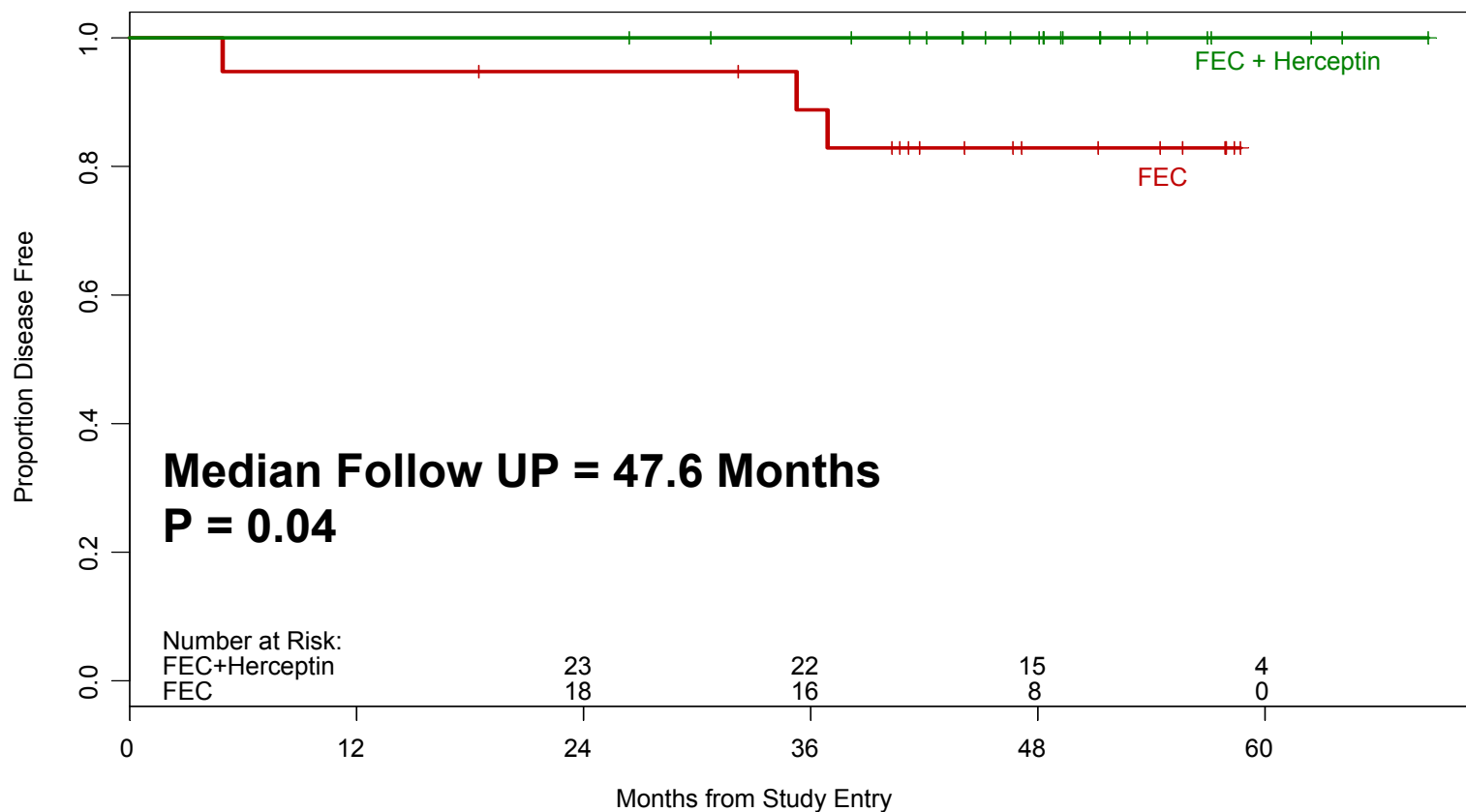
Summary of left ventricular ejection fraction

	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)

Pre-existing Cardiac Risk Factors by Treatment Group

Risk Factors	Randomized Groups		Assigned Treatment
	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

