Late Recurrence and Death in ER Positive Early Stage Breast Cancer

The Next Frontier

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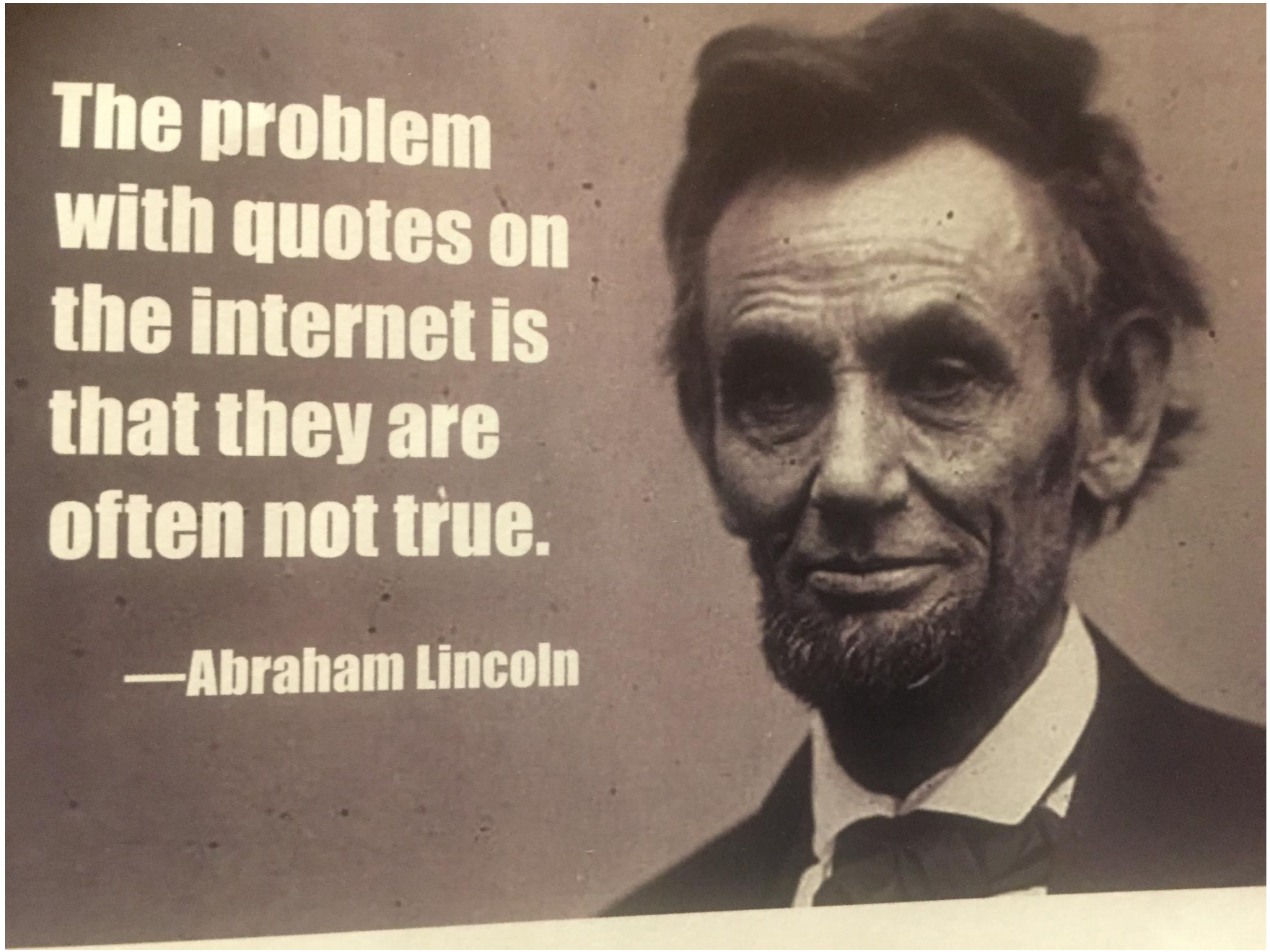
Breast Oncology Program

ROGEL CANCER CENTER
MICHIGAN MEDICINE


The problem with quotes on the internet is that they are often not true.
—Abraham Lincoln

DISCLOSURES

- **Circulating Tumor Cells**
  - **CellSearch**
    - **Laboratory and Clinical research funding from Veridex/Janssen Diagnostics/Menarini Silicon BioSystems (MSB)**
    - **Patent regarding circulating tumor cells licensed to MSB**
- **Other**
  - **Stock Options: InBiomotion**
  - **Consultant: Agendia, Cellworks, Cepheid, CVS Caremark, EPIC Sciences, Freenome, Lexent, Salutogenic Innovations, L-Nutra**
  - **Sponsored Clin Research: Merrimack Pharmaceuticals, Eli Lilly, Menarini/Silicon BioSystems, Puma Biotechnology, Pfizer, Astra Zeneca**
  - **Collaborated with GHI, manufacturer of 21-gene RS**

(no financial support or conflict)

Early Stage Breast Cancer

First: the Good News-

Breast Cancer Mortality in the U.S. Has Decreased Substantially Over the Last 30 Years

Increase in Breast Cancer Incidence but Decrease in Mortality

1975-2012

CA: A Cancer Journal for Clinicians; 66:31-42, 2015

For Black women, proportionally decreased by ~ 20%

For white women, proportionally decreased by ~ 40%

OVERALL: Breast Cancer Mortality Decreased by 36%

CA: A Cancer Journal for Clinicians 66:31-42, 2015

Early Stage Breast Cancer

First: the Good News-

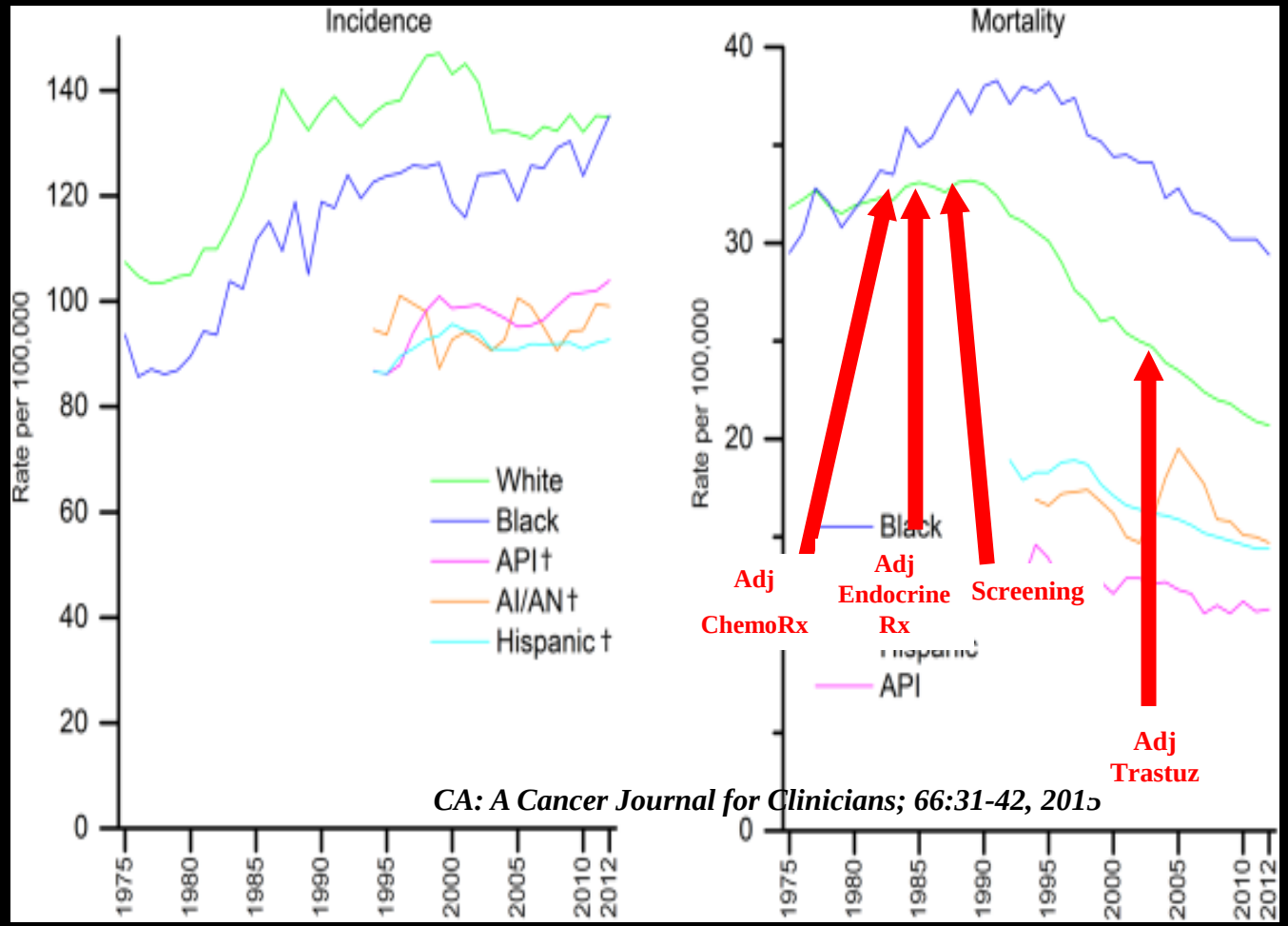
Breast Cancer Mortality in the U.S. Has Decreased Substantially Over the Last 30 Years

Why?

- **Screening**
- **Better and More Well Tolerated Therapies**

Increase in Breast Cancer Incidence but Decrease in Mortality

1975-2012



CA: A Cancer Journal for Clinicians; 66:31-42, 2015

OVERALL: Breast Cancer Mortality Decreased by 36%

CA: A Cancer Journal for Clinicians 66:31-42, 2015

Early Stage Breast Cancer

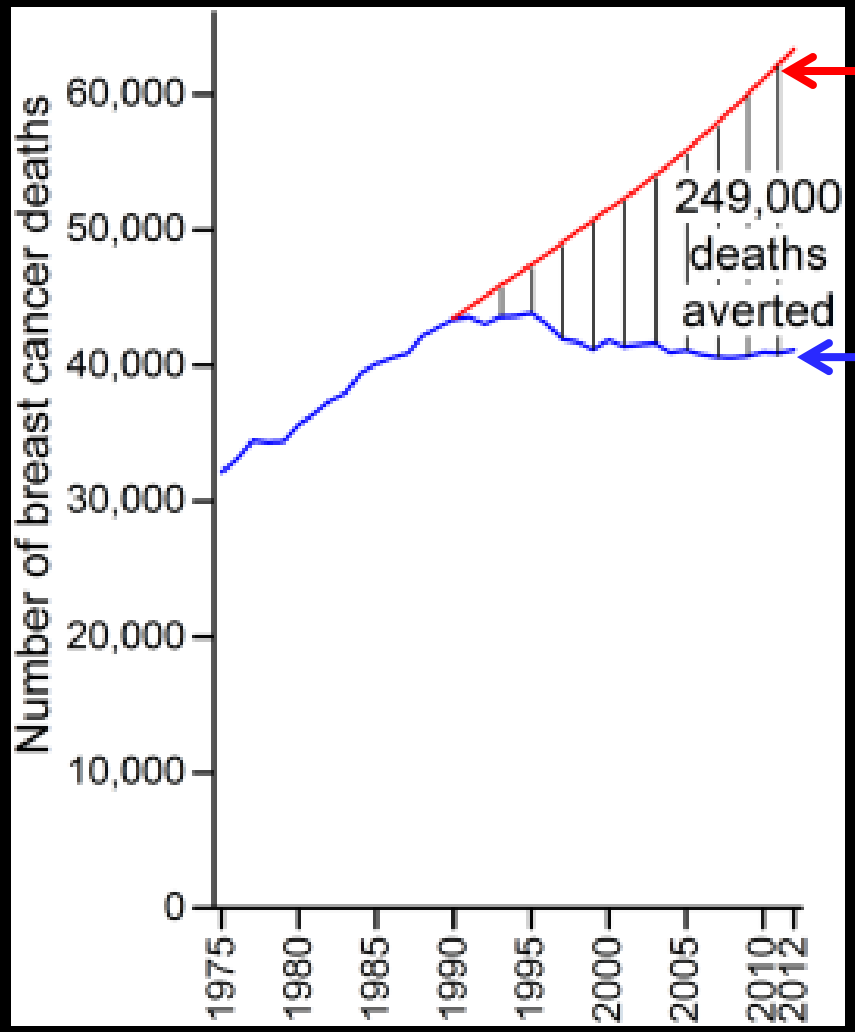
Second: Mixed News-

Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,

~40,000 U.S. Women Will Die of Br Ca in 2019

Deaths Averted by Advances in Breast Cancer Screening and Therapy

1990-2012



Anticipated Breast Cancer Deaths in US at unabated 1989 rate

Actual Number of Breast Cancer Deaths recorded in each year

CA: A Cancer Journal for Clinicians 66:31-42, 2015

Early Stage Breast Cancer

Second: Mixed News-

Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,

~40,000 U.S. Women Will Die of Br Ca in 2019

Who Are These Patients?

- **All Types of Breast Cancers**
- **Disproportionally those with ER Positive Disease Who Will Experience Late Recurrences**

ER Positive Breast Cancer: Adjuvant Endocrine Therapy

Principle #1

5 years of adjuvant ET decreases risk of recurrence and mortality in ER POS BrCa by 40-50%

- **Tam vs. Nil**
- **AI vs. Tam**

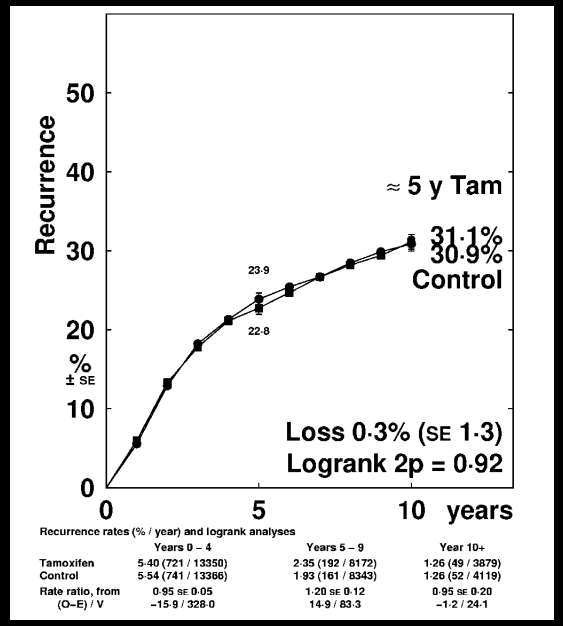
Early Breast Cancer Trialists' Collaborative Group. Lancet. 365:1687-717, 2005

Dowsett, et al. Aromatase Inhibitor Overview Group, J Clin Oncol 28:509-18, 2010

ER Positive Breast Cancer:
Adjuvant Endocrine Therapy

~5 years Tamoxifen vs NOT

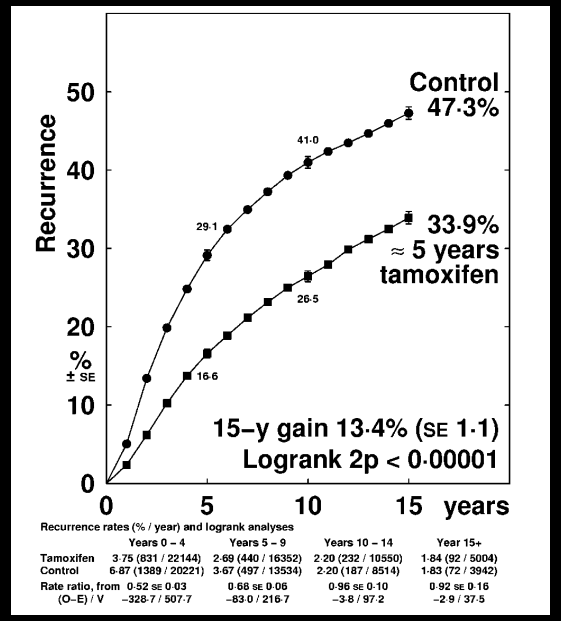
ER Poor



Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Year 10+
Tamoxifen	5·40 (721 / 13350)	2·35 (192 / 8172)	1·26 (49 / 3879)
Control	5·54 (741 / 13366)	1·93 (161 / 8343)	1·26 (52 / 4119)
Rate ratio, from (O–E) / V	0·95 SE 0·05 −15·9 / 328·0	1·20 SE 0·12 14·9 / 83·3	0·95 SE 0·20 −1·2 / 24·1

ER Pos



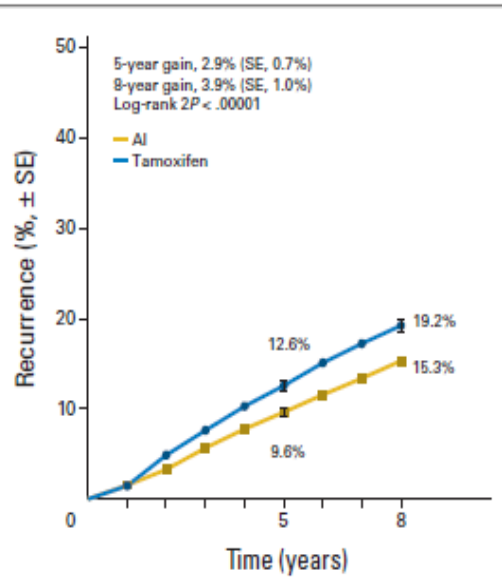
Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	3·75 (831 / 22144)	2·69 (440 / 16352)	2·20 (232 / 10550)	1·84 (92 / 5004)
Control	6·87 (1389 / 20221)	3·67 (497 / 13534)	2·20 (187 / 8514)	1·83 (72 / 3942)
Rate ratio, from (O–E) / V	0·52 SE 0·03 −328·7 / 507·7	0·66 SE 0·06 −83·0 / 216·7	0·96 SE 0·10 −3·8 / 97·2	0·92 SE 0·16 −2·9 / 37·5

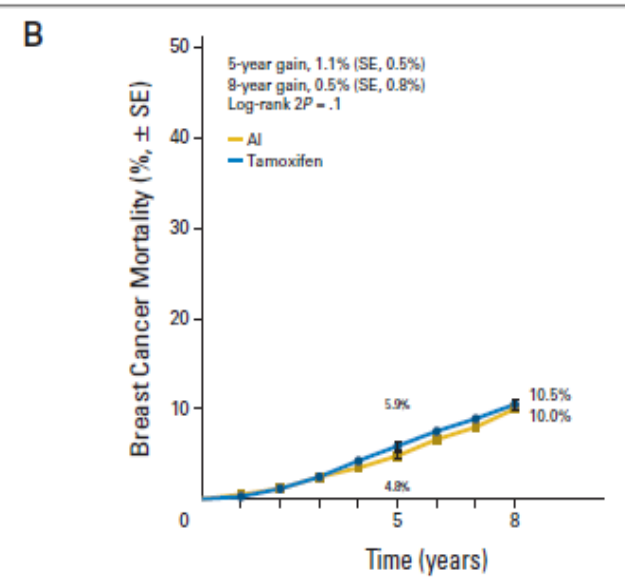
Early Breast Cancer Trialists' Collaborative Group. Lancet. 365:1687-717, 2005

AI vs. Tamoxifen

Recurrence



Br Ca Mortality



Dowsett, et al. Aromatase Inhibitor Overview Group, J Clin Oncol 28:509-18, 2010

ER Positive Breast Cancer: Adjuvant Endocrine Therapy

Principle #2

The risk for recurrence of ER POS BrCa

- **Is highest in first 4-6 years**
- **Never declines to zero, even as long as 20-30 years after diagnosis**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

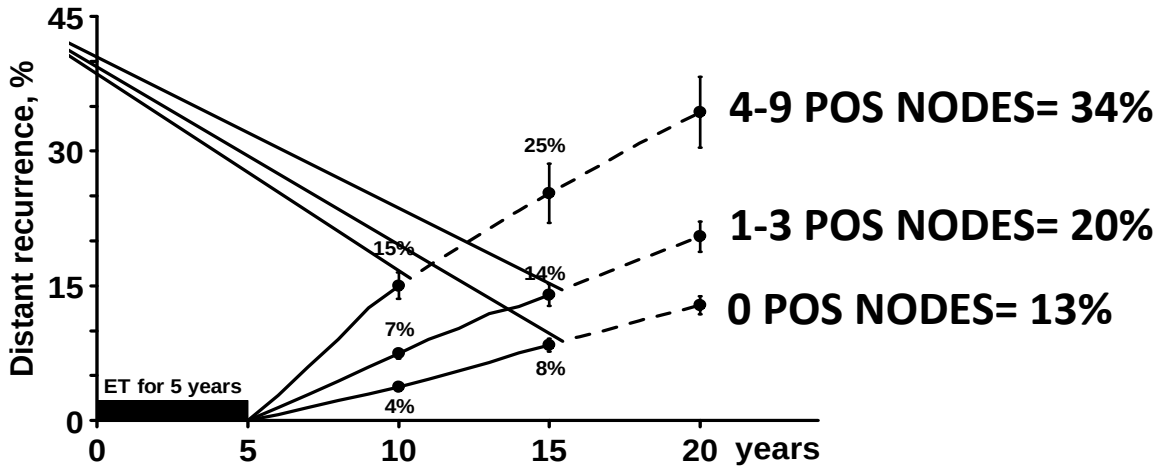
20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D., Christina Davies, B.M., B.Ch., Carolyn Taylor, B.M., B.Ch., Ph.D., Paul McGale, Ph.D., Richard Peto, F.R.S., Kathleen I. Pritchard, M.D., Jonas Bergh, M.D., Ph.D., Mitch Dowsett, Ph.D., and Daniel F. Hayes, M.D., for the EBCTCG*

N Engl J Med 377:1836-1846, 2017

Distant Recurrence by Nodal Status & T Size
Patients Without Recurrence @ 5 Yrs; Years 5-20

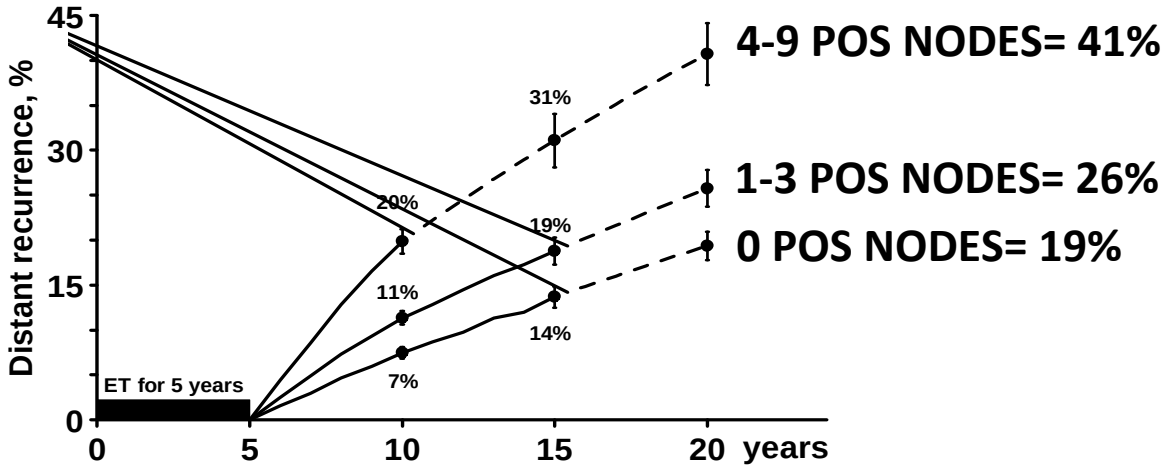
T1 only



No. at risk (and, in each 5-year period, no. of events and annual rate)

T1N4-9	3832	(391, 3.2%)	1193	(68, 2.6%)	214	(11, 2.2%)	32
T1N1-3	14342	(734, 1.5%)	5138	(162, 1.5%)	817	(35, 1.7%)	154
T1N0	19402	(509, 0.8%)	8020	(218, 1.0%)	2345	(58, 1.0%)	440

T2 only



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N4-9	4952	(688, 4.5%)	1517	(106, 3.3%)	285	(12, 1.7%)	51
T2N1-3	10950	(842, 2.4%)	3551	(134, 1.8%)	614	(28, 1.9%)	114
T2N0	9445	(512, 1.6%)	3901	(152, 1.4%)	1129	(37, 1.3%)	218

Pan et al NEJM 2017

Association of TN Status and grade with Distant Recurrence

		Number of women event-free at year 5		Annual rate (%) of distant recurrence		Cumulativ risk, year 5-20 (%)
		Total	Chemotherapy scheduled	Years 5-10	Years 10-20	
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
Diameter in mm, N0 only	**≤10 (T1a/b)**	5,527	910 (16%)	0.5	0.8	10
	11-20 (T1c)	13,875	4,034 (29%)	0.8	1.1	14
	21-30 (T2)	6,700	2,859 (43%)	1.5	1.4	19
	31-50 (T2)	2,745	1,333 (49%)	1.7	1.4	20
Tumor grade, T1N0 only	**Low**	3,524	401 (11%)	0.4	0.8	10
	Moderate	7,363	1,861 (25%)	0.7	1.0	13
	High (poorly differentiated)	3,054	1,414 (46%)	0.9	1.5	17

Pan et al NEJM 2017

Conclusions: Late Recurrence in ER Pos Br Ca

- **The risk of late distant recurrence and Br Ca mortality is relentless in women with ER POS Disease who stop ET at 5 years**
  - **Annual rate is constant for at least 15 years**
- **After 5 years, the annual event rate is a function of original**
  - **Nodal status**
  - **Size**
  - **Grade**
  - **NOT: PgR, HER2, other factors**
- **Modern estimates may be less, tempered by:**
  - **Observed better prognosis over last decade (TailoRx, RxPonder taking longer to report)**
    - **Earlier diagnosis**
    - **Better staging**
    - **More effective ET, chemotherapy and anti-HER2 therapies**
    - **Other?**

ER Positive Breast Cancer: Adjuvant Endocrine Therapy

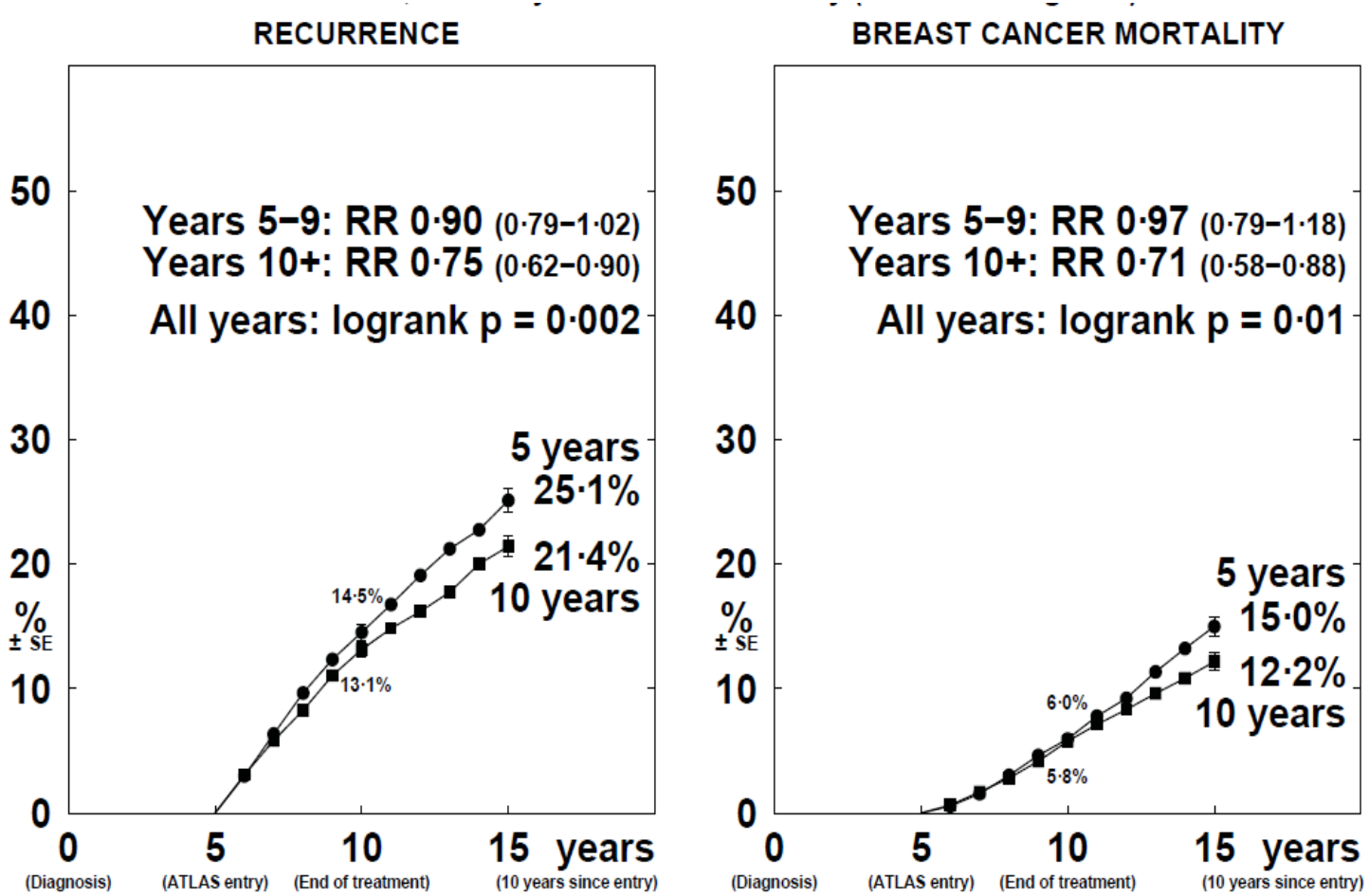
Principle #3

Extended ET beyond 5 years further reduces the risk of recurrence

Extended TAMOXIFEN After 5 Years of Tamoxifen

Reduced Recurrence and Death in ER POS Breast Cancer

ATLAS TRIAL: Tamoxifen after ~ 5 Yrs of TAM



Davies, et al., Lancet 381:805-16, 2013

Extended AI Treatment After 5+ Years of Prior Endocrine Therapy (Mostly Tamoxifen):
Methods

Oxford Overview:

Meta-analysis of individual patient data on postmenopausal women with ER-positive (99%) or ER-unknown (1%) tumours in trials of:

Any third-generation AI (exemestane, anastrozole, letrozole) vs no further adjuvant therapy **following**:

a) ≈ 5 years of tamoxifen alone (n=7,500)

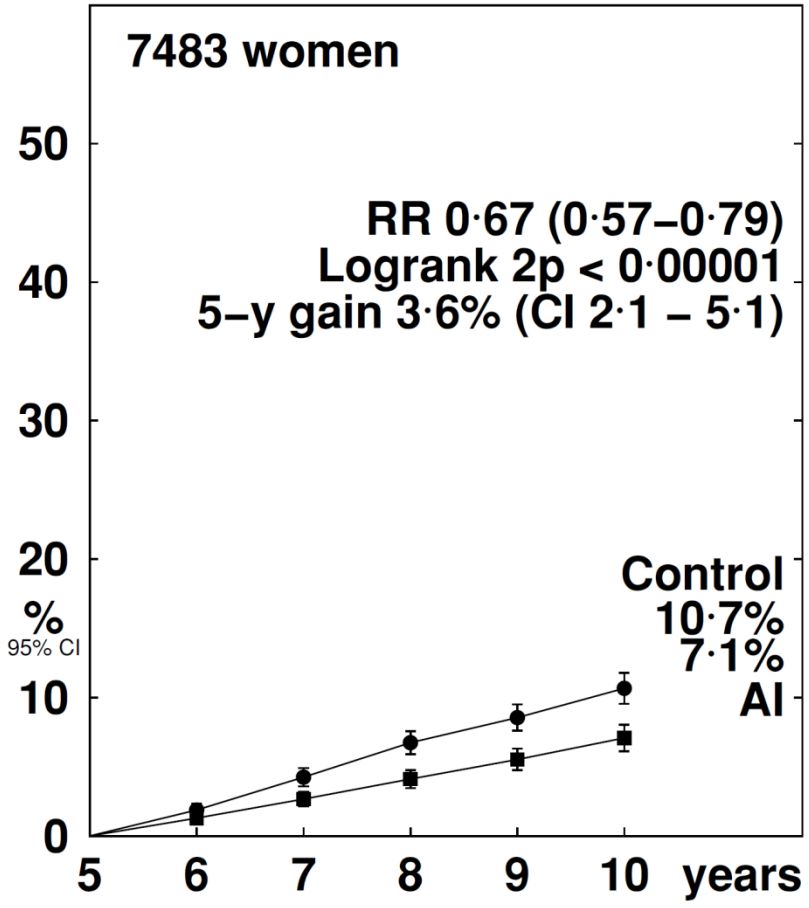
b) ≈ 5-10 years of tamoxifen then AI (n=12,600)

c) ≈ 5 years of AI alone (n=4,800)

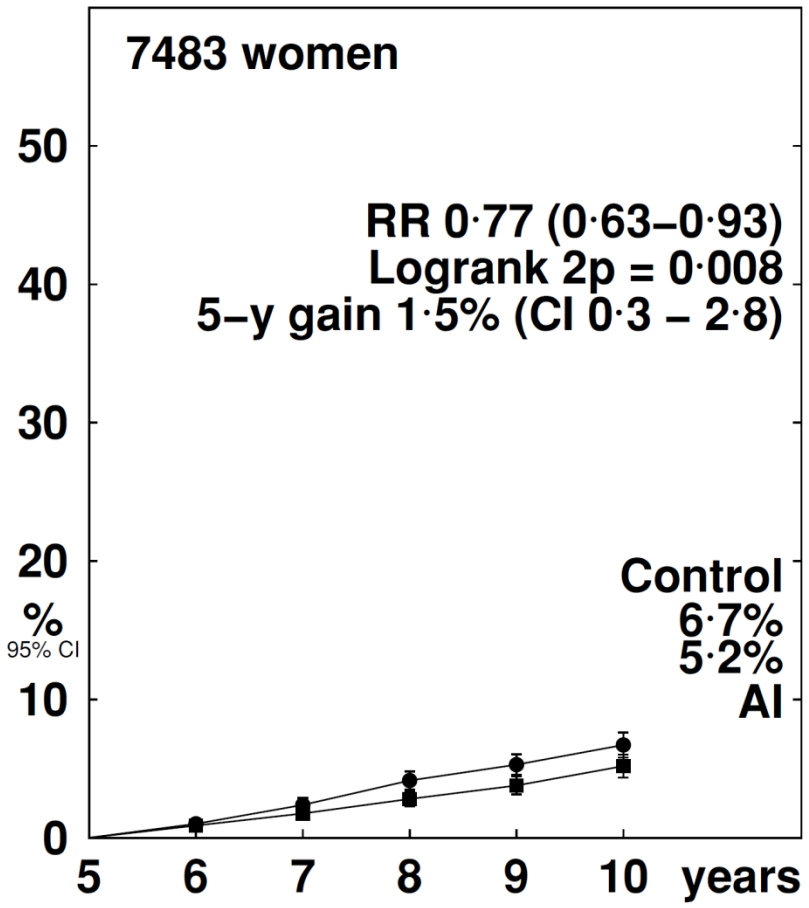
Extended Aromatase Inhibitor After ≈5 Years of Tamoxifen

Reduced Recurrence and Death in ER POS Breast Cancer

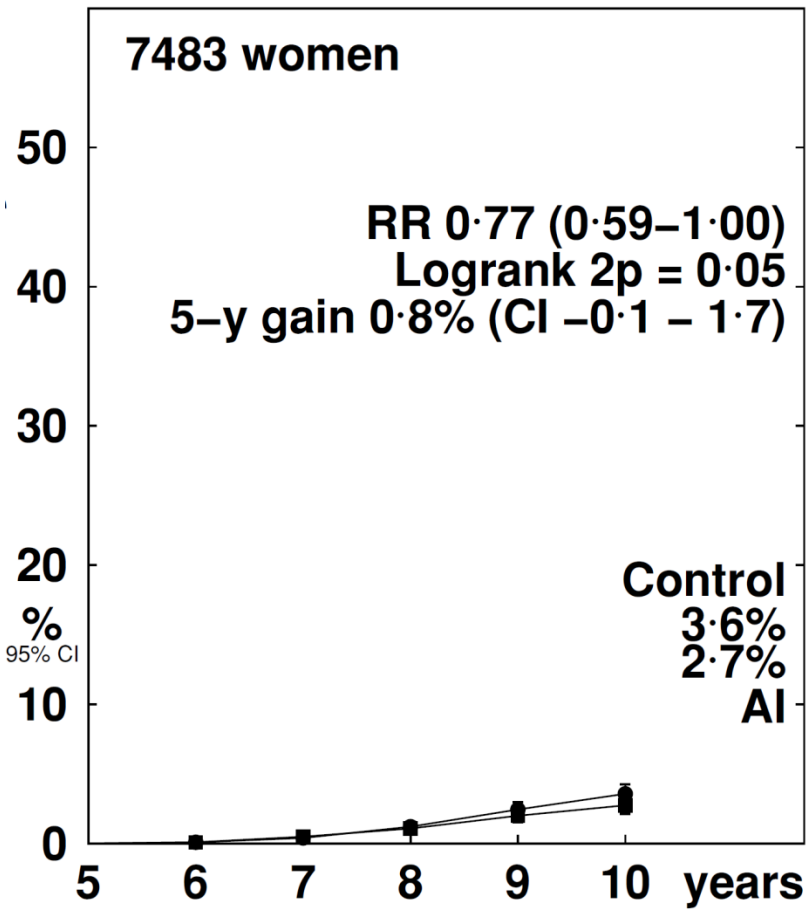
Any recurrence (distant, local or new primary)



Distant Recurrence

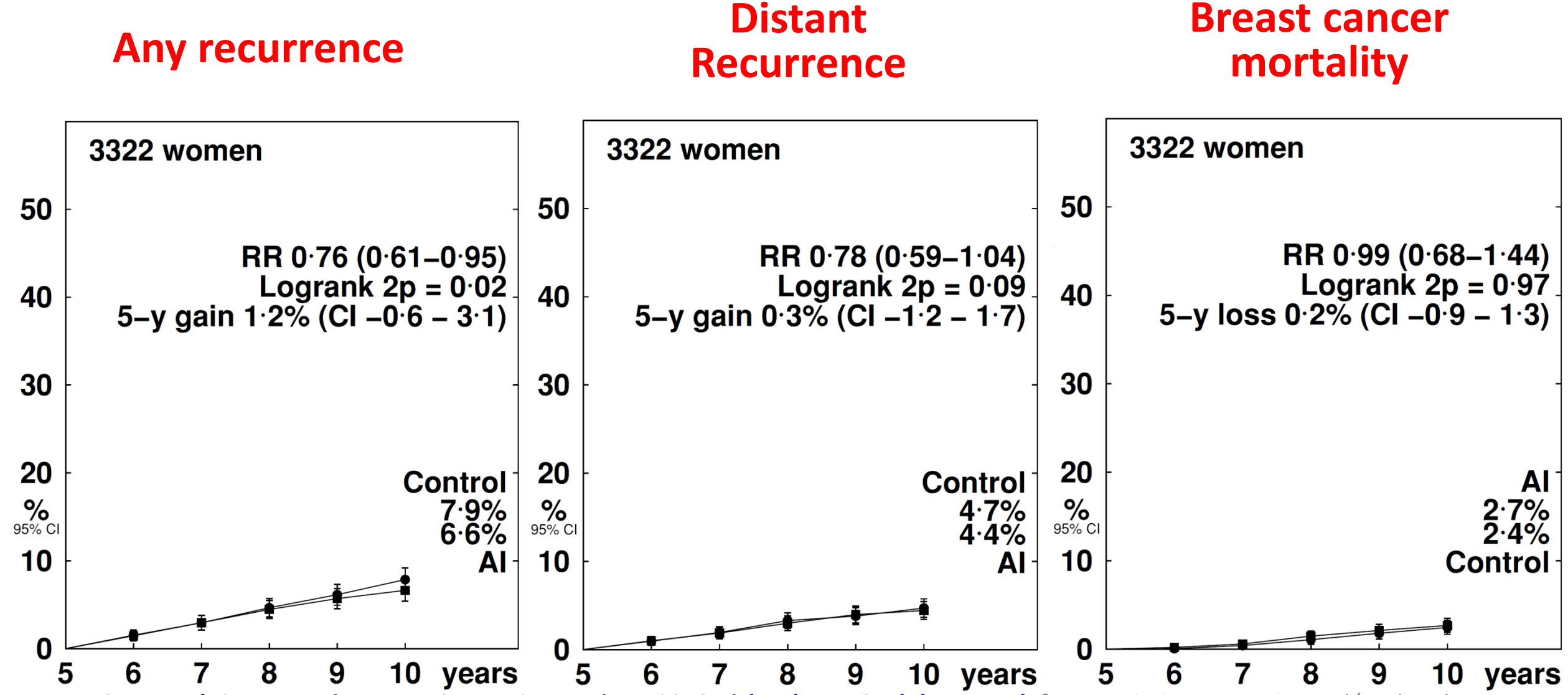


Breast cancer mortality



Gray et al, San Antonio Breast Cancer Symposium, 2018; richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute

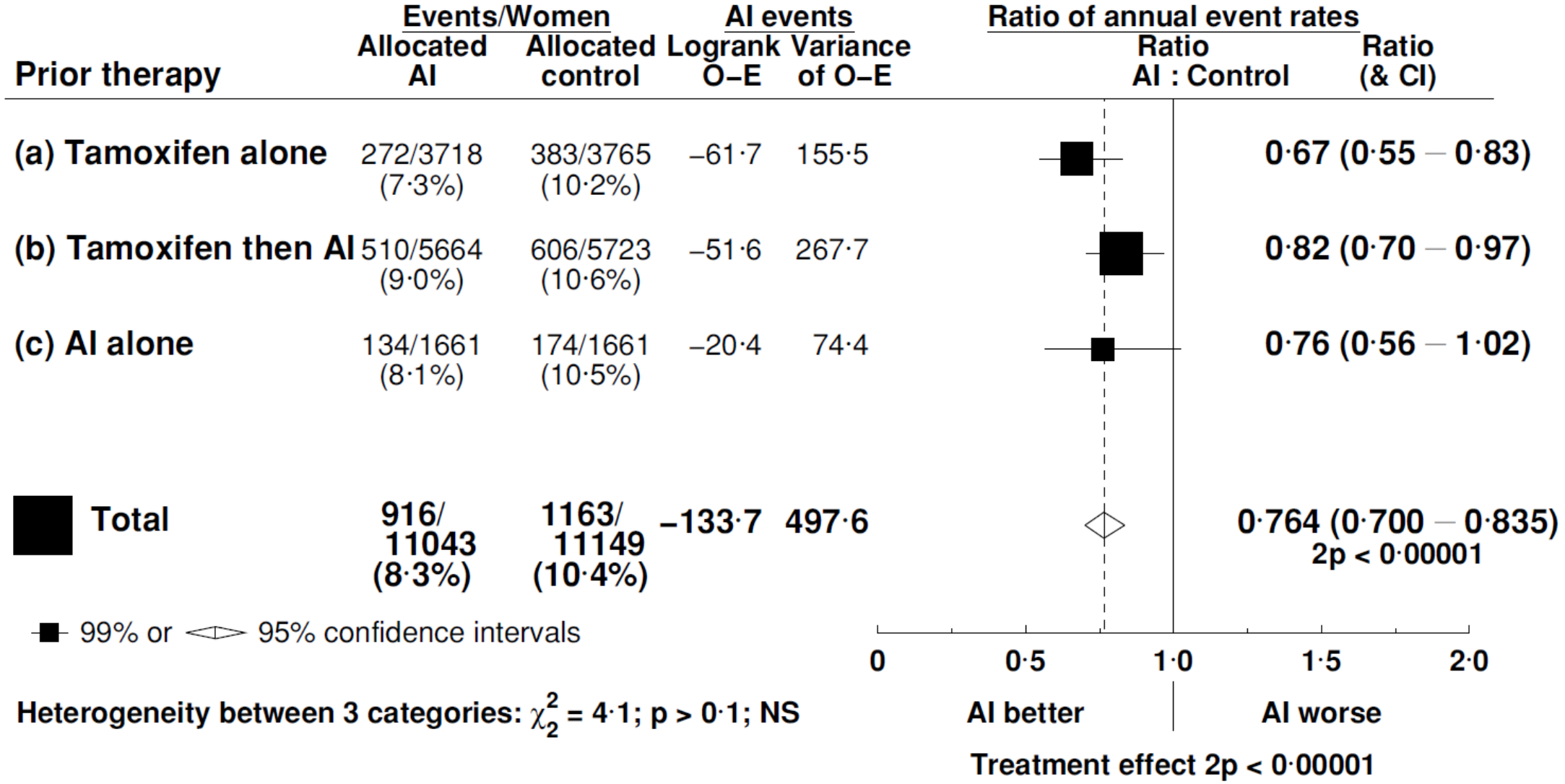
Extended AI Following 5 Years of AI Alone
Unclear if Reduced Recurrence and Death Overall?



Gray et al, San Antonio Breast Cancer Symposium, 2018; richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute

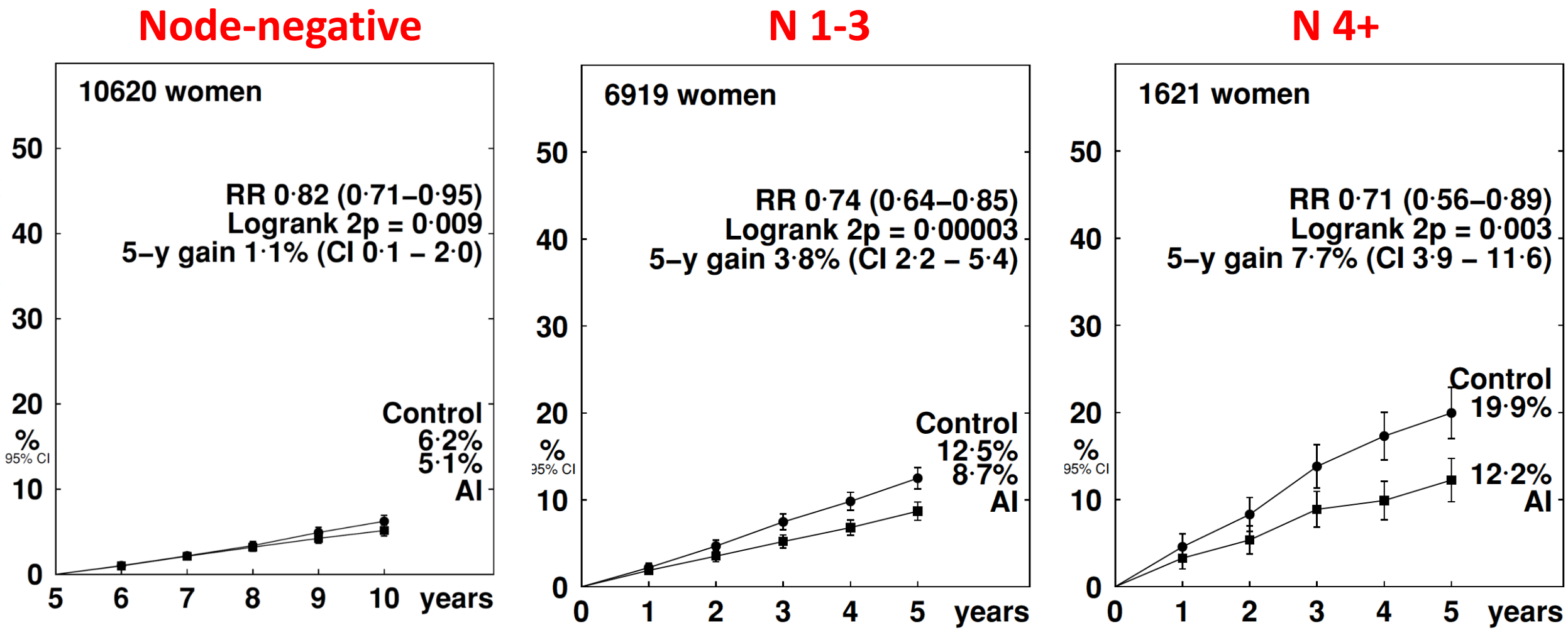
Effect of Extended AI on Recurrence

By Prior Endocrine Therapy



BUT....

Extended AI Following 5 Years of AI Alone by Nodal Status

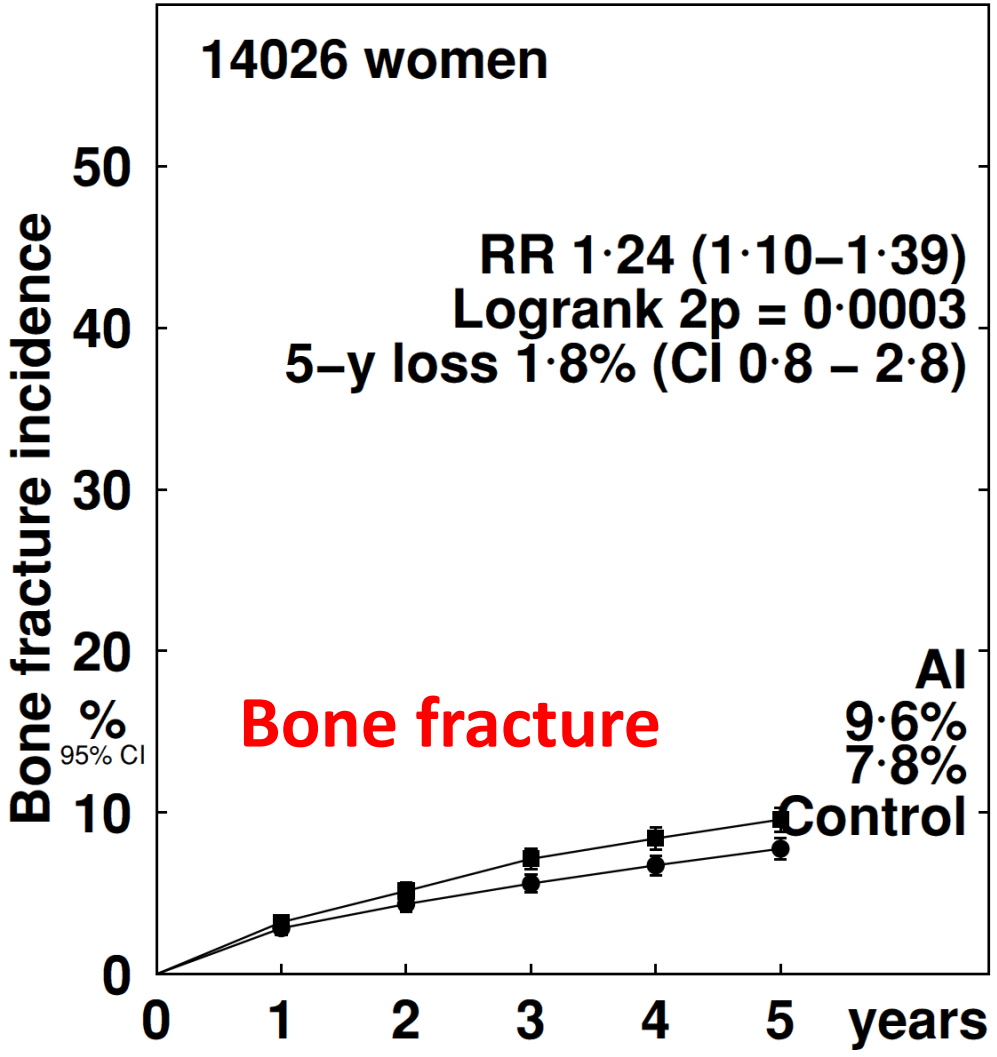


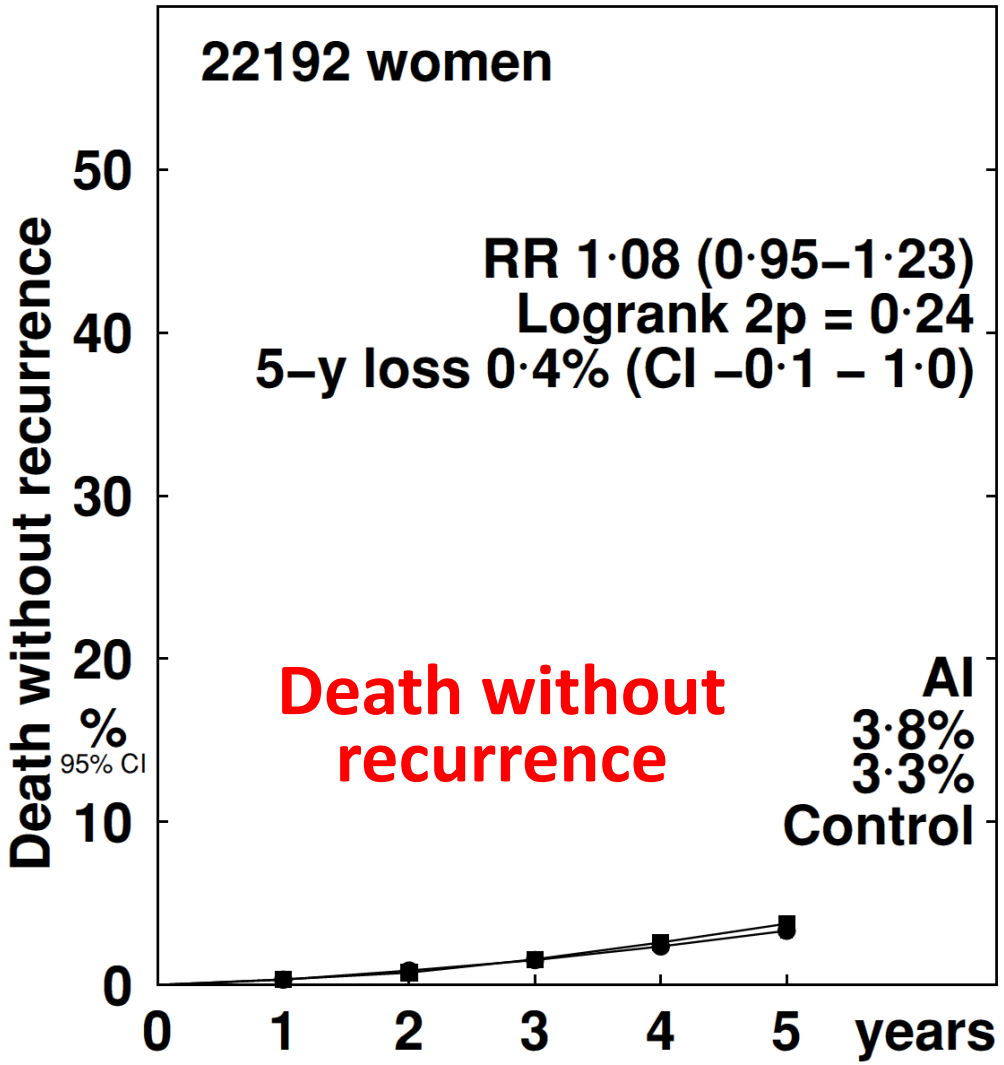
Gray et al, San Antonio Breast Cancer Symposium, 2018; richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute

BUT....

Extended AI Therapy

Bone Fracture and Death Without Recurrence





Gray et al, San Antonio Breast Cancer Symposium, 2018; richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute

Conclusions: Benefits and Risks of Extended AI Rx
ER Positive Br Ca Patient Free of Disease After 5 Yrs of Tamoxifen

- **≈1/3 reduction in recurrence if prior ≈5 years of tamoxifen**
- **≈ 1/5 reduction in risk of recurrence if prior AI**
  - **Preceded or not by prior tamoxifen**
- **Absolute benefits higher if worse prognosis (many + nodes)**
- **Risk of bone fracture increased by ≈1/4**
  - **Can be tempered with bisphosphonate therapy**

Alternating Extended Adjuvant AI Every 3 Months
The SOLE Trial

Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial

Marco Colleoni, Weixiu Luo, Per Karlsson, Jacquie Chirgwin, Stefan Aebi, Guy Jerusalem, Patrick Neven, Erika Hitre, Marie-Pascale Graas, Edda Simoncini, Claus Kamby, Alastair Thompson, Sibylle Loibl, Joaquín Gavilá, Katsumasa Kuroi, Christian Marth, Bettina Müller, Seamus O'Reilly, Vincenzo Di Lauro, Andrea Gombos, Thomas Ruhstaller, Harold Burstein, Karin Ribi, Jürg Bernhard, Giuseppe Viale, Rudolf Maibach, Manuela Rabaglio-Poretti, Richard D Gelber, Alan S Coates, Angelo Di Leo, Meredith M Regan, Aron Goldhirsch*, on behalf of the SOLE Investigators†*

Summary

Background In animal models of breast cancer, resistance to continuous use of letrozole can be reversed by withdrawal and reintroduction of letrozole. We therefore hypothesised that extended intermittent use of adjuvant letrozole would improve breast cancer outcome compared with continuous use of letrozole in postmenopausal women.

Lancet Oncol 2017

Published Online November 17, 2017

http://dx.doi.org/10.1016/

Alternating Extended Adjuvant AI Every 3 Months

The SOLE Trial

4884 Pts after 5 years of AI (with or without Preceding Tam)
Randomly Assigned

Continuous Letrozole

Intermittent Letrozole

15 excluded from ITT population
- 8 at a non-adherent centre
- 2 randomly assigned in error
- 5 withdrew consent for all participation

18 excluded from ITT population
- 2 inadequate documentation of informed consent
- 6 at a non-adherent centre
- 1 major eligibility violation*
- 9 withdrew consent for all participation

2426 included in ITT population
Treatment
- 2411 initiated treatment
  - 15 never started treatment

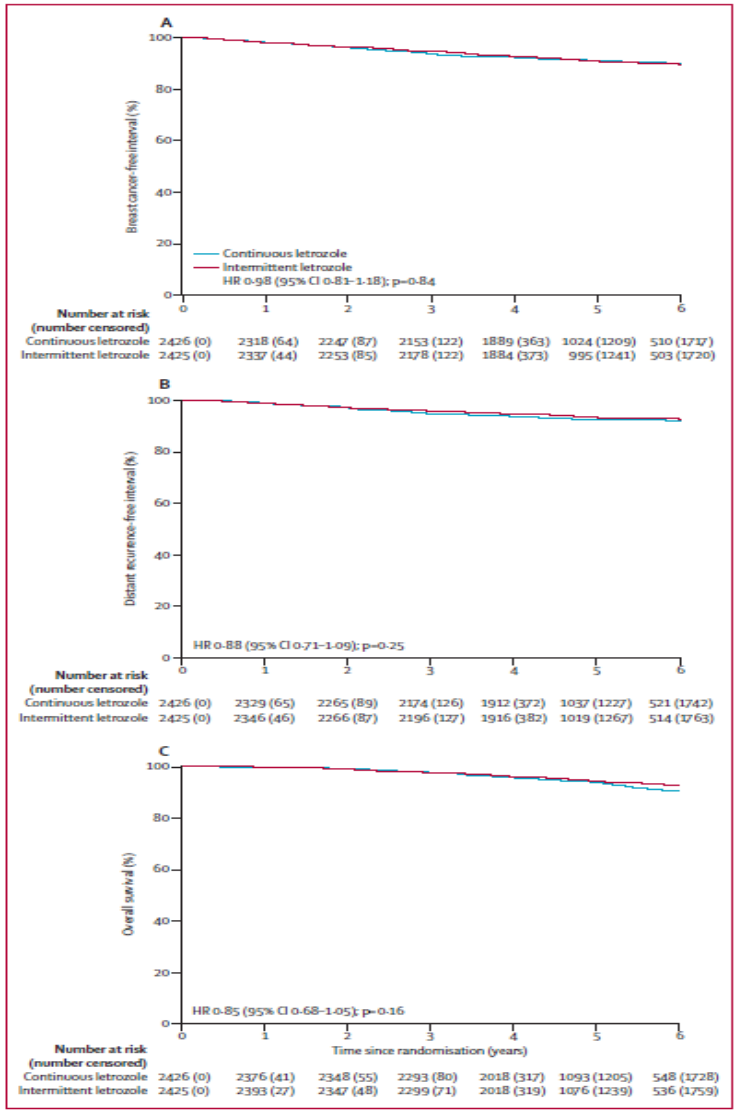
Follow-up
- 109 withdrew consent during follow-up
- 20 lost to follow-up

2425 included in ITT population
Treatment
- 2417 initiated treatment
  - 8 never started treatment

Follow-up
- 89 withdrew consent during follow-up
- 30 lost to follow-up

2426 patients included in ITT analysis
2411 patients included in safety analysis

2425 patients included in ITT analysis
2417 patients included in safety analysis



RS

DRFS

OS

Colleoni, M, et al., Lancet Oncol 19:127-138, 2018

ER Positive Breast Cancer:
Extended Adjuvant Endocrine Therapy

Principle #4

Most (80-90%) patients who have received 5 years of endocrine therapy without a recurrence are unlikely to die of metastatic BrCa

And…

…Adjuvant ET has significant side effects

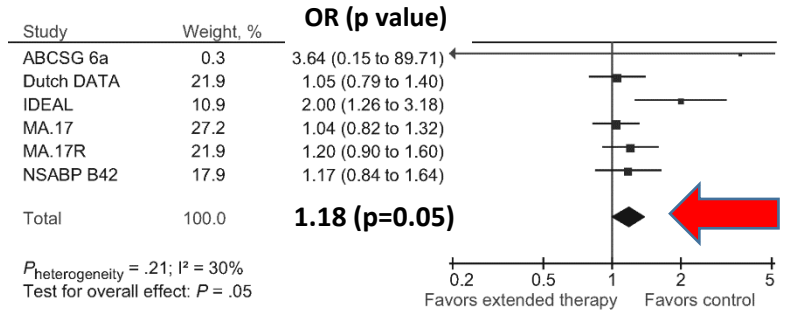
- **Life changing/Quality of Life**
  - ***Tamoxifen and Aromatase Inhibitors***
    - **Hot flushes, sexual dysfunction, myalgias/arthralgias**
    - **? Cognitive dysfunction)**
- **Life threatening (persist as long as Rx Continues)**
  - ***Tamoxifen***
    - **Thrombosis**
    - **Endometrial Cancer**
  - ***Aromatase Inhibitors***
    - **Osteoporosis/Fracture**
    - **? Cardiovascular**

Life Threatening Toxicities of Extended AI Therapy After 5 years ET

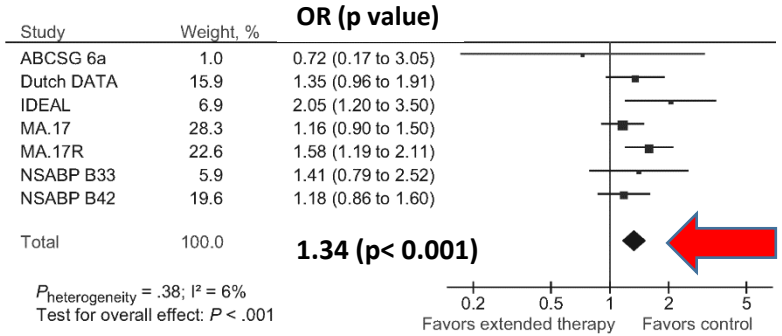
Published Trial Overview

Absolute Diff (Longer vs. Not): *7% vs. 6%*

A Cardiovasc Events



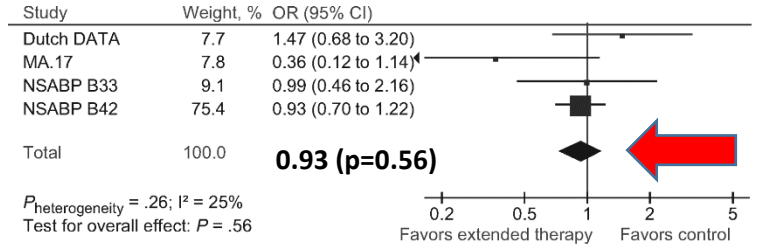
B Bone Fractures



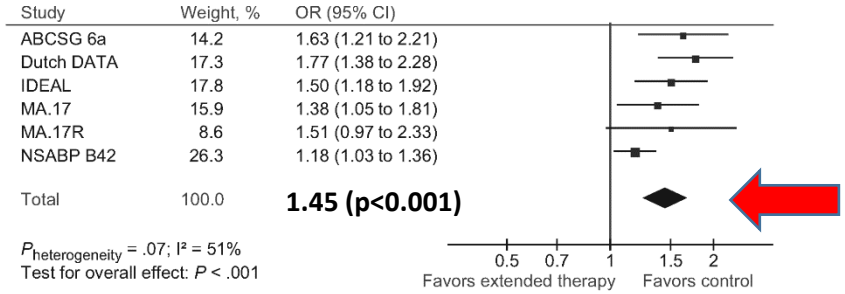
Absolute Diff (Longer vs. not): *6.3% vs. 4.8%*

2.2% vs. 2.4%

C Non-Br 2nd Cancers



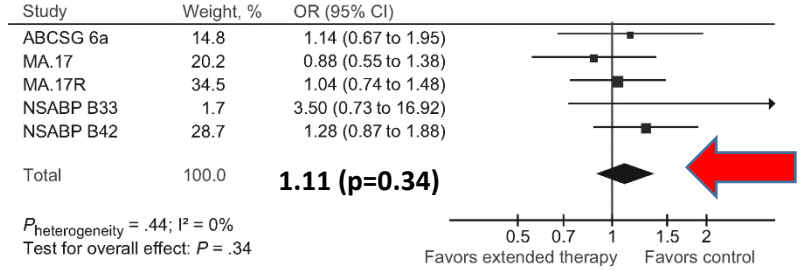
D Discontinuation



17% vs. 13.4%

3.3% vs. 2.9%

E Death without Br Ca Recurrence



Goldvaser, H, et al., J Natl Cancer Inst 110:2018

Taken Together, These Data Support-

- Consideration of extended adjuvant endocrine therapy
  - Reduces risk by 1/3-1/2 for most patients
- There might be a group who could consider stopping
  - Not clear who that is
- Further studies of determination of late risk
  - Biology of primary tumor (multi-gene expression assays, etc)
  - Real time identification of risk

Does Everyone Need to Take Extended ET?

- **Potential determinants of late risk other than nodal status, tumor size and grade**
  - **Biology of primary tumor (multi-gene expression assays, etc)**
  - **Identification of dormant disease with recurrence potential:**
    - **Disseminated or circulating tumor cells (DTC, CTC)**
    - **Circulating cell free tumor DNA (cftDNA)**
    - **Circulating protein or metabolites?**

Does Everyone Need to Take Extended ET?

- **Are there better prognostic factors in the Primary Cancer than just lymph node, tumor size, and grade for recurrence after 5 years of adjuvant ET?**
  - ***Multi-parameter molecular biomarker tests***

In 1 or 2 Retrospective Data Sets, Each of These Assays Has Been Reported to Separate Patients with Low from High Risk for Late Recurrence

HOWEVER:

ASCO Tumor Marker Guidelines Panel did not feel that the evidence was of sufficiently high level to recommend that any one of these assays should be used to decide whether to continue or stop extended ET after 5 years

Harris, Ismaila, McShane, Andre, Collyar, Gonzalez-Angulo, Hammond, Kuderer, Liu, Mennel, Van Poznak, Bast and Hayes, J Clin Oncol 34:1134-50, 2016

Does Everyone Need to Take Extended ET?

- **Potential determinants of late risk other than nodal status, tumor size and grade**
  - **Biology of primary tumor (multi-gene expression assays, etc)**
  - **Identification of dormant disease with recurrence potential:**
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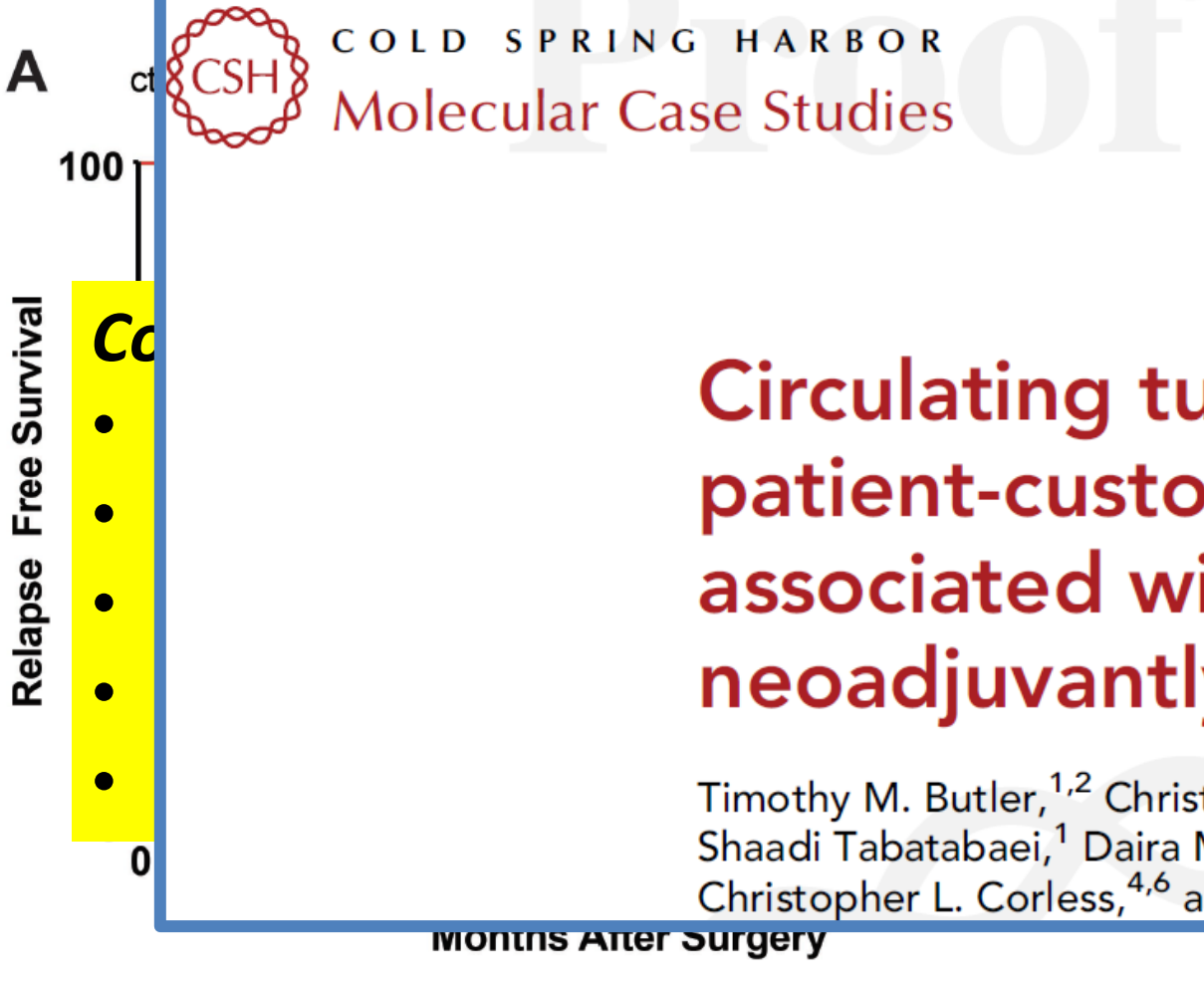
    - **Circulating protein or metabolites?**

Personalized ctDNA to Detect Occult Recurrences



COLD SPRING HARBOR
Molecular Case Studies
RESEARCH REPORT

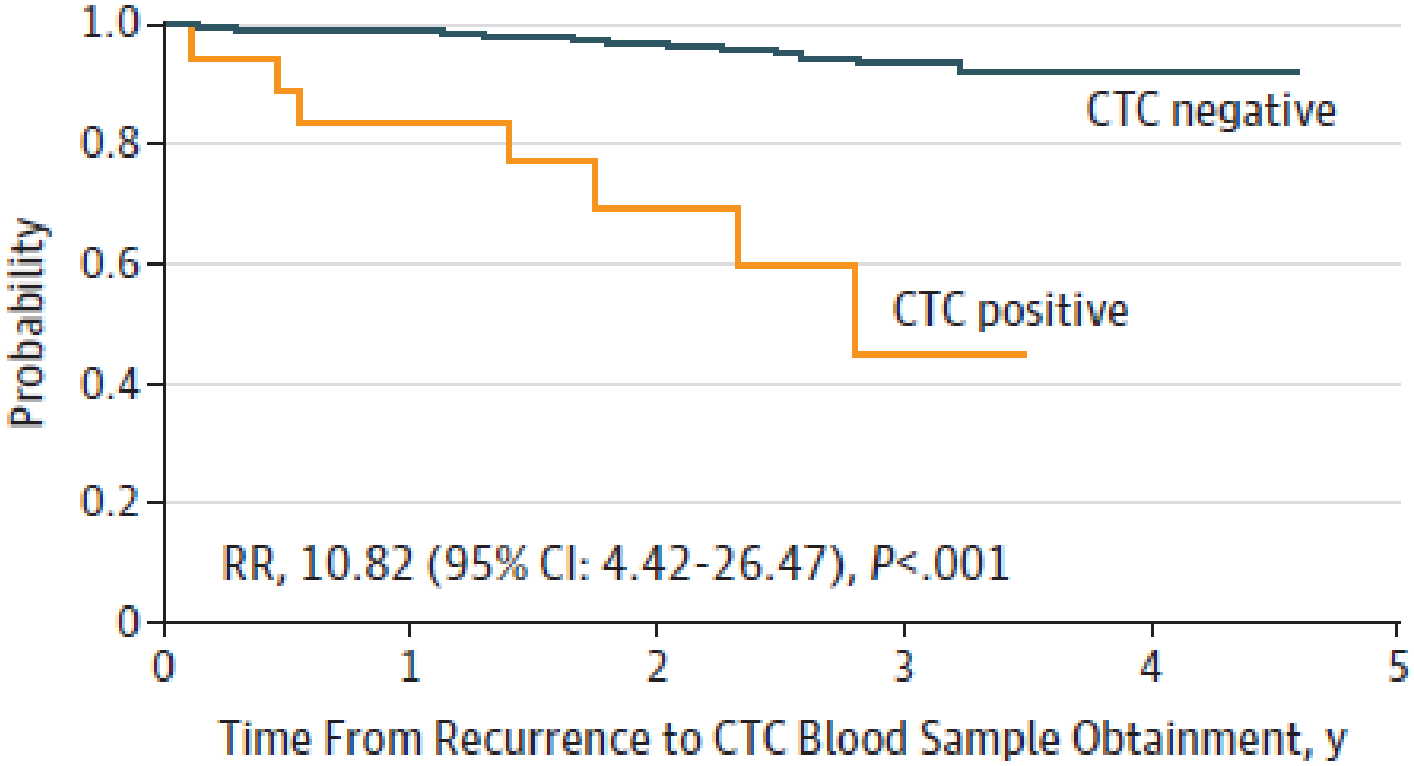
Circulating tumor DNA dynamics using patient-customized assays are associated with outcome in neoadjuvantly treated breast cancer

Timothy M. Butler,[1,2] Christopher T. Boniface,[1] Katie Johnson-Camacho,[1] Shaadi Tabatabaei,[1] Daira Melendez,[1] Taylor Kelley,[1] Joe Gray,[3,4,5] Christopher L. Corless,[4,6] and Paul T. Spellman[1,4,5]

Months After Surgery

Coombes, RC, et al., Clin Cancer Res 2019

Risk of Recurrence According to CTC at ~ 5 Years After Diagnosis



No. at risk						
CTC negative	335	306	211	102	16	0
CTC positive	18	13	7	3	0	0

Sparano, et al., JAMA Oncol 2018

Risk of Late Recurrence

- **Prognostic factors present at time of decision**
  - ***NONE OF THESE HAS BEEN CLINICALLY VALIDATED AND SHOULD NOT BE MONITORED OR USED TO MAKE THE DECISION REGARDING EXTENDED ET!!***
  - *Circulating tumor cells*

Late Recurrence: Conclusions

- **Persistent in ER positive early stage disease X 15-20 yrs**
- **Rate reduced by extended ET, but at a cost**
- **Concerns:**
  - **Treating patients with very good prognosis**
  - **Over-Dx (i.e. assuming that if we find something, it must be true)**
  - **If Rx does not decrease breast cancer recurrence, it could lead to increased mortality**
    - **Tamoxifen: Thrombosis, endometrial CA**
    - **AIs: Fractures, ? CVD**
- **Research Question: Can we identify-**
  - **Very favorable prognosis who can stop therapy**
  - **Poor prognosis who need to**
    - **Continue**
    - **Change**
    - **Add**

Future Research

- **Study women who have reached 5 years on ET**
  - **Liquid biopsies (CTC, cfDNA)**
  - **Bone marrow biopsies**
  - **Quality of life/patient perspectives**
  - **Objectives**
    - **Can we find "positives"**
    - **Do the positives predict recurrence, and when?**
- **Re-conduct new randomized trials of intervention**
  - **Use new diagnostics that are *validated***
  - **Rx with new targeted therapeutics ("Precision Medicine") to determine if this strategy improves survival**

Acknowledgements

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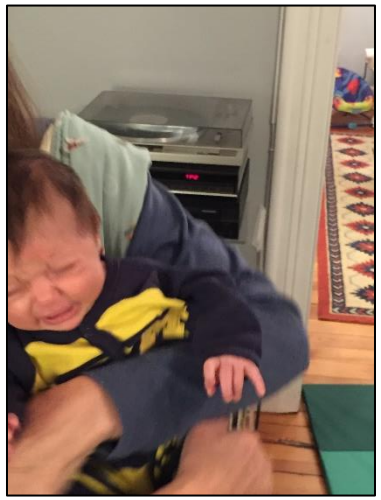
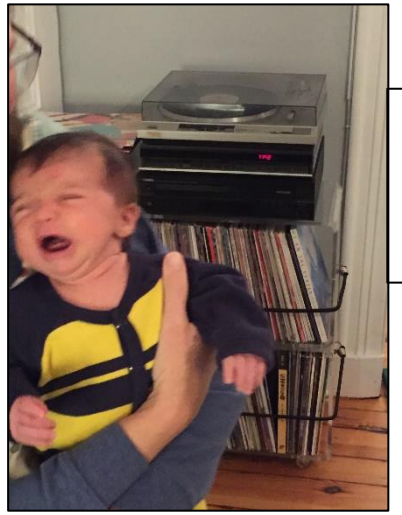
- **UM and other lab and clinical colleagues**
- **Of course, the many thousands of patients who have entered clinical trials to improve the care of those who came after them.**

Why Are We Doing This?
For Our Mothers, Wives, Sisters, Selves, and Granddaughters!

Willa Rao Hayes and her Sister, Parker Mary Hayes, born October 16, 2018





Parker after the UM/OSU game!!

Methods: Study Design

- **Population:** Stage II-III HER2-negative enrolled in E5103 (NCT00433511)
- **Treatment:** AC-weekly paclitaxel ± bevacizumab + endocrine therapy if ER+
- **Selection:** Recurrence-free 4.5-7.5 years after diagnosis & informed consent
- **CTC Assay**: Whole blood (7.5 ml) drawn into fixative-containing tube for CTC identification and enumeration using the CellSearch® system at entry
- **Assay results:** not reported to clinicians or patients due to uncertainty regarding prognostic information

Sparano et al SABCS 2017