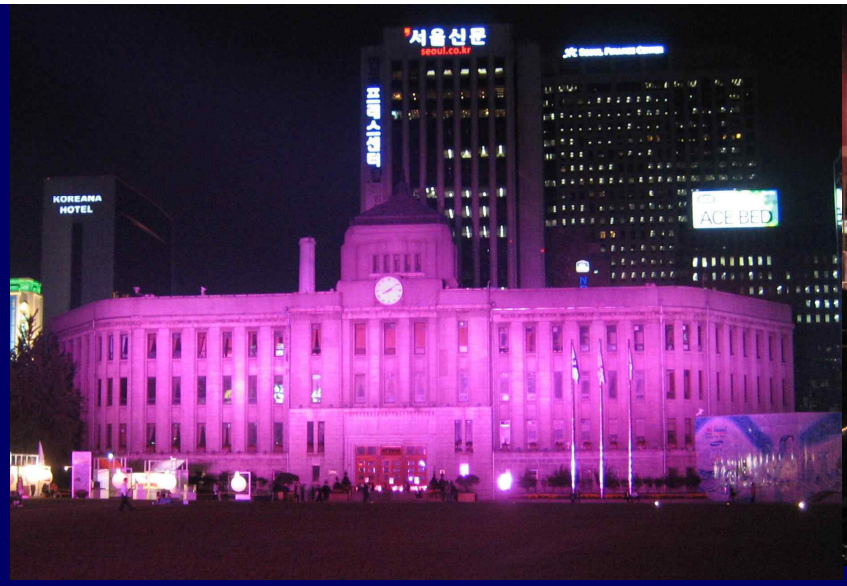
National Cancer Institute



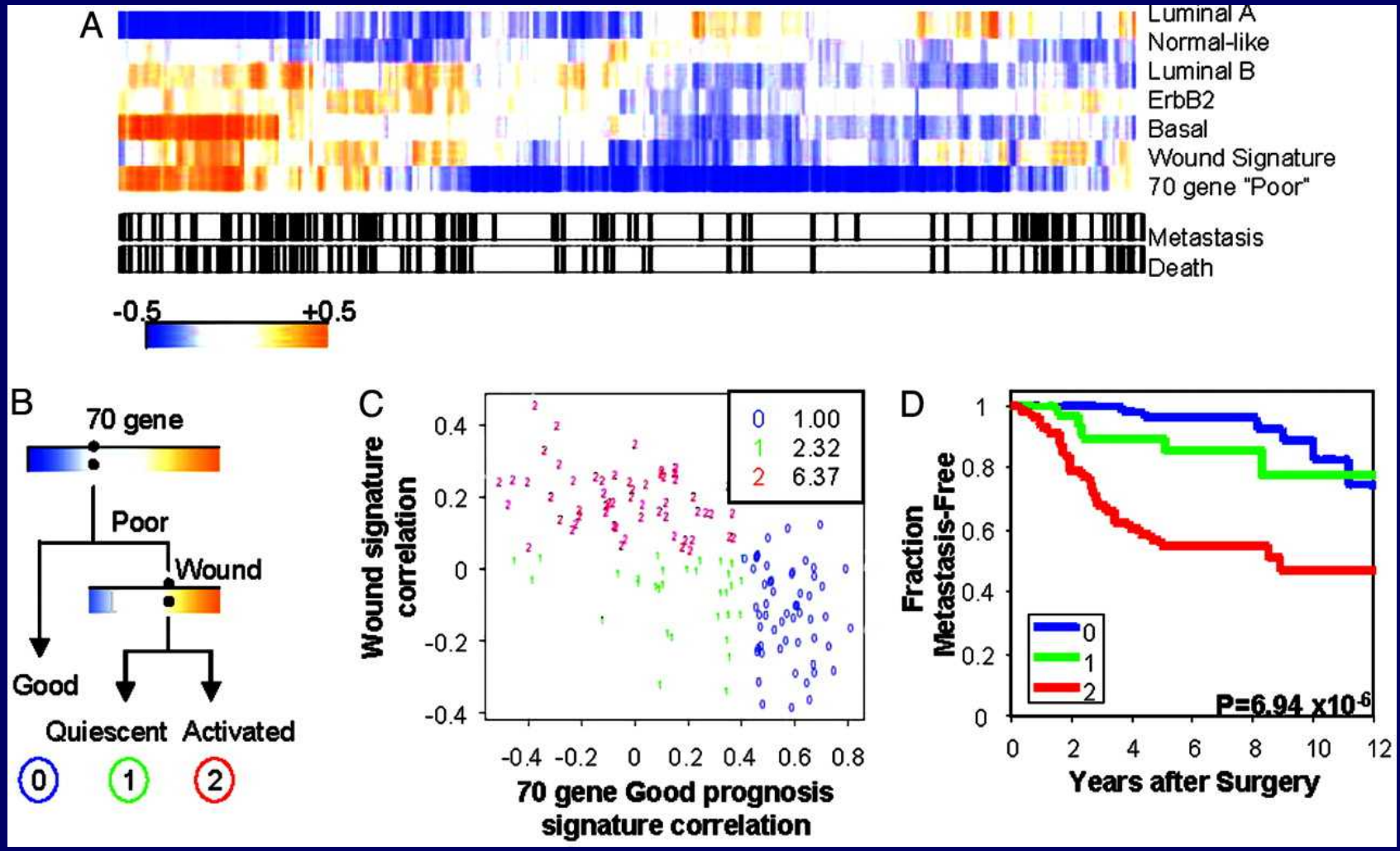
Systemic Therapy Progress 2007-2009

Jo Anne Zujewski, M.D.
Head, Breast Cancer Therapeutics
Clinical Investigations Branch
National Cancer Institute
October 8, 2009

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

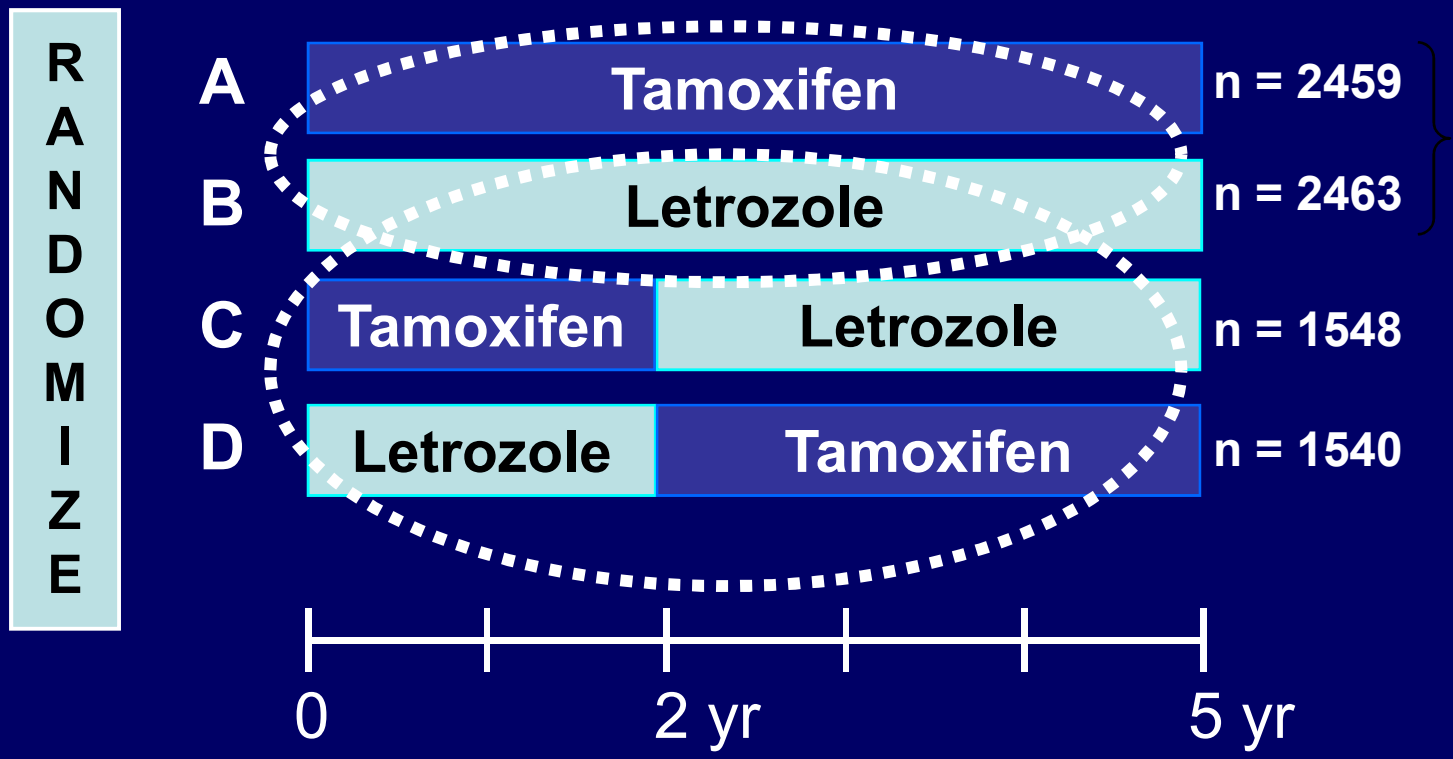
National Institutes of Health

Breast cancer subtypes



PNAS 2005

BIG 1-98: Letrozole and Tamoxifen for the Adjuvant Treatment of Breast Cancer



619 tamoxifen patents crossed over to letrozole after unblinding (mostly years 3-5)

Mouridsen et al. SABCS 2008. Abstract 13.

BIG 1-98: Letrozole monotherapy improves DFS compared with tamoxifen monotherapy

Tamoxifen vs. letrozole (intent-to-treat) median follow-up 76 months

	Tam (n = 2459)	Let (n =2463)	HR	*P* Value
DFS	**565 events**	**509 events**	**0.88**	**.03**
OS	343 events	303 events	0.87	.08

Mouridsen et al. SABCS 2008. Abstract 13.

BIG 1-98: Sequential Treatment Letrozole and Tamoxifen

Sequential treatment: Median follow-up 71 months*

	Let (n=1546)	Let→Tam (n = 1540)	Tam→Let (n = 1548)
DFS	88%	88%; HR 0.96	86%; HR 1.05
OS	–	HR 0.90	HR 1.13

- **Hazard ratios numerically lower with starting with Letrozole**
  - **Differences have not reached significance for any endpoint.**

Mouridsen et al. SABCS 2008. Abstract 13.

BIG 1-98: Breast Cancer Events for Letrozole Versus Sequential Strategies

Breast Cancer Recurrence Events at 5 Years (%)

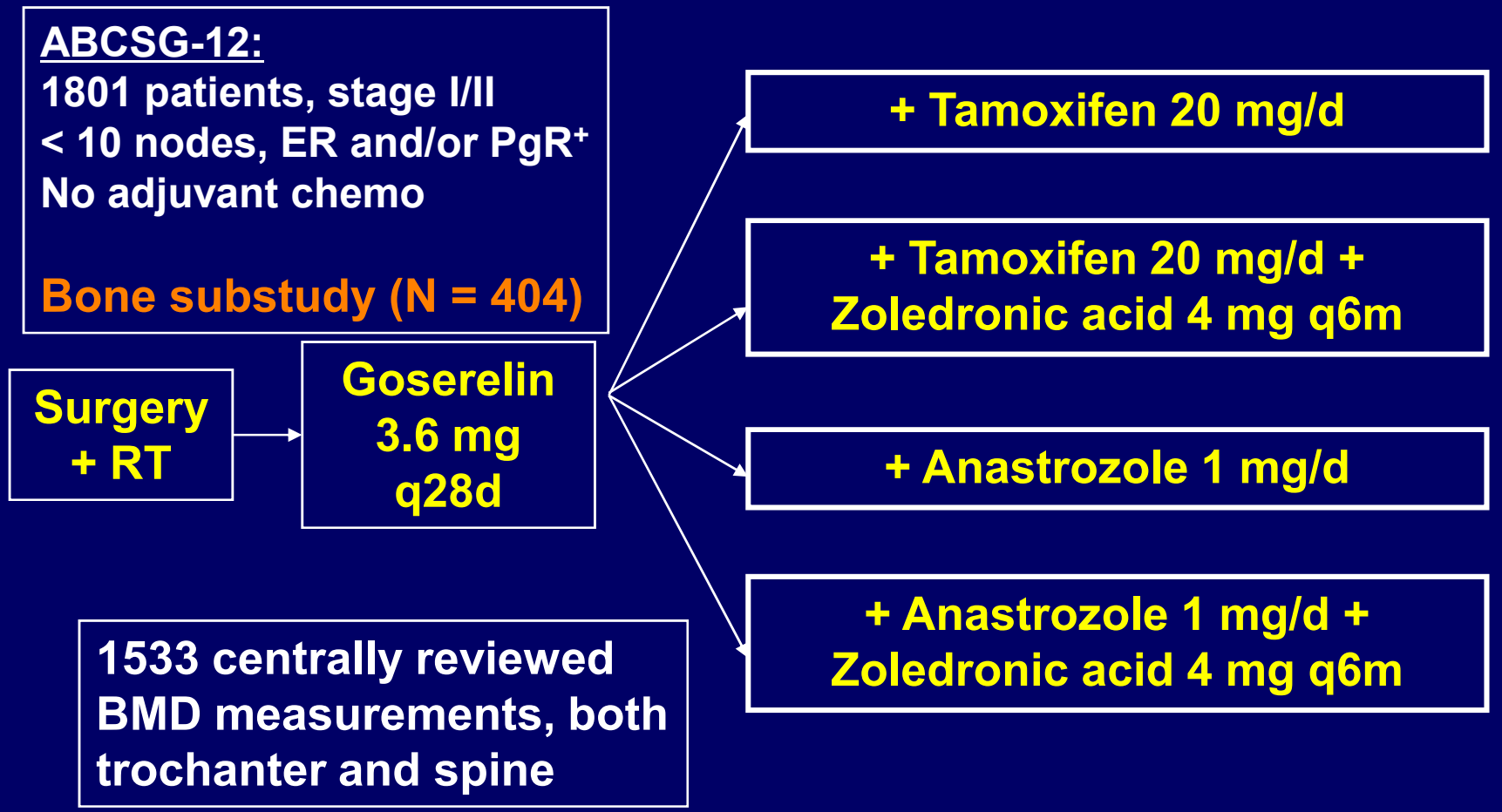
	Let	Let→Tam	Tam→Let
Overall	7.3%	7.3%	9.1%
Node Negative	3.5%	3.9%	4.9%
Node Positive	12.4%	12.5%	14.7%

Mouridsen et al. SABCS 2008. Abstract 13.

BIG-1-98 Summary

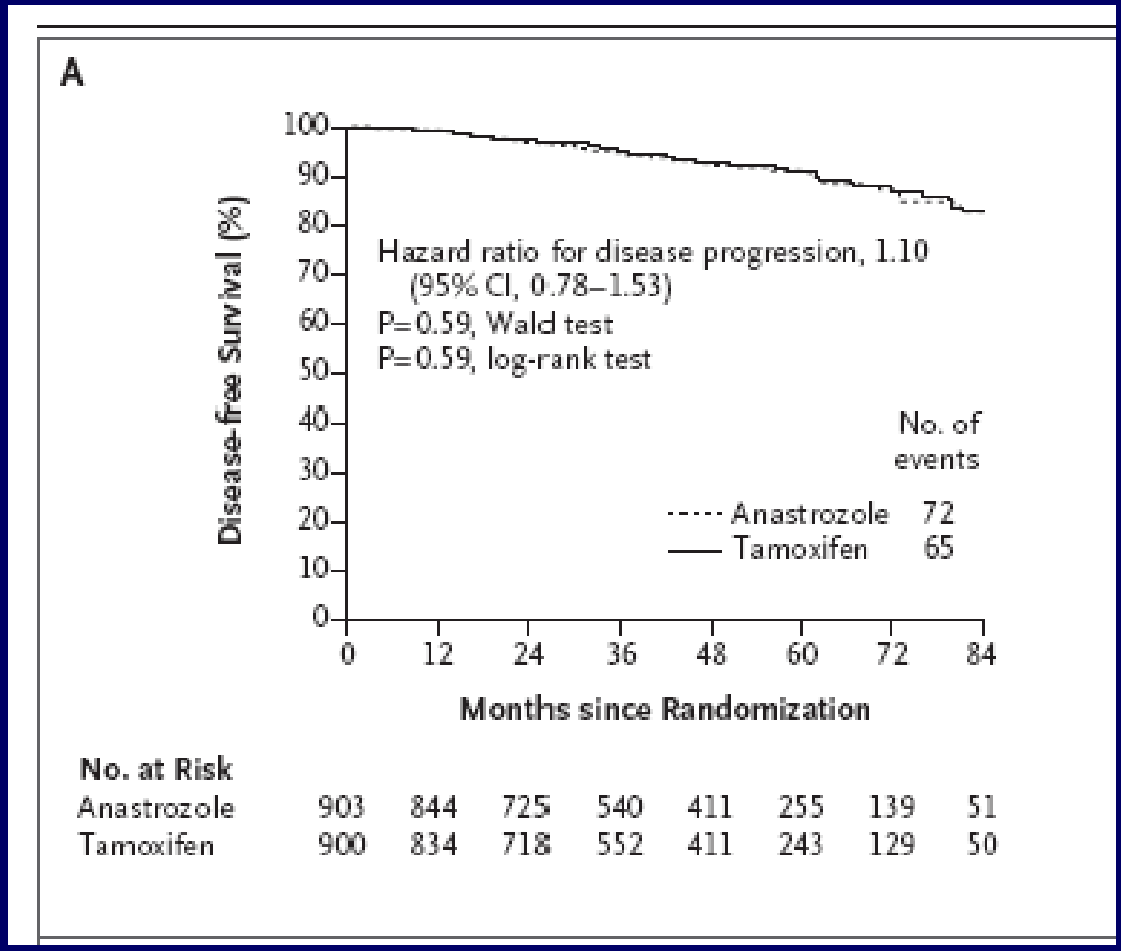
- Initial letrozole indicated, especially in high-risk patients
- Patients can be switched to tamoxifen after 2 years, if needed