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

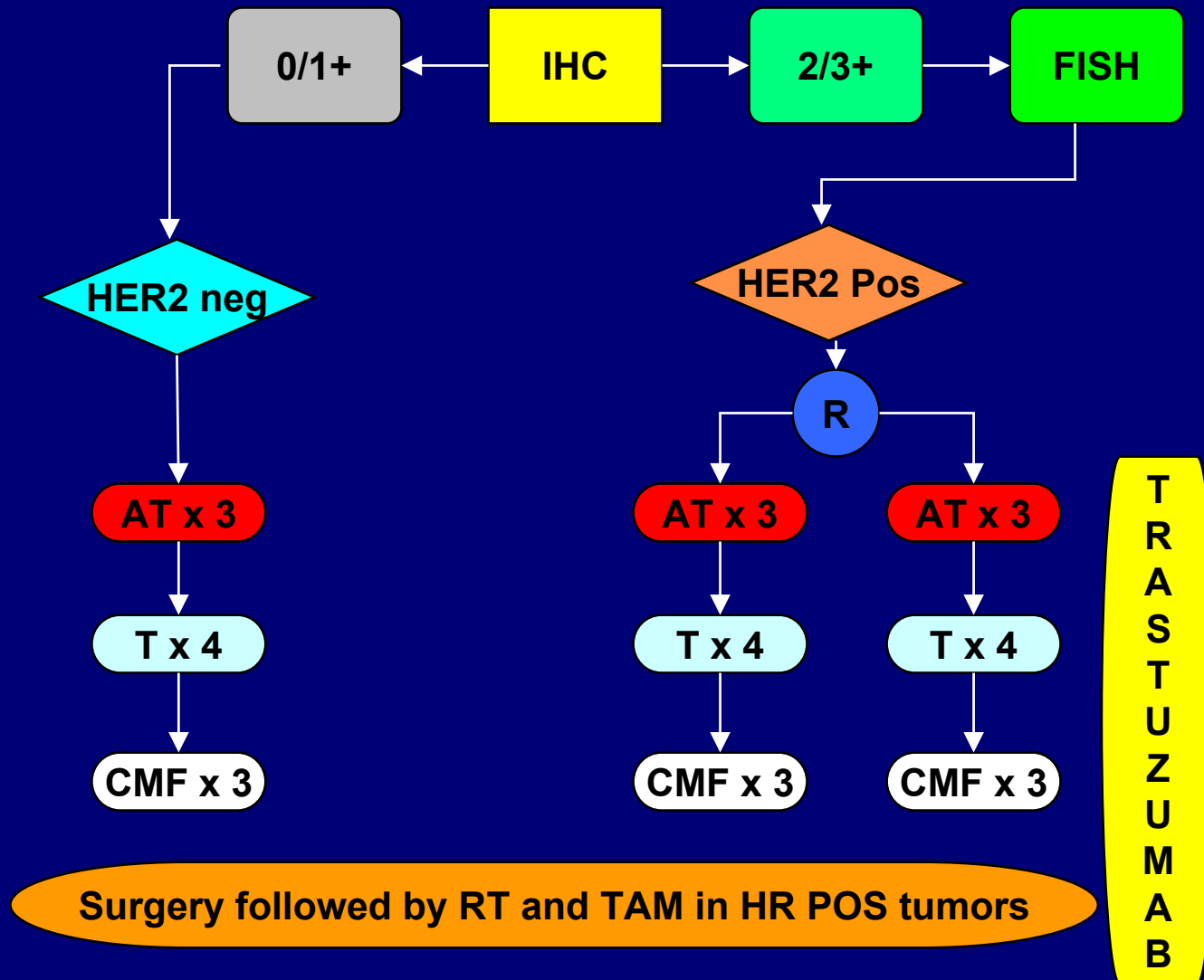
*Chemotherapy duration = 24 weeks

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/m²) and Paclitaxel (150 mg/m² over 3 h) q 3 weeks

T: Paclitaxel (200 mg/m² over 3 h) q 3 weeks

CMF: Intravenous on days 1 and 8 q 4 weeks

Herceptin:

