National Cancer Institute

Challenges in Breast Cancer Clinical Trials

Jo Anne Zujewski, MD
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Diagnosis and Treatment

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Relative 5 Year Survival (%) by Cancer Site

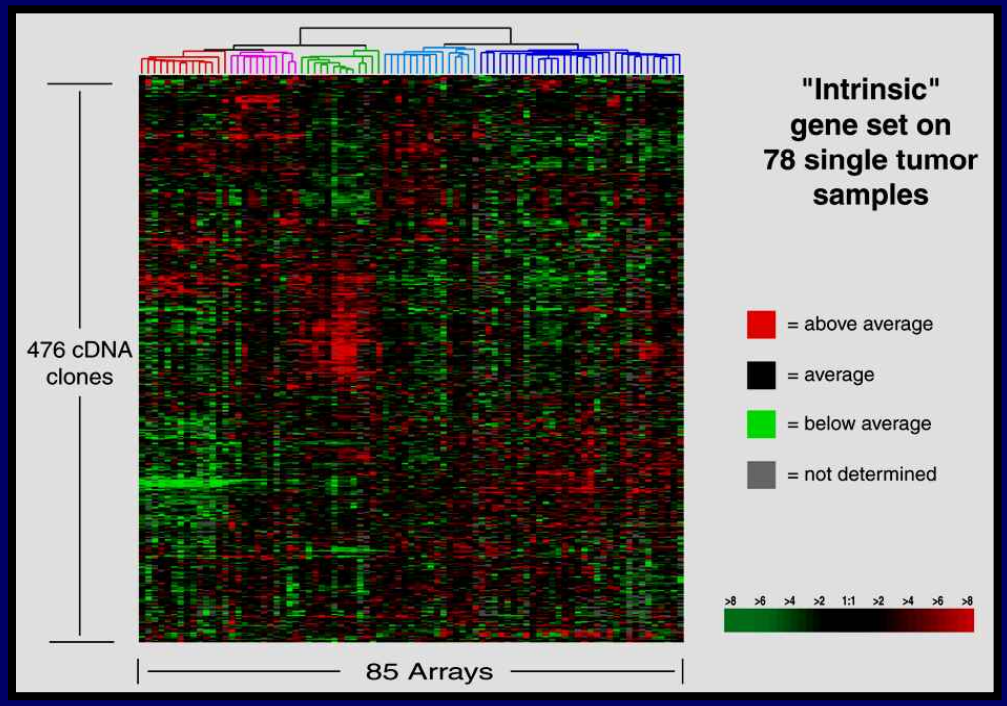
Site	1974-1976	1983-1985	1992-1997	1996-2003
Breast	75	78	86	89.8
Colon	50	58	61	64.9
Lung	12	14	15	15
Ovary	37	41	52	44.9

SEER, 1973-2003, DCP, NCI, 2009

2009

- Paradigm for treatment changes with continued understanding of biology of disease
- Breast cancer more than one disease
- Metastatic breast cancer: our greatest challenge

"Seminal observations that have led to the current understanding of breast as a family of related diseases, not a single monolithic process."