Trial ABCSG-12: Endocrine Therapy With or Without Zoledronic Acid



Gnant, SABCS 2007, Abstract 26

ABCSG -12 Disease Free Survival Tamoxifen versus OFS anastrazole



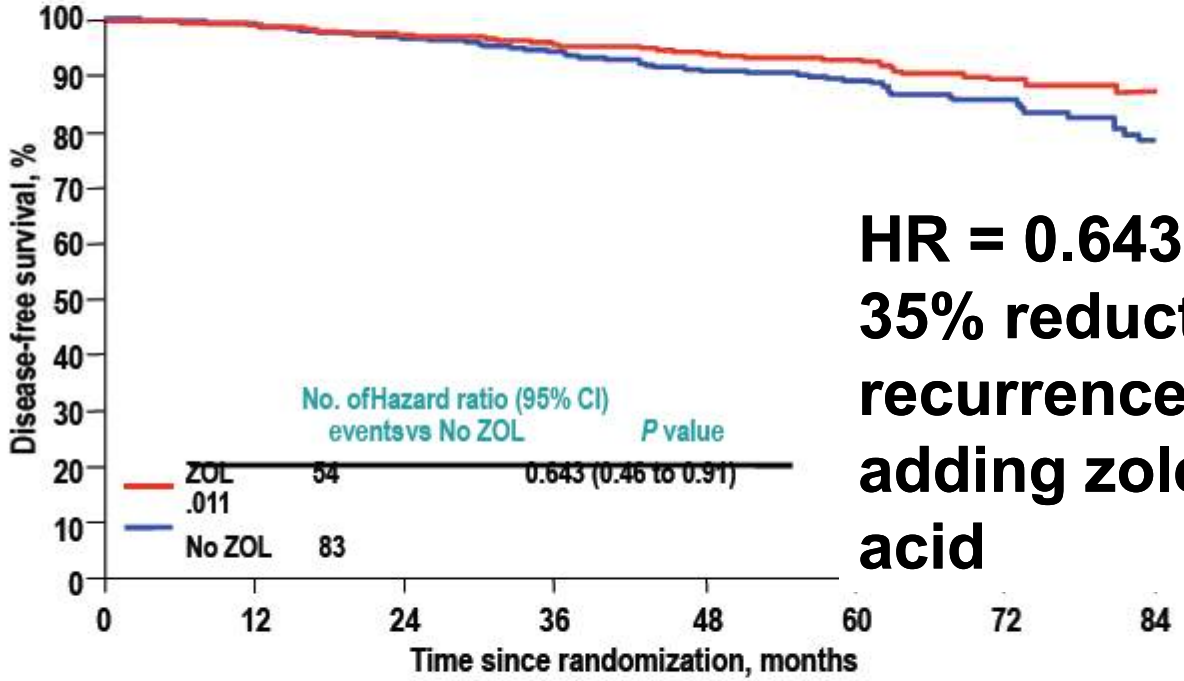
Gnant M, et al NEJM 2009

Cancer and the Bone Microenvironment

Bisphosphonates prevent bone resorption

Primary Endpoint: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



HR = 0.643 (0.46-0.91)
35% reduction in recurrences from adding zoledronic acid

Number at risk

No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

S0307 Intergroup/NSABP: Phase III Comparison of 3 Bisphosphonates as Adjuvant Therapy for Breast Cancer

PIs: J Gralow, A Paterson

- Patients: 5,400 stage I, II, III breast cancer patients receiving "standard" systemic therapy
- Treatment: (3 years)

Clodronate 1,600 mg po qd

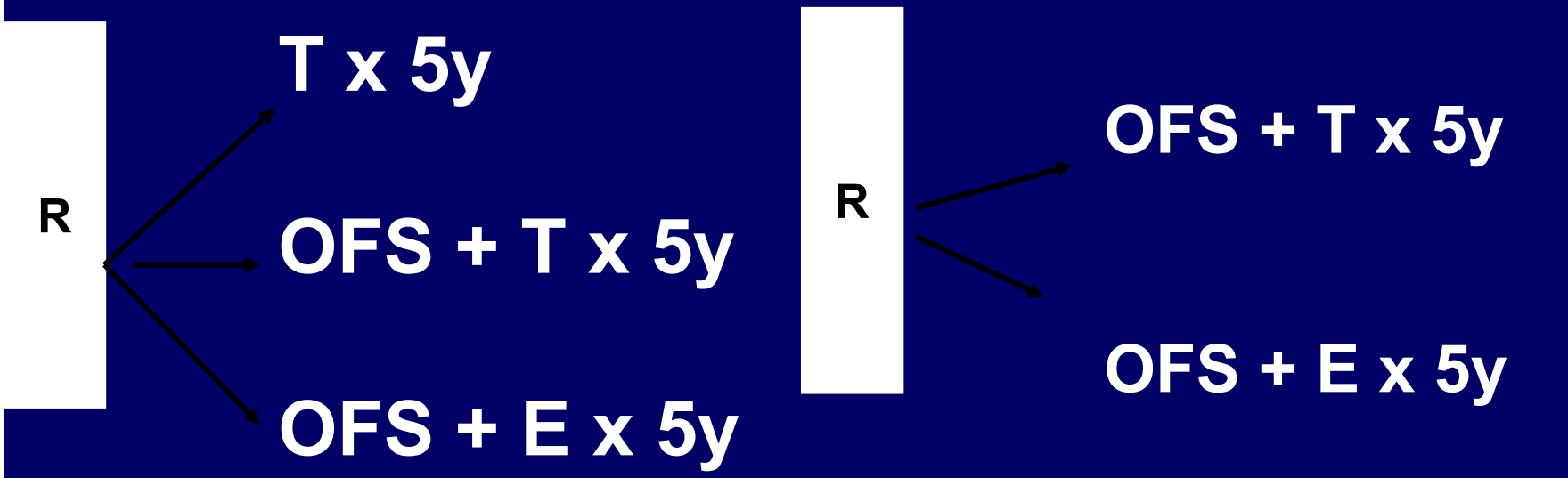
vs.

Ibandronate 50 mg po qd

vs.

Zoledronic acid 4 mg IV q month x 6, followed by q3 month

SOFT and TEXT in pre-menopausal breast cancer



Accrual 31 Jan 09: 2173 / 3000

Original target reached (n=2039)
extension for 600 patients approved

Endocrine therapy 2009

- Aromatase inhibitors demonstrate a modest improvement in DFS
  - Start with an AI in postmenopausal women unless contraindications
- Not yet clear
  - Duration of endocrine treatment
  - Which AI?
  - Role of OFS
  - Tailored endocrine therapy
- Promising early data with zoledronate in improving DFS

NSABP B-30: Combinations of doxorubicin, cyclophosphamide and docetaxel for early-stage node-positive breast cancer

Stage I, II or IIIA BC
N0-1, M0
HR+ or HR-
No metastatic disease

Stratification:
Nodes
Radiotherapy
Surgery
Tamoxifen

Randomize

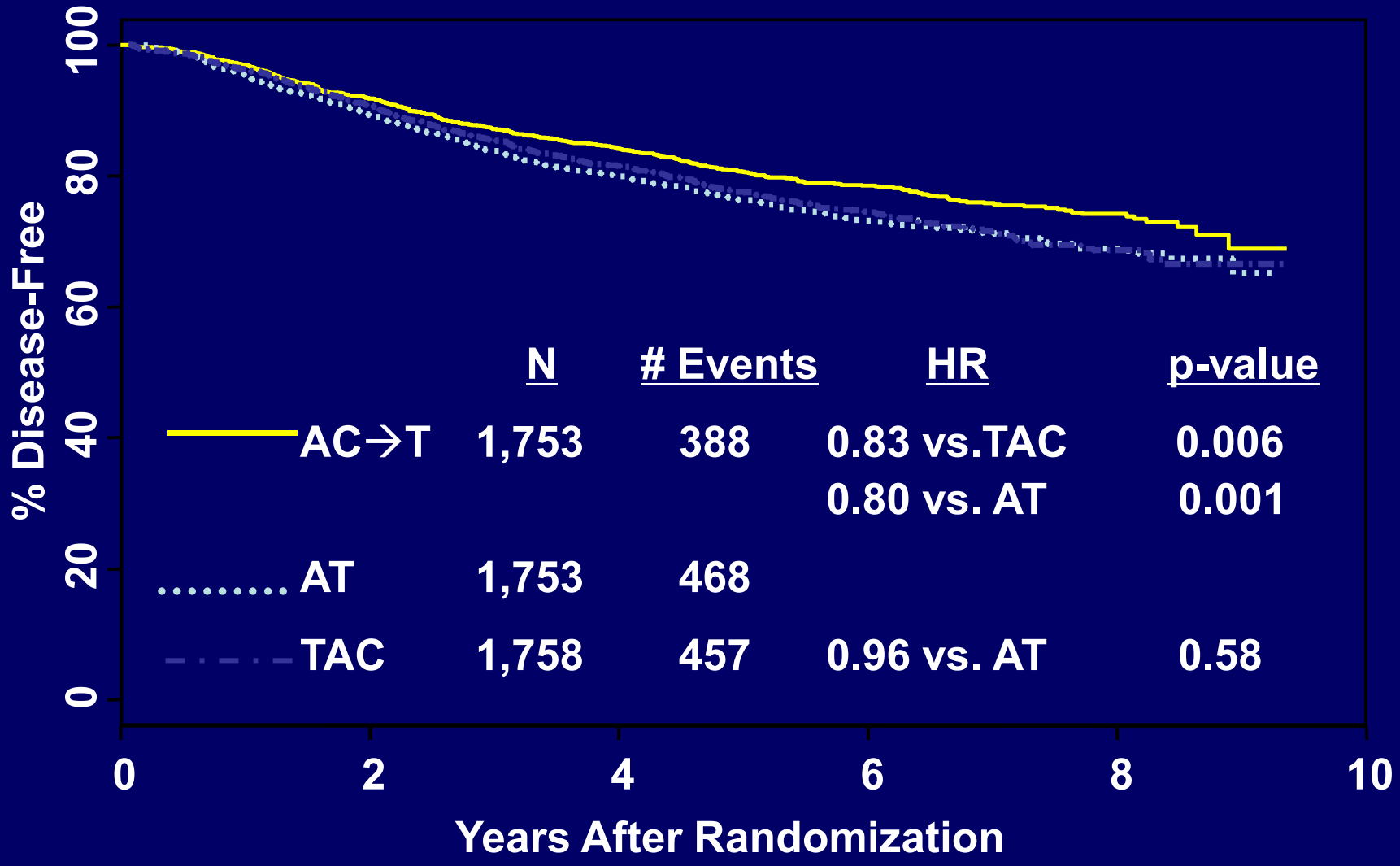
N=5351

- AC→T: A (60 mg/m2) + C (600 mg/m2) q3w x 4 → T (100 mg/m2) q3w x 4
- AT: A (50 mg/m2) + T (75 mg/m22) q3w x 4
- TAC: A (50 mg/m2) + C (500 mg/m2) + T (75 mg/m2) q3w x 4

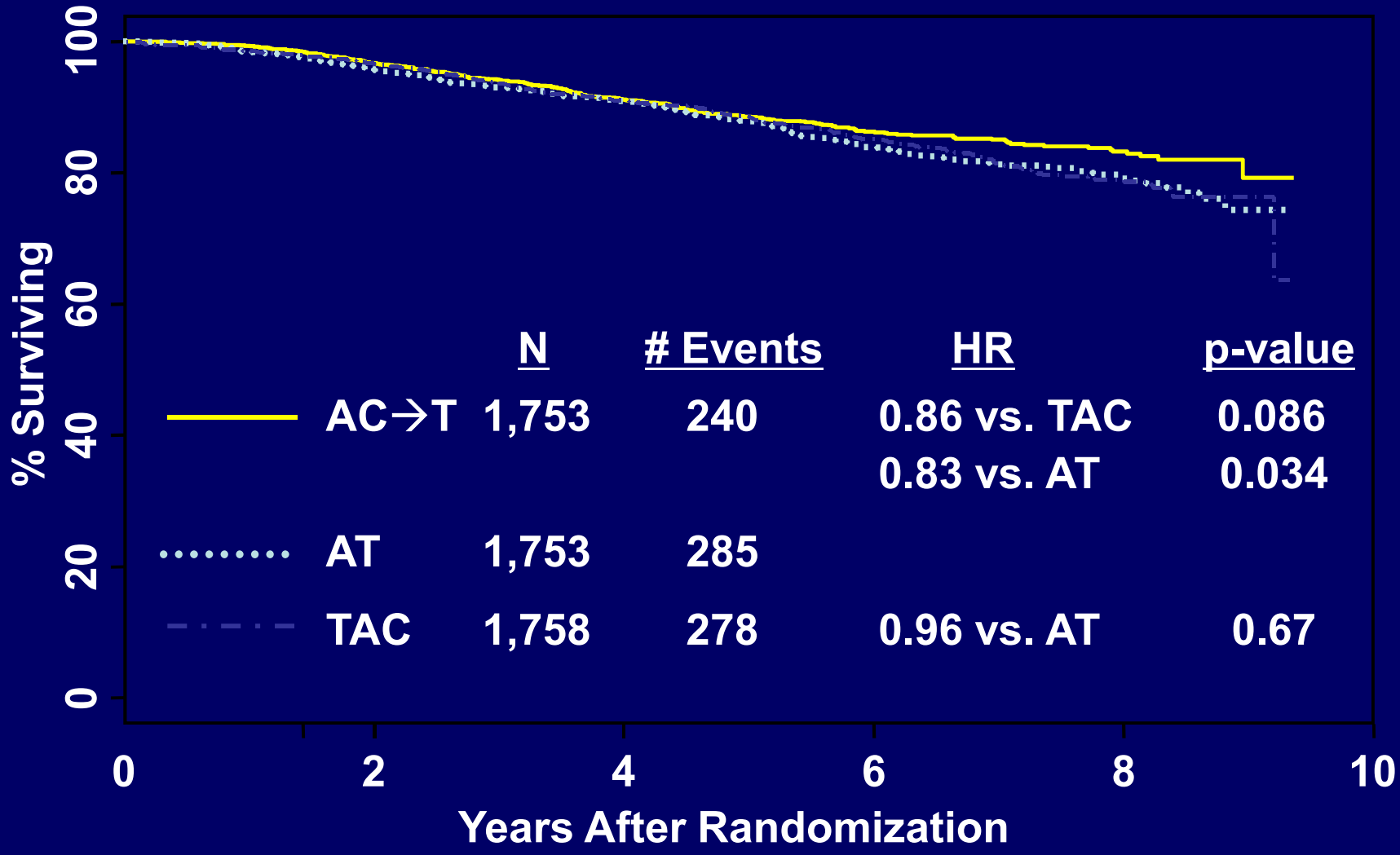
Primary aims:
- Concurrent vs. sequential: effect on DFS, OS
- Utility of cyclophosphamide

Swain, SABCS 2008, Abstract 75

NSABP B-30 Disease-Free Survival

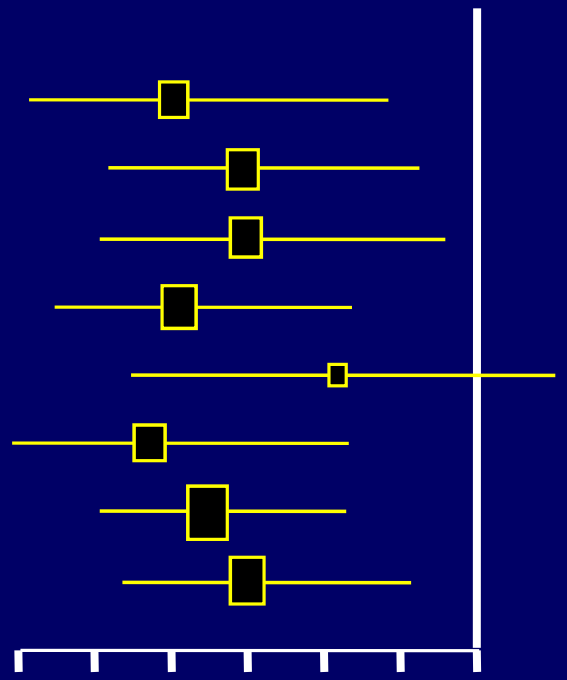


NSABP B-30 Overall Survival



NSABP B-30
Amenorrhea Data (DFS) by Subgroups (Adjusted by ER, LN, Tumor Size) HR with 95% CI

Factor	HR
AC → T	0.60
AT	0.69
TAC	0.69
<40 years	0.61
40-44	0.81
>44 years	0.57
Hormonal Tx	0.64
No Hormonal Tx	0.70