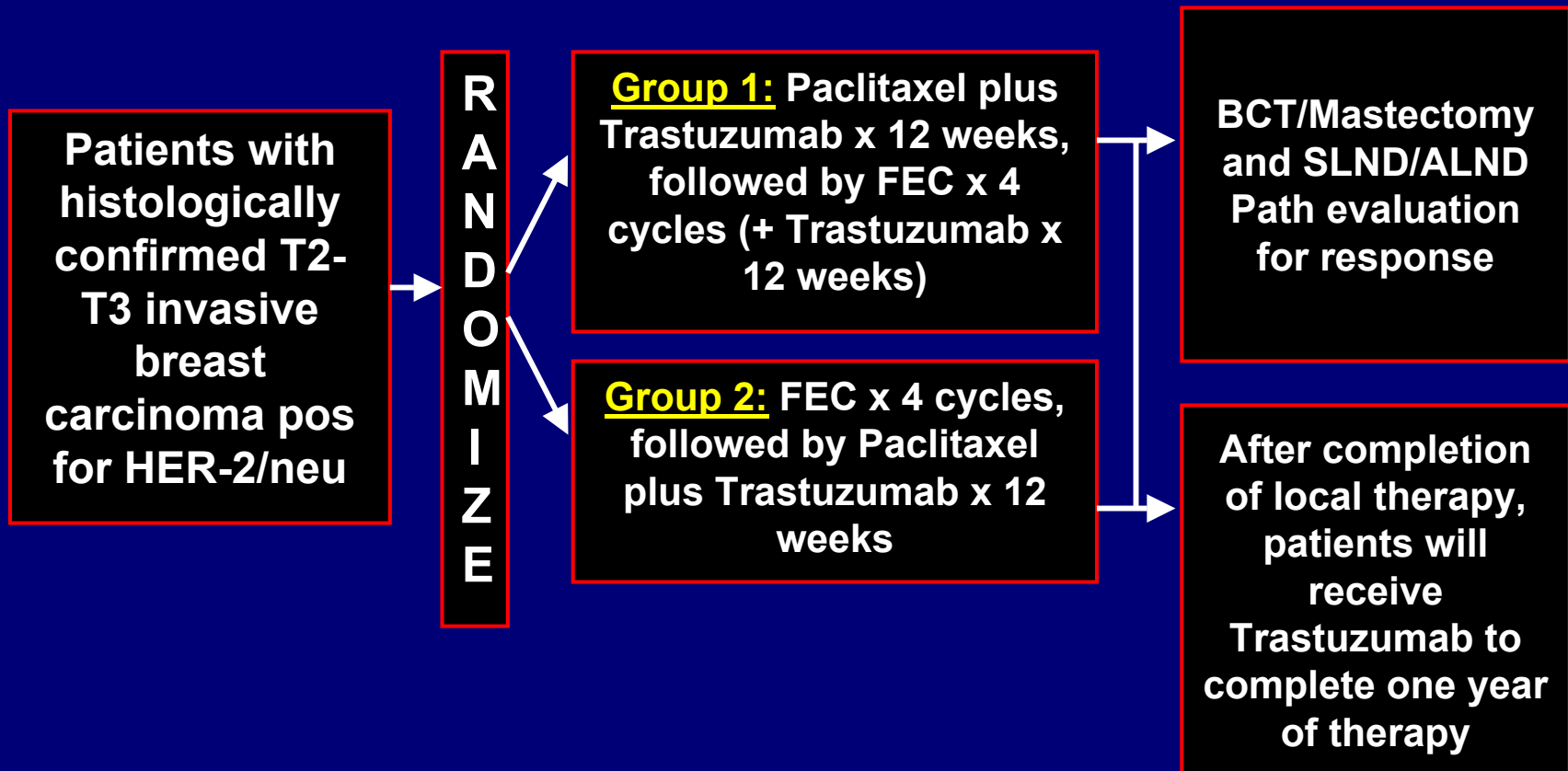
8 mg/kg loading dose followed by 6 mg/kg q3 weeks for 1 year

Patients Population

Enrollment completed on December 2005

<u>Total enrolled patients</u>	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



Thank You !

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER