Treatment Strategies for Early Stage Breast Cancer: Past, Present, and Future

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The Plan

- A brief look back
- The progress we have made, and state of the science today
- A look into the future

Breast Cancer: circa 1990 in the U.S.

- 150,000 cases and 44,300 deaths
- Seen as single monolithic disease
- Most cancers presented as lump/mass
- Extensive surgery often performed and resulted in psychological and physical distress
- Adjuvant chemotherapy and hormonal therapy were recent additions to treatment approach

Progress Over the Past 25 Years
A Few Comments About Local Therapy

- Less extensive surgery to breast
  - Widespread acceptance of conservative surgery and radiation, though still underutilized
  - Less extensive axillary surgery – in patients with and without axillary involvement
- Reduction in late radiation toxicity and more convenient fractionation schedules
- More rational use of radiation – with appropriate increase and reduction in use in selected patients
- Improvement in reconstructive surgery
- Greater individualization based on stage, subytpe, and patient preferences

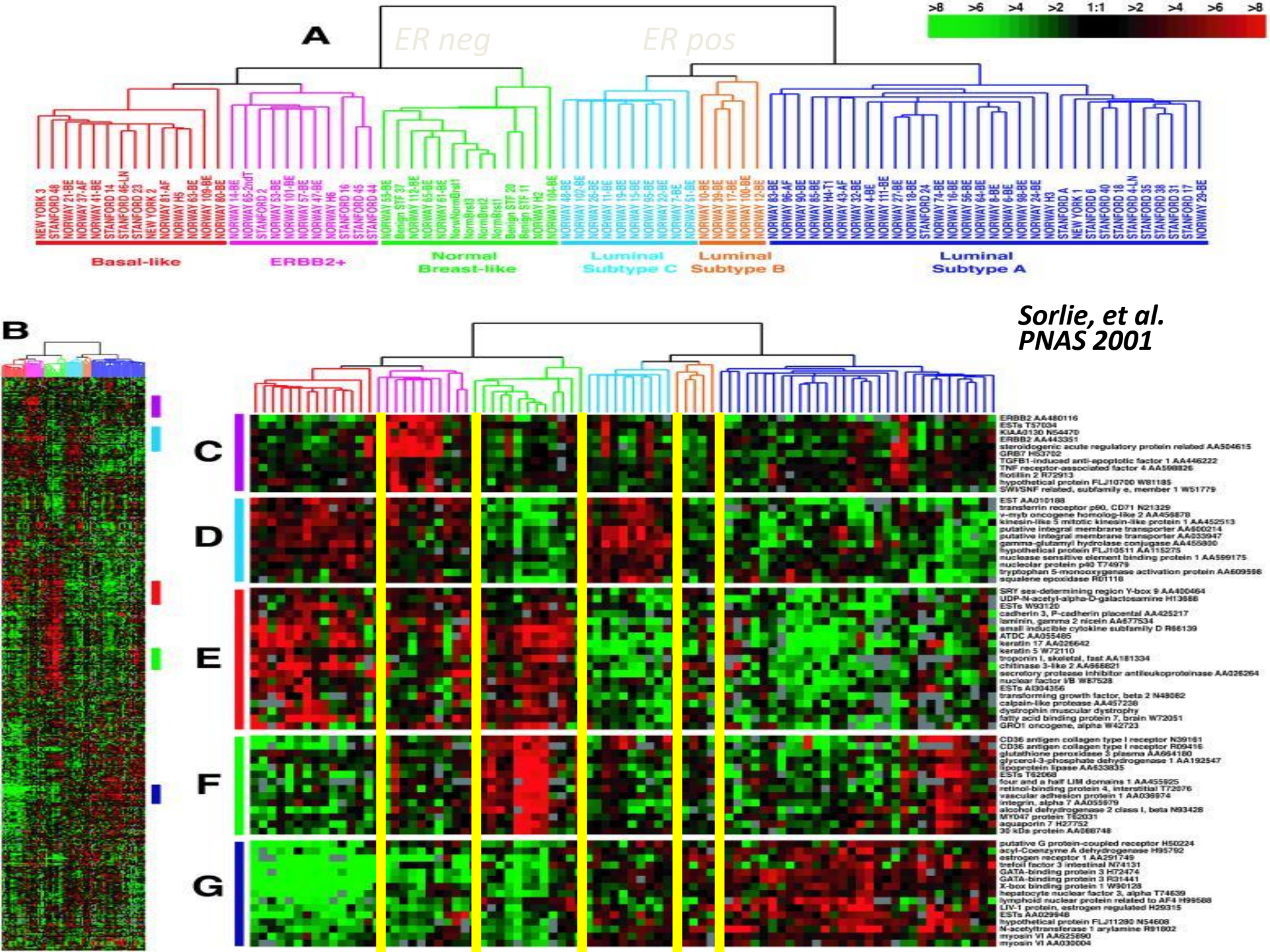
NCI Consensus Conference: 2001
Little Variation in Treatment Among Patients

- All women with tumors > 1 cm with or without nodal involvement should receive adjuvant chemotherapy
- As a result, vast majority of patients were treated with chemotherapy, often with considerable toxicity
- Only endocrine treatment was tamoxifen which was added to all patients with ER+ tumors
- There was no adjuvant anti-HER2 therapy

Three Major Changes That Have Changed The Approach to Systemic Therapy

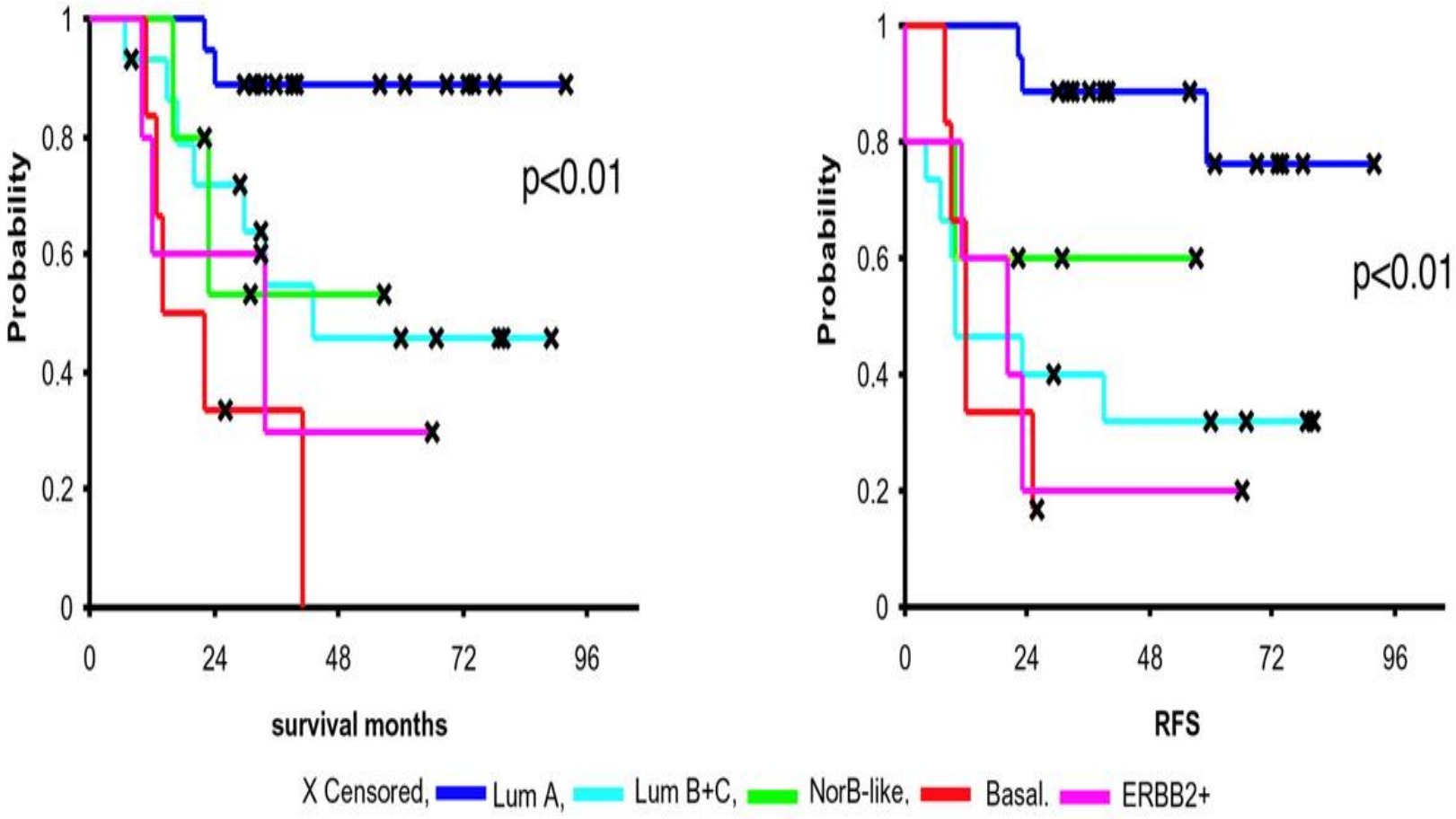
- Understanding of heterogeneity across breast cancer – prognosis varies by subtype
- Recognition that benefits of treatment track with subtype
- Development of targeted therapeutics, particularly for HER2+ disease

HETEROGENEITY



Sorlie, et al. PNAS 2001

Overall and Relapse Free Survival by Tumor Types Defined with Gene Expression Patterns

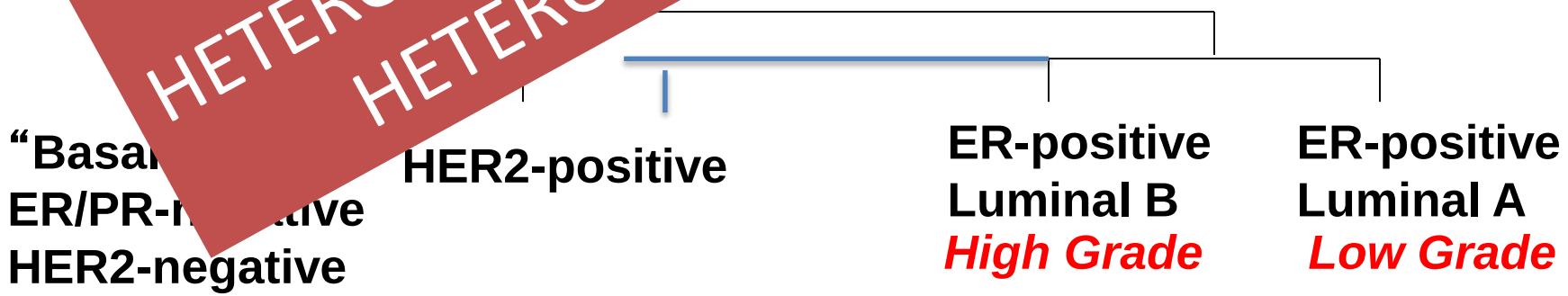


Sorlie, et al. PNAS 2001

Breast Cancer is a Family of Diseases

- Convergence of clinical and genomic data
- Still uncertain how many members of
- At a minimum:
  - HER-2 +
    - HER-2 enriched
    - Luminal
  - Basal-like or
    - Sev
  - L
    - minal A)

WE WILL RETURN TO THE CONCEPT OF HETEROGENEITY LATER IN THE TALK, THAT IS HETEROGENITY WITHIN SUBTYPES

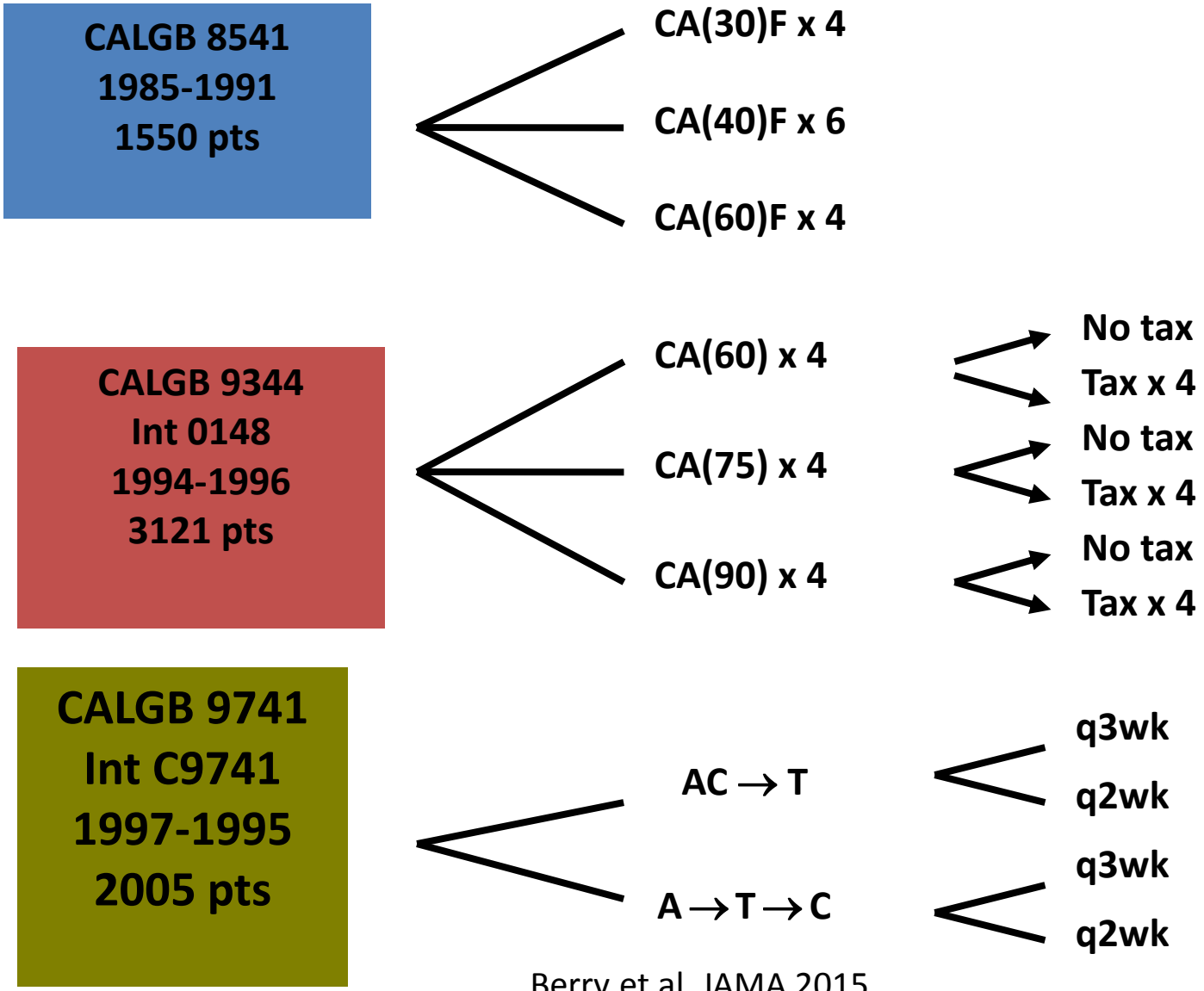


Reduction in Breast Cancer Recurrence from Chemotherapy by Age and Receptor Status

Patient Population	#	% Node Positive	Absolute Gain
< 50, ER-poor	1757	20%	13.2% p<0.00001
< 50, ER+ tamoxifen	2254	34%	7.6% p<0.00001
50-69 ER- poor	4071	67%	9.6% p<0.00001
50-69, ER+ tamoxifen	11,333	73%	4.9% p<0.00001

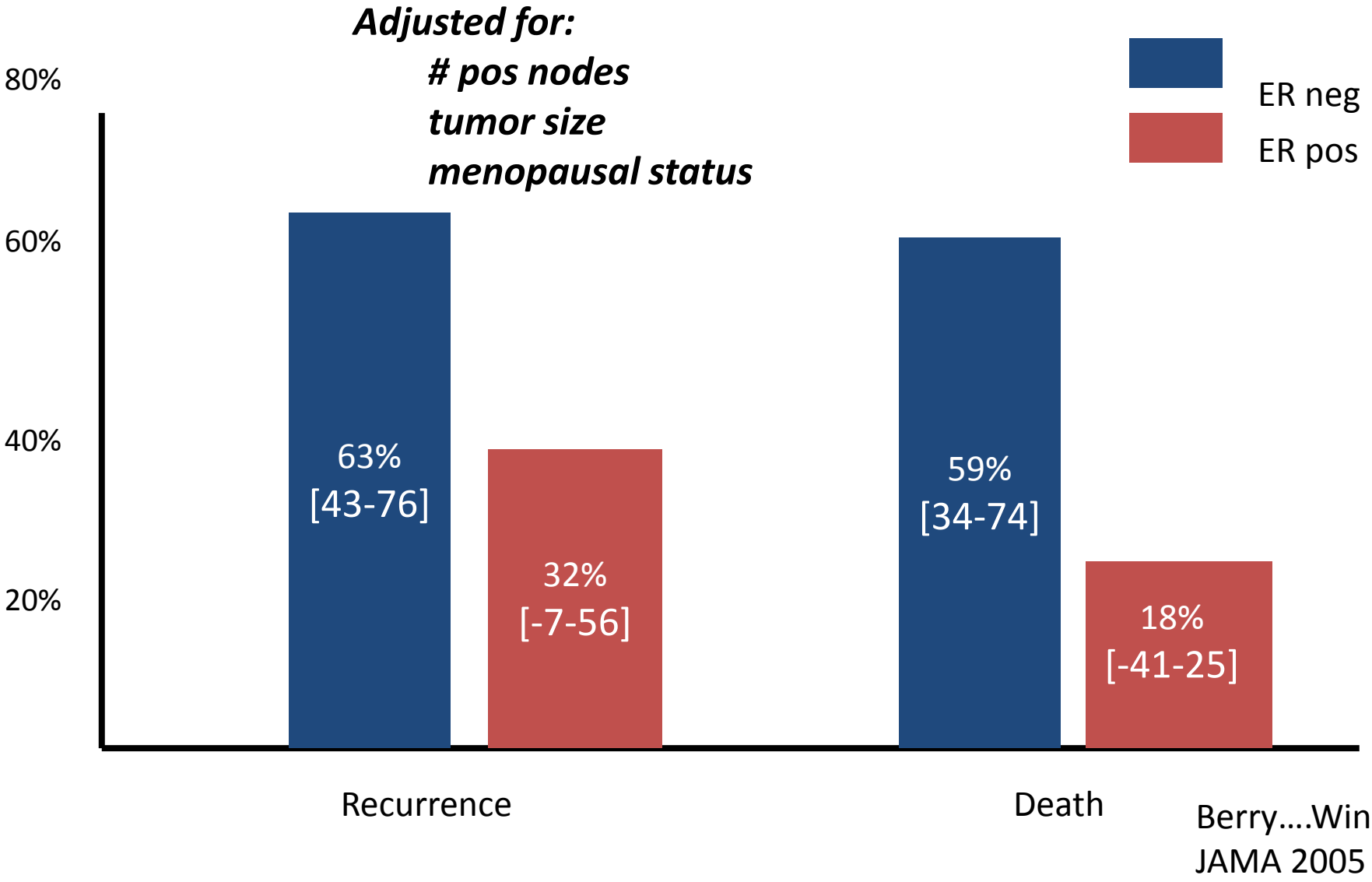
EBCTCG, Lancet 2005

Impact of ER Status and on Benefits of More Effective Chemotherapy



Berry et al, JAMA 2015

Reduction in Hazards
(Lower Dose CAF→Dose Dense AC-T)



Berry….Winer;
JAMA 2005

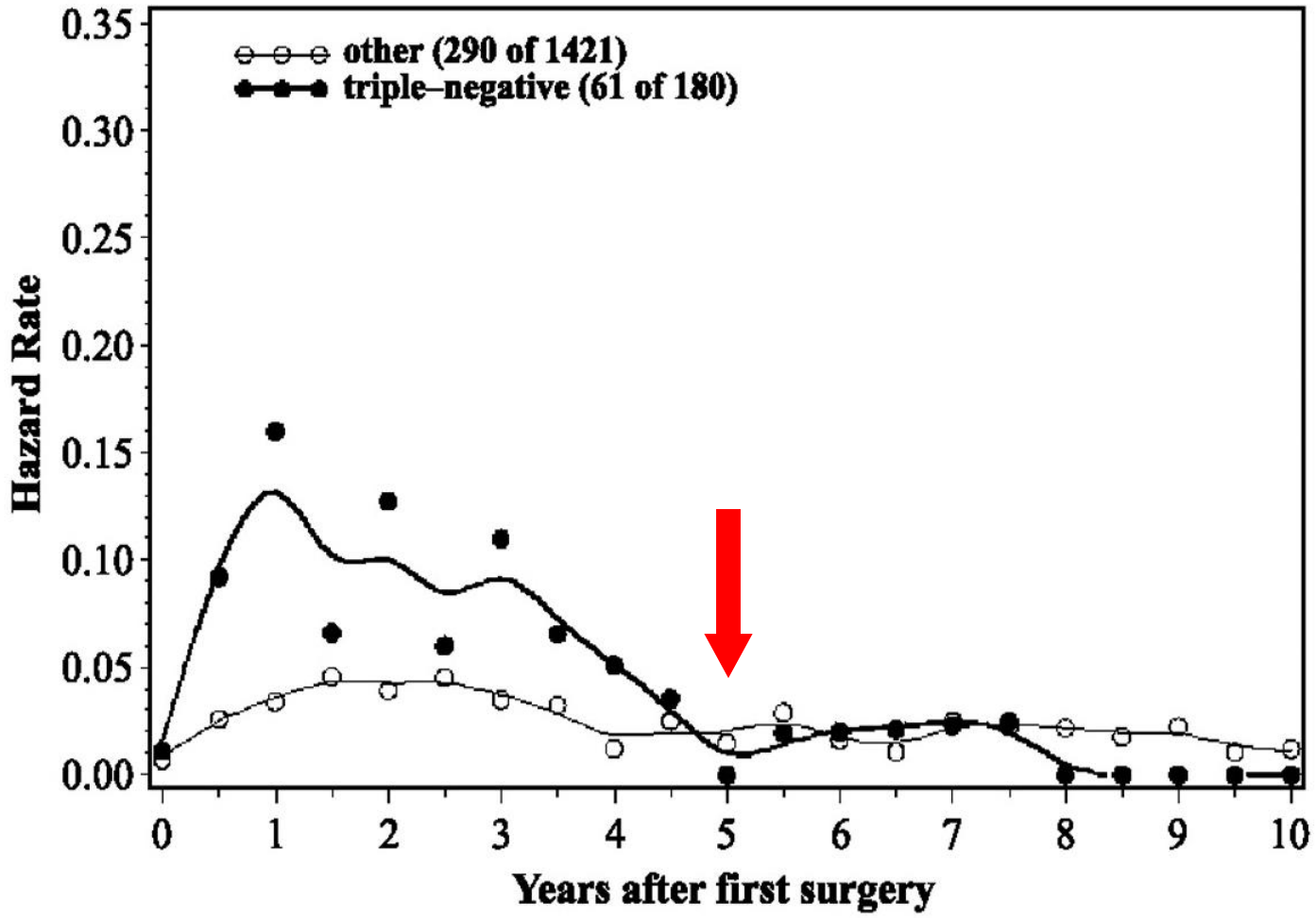
Prevention of Recurrence is Now Subtype Dependent

- Triple Negative
- ER+/HER-
  - Low grade (Luminal A)
  - High grade. (Luminal B)
- HER2+

Why get it right?

Still over 40,000 deaths per year from breast cancer in U.S. and >500,000 worldwide

Timing of TNBC Recurrence is Early

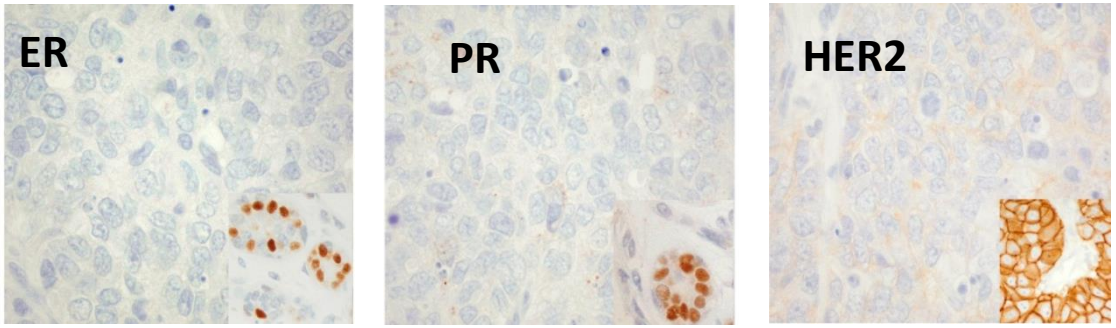


Rates of distant recurrence following surgery in triple-negative vs other breast ca

Dent et al, Clin Cancer Res 2007

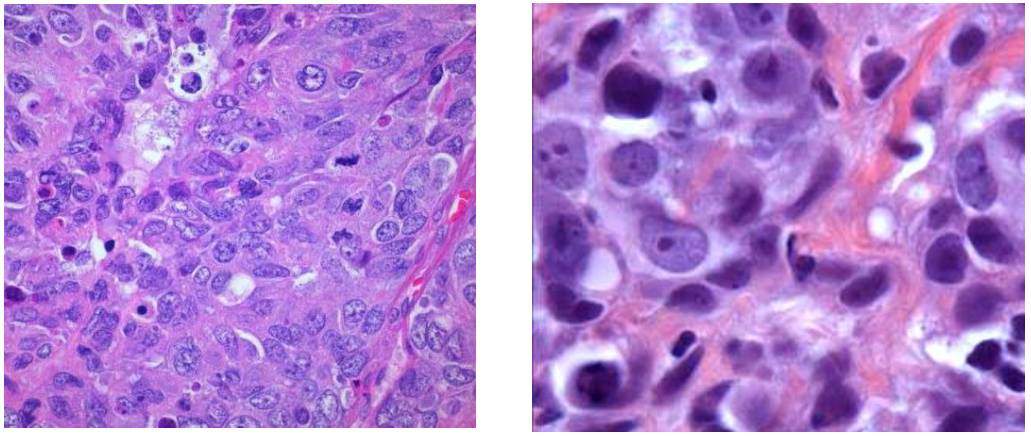
What is Optimal Therapy for Early TNBC?

Immunohistochemistry



- ER and PR <1% nuclear with positive normal breast internal control
- HER2 "negative" is 0 or 1+ staining or 2+ staining with negative FISH – usually HER2 is 0
- Rarely lobular

High grade ductal



slide courtesy of Andrea Richardson, MD, PhD

Adjuvant = Neoadjuvant

Purpose of Neoadjuvant Therapy is Given to Minimize Extent of Surgery and to Decrease Risk of Disease Recurrence

Neoadjuvant Therapy Should Never Be Given If There Is a Question About the Need for Adjuvant Treatment

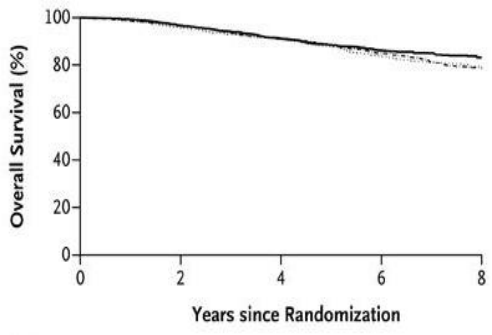
A Sequential Antracycline-Taxane Combination is the Standard of Care for Moderate-Risk TNBC

NSABP-B30

AC-T x 8 vs AT x 4 vs TAC x 6

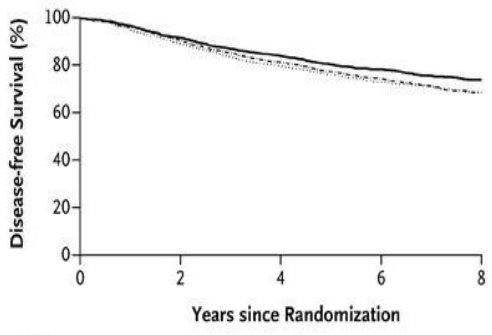
A

	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	240	0.86 vs. concurrent ACT	0.09
			0.83 vs. doxorubicin–docetaxel	0.03
Doxorubicin–docetaxel	1753	285		
Concurrent ACT	1758	278	0.96 vs. doxorubicin–docetaxel	0.67



B

	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	388	0.83 vs. concurrent ACT	0.01
			0.80 vs. doxorubicin–docetaxel	0.001
Doxorubicin–docetaxel	1753	468		
Concurrent ACT	1758	457	0.96 vs. doxorubicin–docetaxel	0.58



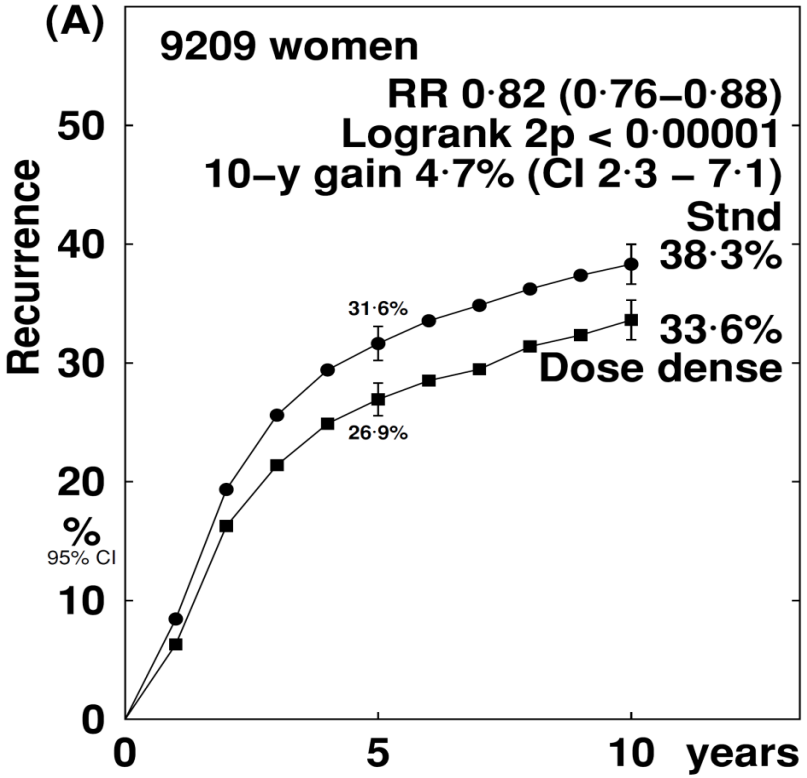
POSSIBLE REGIMENS

1. AC-paclitaxel (dose dense)
2. AC- paclitaxel (weekly)
3. AC-docetaxel (every 3 weeks)
4. FEC-docetaxel

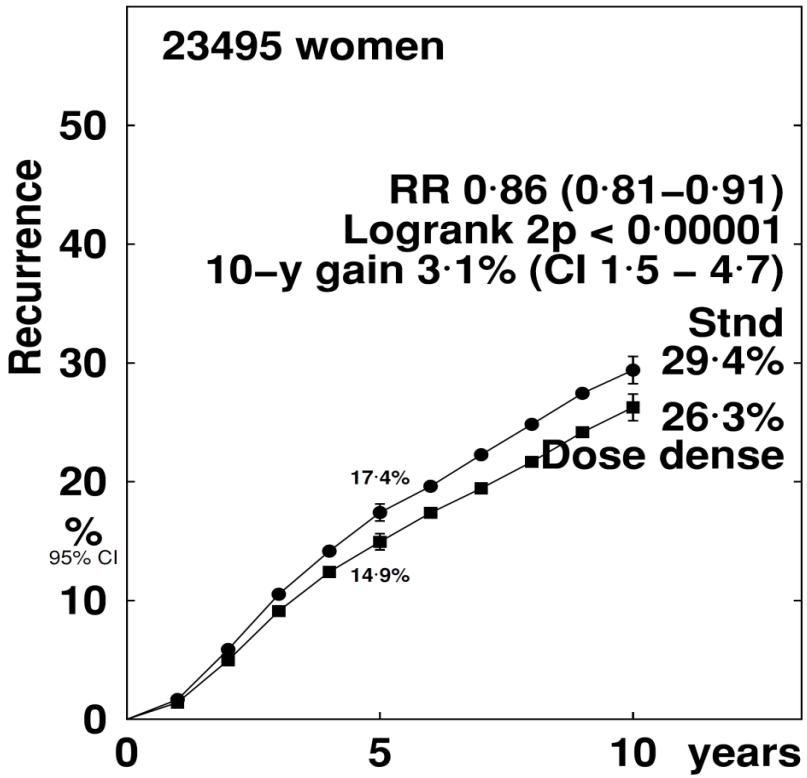
Swain SM et al. N Engl J Med 2010;362:2053-2065

Pooled Analysis of Dose Dense vs Not
Fewer Recurrences with Dose Dense Approach

ER Negative



ER Positive



Grey et al, SABCS 2017
For EBCTCG

AC-T vs TC: Results

	Pts		Events		4 yr IDFS		4 yr IDFS	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC	Delta	
ER/PgR (-)								
N-	459	488	37	52	89.5	87.0	2.5%	1.31 (0.86-1.99)
1-3 N+	153	119	21	28	85.5	74.6	10.9%	1.58 (0.90-2.79)
4+ N+	42	40	11	16	71.8	60.8	11.0%	1.34 (0.62-2.91)
ER or PgR (+)								
N-	358	378	29	22	91.5	94.2	- 2.7%	0.69 (0.39-1.19)
1-3 N+	771	789	46	53	94.3	92.3	2.0%	1.14 (0.77-1.69)
4+ N+	279	280	35	49	87.2	81.4	5.8%	1.46 (0.95-2.26)

Suggests all groups aside from ER+ N0 benefit from A-containing regimens, especially ER- N+

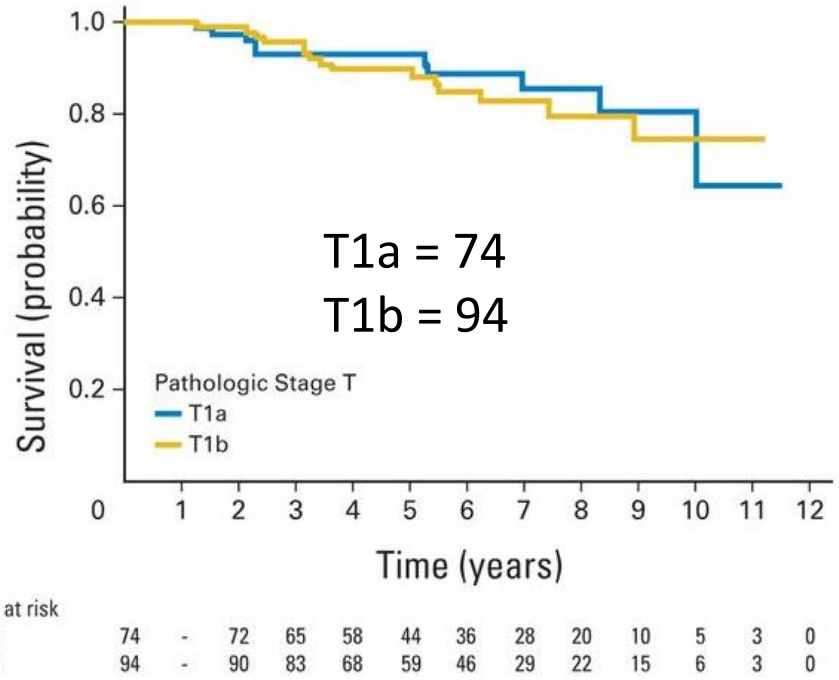
Should Stage Affect the Choice of of a Treatment Regimen?

What is the optimal treatment for small, node negative TNBC tumors?

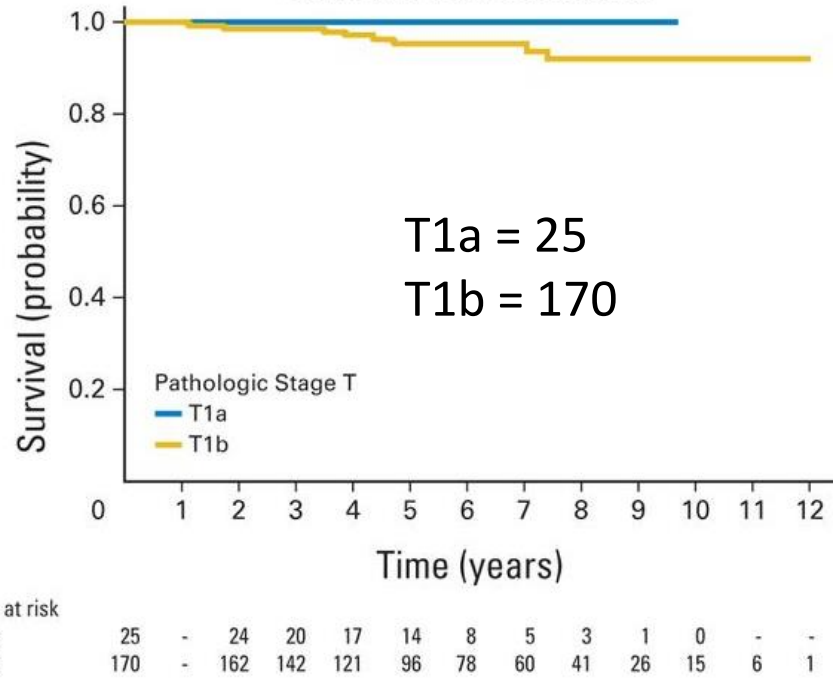
Do all patients need to be treated with AC-T?

Outcome in National Comprehensive Cancer Network Distant Relapse Free Survival HR-HER2-

No chemotherapy



Chemotherapy



T1a 5- year estimate : 93% (84-97)
T1b 5-year estimate : 90% (81-95)

T1a 5- year estimate : 100%
T1b 5-year estimate : 96% (90-98)

Vaz-Luis et al. JCO 2014;32:2142-2150

Options for Stage 1 TNBC

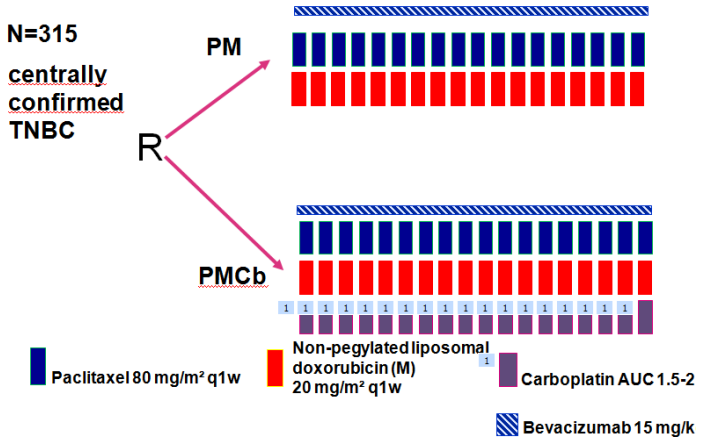
- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

	Enthusiasm for Chemotherapy	Possible Regimens
Microinvasion only	**Virtually none**	**---**
T1a	**Low to moderate**	**Simple**
T1b	**Moderate to high**	**Simple**
T1c	**High**	**Simple or selectively sequential approach**

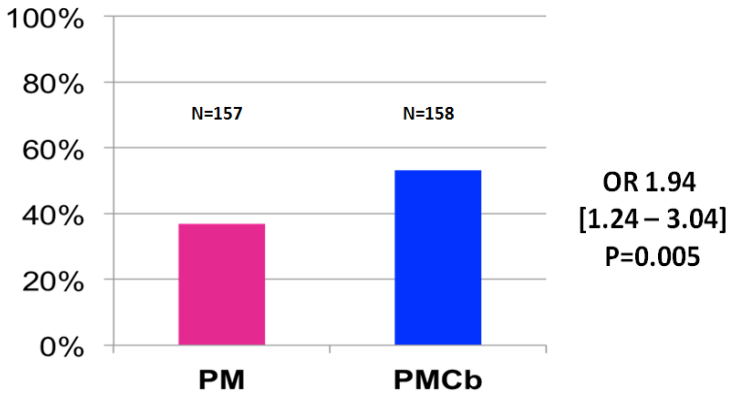
Is There a Role for Platinum Chemotherapy in the Neo/Adjuvant Management of Triple Negative Breast Cancer?

Randomized Trials of Preoperative Platinum Chemotherapy for TNBC

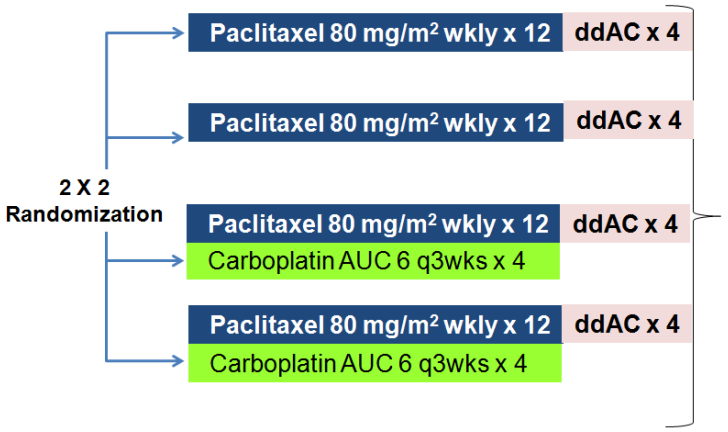
GeparSixto Schema



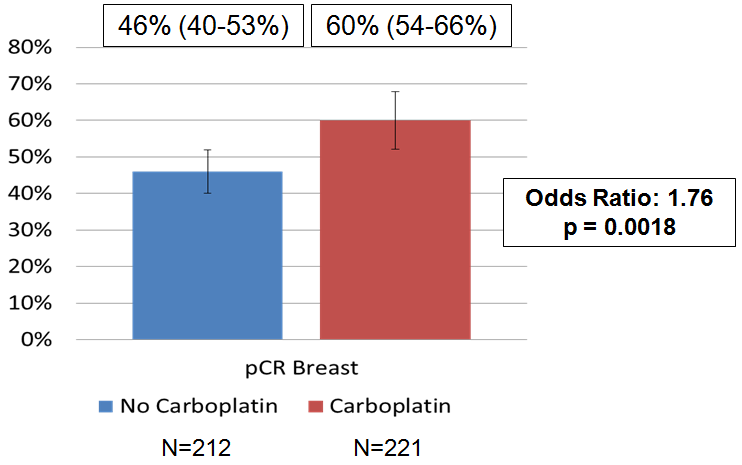
GerparSixto pCR: platinum vs not



CALGB 40603 Schema



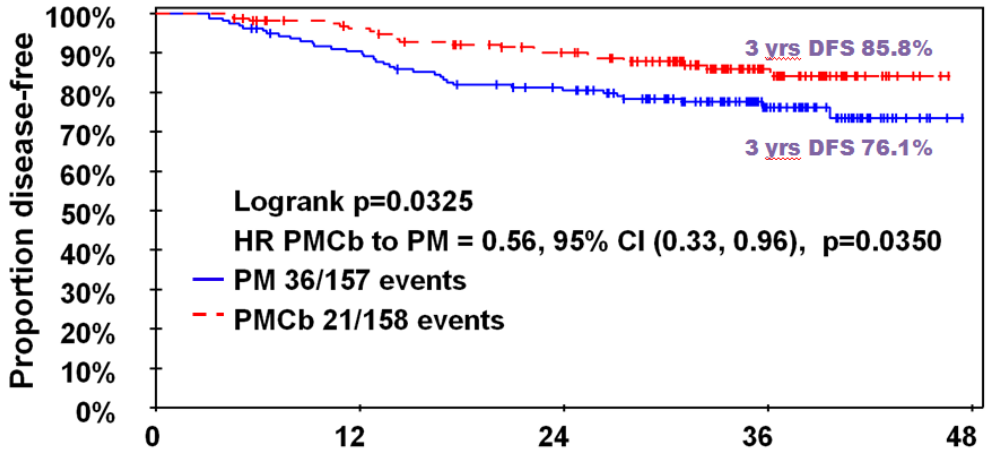
CALGB pCR: platinum vs not



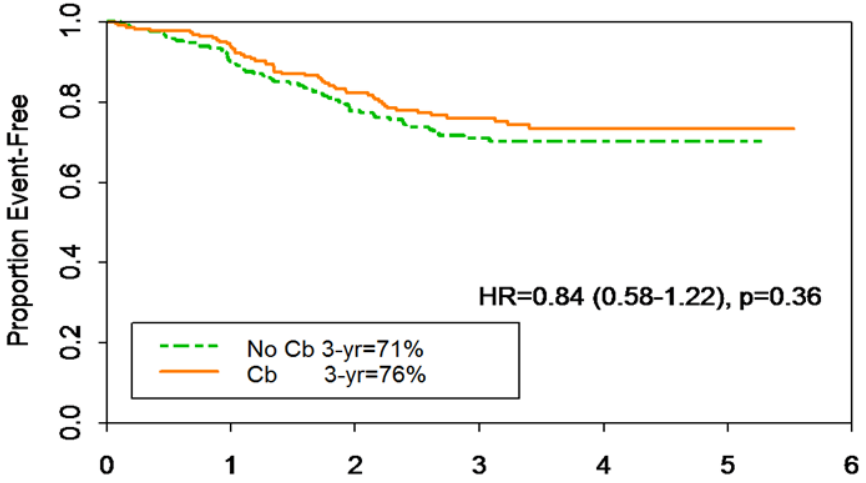
Sikov et al. JCO 2015;33:13-21; von Minckwitz et al. Lancet Oncology, May 2014

Does Addition of Preoperative Platinum Improve Survival Outcomes for TNBC?

GeparSixto 3Y DFS: Improved with Carbo



CALGB 40603 3Y EVS: Not Improved with Carbo



- Mixed results on survival benefits from preop platinum in TNBC
- Achieving pCR is a good surrogate for long-term outcomes on a patient level
- No evidence that pCR rates can be used as a surrogate for survival on a trial level to compare regimens in TNBC

Sikov et al. SABCS 2015; von Minckwitz et al. SABCS 2015

Is Carboplatin Ready for Primetime in Unselected TNBC in the Adjuvant or Neoadjuvant Setting?

NO

- Need definitiv ovement in DFS and/or OS
- If platinum is ultimately used, should it be added to standard therapy or substituted for one or more drugs?
- Are there triple negative subtypes that are particularly sensitive to platinum, ie biomarker driven?

ER+ Disease:
Hormonal Therapy

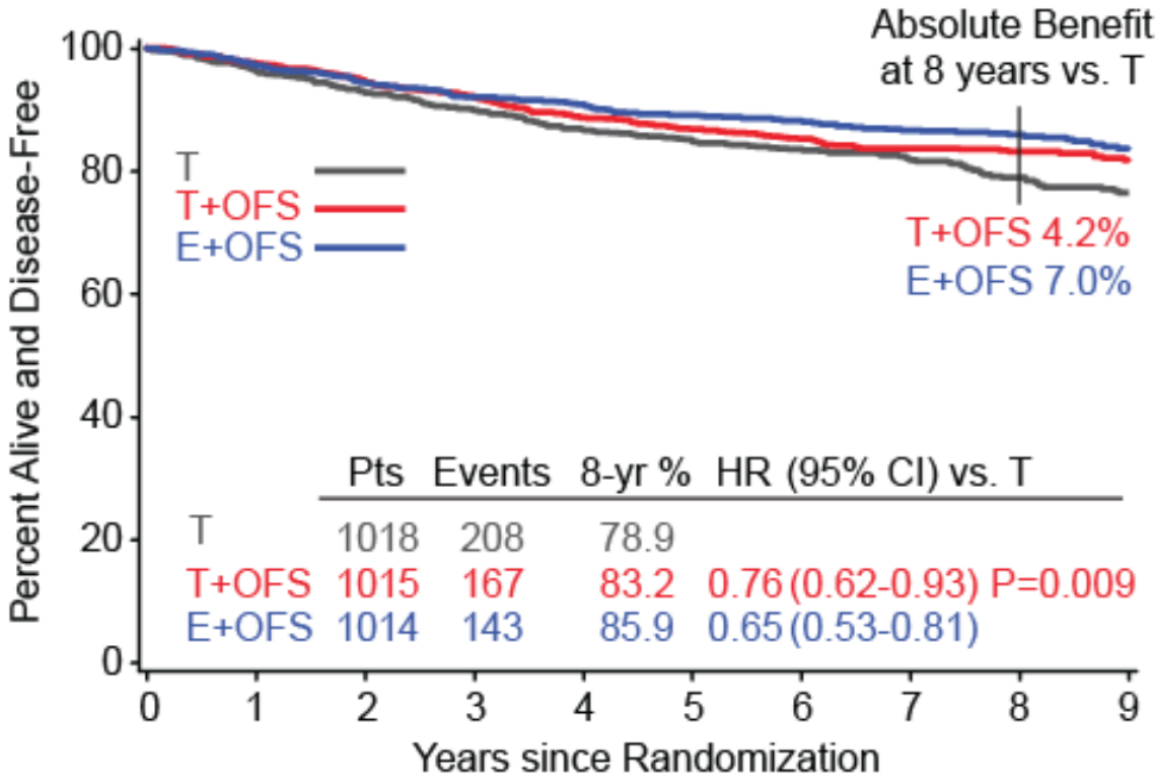
- Premenopausal
- Postmenopausal
- Extended Duration

Premenopausal

- When to use OS?
- When to use AI?

SOFT DFS

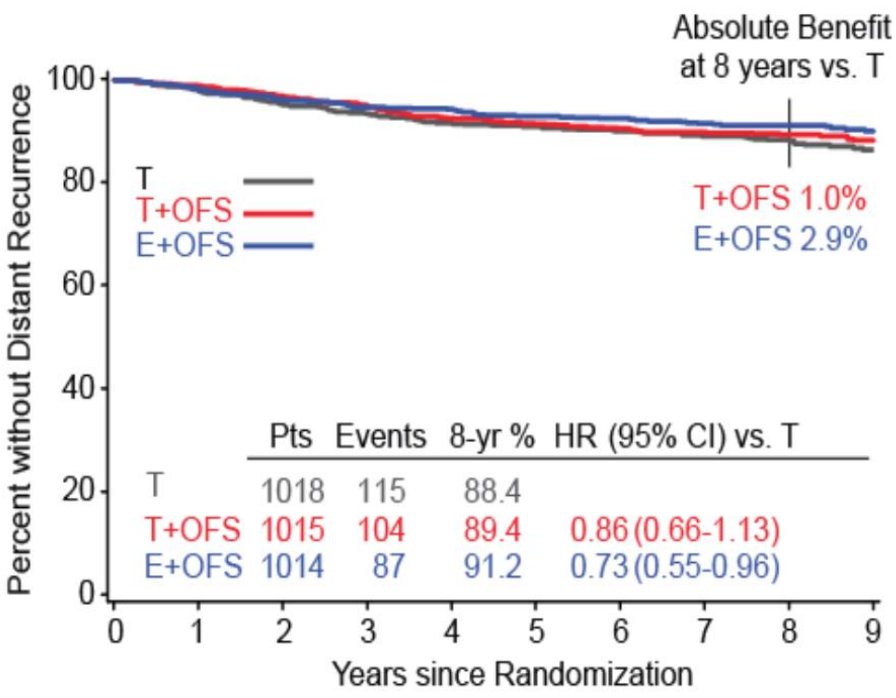
8 years median follow-up



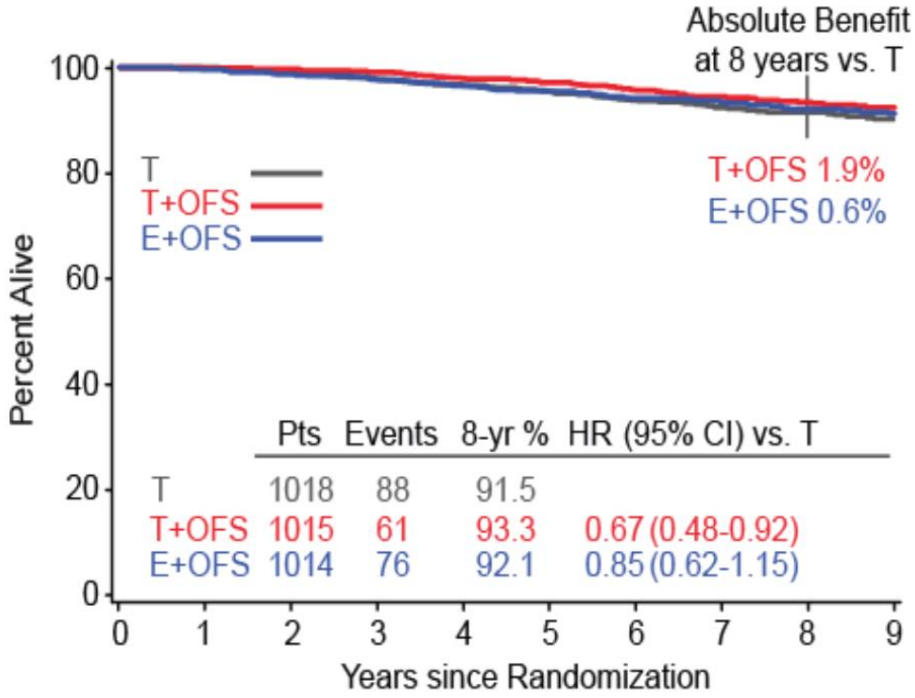
Francis et al, SABCS 2017

SOFT Secondary Endpoints

Distant Recurrence-Free Interval

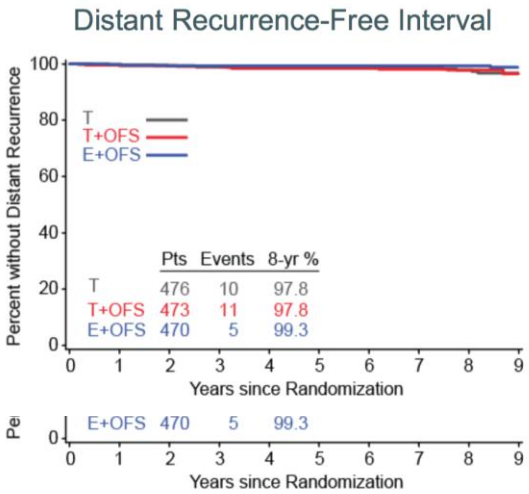


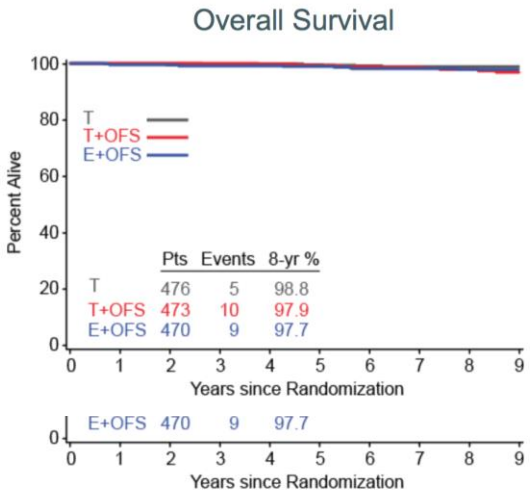
Overall Survival



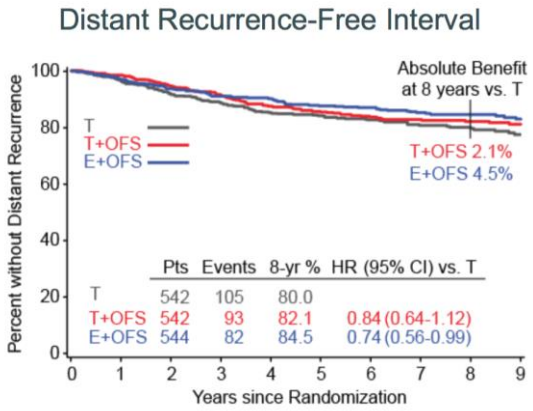
Francis et al, SABCS 2017

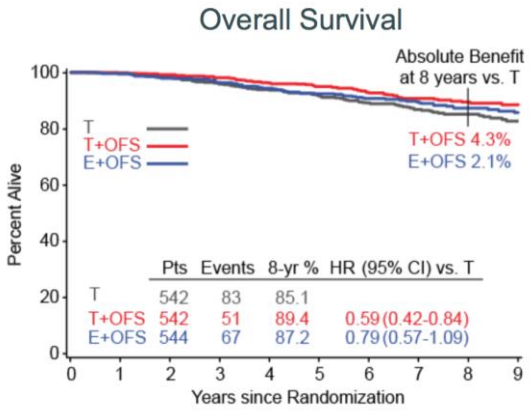
SOFT Secondary Endpoints: No Chemo





SOFT Secondary Endpoints: Chemotherapy





Francis et al, SABCS 2017

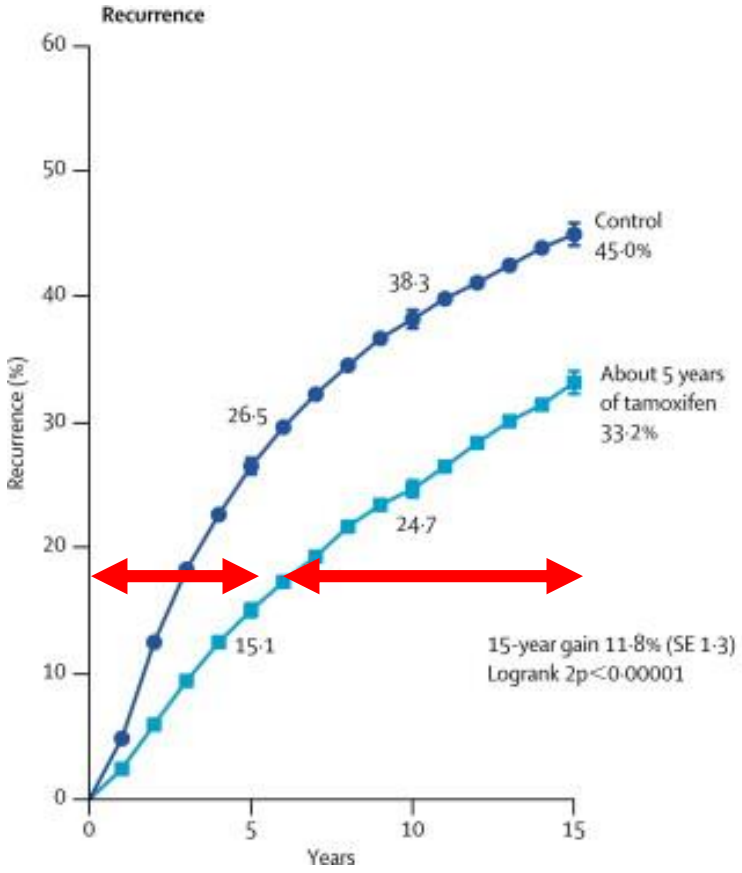
Who Should Receive Ovarian Suppression +/- AI?

- High risk patients (node positive, larger node negative, higher grade)
- What about choice of OS + tam vs OS + AI
  - OS + AI is challenging treatment – may be best to start with tamoxifen
  - AI can always be substituted, though no data using switch strategy in premenopausal women apart from MA-17

Postmenopausal

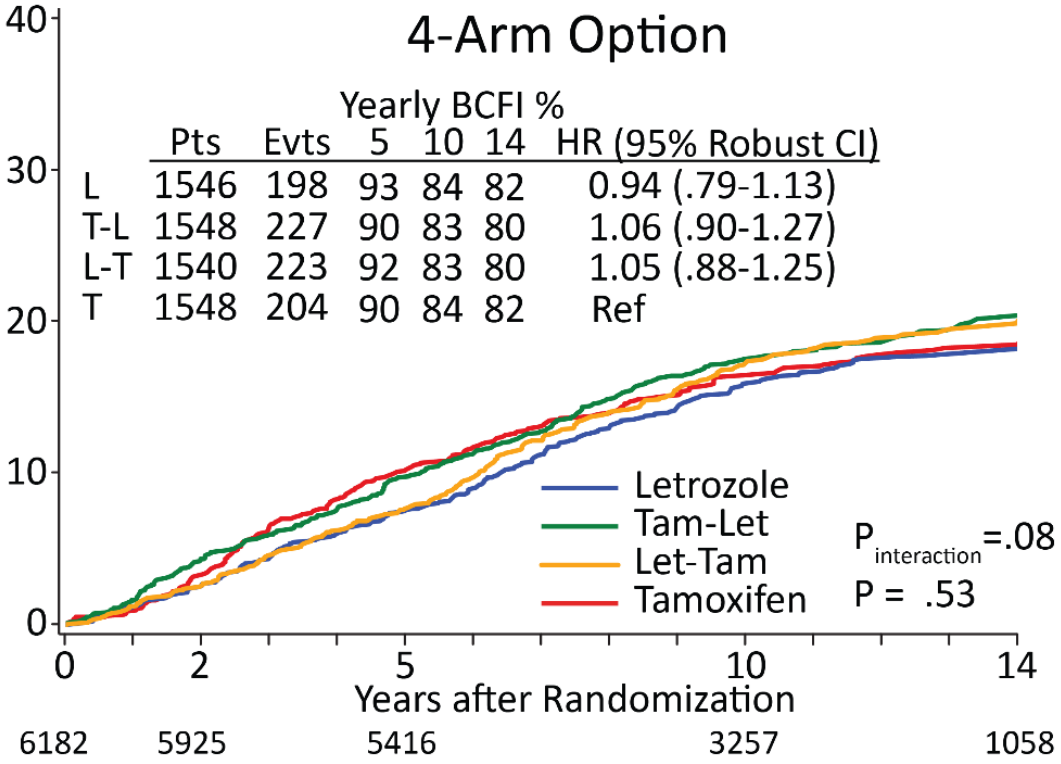
- ASCO Guideline: AI should be given either upfront, after 2-3 years, or after 5 years
- Very high risk patients should start with AI
- Very low risk patients probably fine with tamoxifen
- Side effects need to be considered carefully and managed effectively
- Far better to substitute one agent for another than to risk non-adherence

Effects of Hormonal Therapy for Early Breast Cancer on Recurrence: EBCTCG Analysis



Early Breast Cancer Trialists' Collaborative Group. The Lancet 2005:365:1687-1717.

BIG 1-98: Long-term Outcomes
Initially Therapy Has Little Impact on Late Recurrence



Thurlimann B, et al. SABCS 2016

The Problem of Late Recurrence
Annual and Cumulative Risk by Subset

Variable	Women Who Were Event-free at 5 Yr		Annual Rate of Distant Recurrence		Cumulative Risk from 5 Yr to 20 Yr
	Total	Chemotherapy Scheduled	5 to <10 Yr	10 to 20 Yr	
	no.	*no. (%)*	*percent*		*percent*
Nodal involvement					
N0	28,847	9,136 (32)	1.0	1.1	15
N1–3	25,292	17,280 (68)	1.9	1.7	23
N4–9	8,784	6,664 (76)	3.9	2.8	38
Tumor diameter in N0 only					
T1a or T1b: ≤1.0 cm	5,527	910 (16)	0.5	0.8	10
T1c: 1.1–2.0 cm	13,875	4,034 (29)	0.8	1.1	14
T2: 2.1–3.0 cm	6,700	2,859 (43)	1.5	1.4	19
T2: 3.1–5.0 cm	2,745	1,333 (49)	1.7	1.4	20
Tumor grade in T1N0 only					
Low	3,524	401 (11)	0.4	0.8	10
Moderate	7,363	1,861 (25)	0.7	1.0	13
High	3,054	1,414 (46)	0.9	1.5	17

All Patients Cancer Free at 5 Years and Received Adjuvant Tamoxifen

Hayes et al NEJM 2017

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

*Christina Davies, Hongchao Pan, Jon Godwin, Richard Gray, Rodrigo Arriagada, Vinod Raina, Mirta Abraham, Victor Hugo Medeiros Alencar, Atef Badran, Xavier Bonfill, Joan Bradbury, Michael Clarke, Rory Collins, Susan R Davis, Antonella Delmestri, John F Forbes, Peiman Haddad, Ming-Feng Hou, Moshe Inbar, Hussein Khaled, Joanna Kielanowska, Wing-Hong Kwan, Beela S Mathew, Bettina Müller, Antonio Nicolucci, Octavio Peralta, Fany Pernas, Lubos Petruzelka, Tadeusz Pienkowski, Balakrishnan Rajan, Maryna T Rubach, Sera Tort, Gerard Urrútia, Miriam Valentini, Yaochen Wang, Richard Peto, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group**

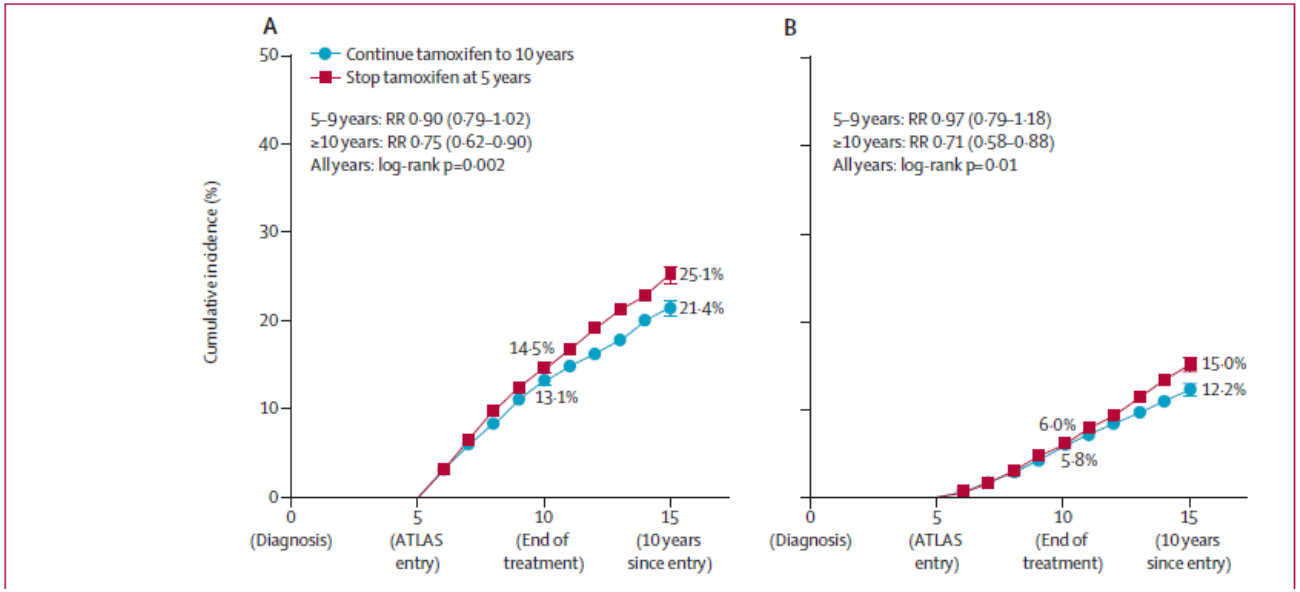
Summary

Background For women with oestrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis. We aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years.

Published Online
December 5, 2012
http://dx.doi.org/10.1016/
S0140-6736(12)61963-1

Disease-free Survival

Overall Survival



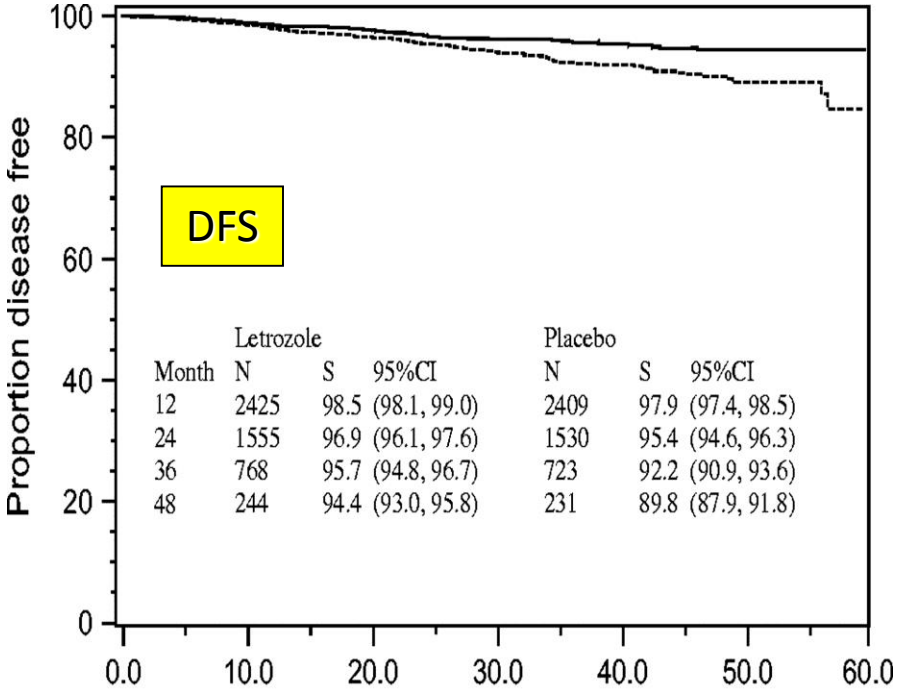
Extended Letrozole After 5 yrs of Tamoxifen (MA17)

Tamoxifen for 4.5-6 yrs
Postmenopausal
N=5,187

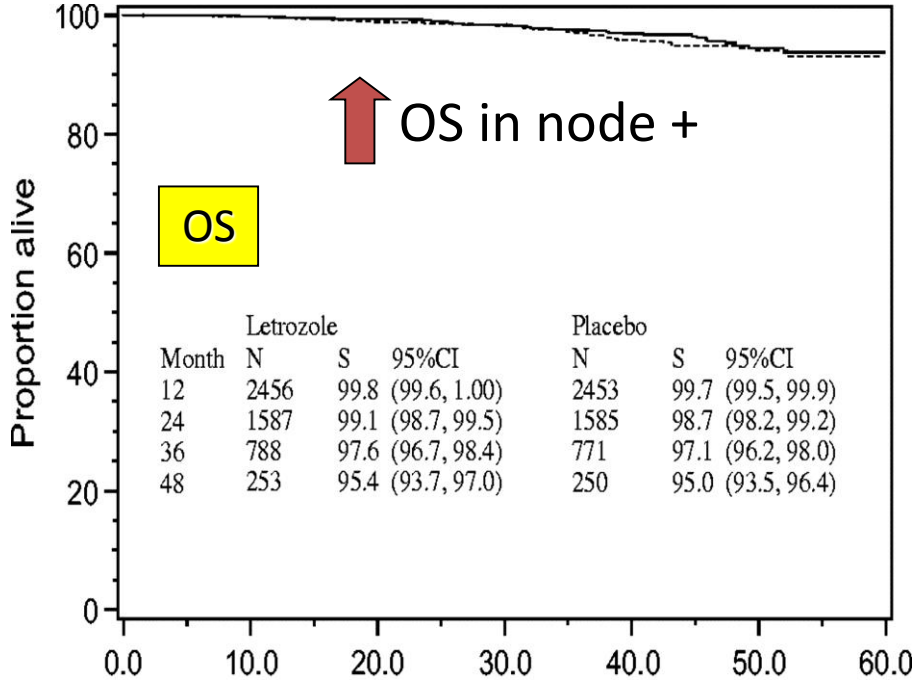
PLACEBO

5 yrs rx planned

LETROZOLE



Month	Letrozole N	S	95%CI	Placebo N	S	95%CI
12	2425	98.5	(98.1, 99.0)	2409	97.9	(97.4, 98.5)
24	1555	96.9	(96.1, 97.6)	1530	95.4	(94.6, 96.3)
36	768	95.7	(94.8, 96.7)	723	92.2	(90.9, 93.6)
48	244	94.4	(93.0, 95.8)	231	89.8	(87.9, 91.8)

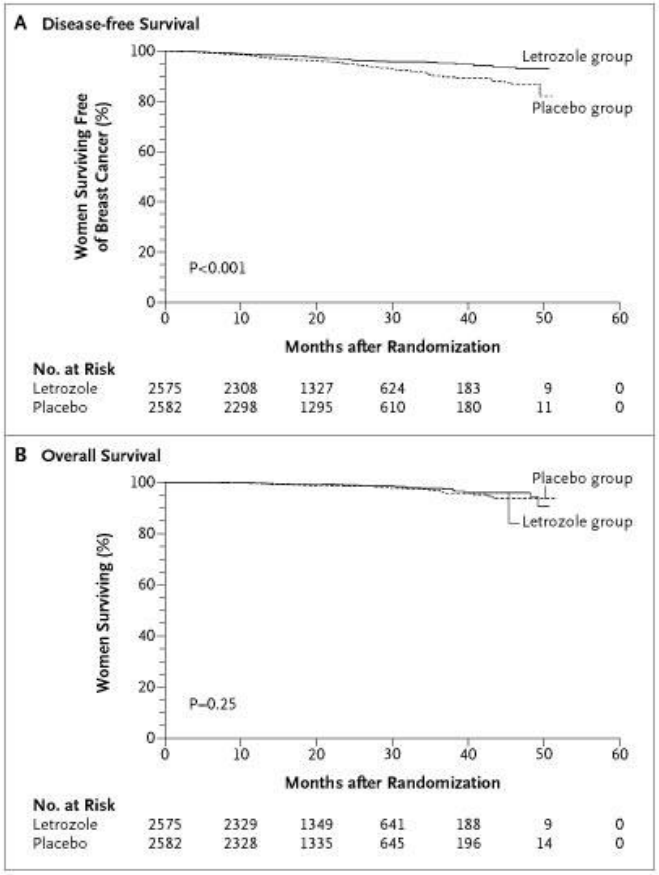


Month	Letrozole N	S	95%CI	Placebo N	S	95%CI
12	2456	99.8	(99.6, 1.00)	2453	99.7	(99.5, 99.9)
24	1587	99.1	(98.7, 99.5)	1585	98.7	(98.2, 99.2)
36	788	97.6	(96.7, 98.4)	771	97.1	(96.2, 98.0)
48	253	95.4	(93.7, 97.0)	250	95.0	(93.5, 96.4)

Goss *et al*. JNCI 2005

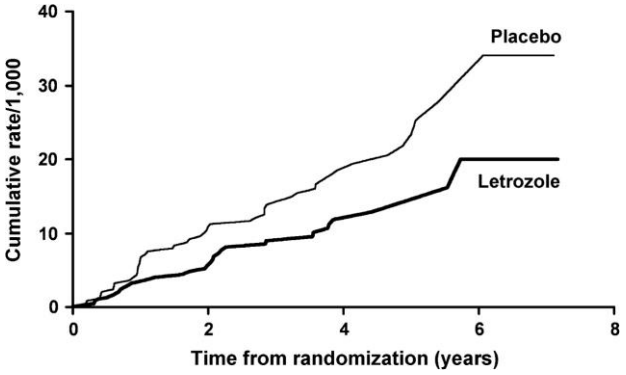
MA 17: Letrozole or Placebo after 5 years of Tamoxifen

DFS and OS



Goss PE et al. N Engl J Med 2003;349:1793-1802.

Contralateral BC



Ingle J N et al. Ann Oncol 2008;19:877-882

Difference in distant recurrences is only 10 events!

Frequency of ctDNA ESR1 mutations in ER+ MBC

Study	ESR1 mut
BOLERO2* (N=541)	28.8%
SOFeA** (N=161)	39.1%
PALOMA 3** (N=360)	25.3%
FERGI§ (N=70)	37%

*D538G and Y537G
**E380Q, L536R, Y537C, D538G, S463P, Y537N, and Y537S
§E380Q, S463P, P535H, L536Q, L536R, L536H, L536P, Y537C, Y537N, Y537S, D538G

.
Courtesy of Mafalda Oliveira

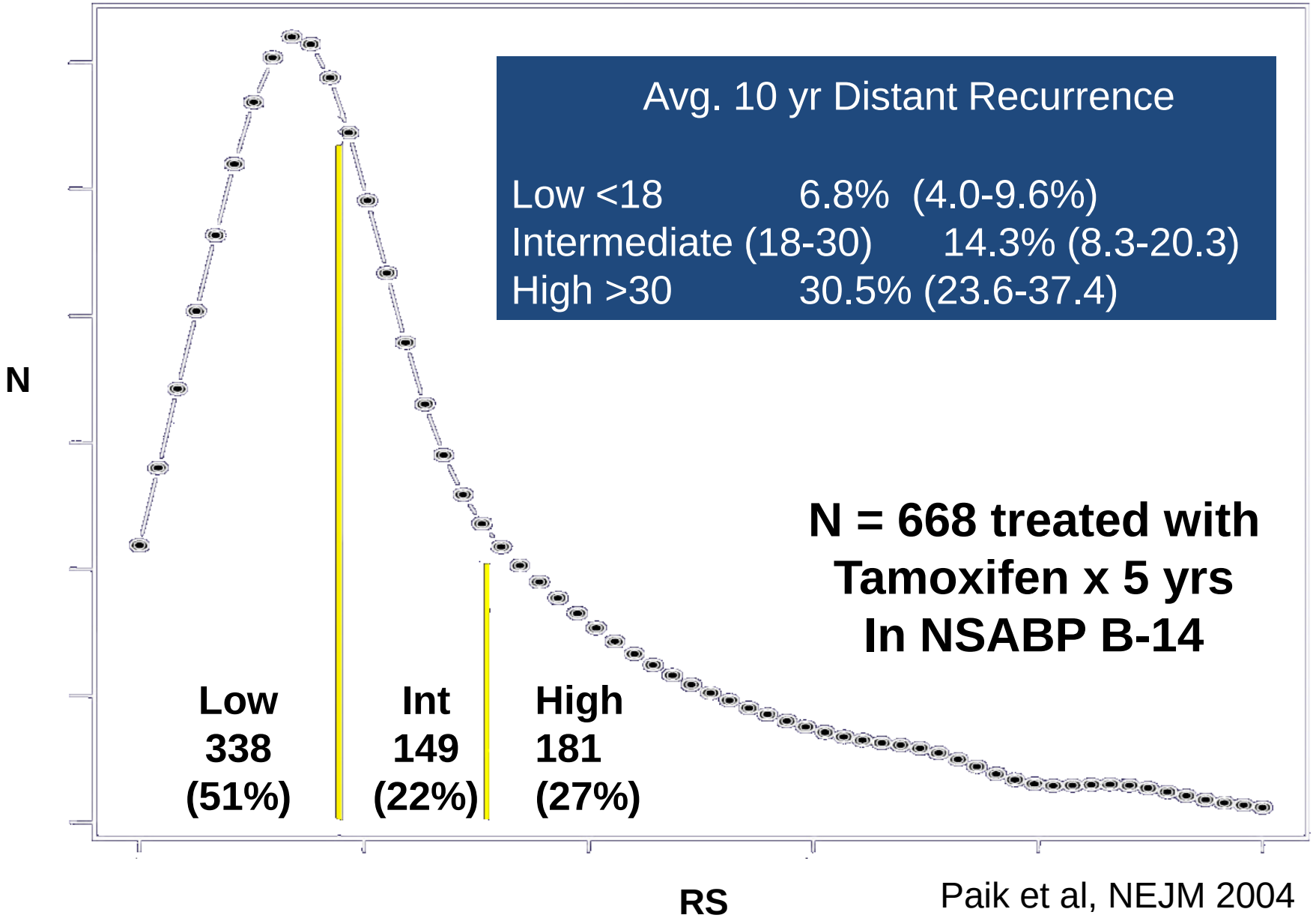
Chandarlapaty S. et al. JAMA Oncol. 2016;2(10):1310-1315
Fribbens C. et al. J Clin Oncol. 2016 Sep 1;34(25):2961-8
Gendreau S. et al. SABCS 2015

Duration of Therapy

- 5 years adequate for many patients
- Longer duration reasonable for those at higher risk
  - 10 years of tamoxifen (in premenospausal)
  - 5 years of tamoxifen followed by 5 years of AI
  - 2-3 years of tamoxifen followed by 5-8 of AI
  - 10 years of AI

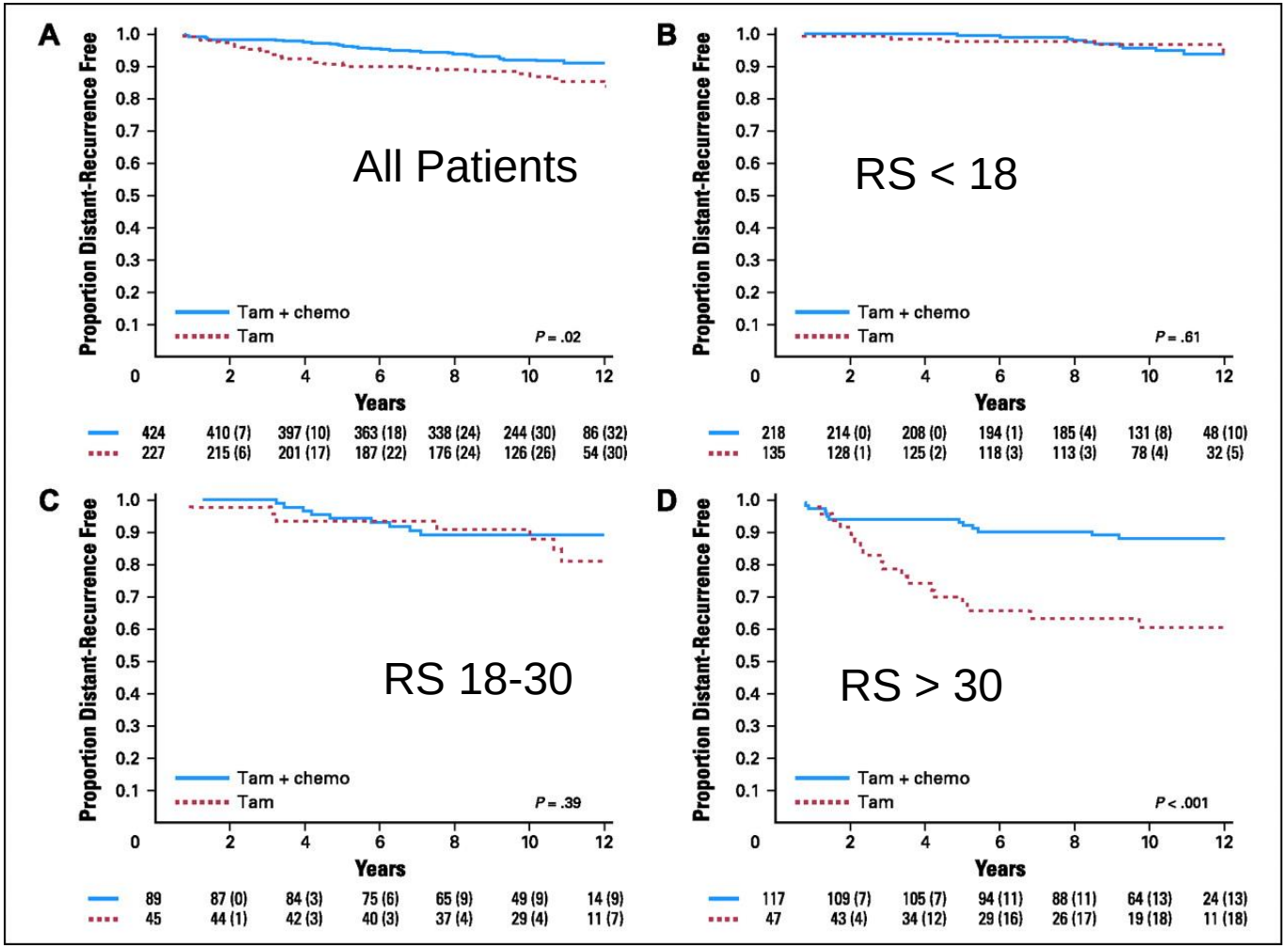
Which ER+ Patients Need Chemotherapy?

RS in Node Negative Pts Treated With Tamoxifen



Paik et al, NEJM 2004

Benefit of Chemotherapy By Oncotype Dx Recurrence Score In Node Negative Breast Cancer Treated With Tamoxifen



Paik S et al. JCO 2006;24:3726-3734

JOURNAL OF CLINICAL ONCOLOGY

Recurrence Score and Benefit from Chemotherapy in NSABP B-20

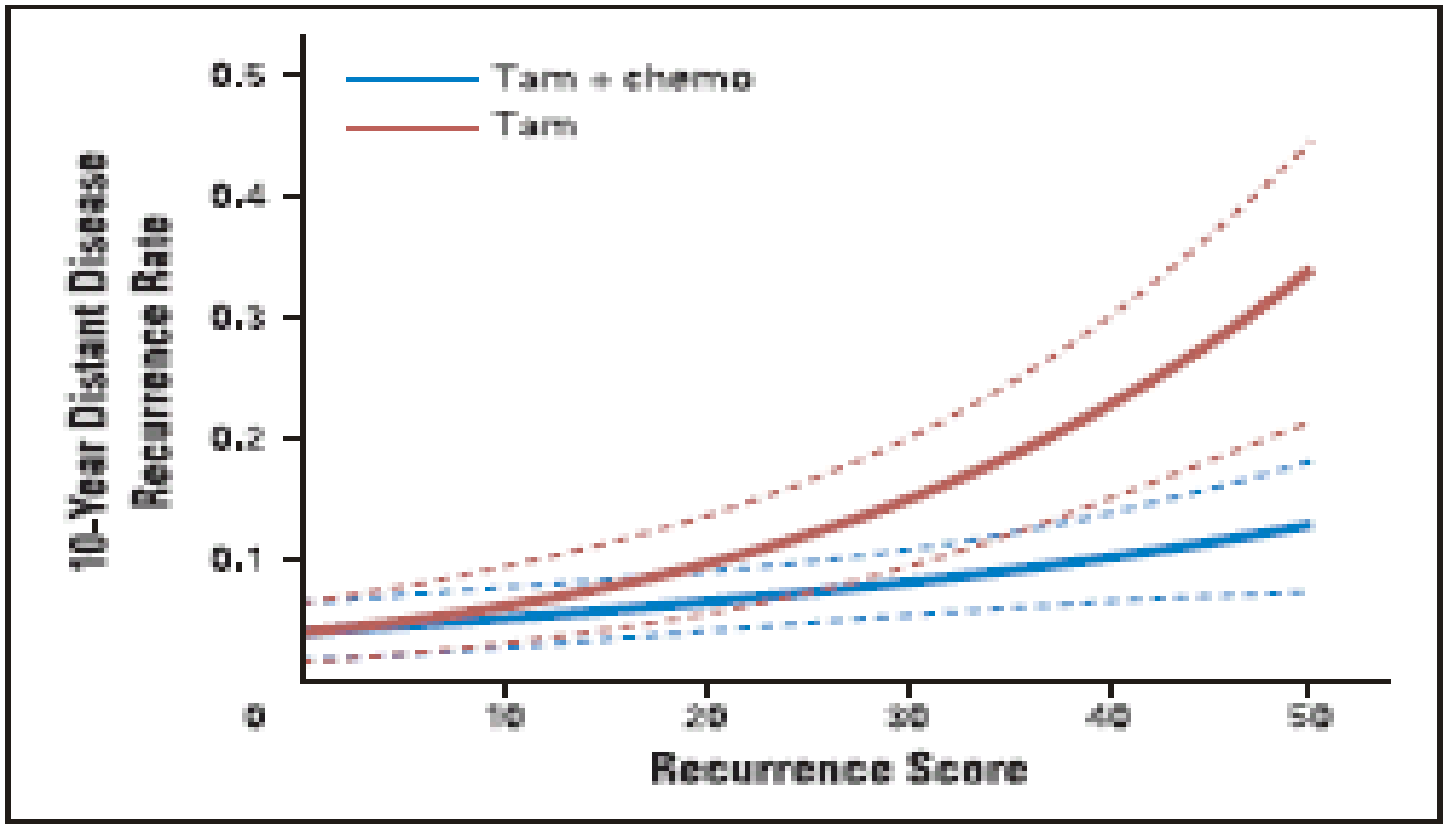
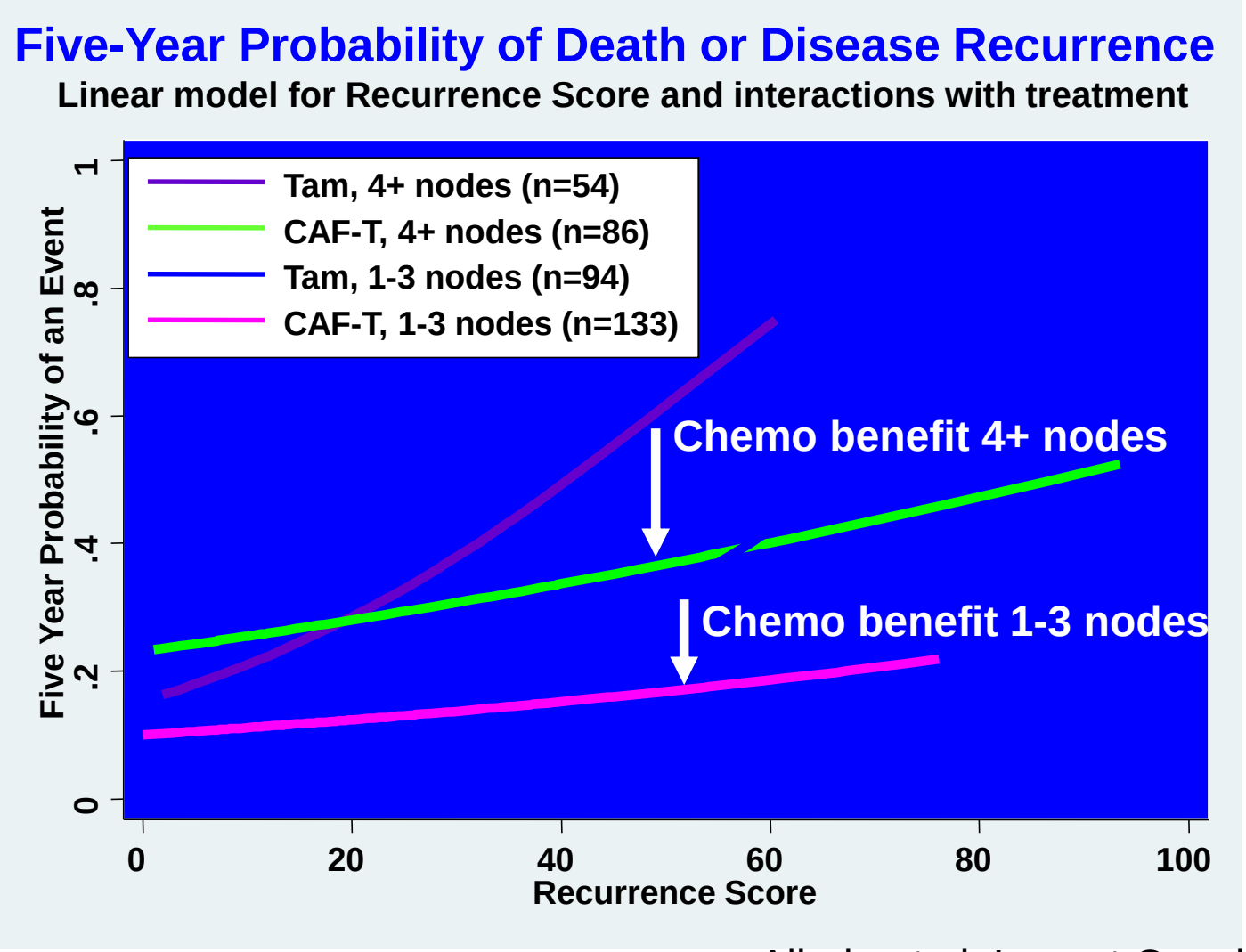


Fig 4. Linear fit of the likelihood of distant recurrence as a continuous function of recurrence score for the tamoxifen alone (TAM) and tamoxifen plus chemotherapy (TAM + chemo) treatment groups.

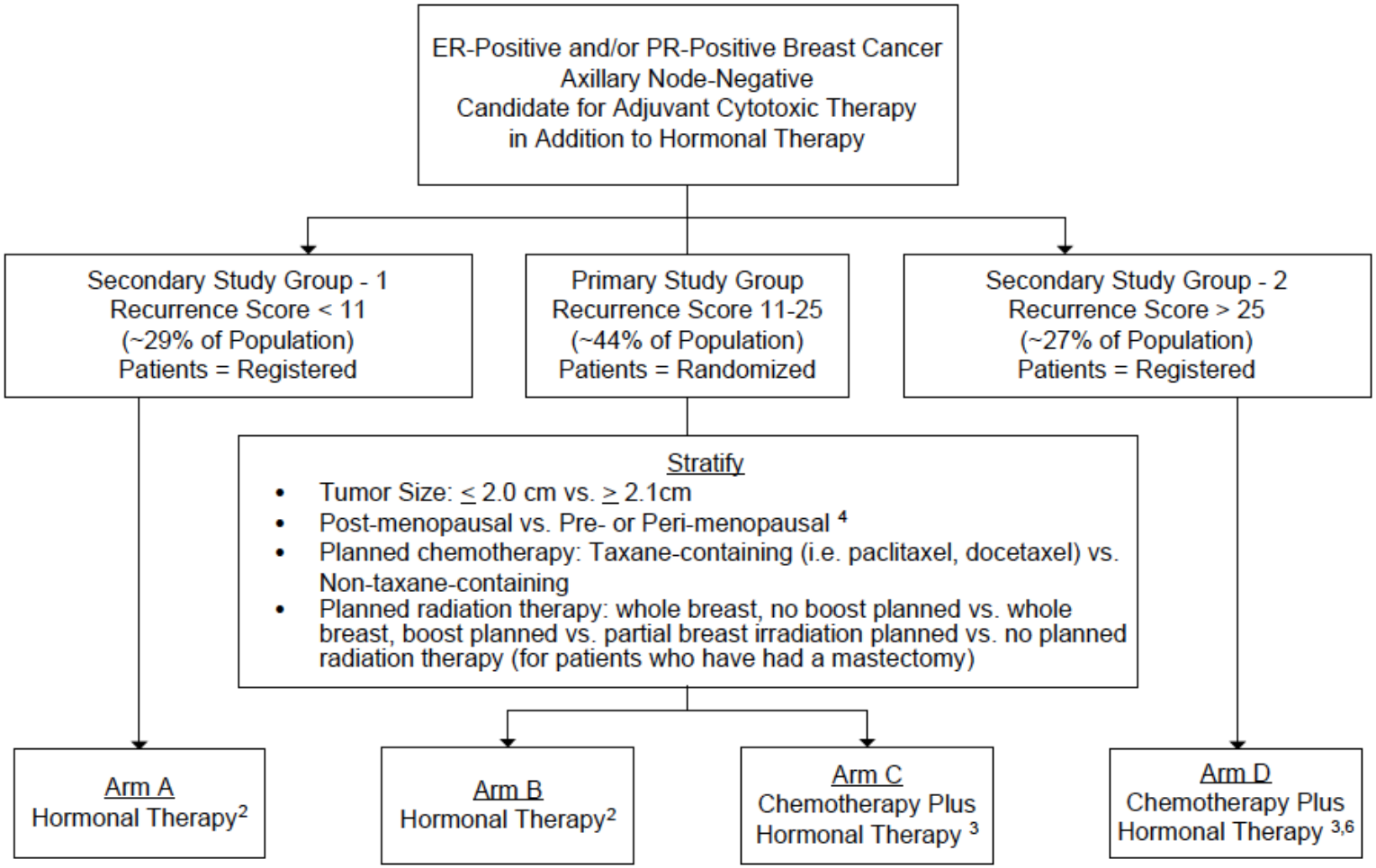
Paik et al, JCO2006

CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS



Albain et al, Lancet Oncology 2011

Prospective Validation of 21-Gene RS in Node-Negative Patients: TAILORx



Sparano JA et al. NEJM 2015

Prospective Validation of 21-Gene RS in Node-Negative Patients: TAILORx

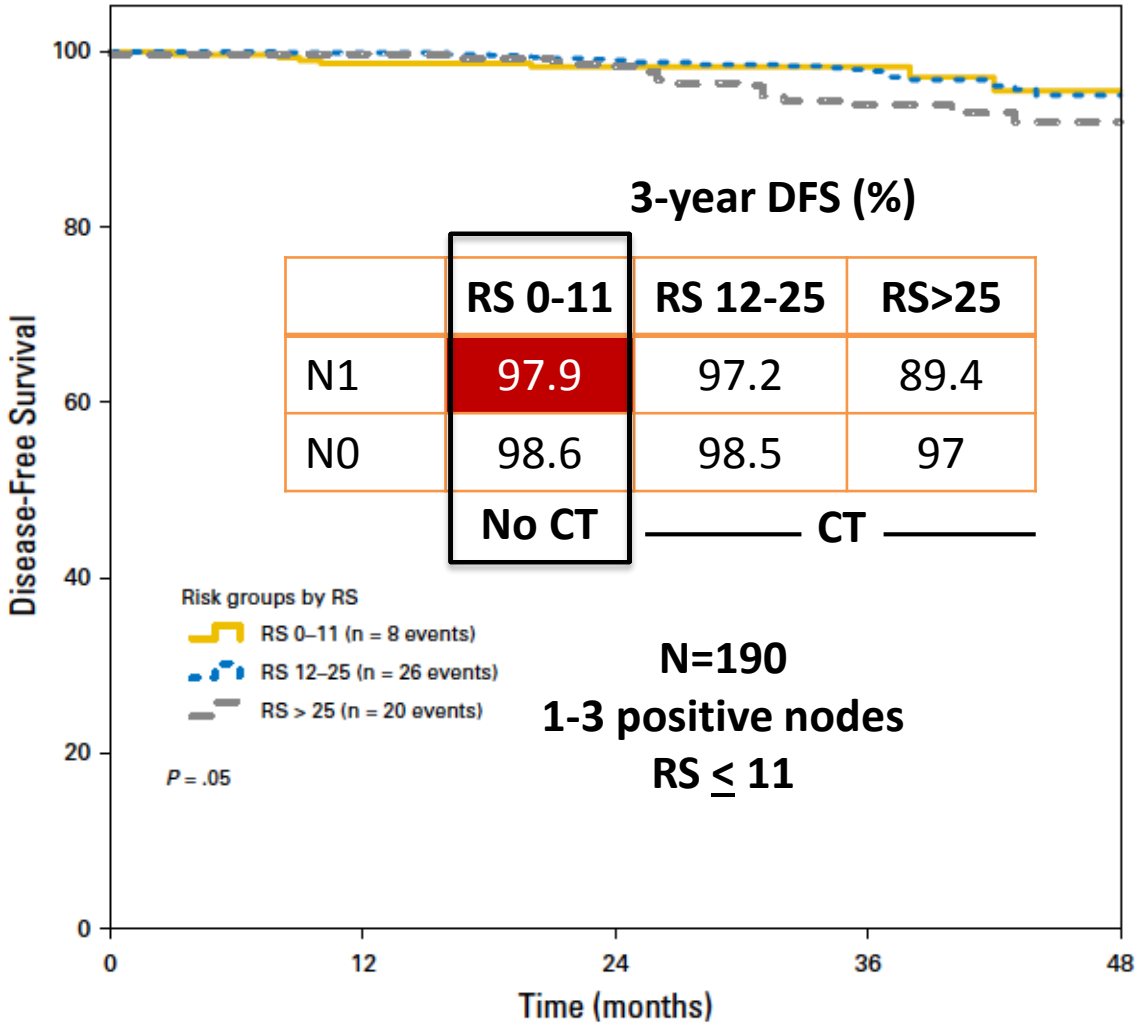
Secondary Group
RS <11
Assigned to Hormonal Therapy Only

5 Year Results

Distant Relapse Free Survival	99.3%
Invasive Disease Free Survival	93.8%
Overall Survival	98.0%

Sparano JA et al. NEJM 2015

Prospective Outcome Data for 21-Gene RS in Node-POSITIVE Patients: PlanB



3-year DFS (%)

	RS 0-11	RS 12-25	RS>25
N1	97.9	97.2	89.4
N0	98.6	98.5	97
	No CT	CT	

N=190
1-3 positive nodes
RS ≤ 11

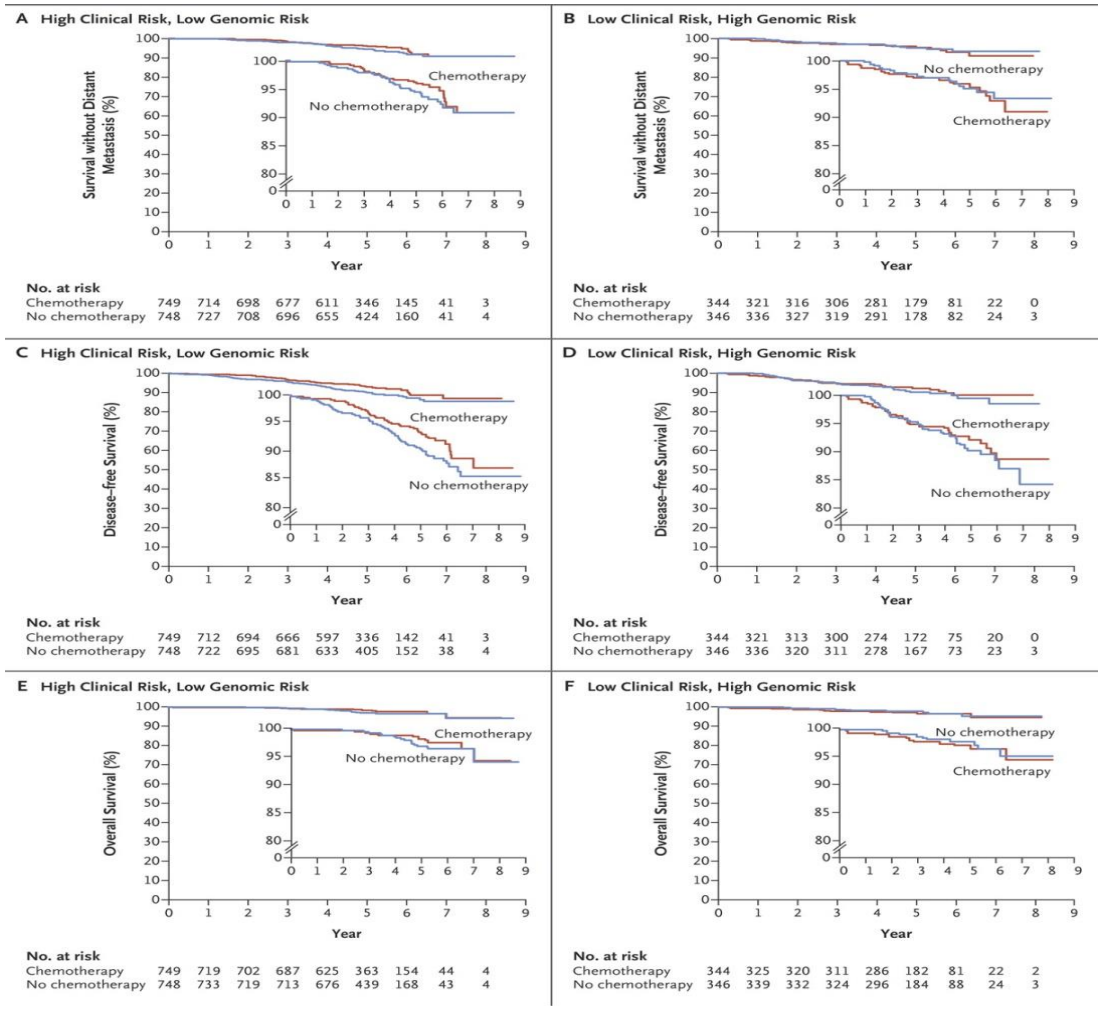
Update:
EBCC 2016
5 year DFS = 94%

Gluz O et al. JCO 2016

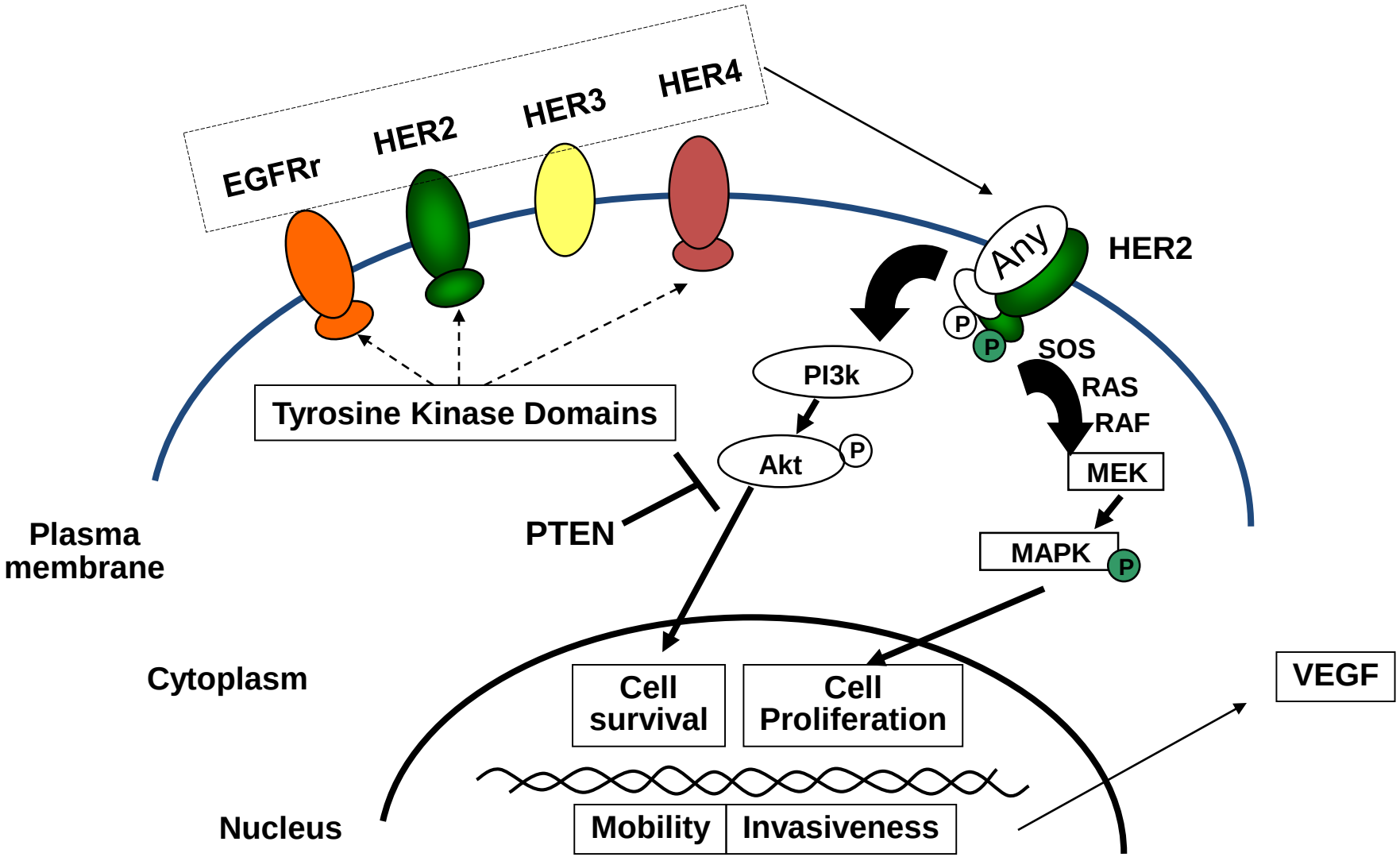
Results From Tailorx Will Be Presented At ASCO

- Most investigators expect trial will demonstrate minimal or no benefit from chemotherapy
- What will the implications be for patients with positive nodes, especially those with 1-3 nodes?
- Do we have to wait for results of Rxponder? If so, many of us may no longer be practicing medicine!

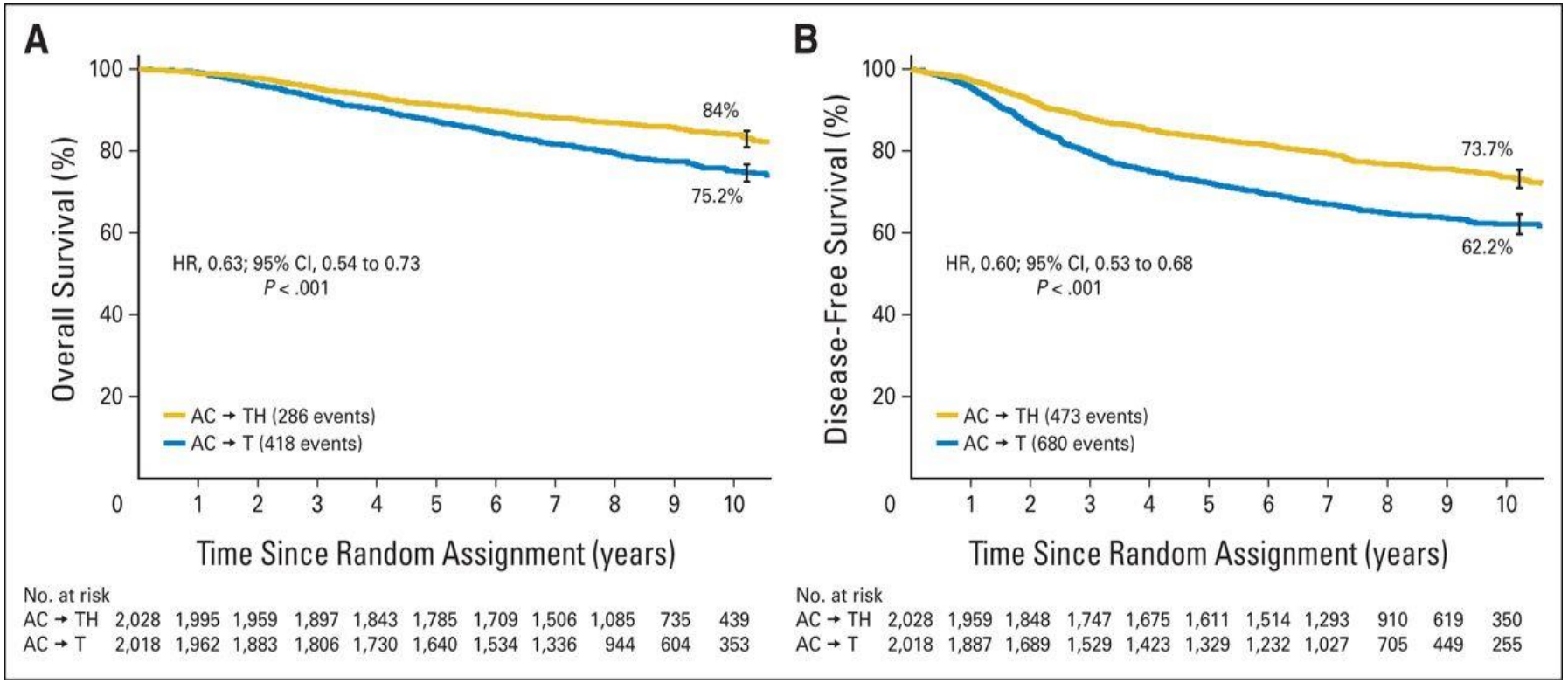
MINDACT: Survival without Distant Metastasis, Disease-free Survival, and Overall Survival in the Two Discordant-Risk Groups, According to Randomized Treatment



HER2 Signaling Pathways



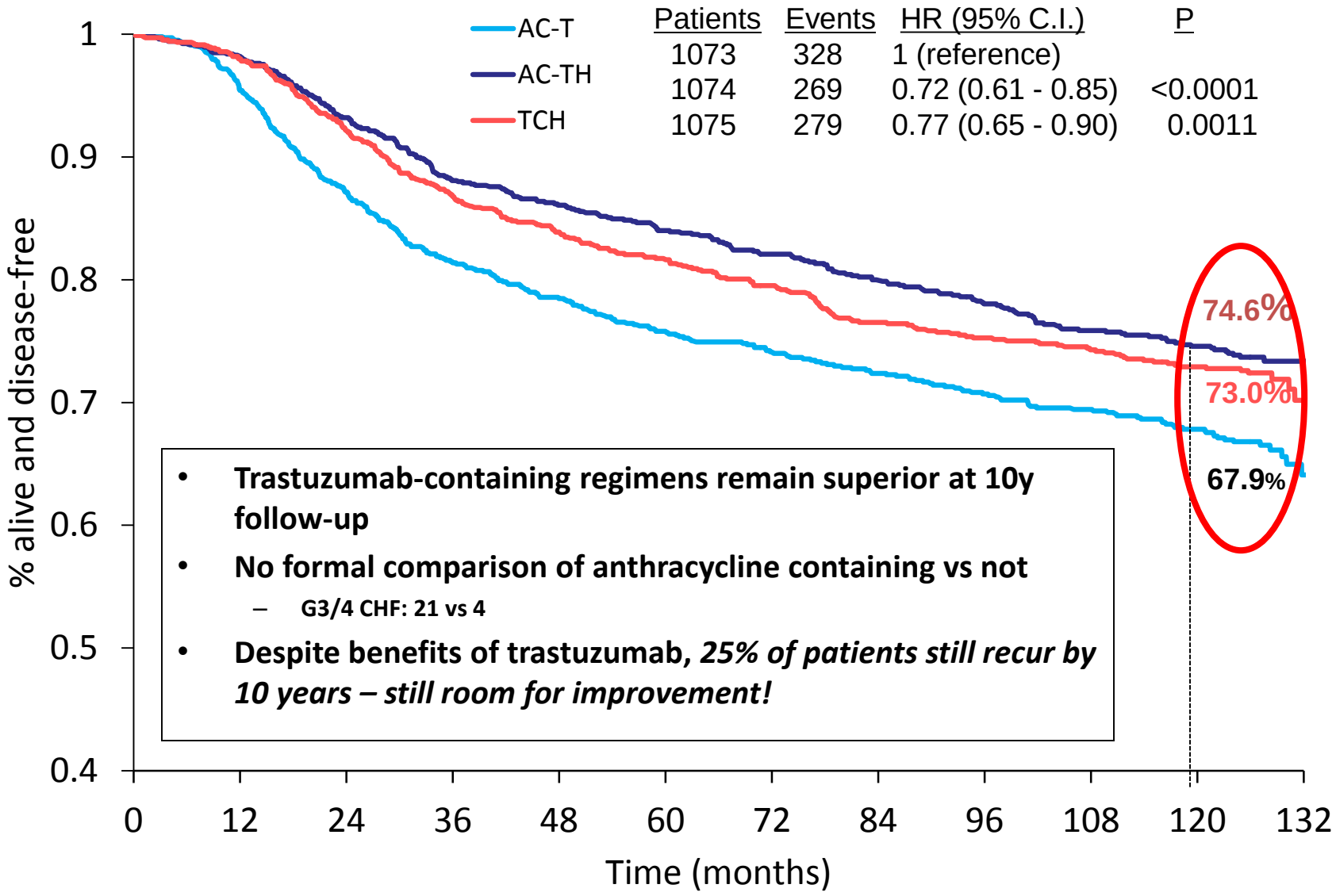
Update Overall Survival and Disease-free Survival From Combined Data Analysis for N9831 and NSABP B-31 (AC-T +/- Trastuzumab)



Significant difference maintained over time in both ER- and ER+ cohorts. Late events more common in ER+ disease (not shown).

Perez E A et al. JCO 2014;32:3744-3752

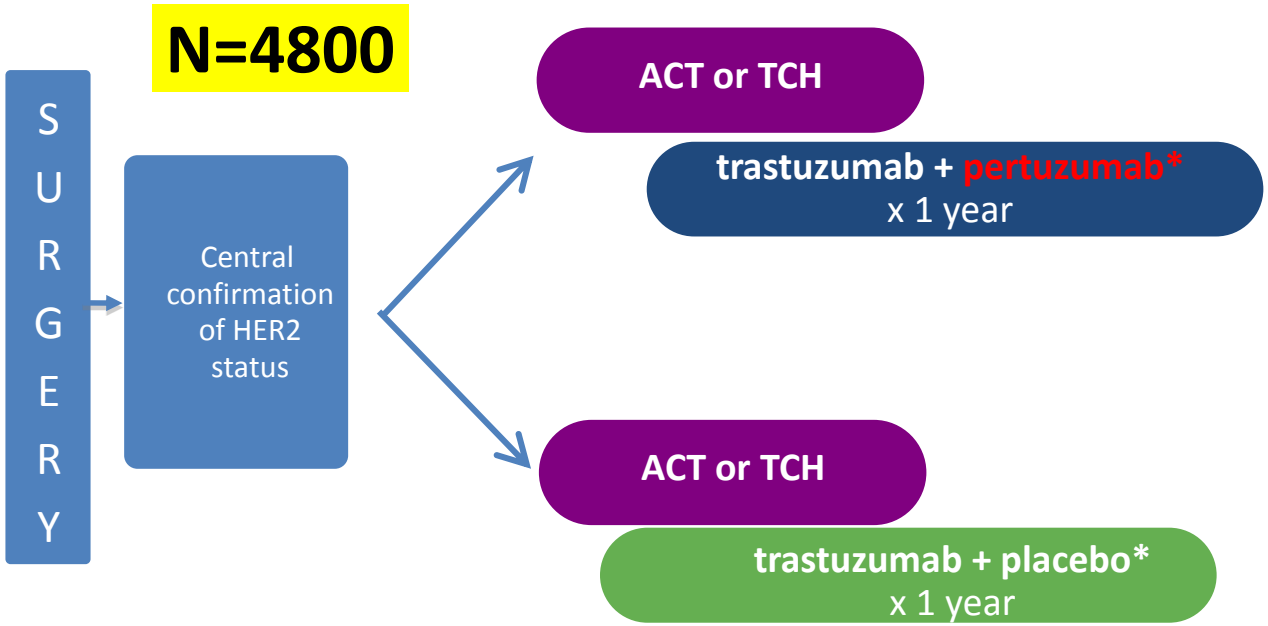
BCIRG-006 DFS Final Analysis (10.3yrs)



- **Trastuzumab-containing regimens remain superior at 10y follow-up**
- **No formal comparison of anthracycline containing vs not**
  - **G3/4 CHF: 21 vs 4**
- **Despite benefits of trastuzumab, *25% of patients still recur by 10 years – still room for improvement!***

Slamon et al, SABCS 2015

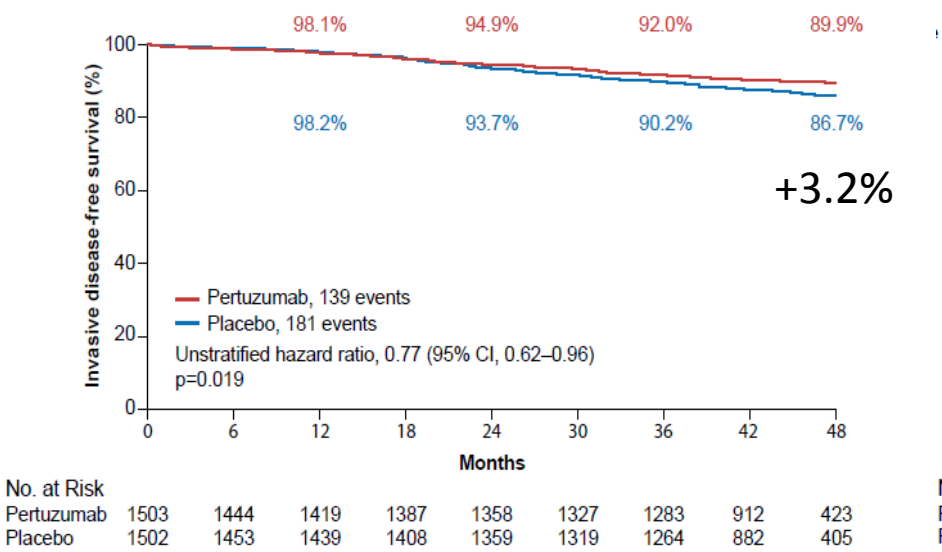
APHINITY Schema



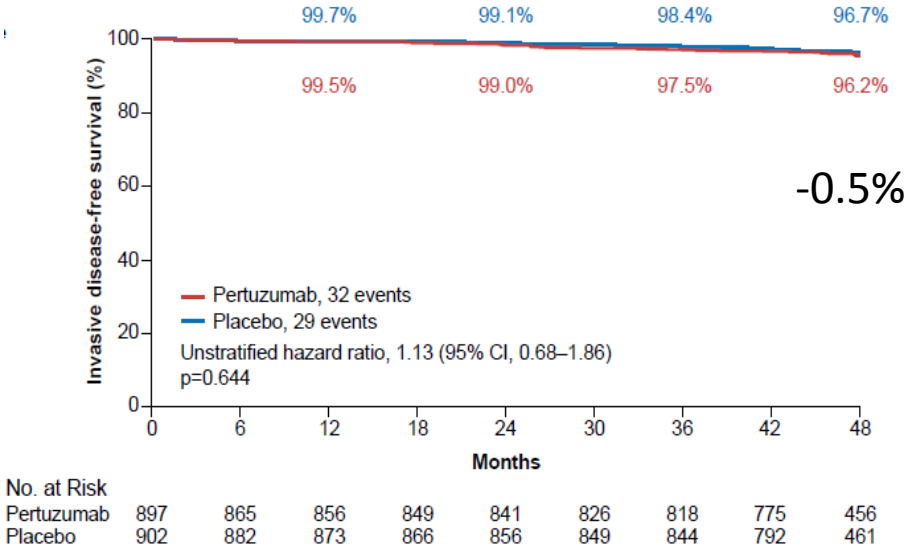
Population: Node + *or* high risk node negative

*antibody therapy started with taxane

APHINITY: By Nodal Subgroups



Node Positive



Node Negative

Also greater impact in ER- than ER+

Adjuvant Paclitaxel/Trastuzumab Trial
Study Design

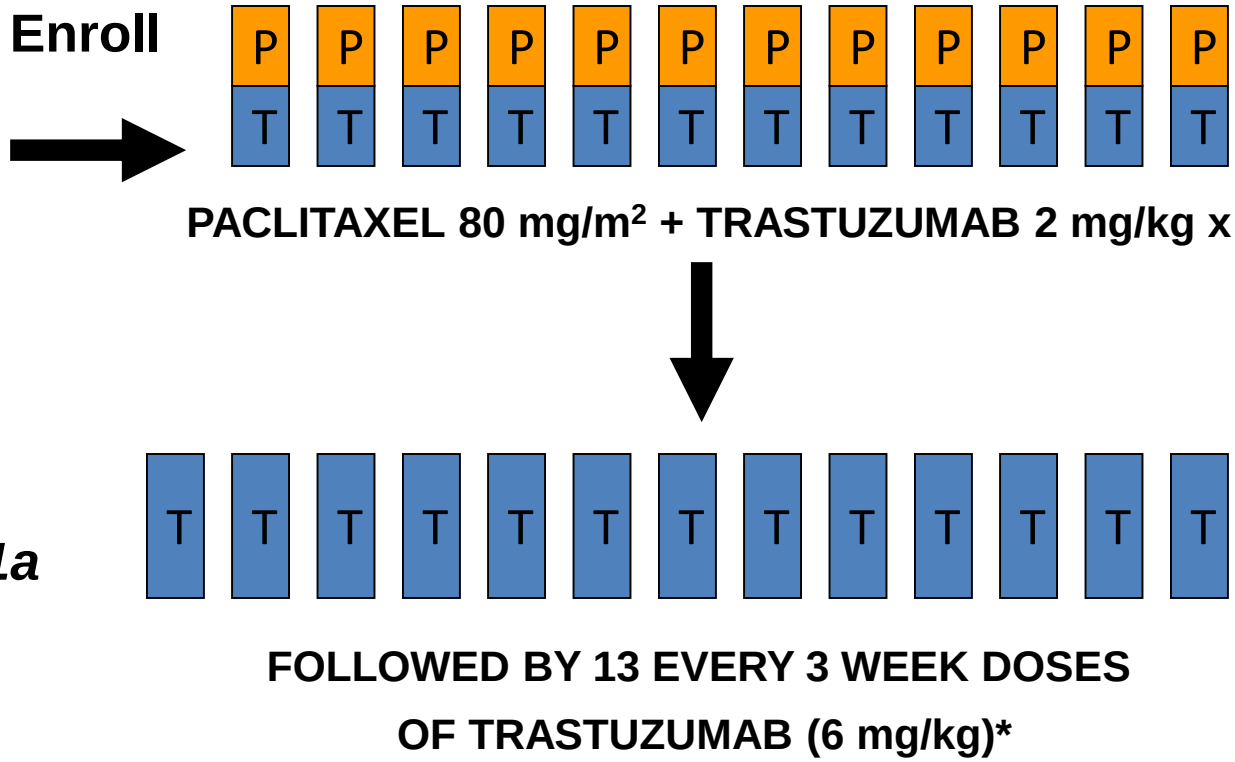
HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Accrual N=406

Less than 20% had T1a

50% had T1c or T2

Enroll



** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney et al, NEJM 2015

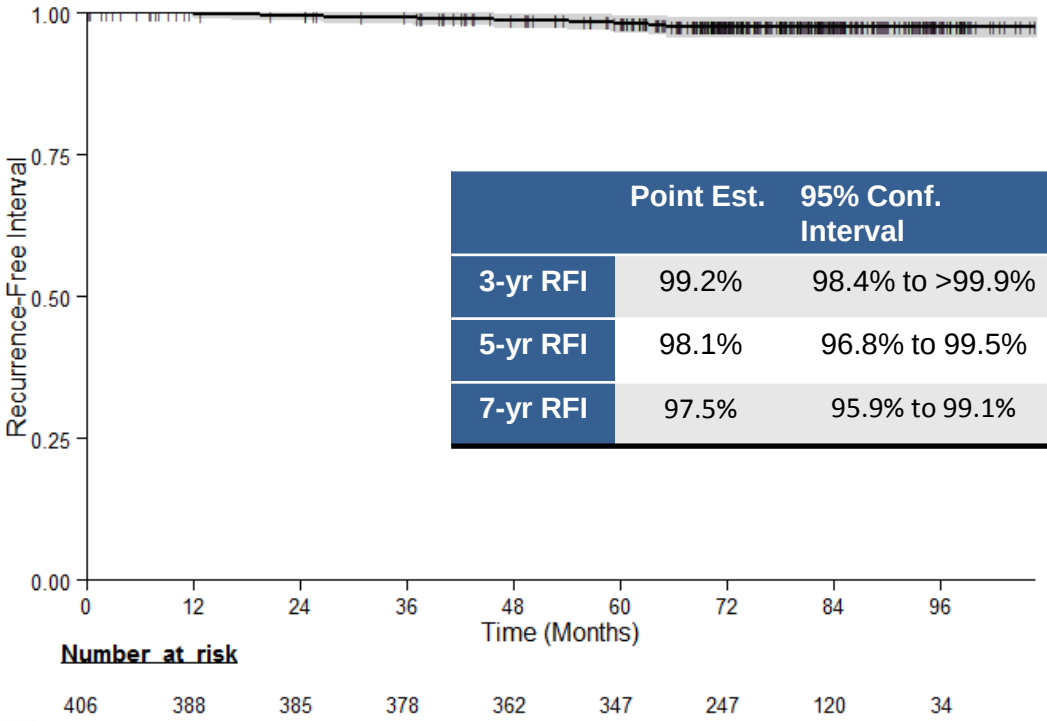
APT: Updated Recurrence Free Interval

RFI Events

Invasive Local/Regional Recurrence

Distant Recurrence

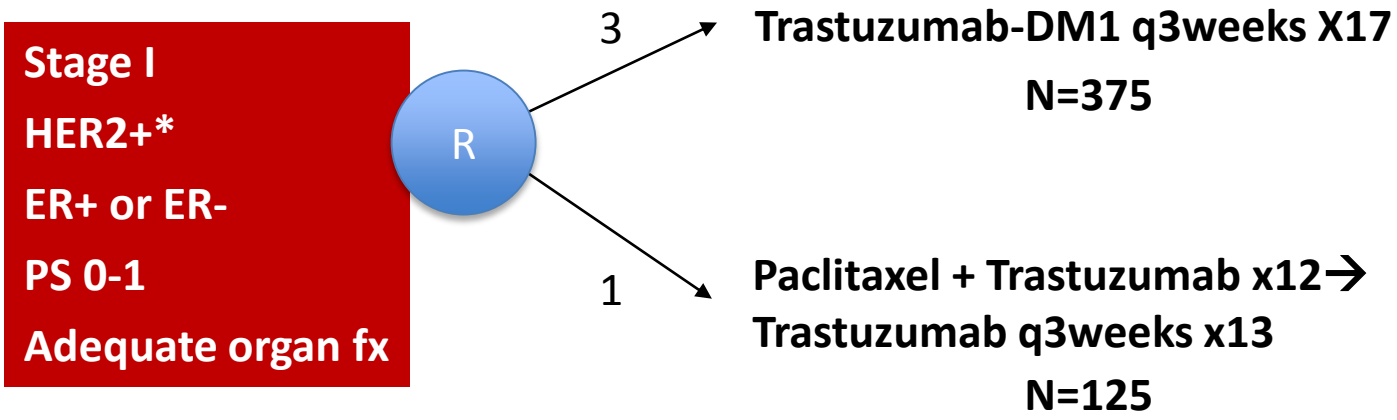
Death from Breast Cancer



	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

Tolaney et al, ASCO 2017

ATEMPT Trial Schema



N=500

All HER2 testing centrally confirmed

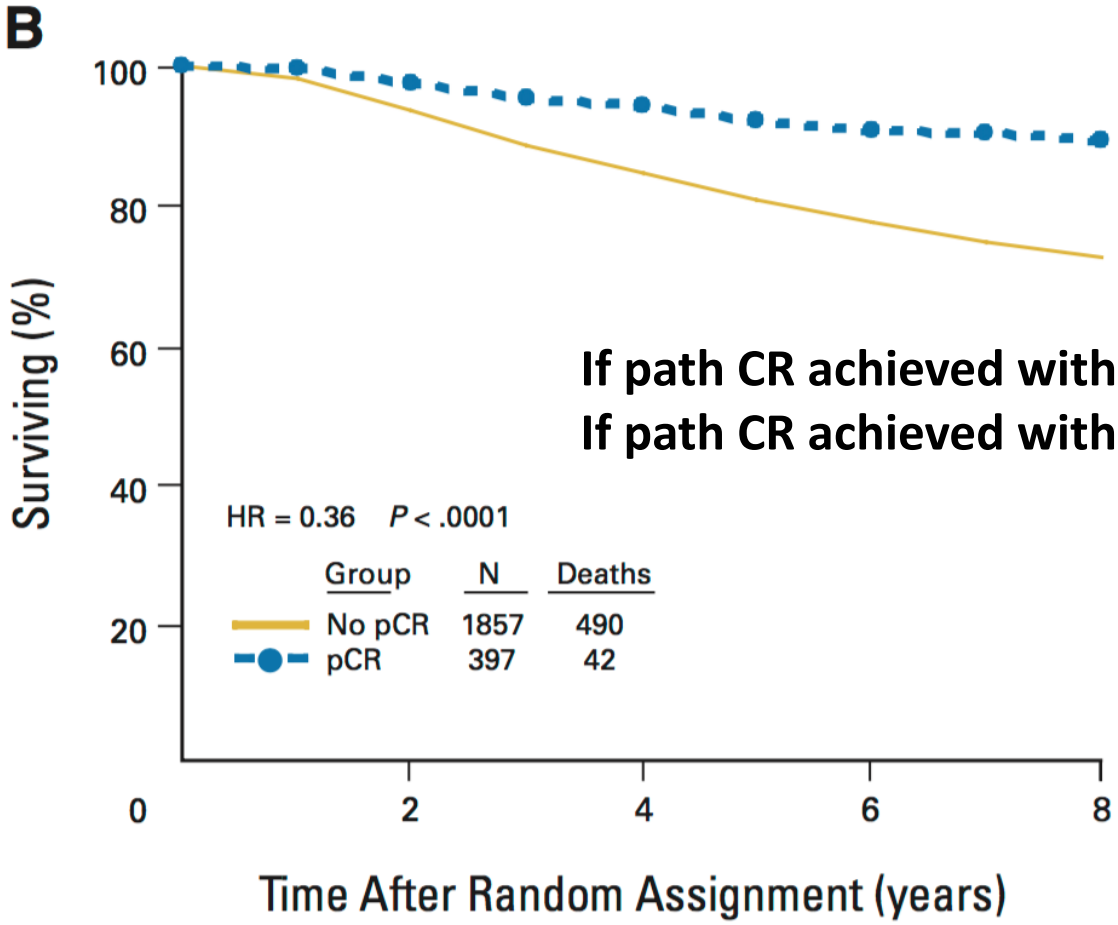
Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy

Adjuvant radiation therapy can be administered concurrently with study treatment.

ACCRUAL COMPLETED 2016

PI: Sara Tolaney, MD, MPH

Path CR is Predictive of Outcome in NSABP B-27
(and MAYBE it does not matter how path CR is achieved)



5 year DFS

If path CR achieved with AC 82%

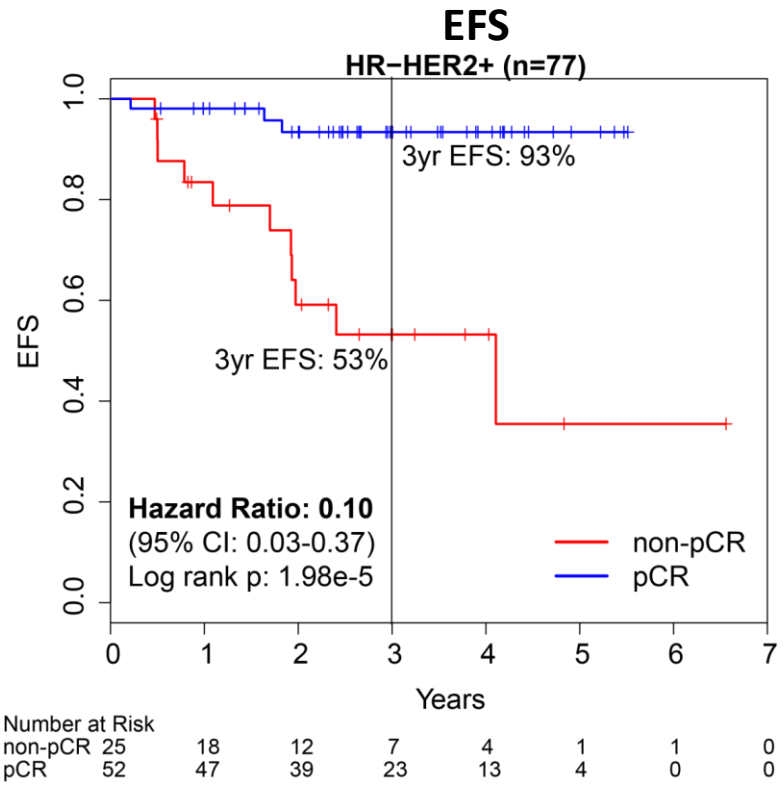
If path CR achieved with AC-T 84%

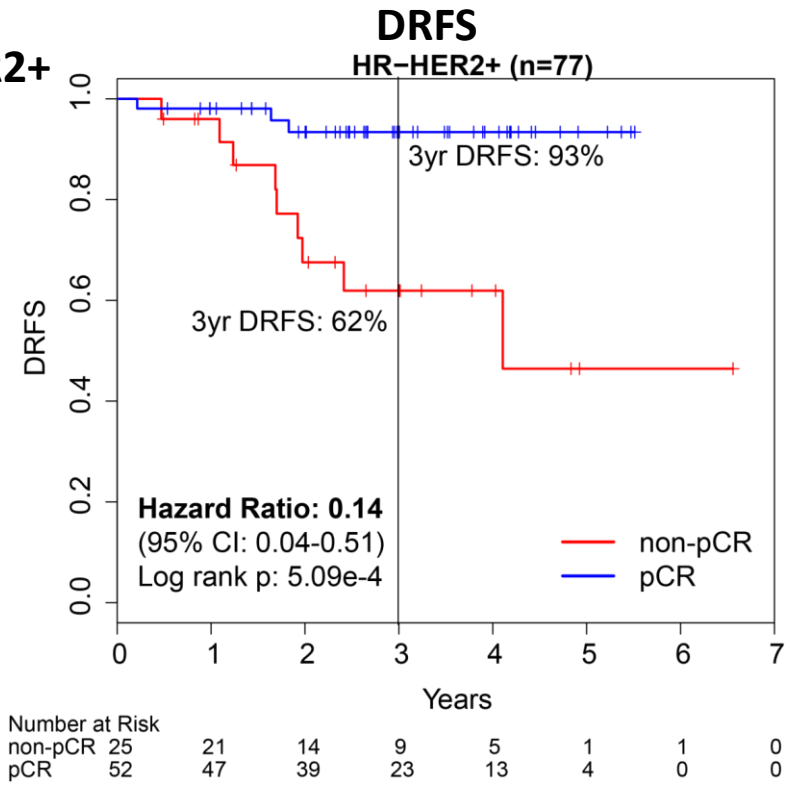
Rastogi, Anderson, Bear et al JCO 2008

Personal communication Terry Mamounas

pCR is Predictive of EFS and DRFS in HR–/HER2+

HR-HER2+



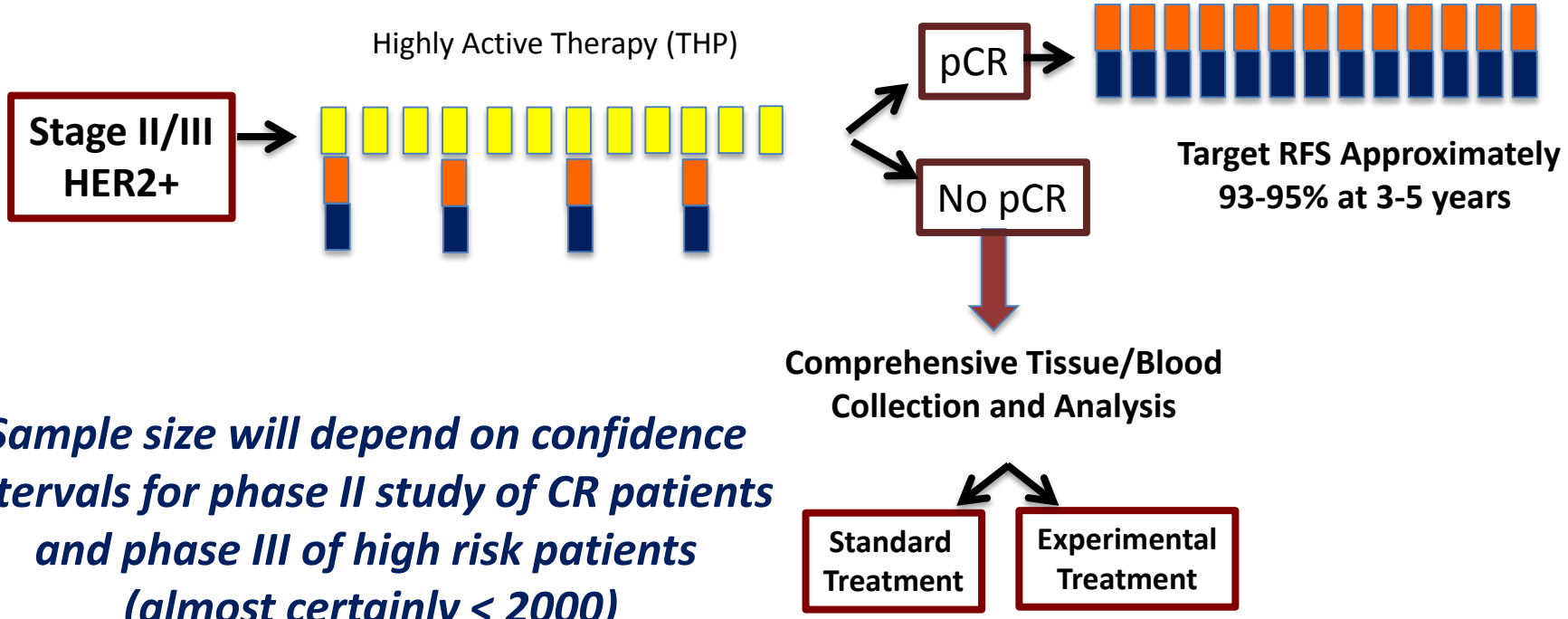


Yee et al, SABCS 2017

Maybe We Are Looking At The Role of Neoadjuvant Therapy The Wrong Way….

- Looking for new treatment approaches based on higher rates of path CR has not paid off to date (e.g. lapatinib, bevacizumab)
- Perhaps we should attempt treatment de-escalation in those with a path CR
- At the same time, we can evaluate resistance mechanisms and new treatments in those who do not obtain a path CR

A Design to Decrease Treatment, Assess Resistance, and Test New Therapies



Sample size will depend on confidence intervals for phase II study of CR patients and phase III of high risk patients (almost certainly < 2000)

A Trans-Atlantic Collaboration is Planned

The Future…
but not so far from now

Adjuvant vs Neoadjuvant Therapy

- Increasing use of neoadjuvant therapy for majority of HER2+, triple negative, and high grade ER+ breast cancer
- Goal will be to decrease extent of surgery and guide radiation
- May be used, particularly in HER2+ setting, as an *in vivo* "experiment" that will allow escalation and de-escalation of therapy

Triple Negative Disease

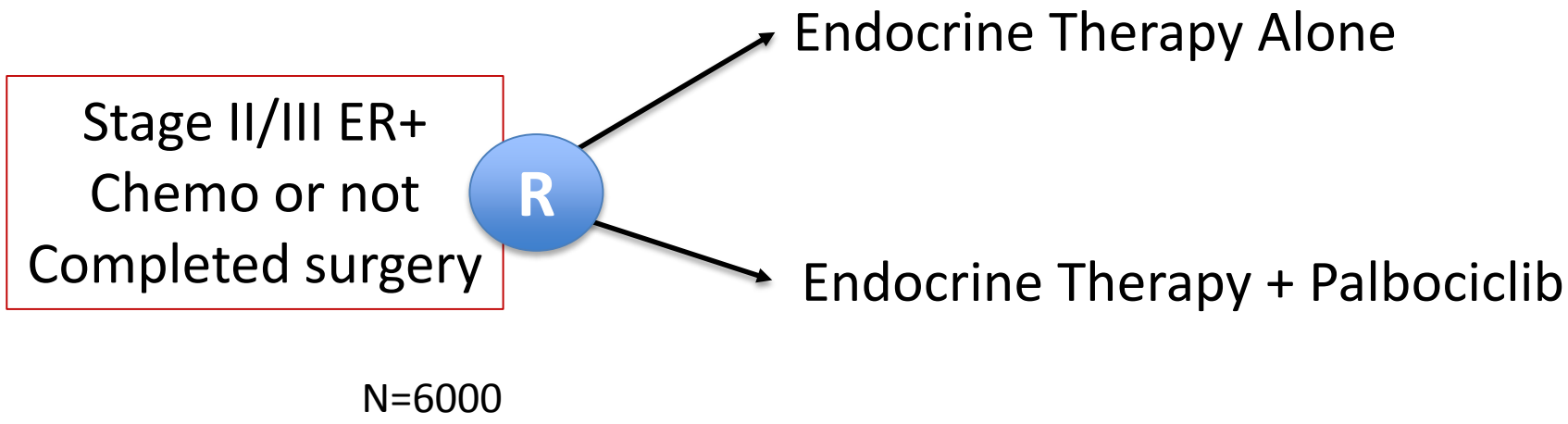
- Better characterization of subtypes, particularly in terms of responsiveness to immunotherapy
- Incorporation of new agents into early stage treatment
  - Immuno-oncology agents
  - Antibody drug congugatges
  - ?? Androgen receptor antagonists
  - PARP inhibitors for patients with BRCA mutations

ER+ Disease

- Continued decline in chemotherapy use
- Ultimately, I suspect will only give chemotherapy to a relatively small minority
- Better delineation of role/need for ovarian suppression
- No new hormonal agents, except perhaps for the selective estrogen receptor degraders, on the horizon
- But…

What About the CDK 4/6 Inhibitors?

Pallas Trial



Trial will complete accrual in next year
Analysis in next 2-3 years

Similar Trial Being Conducted with Abemaciclib

Late Recurrence

- Hormonal therapy has not eliminated problem, and simply extending hormonal therapy is unlikely to be the primary solution
- CDK 4/6 inhibitors may lessen problem
- We need a better understanding of the biology…why are so many tumors dormant and what leads them to be awakened?
- Watch for studies in this area

HER2+ Disease

- Huge successes have been made
- Need more/better therapy for a small percentage
- For others, the major question will be how much chemotherapy can be eliminated
- Testing will likely improve
- And subsets of HER2+ disease are likely to need somewhat different treatment strategies

Getting it right for each patient…

We need to allow biologic insights and thoughtful clinical trials to lead us to “just right”

Thanks to my group at Dana-Farber

- Nancy Lin
- Ian Krop
- Hal Burstein
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- Jennifer Ligibel
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- Judy Garber
- Craig Bunnell
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- Rachel Freedman
- Sara Tolaney
- Mike Hassett
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- Mehra Golshan
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- Tari King
- Beth Mittendorf
- Jennifer Bellon
- Julia Wong
- Rinna Punglia
- Stuart Schnitt
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- Rinath Jesselsohn
- Phil Poorvu
- Ada Waks
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- Otto Metzger
- Caroline Block
- Meredith Regan
- Christina Herold
- Brittany Bychkovsky