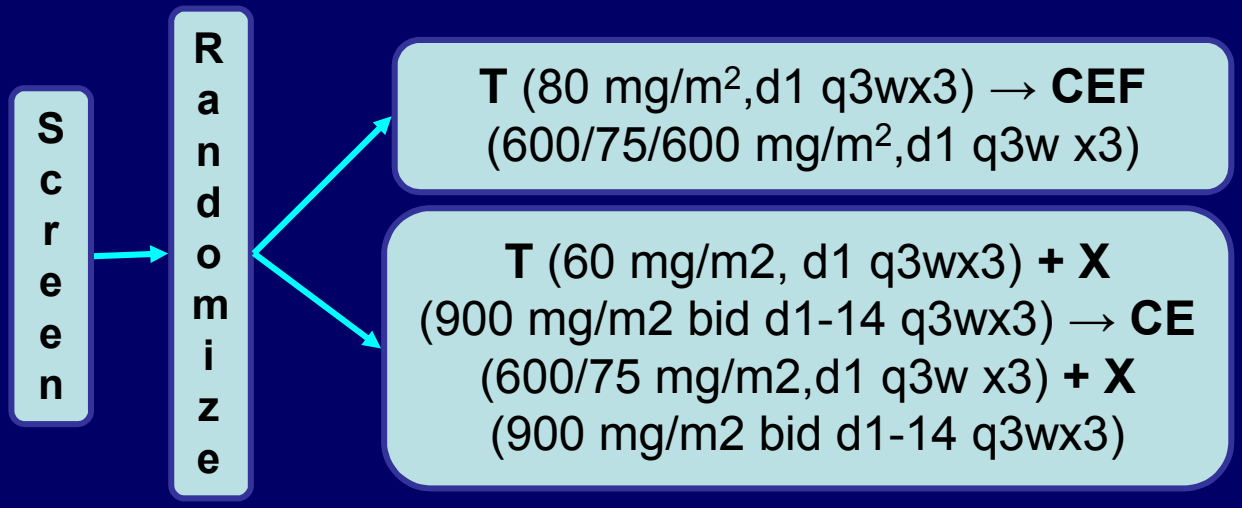
NSABP B-30: Summary

- AC→T superior to TAC and AT for DFS
- AC→T superior to AT, and marginally better than TAC for OS
- No treatment interactions between outcome and nodal, ER or menopausal status
- Significantly improved OS and DFS across all arms in patients with amenorrhea ≥ 6 months

Swain, SABCS 2008, Abstract 75

FinXX trial: Capecitabine added to a taxane-anthracycline

Capecitabine /docetaxel improves survival in MBC



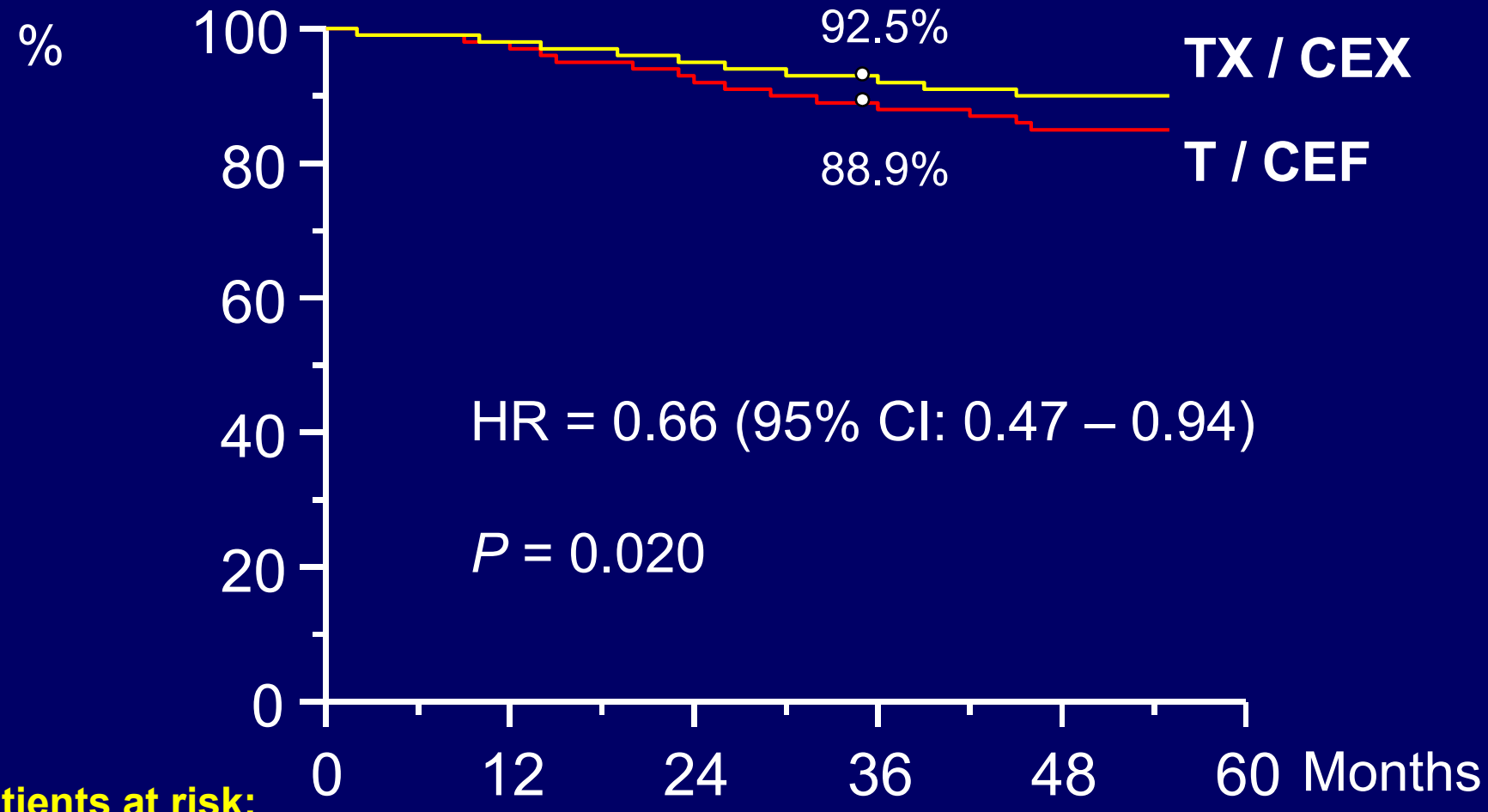
Primary:
- **RFS**

Secondary:
- **OS, safety**

T: Docetaxel; X:Capecitabine

Joensuu et al. SABCS 2008, Abstract 82

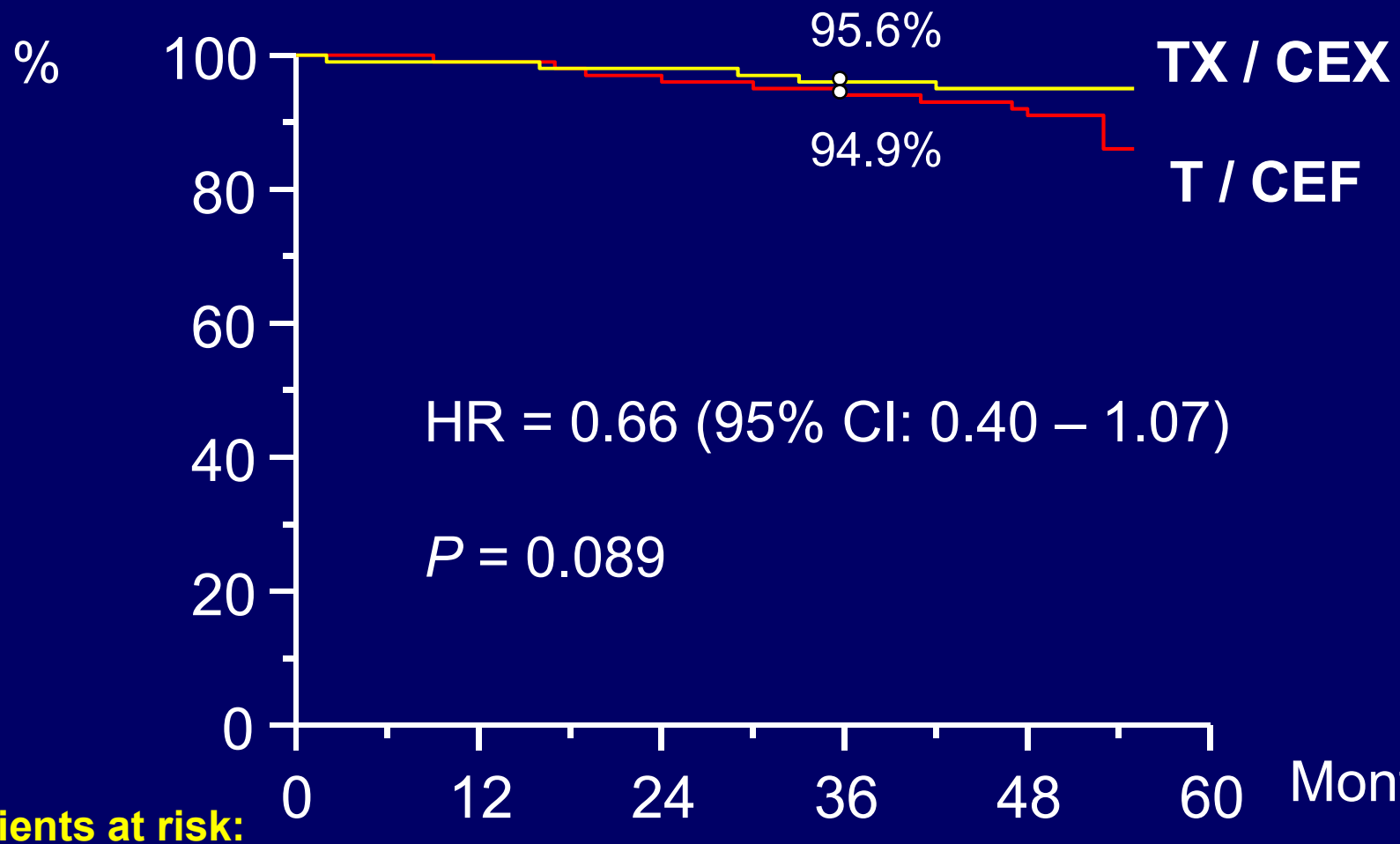
FinXX Recurrence-free survival



Patients at risk:

T + CEF	745	727	563	336	94	0
TX + CEX	751	739	577	337	98	0

FinXX Overall survival



Patients at risk:						
T + CEF	745	738	589	362	105	0
TX + CEX	751	745	595	352	103	0

Summary FinXX: Capecitabine added to a taxane-anthracycline

- TX/CEX improves RFS over T/CEF
  - Despite lower docetaxel dose
  - 34% risk reduction
- TX/CEX: higher rate of treatment discontinuation (25% over 6 cycles vs. 4% for T/CEF)

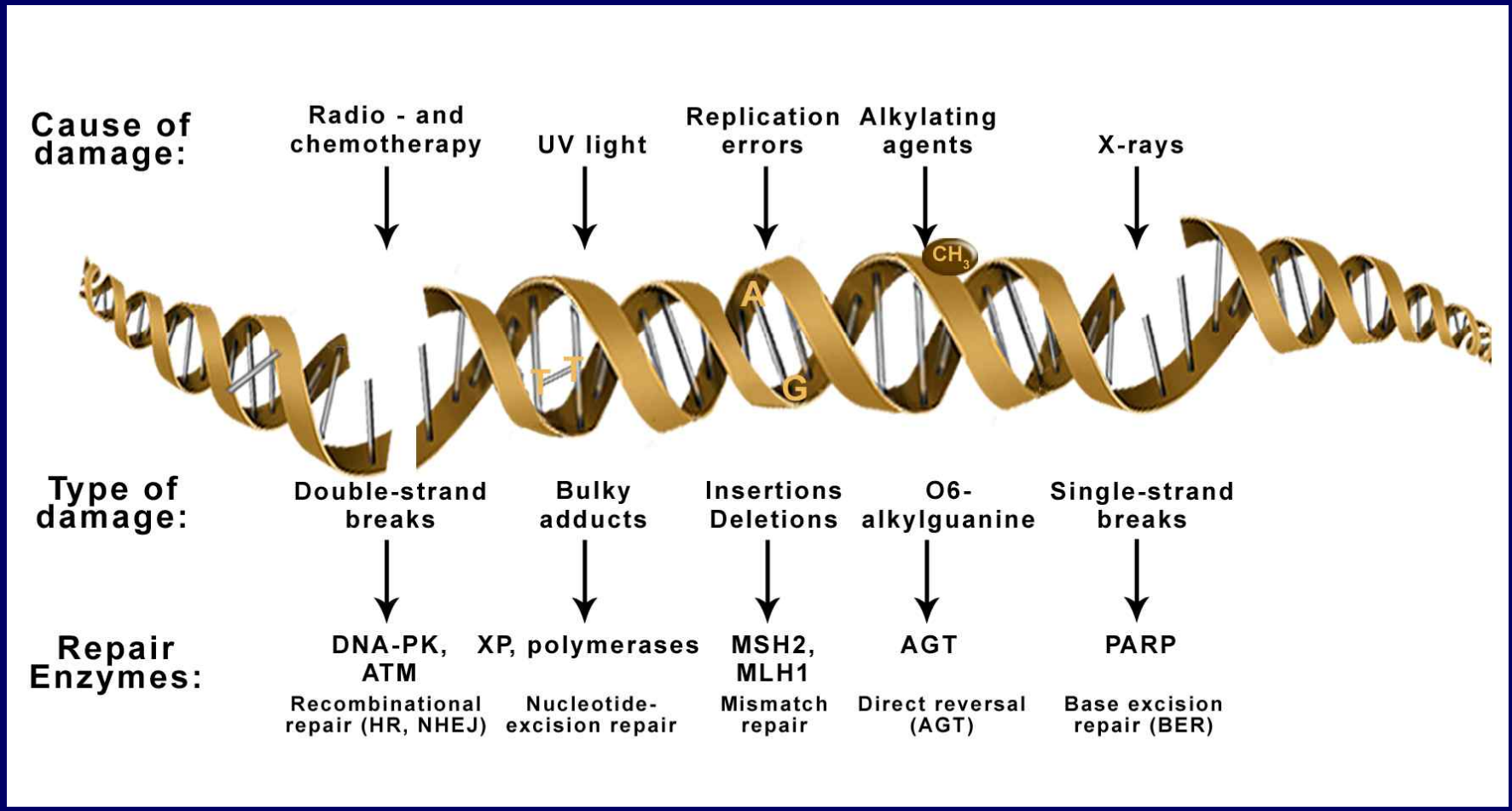
Joensuu et al. SABCS 2008, Abstract 82

Efficacy of BSI-201, a PARP Inhibitor, in Combination with Gemcitabine/Carboplatin in Triple Negative Metastatic Breast Cancer: Results of a Phase II Study

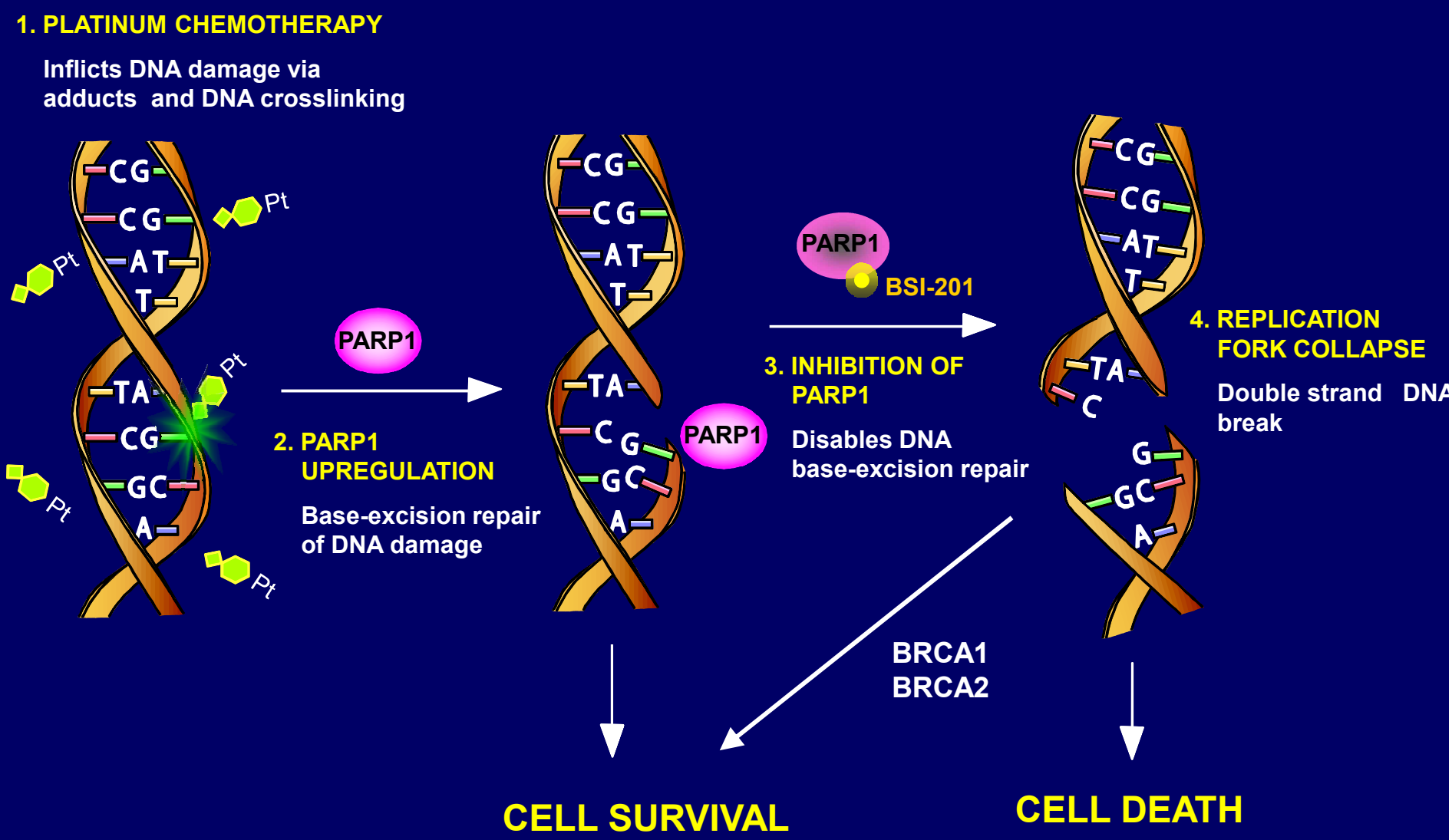
Joyce O'Shaughnessy,[1,2,4] Cynthia Osborne,[1,2,4] John Pippen,[1,2,4], Debra Patt,[3,4]
Christine Rocha,[5] Valeria Ossovskaya,[5] Barry M. Sherman,[5] Charles Bradley [5]

[1]Baylor Sammons Cancer Center, [2]Texas Oncology, Dallas, TX;
[3]Texas Oncology Cancer Center, Austin, Texas; [4]US Oncology, Dallas, TX;
[5]BiPar Sciences, Inc., Brisbane, CA

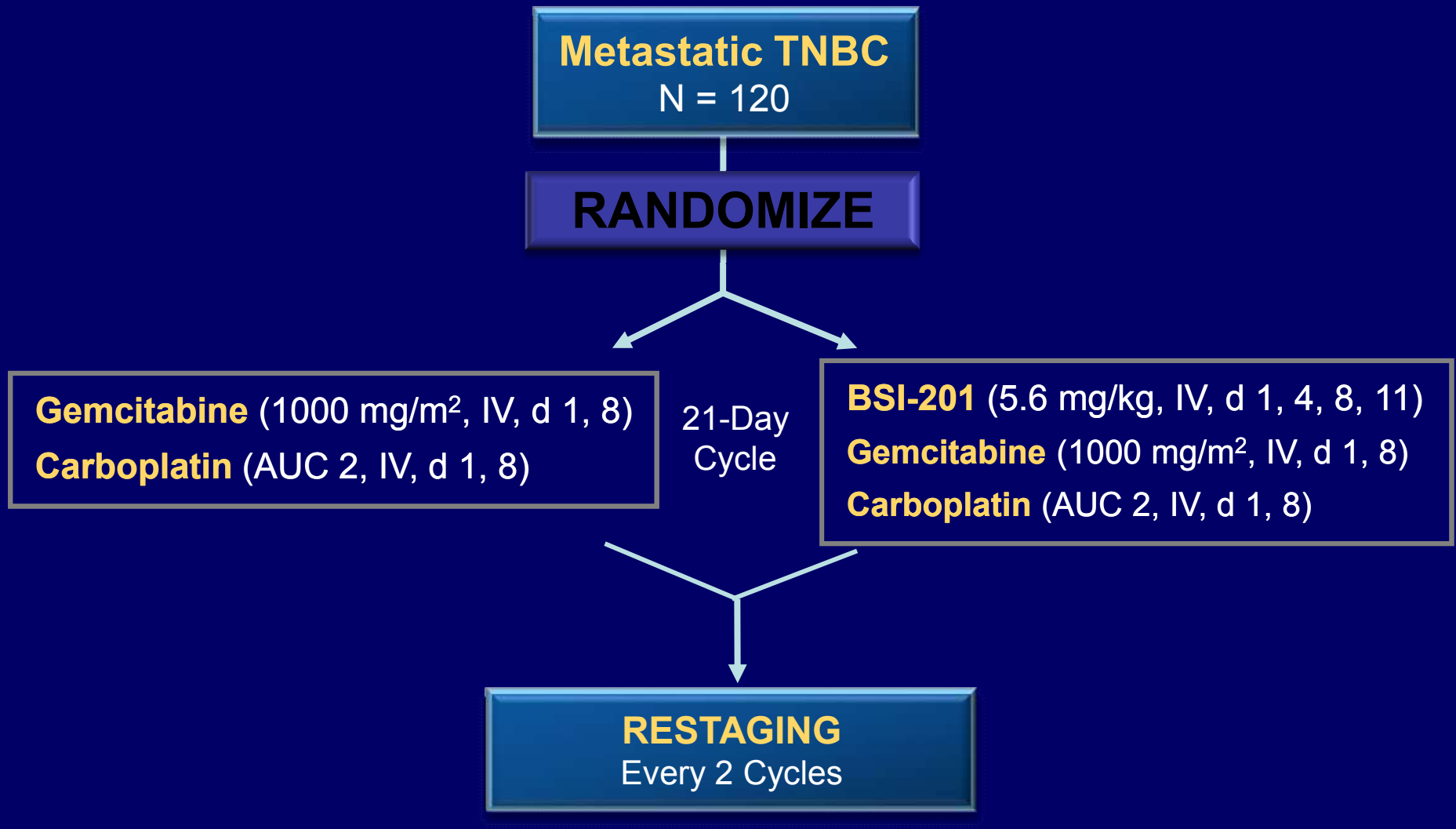
DNA damage and repair



PARP Inhibitor Mechanism of Action

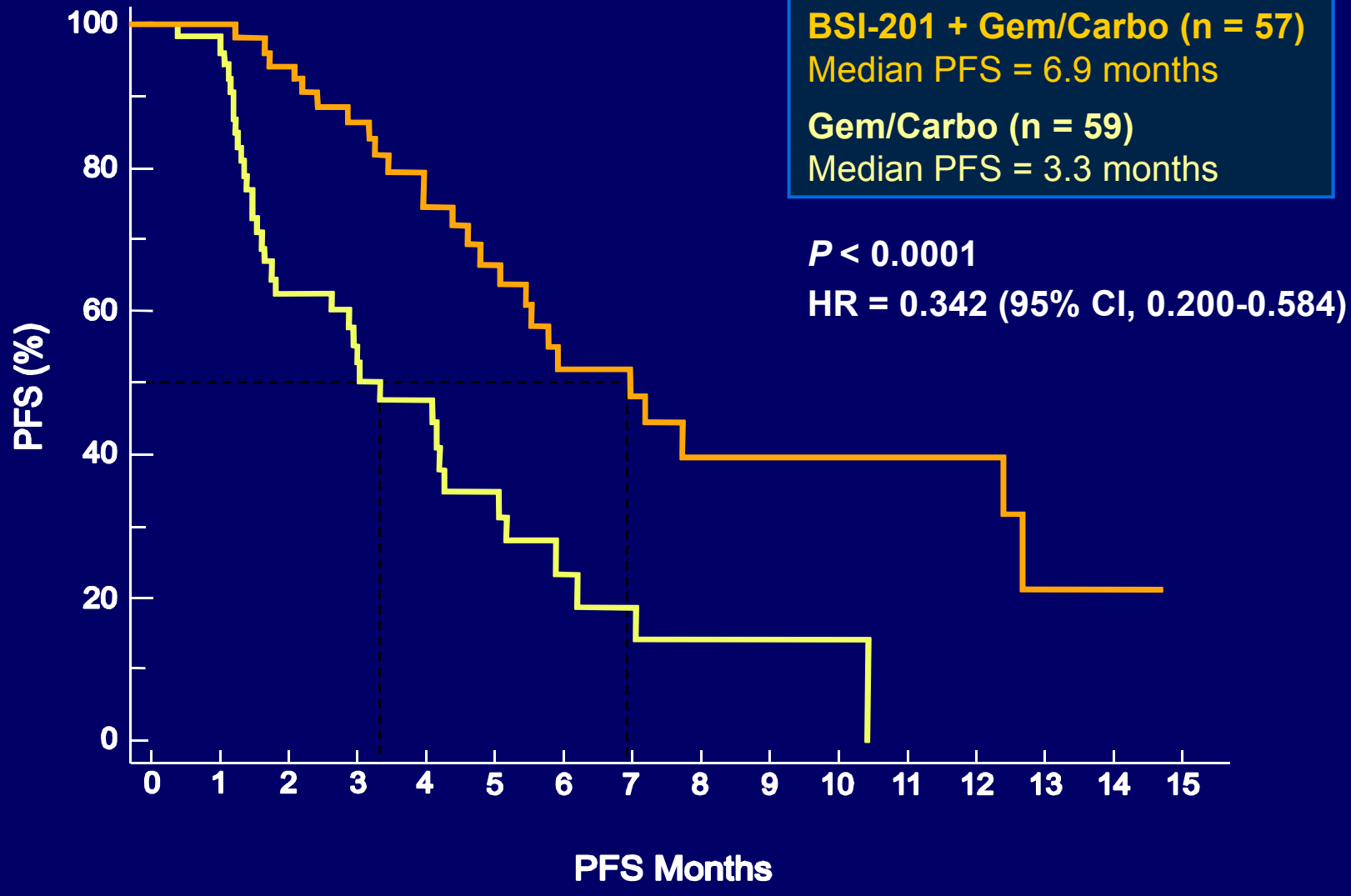


Phase II TNBC Study: Treatment Schema



* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

Progression-Free Survival



BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 months

Gem/Carbo (n = 59)
Median PFS = 3.3 months

P **< 0.0001**

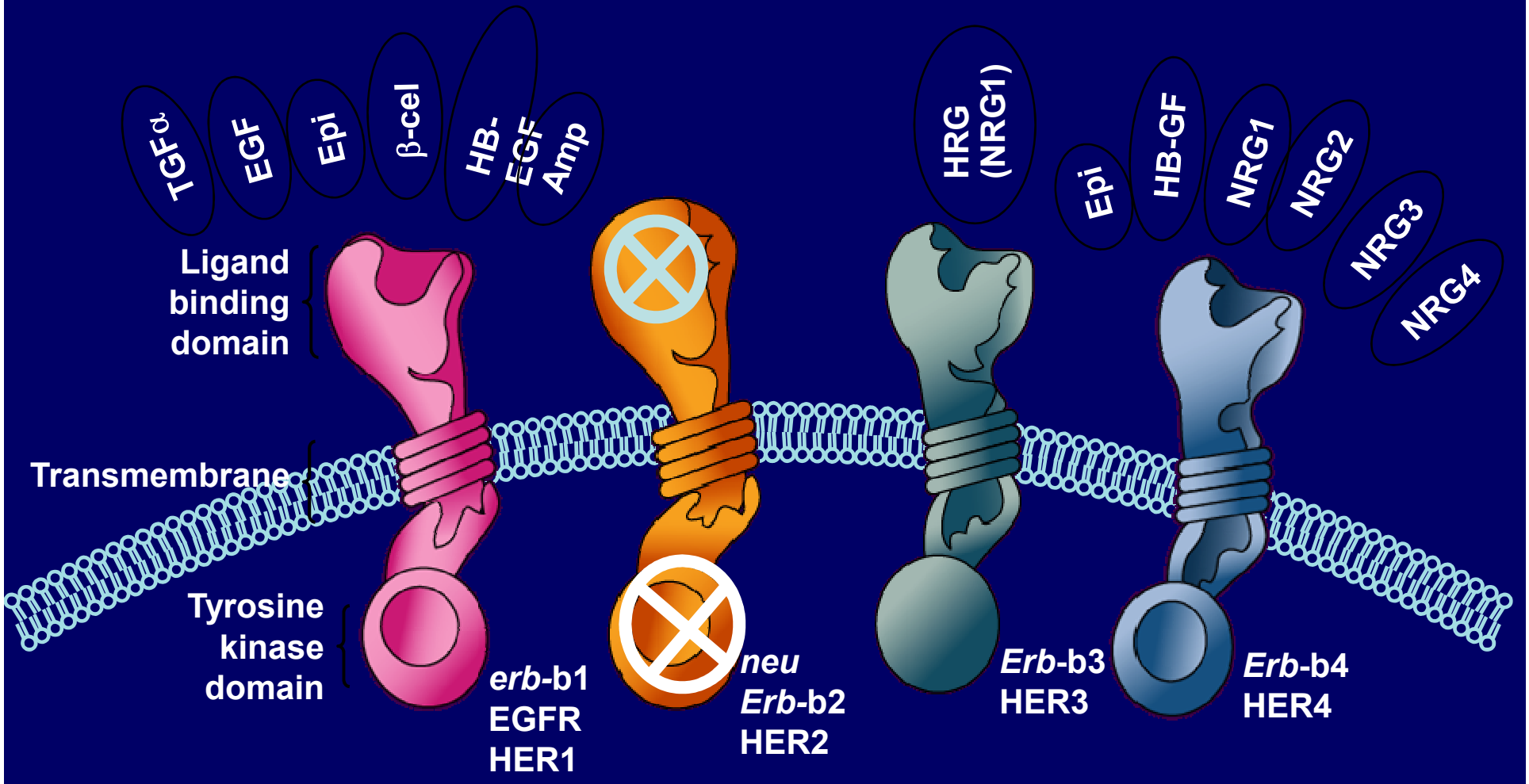
HR = 0.342 (95% CI, 0.200-0.584)

Conclusions

- PARP1 was upregulated in most evaluated TNBC patients
- BSI-201 + gemcitabine/carboplatin was well tolerated and did not potentiate chemotherapy-related toxicities
- BSI-201 improved patients' clinical outcomes
  - Clinical Benefit Rate (62% vs. 21%; $P = 0.0002$)
  - ORR (48% vs. 16%; $P = 0.002$)
  - Median PFS (6.9 months vs. 3.3 months; $P < 0.0001$)
  - Median OS (9.2 months vs. 5.7 months; $P = 0.0005$)

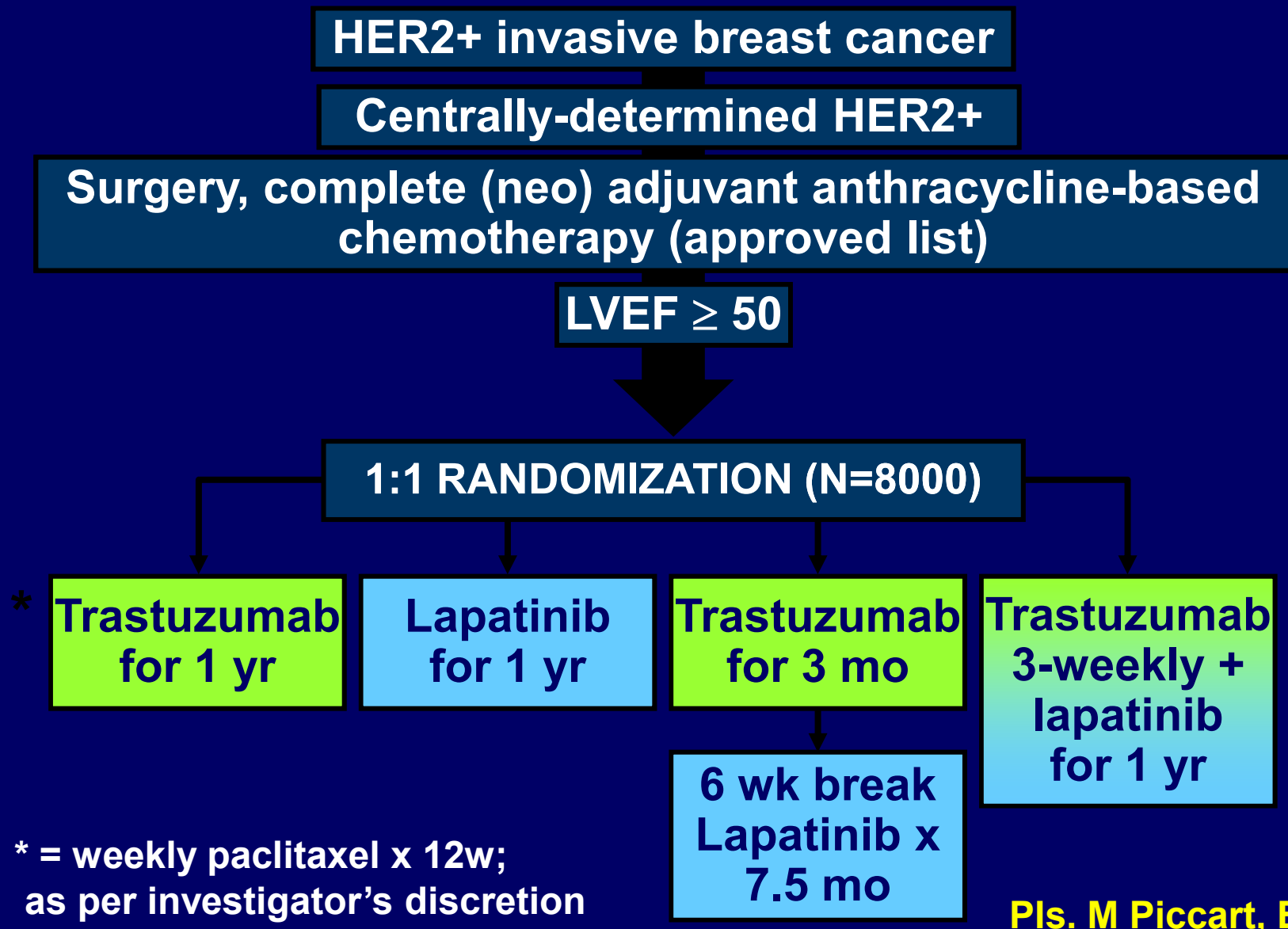
Promising safety and efficacy data from this Phase II study justify further investigation of BSI-201 in a Phase III study

The EGFR/HER Family



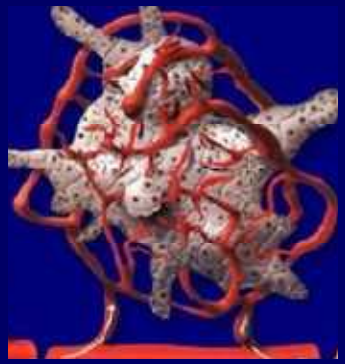
Mendelsohn and Baselga. *Oncogene*. 2000;19:6550.
Olayioye et al. *EMBO J.* 2000;19:3159.
Prigent and Lemoine. *Prog Growth Factor Res.* 1992;4:1.
Harari and Yarden. *Oncogene*. 2000;19:6102.
Earp et al. *Breast Cancer Res Treat.* 1995;35:115.

ALTTO Study Design



* = weekly paclitaxel x 12w;
as per investigator's discretion

PIs. M Piccart, EA Perez



BETH Trial

Node-Positive or High Risk Node-Negative Breast Cancer HER2 Positive by Central Testing

STRATIFICATION

- Number of positive Nodes (0, 1-3 4+)
- Hormone Receptor Status (+/-)

Chemotherapy* q3wks x 6 + Trastuzumab x 1 yr

Chemotherapy* q3wks x 6 + Trastuzumab x 1 yr + Bevacizumab x 1 yr

*CIRG/NSABP/Investigators - Docetaxel/Carbo q3wk x 6

*Independent Investigators - Docetaxel q3wk x 3 -> FEC-90 x 3

(Targeted therapy held during FEC-90)

Thank you !!