Hormone positive

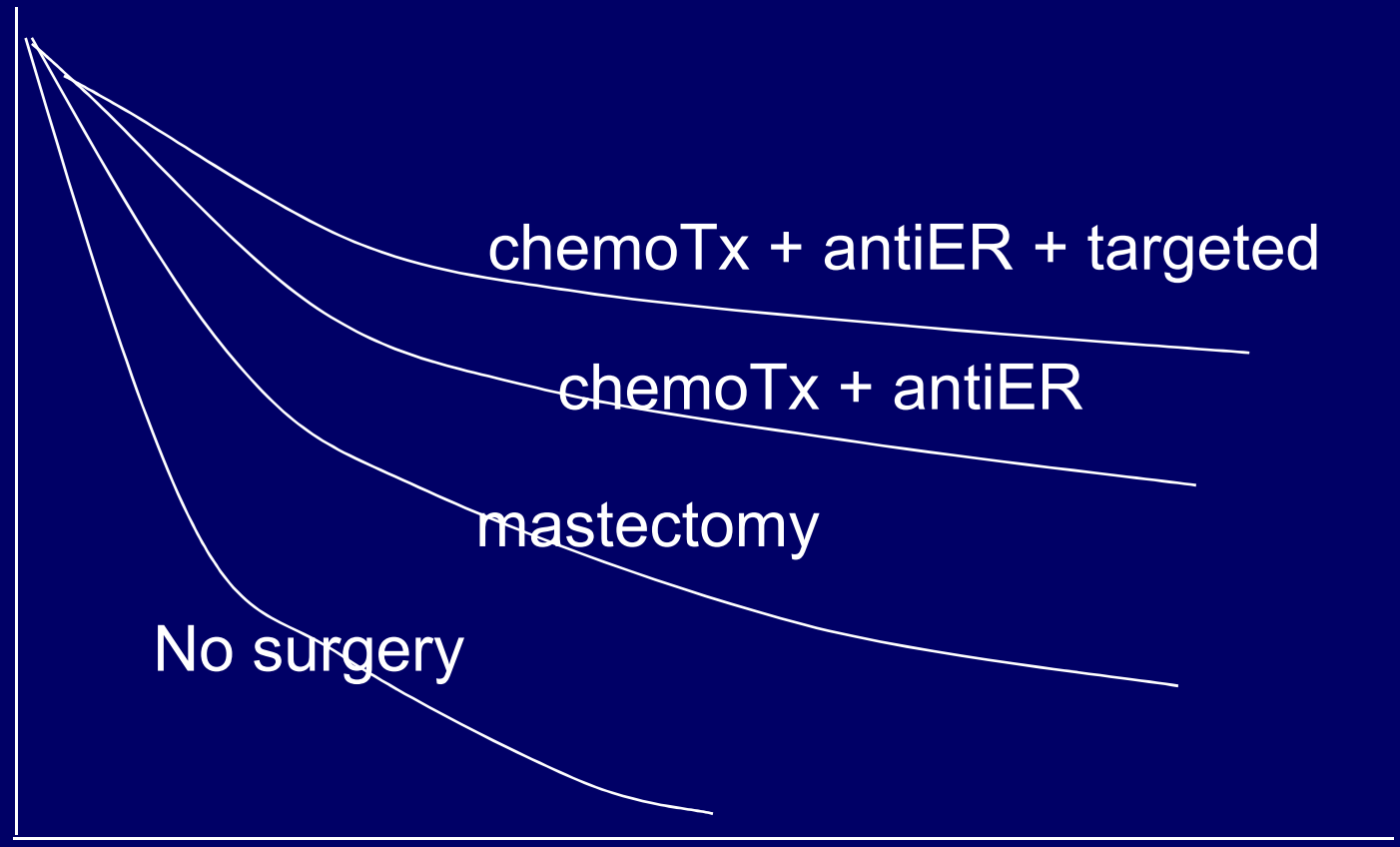
HER-2 positive

Hormone Refractory

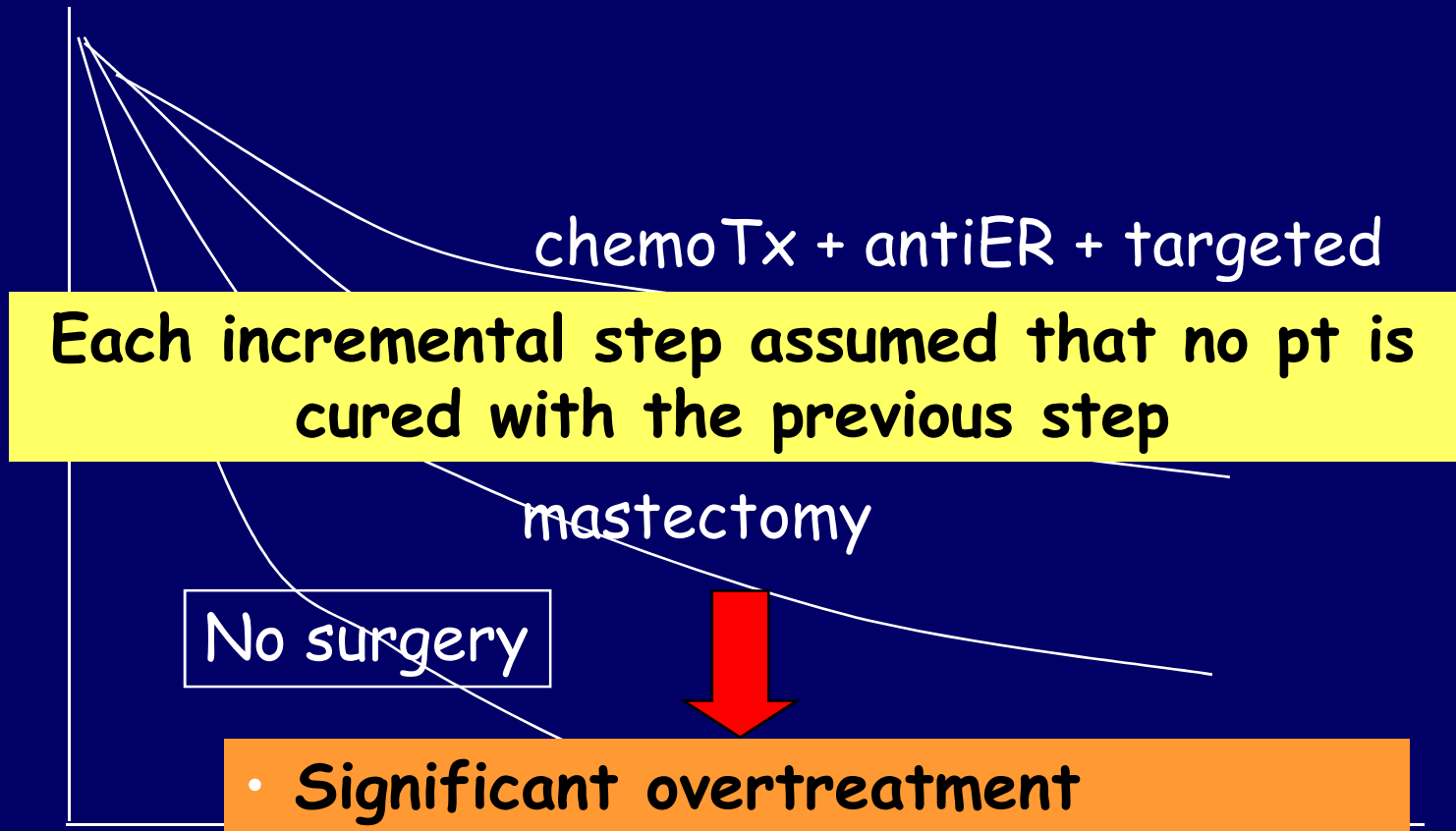
Triple Negative
Secondary Resistance

Sorlie T et al, PNAS 2001

Incremental Benefit



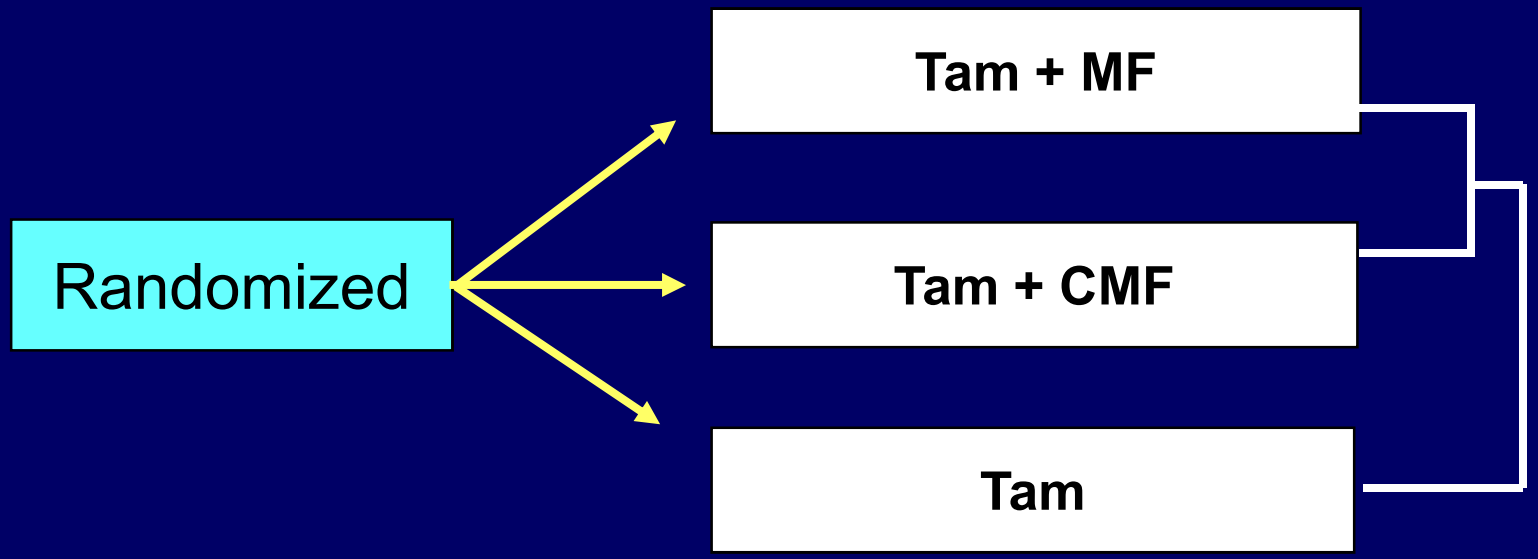
Incremental benefit



Each incremental step assumed that no pt is cured with the previous step

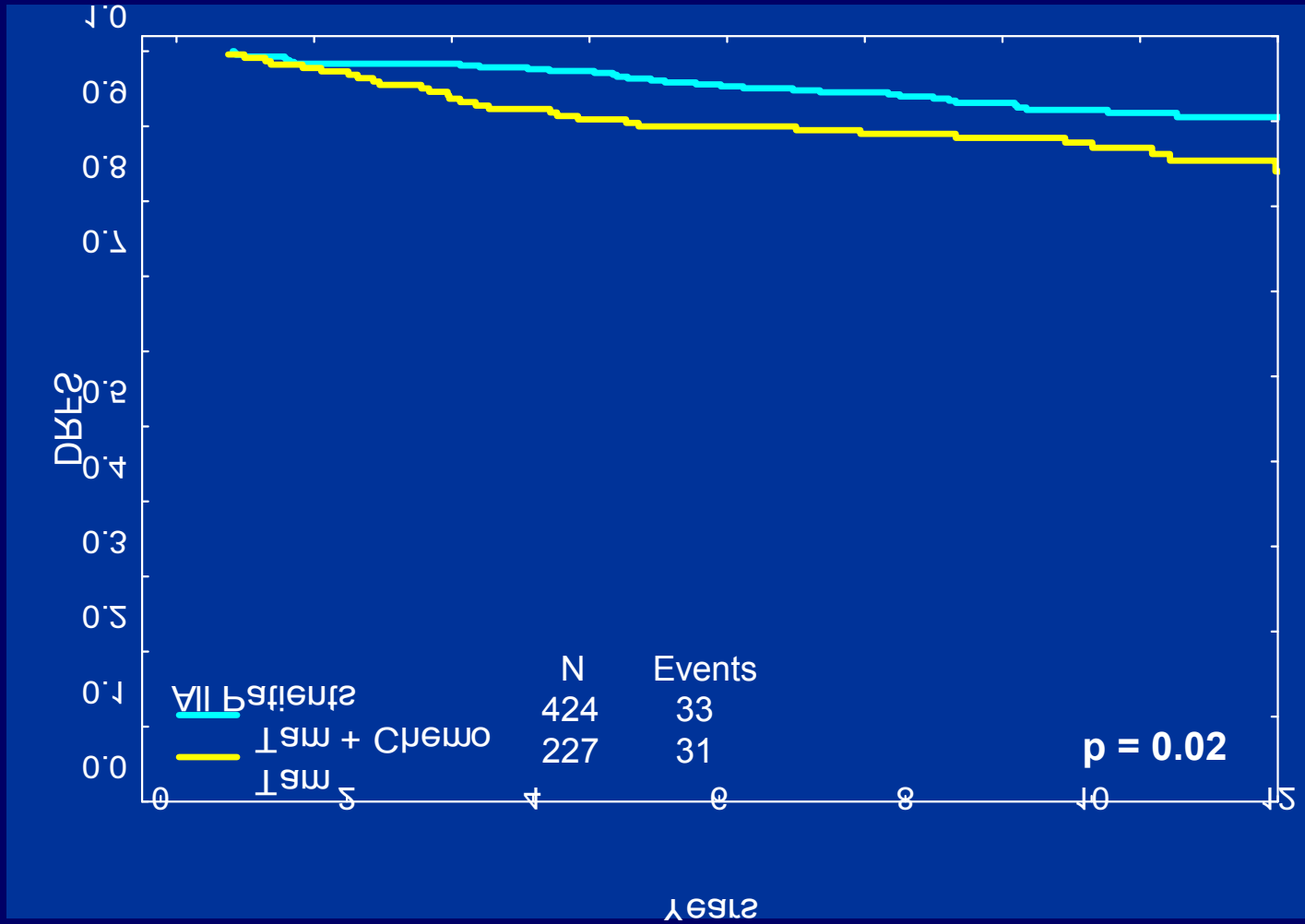
- **Significant overtreatment**
- **Necessity to conduct large trials to demonstrate small benefit**

NSABP B-20 Chemotherapy Response



B-20 Results

- Tam vs Tam + Chemo – All



B-20 Evaluable Patients (n=651) Similar to All Patients (n=2299)

Number of Eligible patients				
	Tam	Tam+MF	Tam+CMF	Total
All B20	770	763	766	2299
GHI-B20	227 (29.5%)	203 (26.6%)	221 (28.9%)	651 (28.3%)

GHI-B20 study subjects were largely similar to All Patients with regard to baseline characteristics

Oncotype DX (ODX) Recurrence Score (RS)

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromolysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

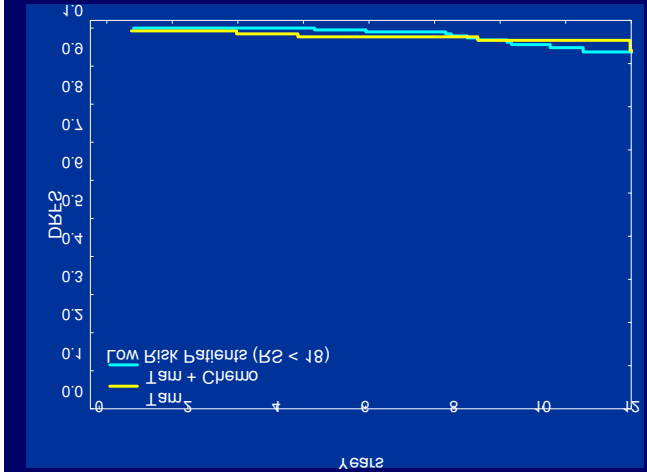
RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

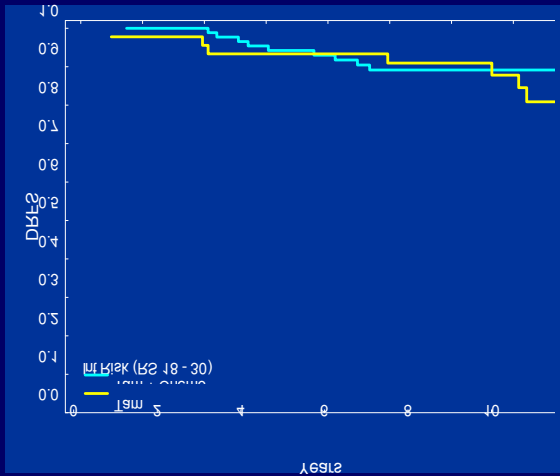
St Gallen 2005

B-20 Summary

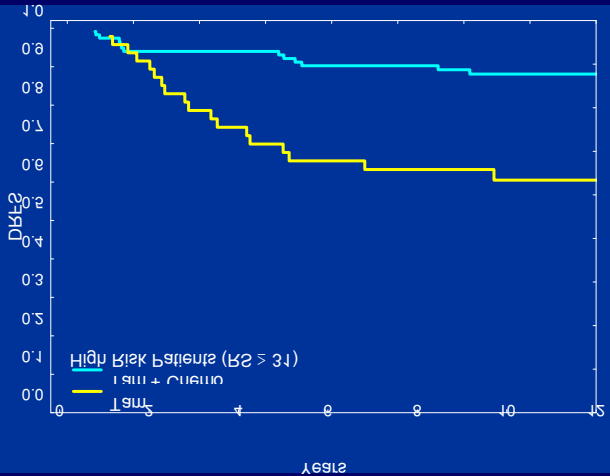
RS < 18



RS 18-30

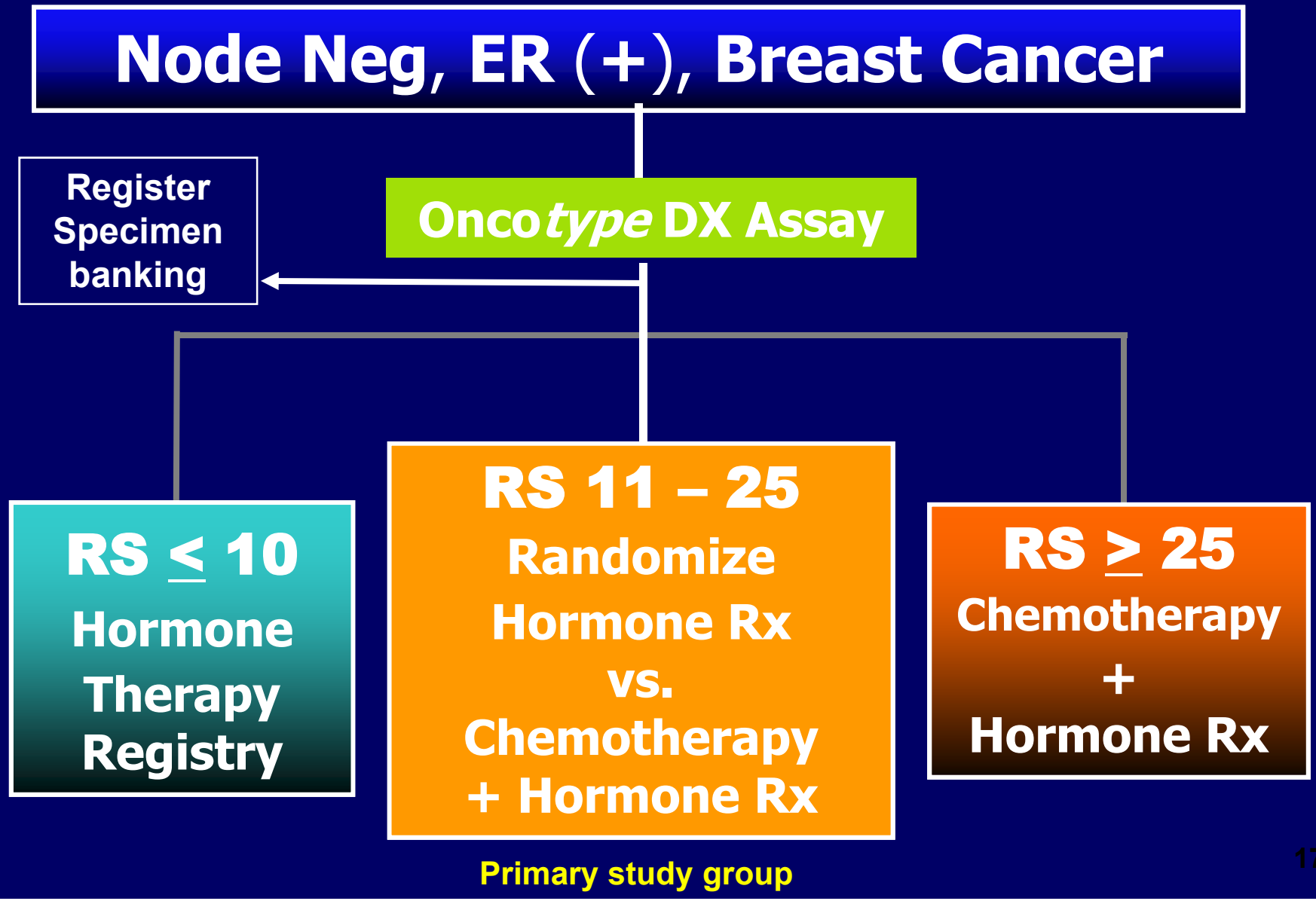


RS ≥ 31



- Patients with tumors that have high Recurrence Scores have a large absolute benefit of chemotherapy (similar results with CMF and MF)
- Patients with tumors that have low Recurrence Scores derive minimal, if any, benefit from chemotherapy

*T*rial *A*ssigning *I*ndividua*L*ized *O*ptions for T*R*eatment (*TAILORx*)



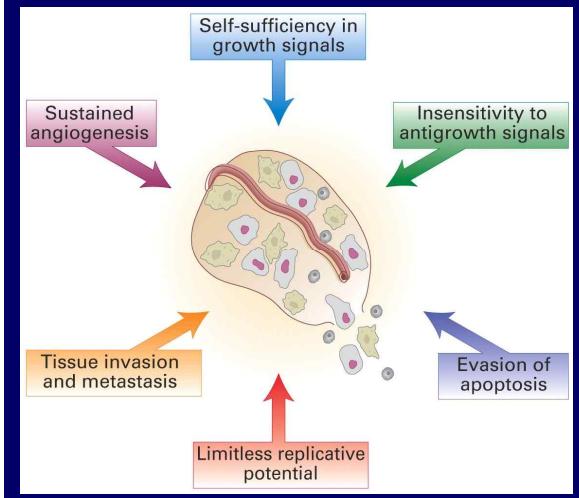
Basic Biologic Features of Neoplasms

Differentiation

Abnormal Proliferation

Angiogenesis

Invasion

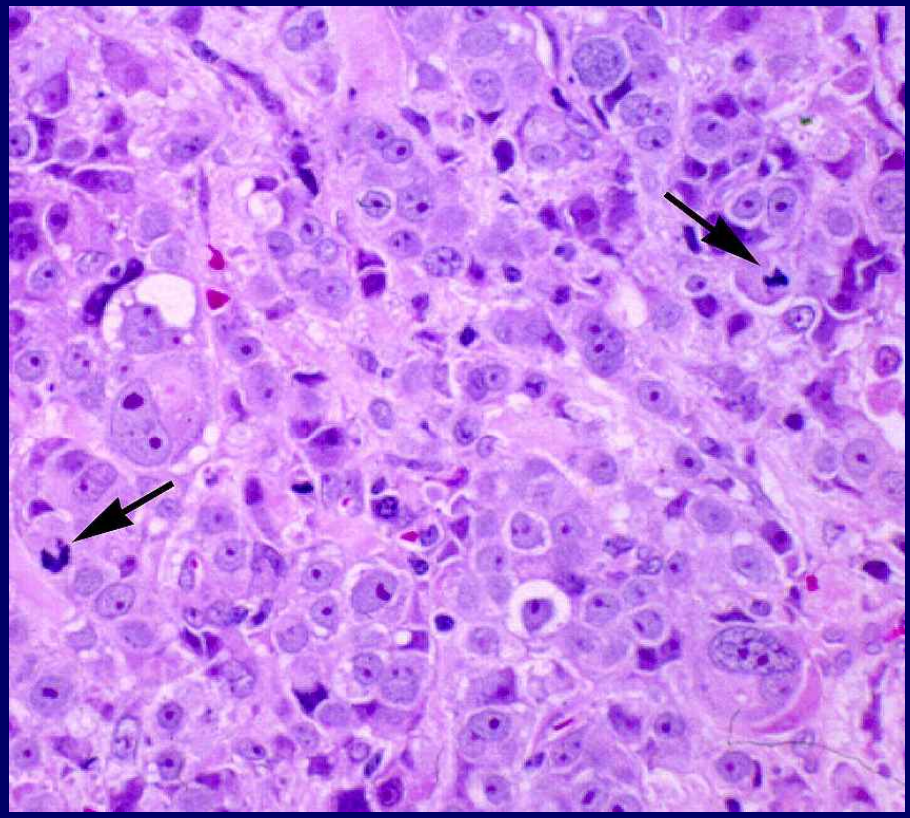


Oncogenic Lesion
(e.g. RAS, MYC, E2F Activation)

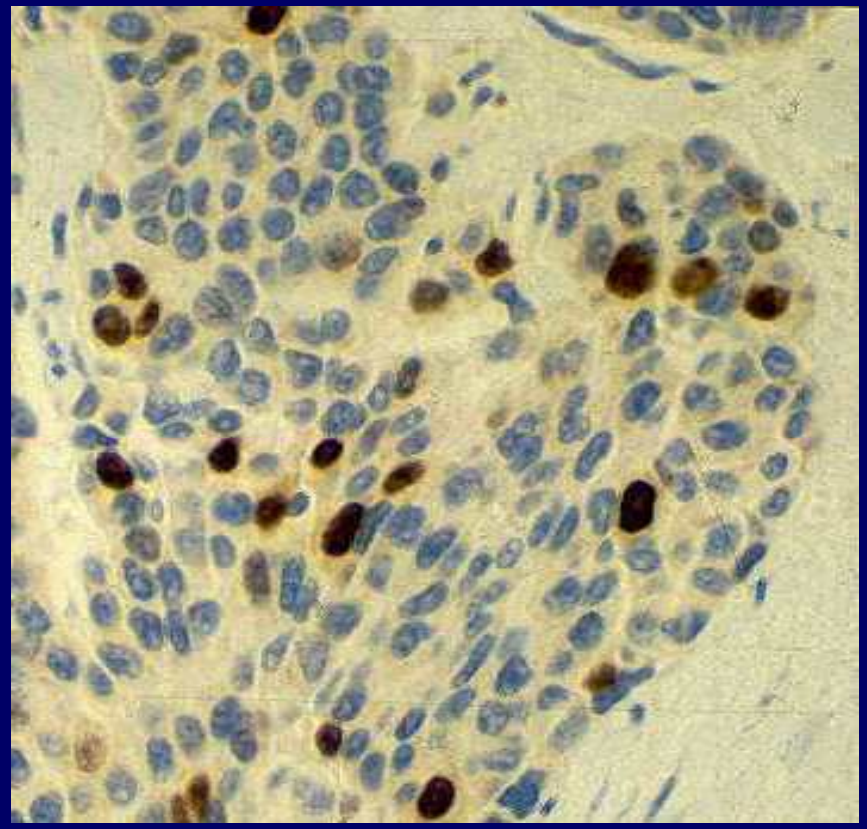
Apoptosis

Senescence

Proliferation



Mitotic bodies



Ki67, MIB1 antibody

Proliferation in multigene signatures

- Desmedt et al (Clin Cancer Res 2008, 14, 5158)
- 7 molecular modules (invasion, immune response, angiogenesis, apoptosis, proliferation, ER signaling, HER2 signaling) + clinical variables (size, grade, age, ER protein)
- 628 ER+HER2- from public databases
- Only proliferation module ($p<10^{-11}$) and grade ($p=0.01$) significant in multivariate analysis

Also genomic grade

Oncotype DX (ODX) Recurrence Score (RS)

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromolysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

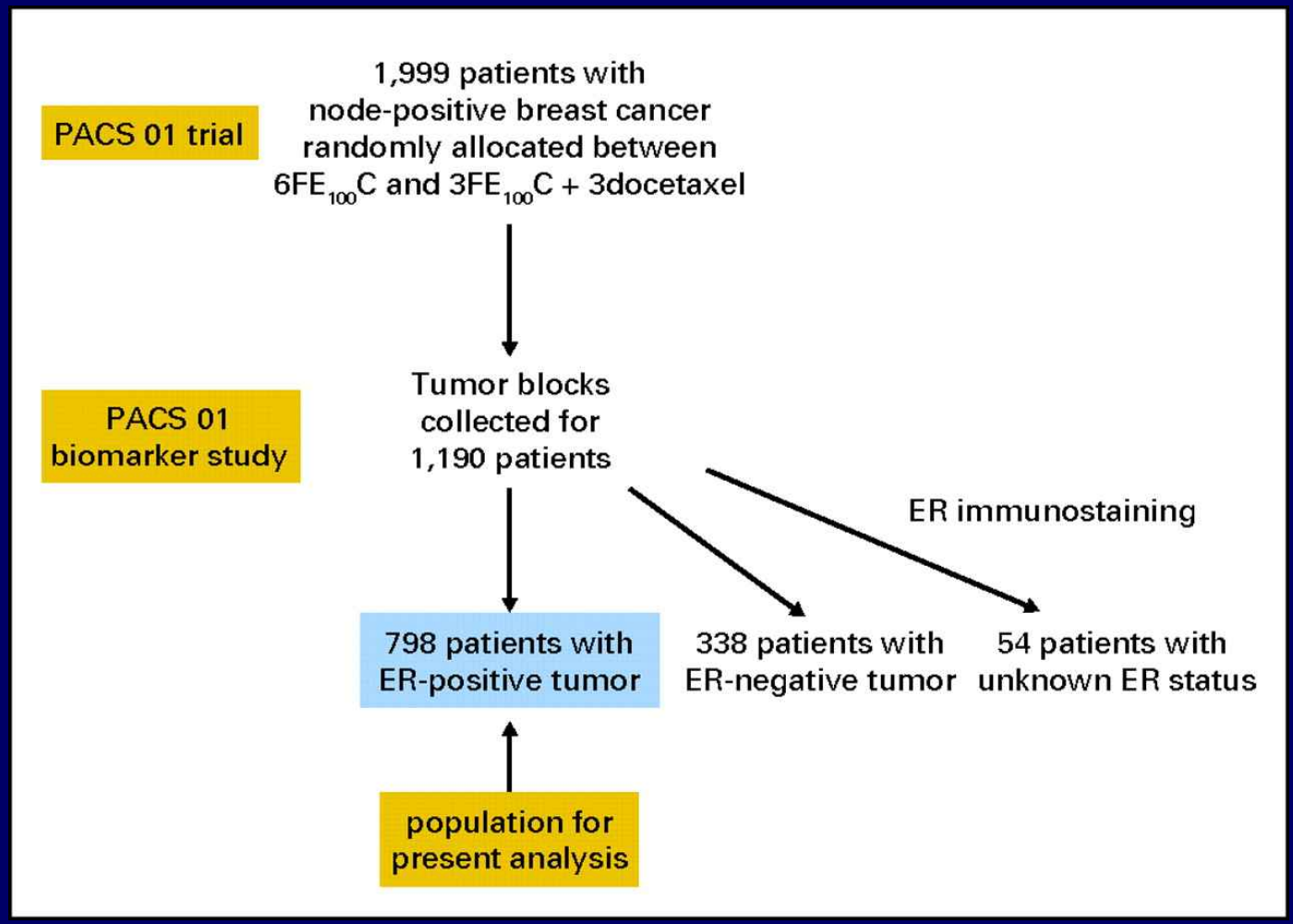
REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

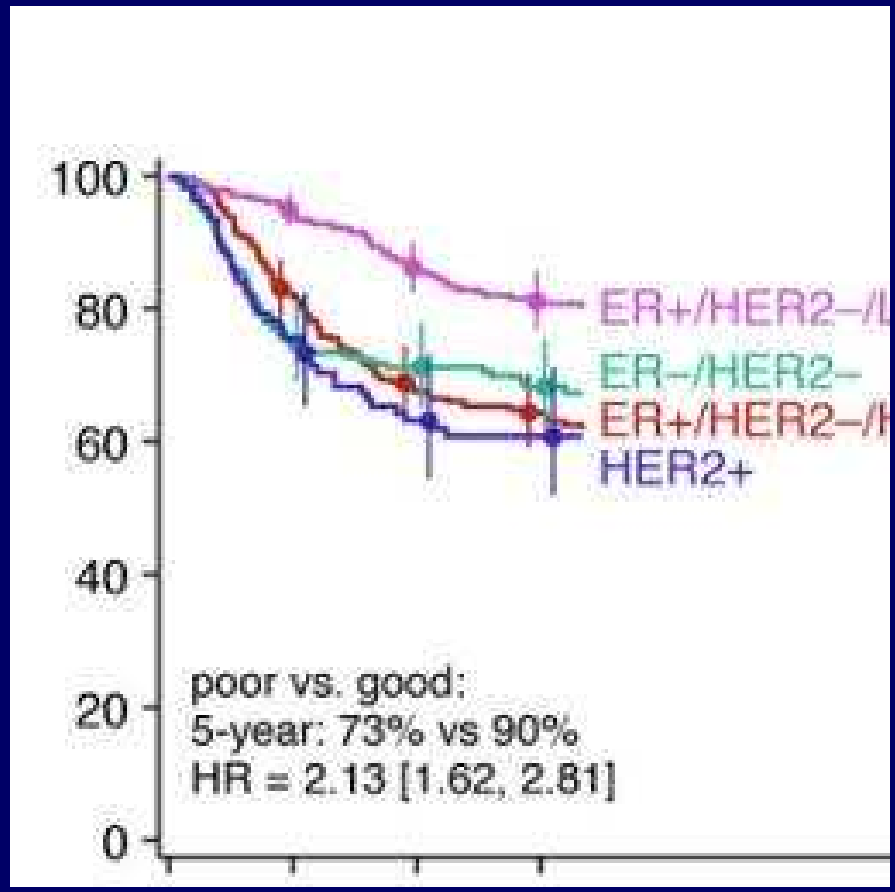
St Gallen 2005

Fig 1. Study flowchart shows the process for tumor blocks and patient selection



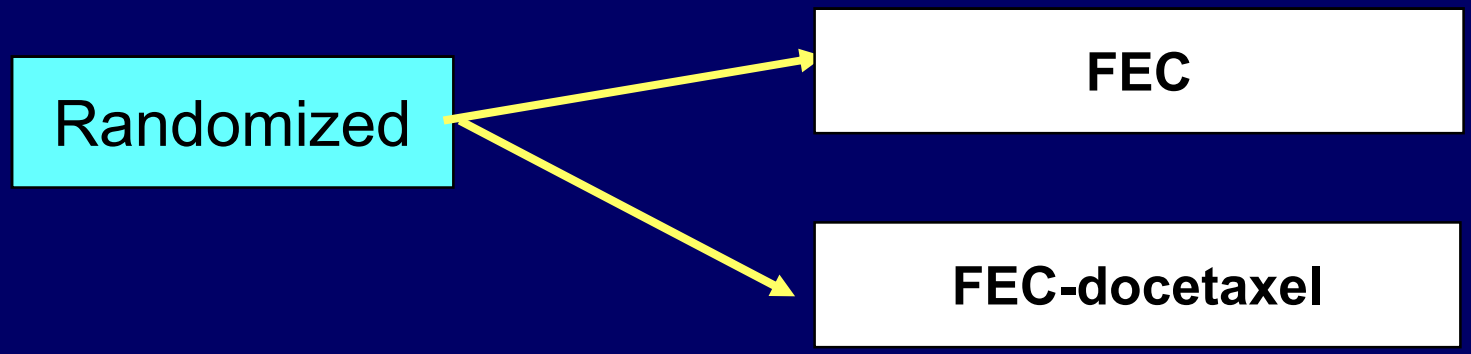
Penault-Llorca, F. et al. J Clin Oncol; 27:2809-2815 2009

Proliferation: Prognostic marker



Wirapati

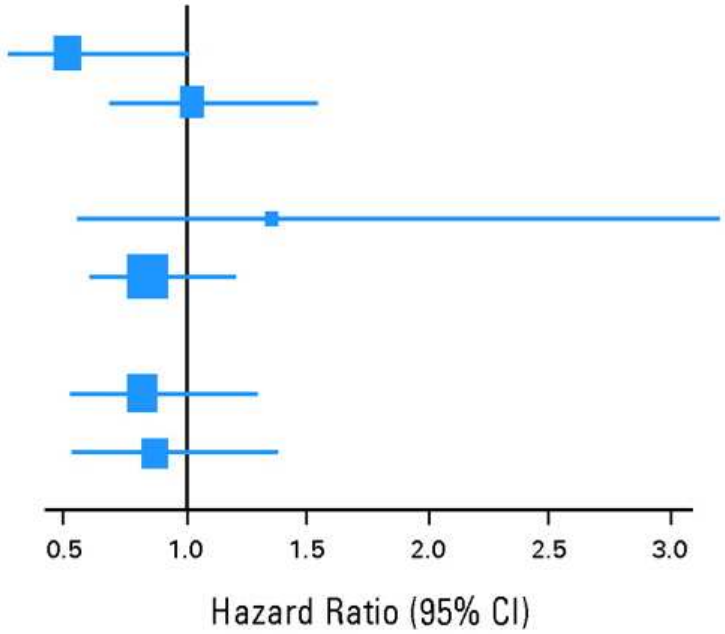
FEC versus FEC-docetaxel



FEC: flurouracil, epirubicin. Cyclophosphamide
FEC-docetaxel

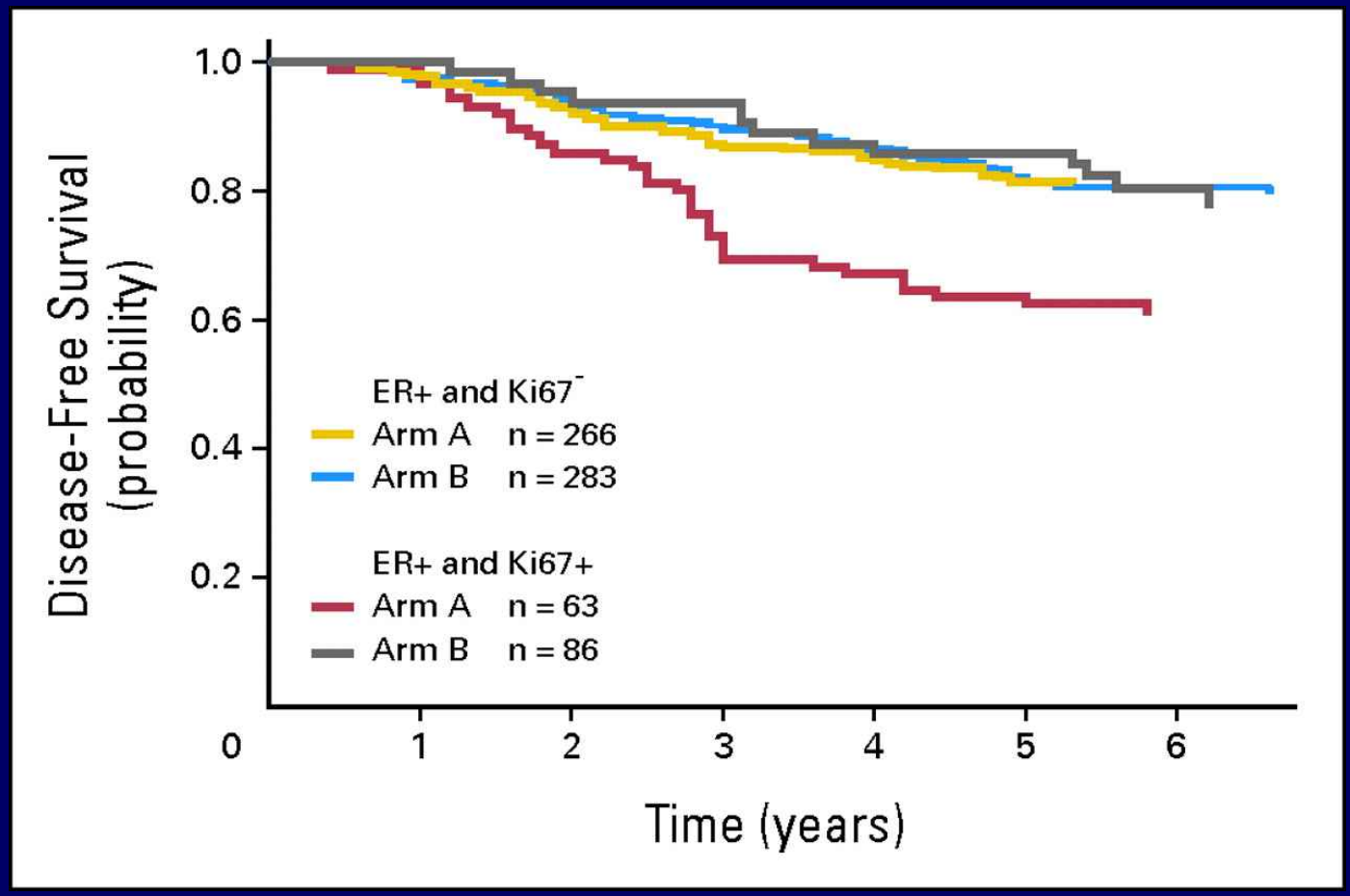
Hazard ratios associated with docetaxel according to biomarker expression

Biomarker	Hazard ratio for relapse associated with docetaxel (95% CI)	Hazard ratio for interaction with docetaxel (95% CI), *P*
Ki67		
Positive (n = 150)	0.51 (0.26 to 1.01)	0.53 (0.24 to 1.16),
Negative (n = 549)	1.03 (0.69 to 1.55)	.11
HER-2		
Overexpressed (n = 73)	1.34 (0.55 to 3.21)	0.83 (0.35 to 1.94),
Normal (n = 705)	0.85 (0.60 to 1.20)	.66
PR		
Positive (n = 454)	0.83 (0.53 to 1.30)	0.89 (0.47 to 1.66),
Negative (n = 279)	0.86 (0.54 to 1.39)	.71



Penault-Llorca, F. et al. J Clin Oncol; 27:2809-2815 2009

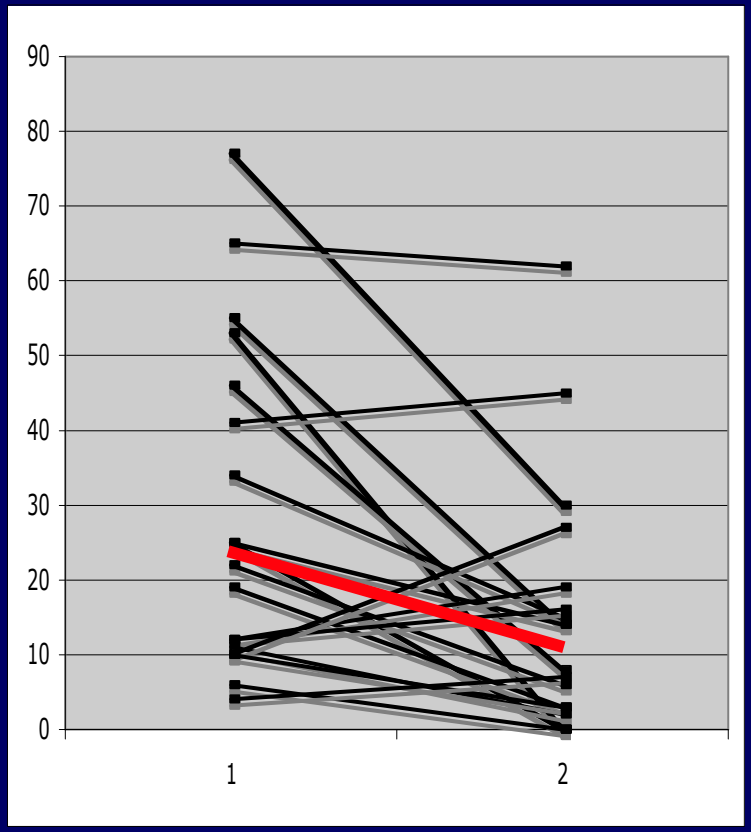
Disease-free survival (DFS) according to treatment and Ki67 expression in patients with estrogen receptor (ER) -positive tumors



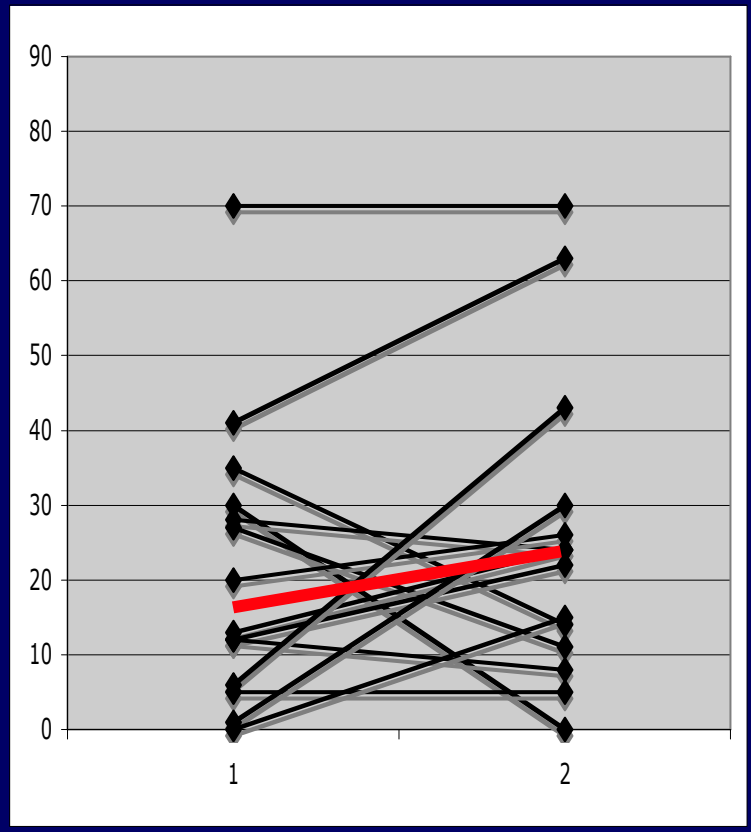
Penault-Llorca, F. et al. J Clin Oncol; 27:2809-2815 2009

Change in Ki67 (FNAs) after 21 days chemotherapy: responders vs non-responders

Responders



Non-responders



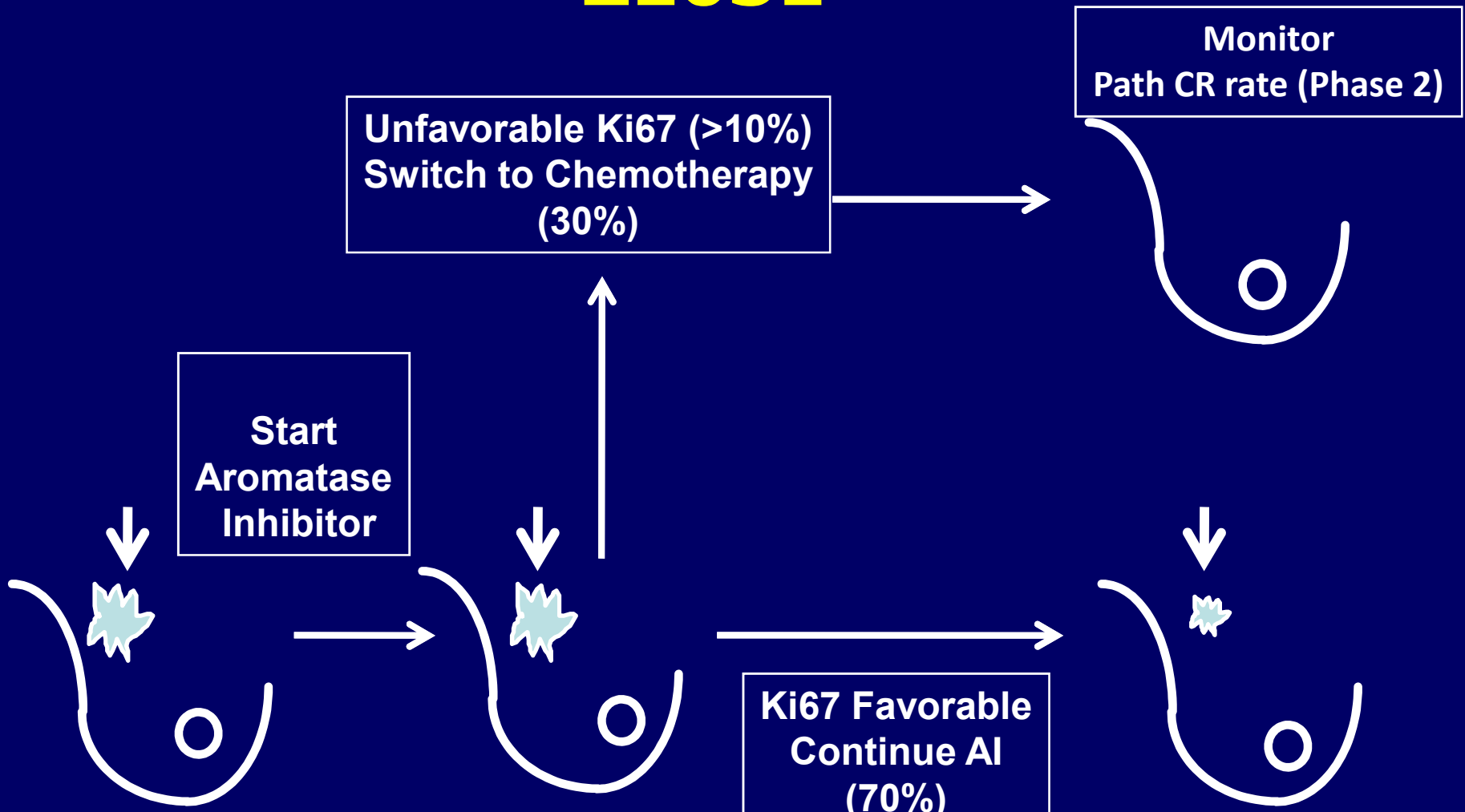
Median Ki67

Assersohn et al BCRT 82, 113, 2003

Ki67 after neoadjuvant therapy

- Prognostic evaluation with Ki67 may be better after presurgical therapy
- May extend to multi-parameter profiling
- Need further validation of change in Ki67 at 2 weeks as a surrogate marker of effectiveness
  - drug development
  - mechanisms of resistance

Z1031



One month biopsy with Ki67 analysis CLIA lab analysis with (DC Allred, cross validated with M Dowsett)

Are we there yet?
How much is enough? – what amount of benefit is meaningful to a patient, society?

Challenges in the evaluation of new agents for MBC

Concurrent versus sequential chemotherapy E1193: doxorubicin, paclitaxel, and combinations in MBC

	doxorubicin	Paclitaxel	Doxorubicin /paclitaxel
Overall response	36%	34%	47%
Time to Tx failure	6.0	6.3	8.2
Median survival mo.	18.9	22.2	22.0

Absent the demonstration of a meaningful benefit in survival, time to progression, or quality of life from such an endeavor, this trial, E1193, argues strongly for monochemotherapy and realism, rather than polychemotherapy, for metastatic breast cancer

Sledge GW, et al JCO 2003; Seidman A JCO 2003

E1193: First line MBC (2003)
PLD plus docetaxel: (2008)
96-97% had no prior cytotoxic chemo for MBC

	doxorubicin	Paclitaxel	Doxorubicin /paclitaxel
Overall response	36%	34% **26 % (docetaxel)**	47% **35% (Combo/PLD)**
Time to Tx failure Mo. **TTP**	6.0	6.3 **7.0(docetaxel)**	8.2 **9.8 (Combo /PLD)**
Median survival mo.	18.9	22.2 **20.7(docetaxel)**	22.0 **20.6 (Combo /PLD)**

Sparano, SABCS 2008, Abstract 80

Sledge GW, et al JCO 2003; Seidman A JCO 2003

Phase II trials –JCO

Life for the clinical investigator was much simpler 30 years ago.

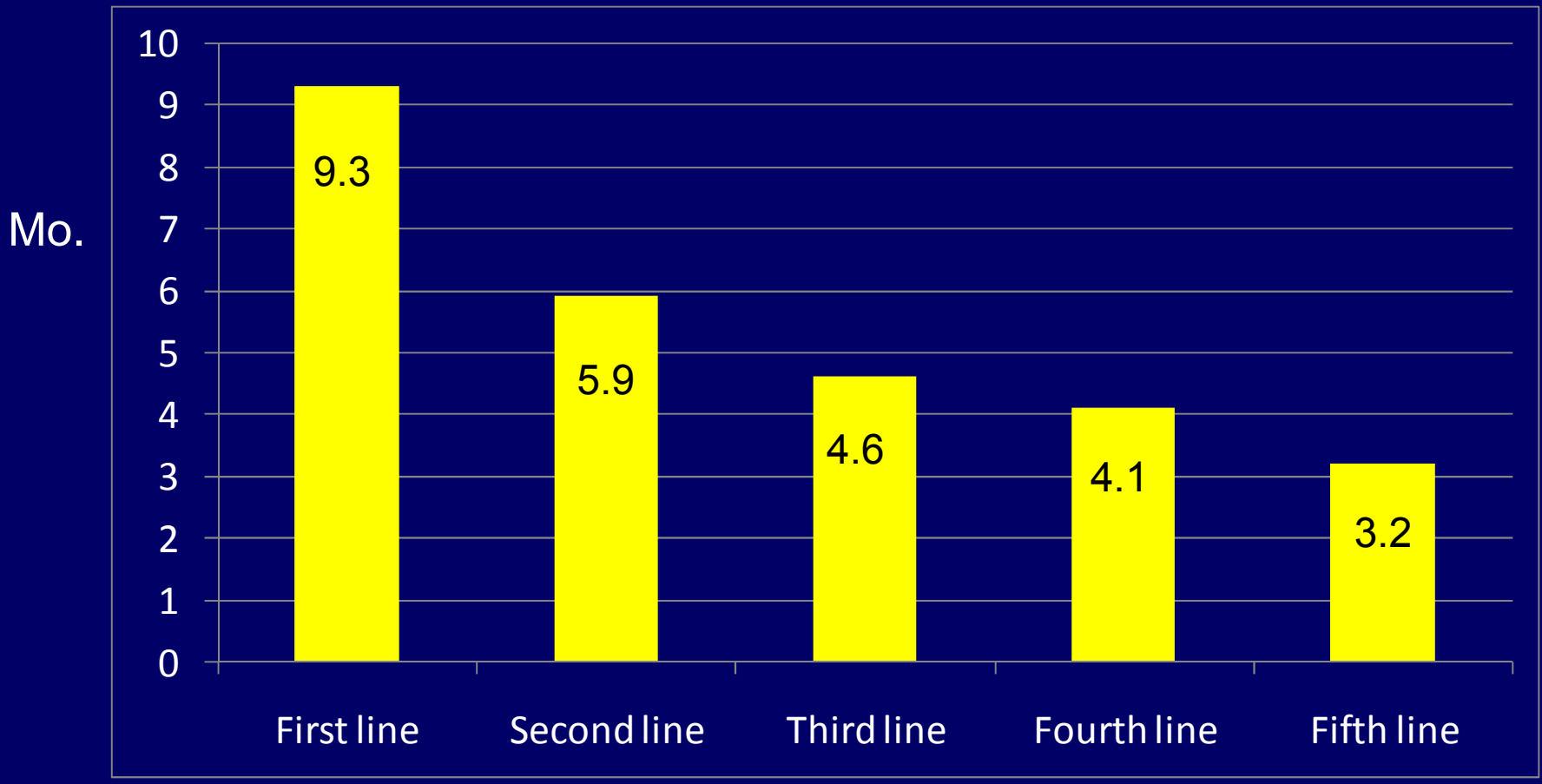
- Historical control data are moving targets
- Shifts is disease presentation and patient referral patterns
- Improvements in radiographic and surgical staging techniques
- Changes in techniques to assess response
- Response rates to not translate into overall survival benefit
- Cytostatic agents may prolong survival without a response

S.A. Cannistra JCO 27, 2009, pp3073-3076

Metastatic trials: historical control drift

Agent	Year	Paclitaxel q 3 wk			Comparator		
		RR	TTP (mo)	OS (mo)	RR (%)	TTP (mo)	OS (mo)
Paclitaxel weekly	1998-2000+	**28**	**5**	16	**40**	**9**	24
Docetaxel q3	1994-2001	25	**3.6**	**12.7**	32	**5.7**	**15.4**
Abraxane q3	2001-2002	**27**	**3.8**	13	**42**	**5.1**	15.2
Bevacizumab + Paclitaxel weekly	2002-2004	**16**	**6.1**		**34**	**11**	
Bevacizumab + docetaxel q3	2006-2008	**44**	**8.0**		**55-63**	**8.8**	
Bevacizumab + anthra/taxane	2006-2009	**38**	**8.0**	**23.8**	**51**	**9.2**	**25.2**

Time of Disease Control by Line of Chemotherapy



Dufresne, A et al. Breast Cancer Res and Treat 2008

Single Arm Phase II

- Historical control required and stable over time
- Likelihood of a response to standard options is low
- Desired effect of agent is large
- MOA cytostatic allowing RR as endpoint

  - May require less than half sample size of some randomized phase II trials with comparable type I (α) and type II (β) error

S.A. Cannistra JCO 27, 2009, pp3073-3076

Randomized Phase II: Selection design

- Selection design "pick the winner"
  - Appropriate for prioritizing between two experimental regimens when no a priori preference (e.g., based on cost, toxicity)
  - Not appropriate for comparing experimental agent to standard treatment control arm (50% chance of choosing experimental arm if truly no difference)
  - Possible neither experimental regimen is effective

(Rubinstein et al., *JCO* 2005; Cannistra S JCO 2009)

Phase II Screening design

- Screening design
  - Compare experimental regimen to standard treatment control arm
  - Economize on sample size by using larger than usual type I and type II errors, and targeting larger effect size (e.g., $\alpha=\beta=0.20$, PFS hazard ratio = 1.5 or RR difference = 20%)
- Other designs
  - Randomized phase II (2 experimental regimens) plus reference control arm
  - Phase II/III

Implications for clinical care….

- **"Tailor" systemic therapy**

  Therapeutic targeting based on biologic sub-setting (ER, HER-2)

- **Every treatment plan is multidisciplinary and individualized**

Implications for research….

- Genomic/proteomic approaches for therapeutic individualization of systemic therapies
- Clinical trials specific for biologic sub-type, with incorporation of biomarkers and development of robust diagnostics
- Identify and target mechanisms of drug resistance- optimize treatment of metastatic breast cancer

THANK YOU !!