Neoadjuvant and Adjuvant Breast Cancer

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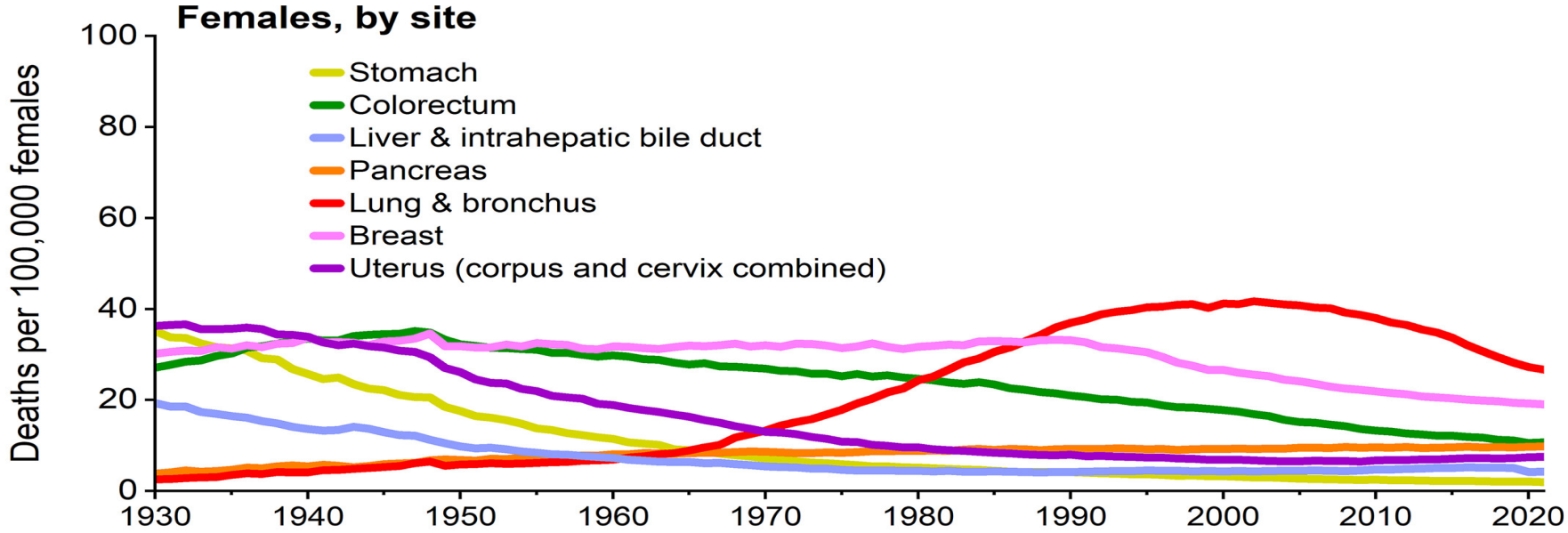
  - Astra Zeneca, Gilead, CoreA Therapeutics, Puma Biotechnology

Overview

- Breast Cancer epidemiology
- Breast Cancer local therapy
- ER/PR+ Breast Cancer
  - Adjuvant Anti-Estrogen Therapy
  - Indications for Chemotherapy
- HER2+ Breast Cancer
  - Adjuvant Trastuzumab
  - Neoadjuvant Pertuzumab
- Adjuvant Chemotherapy
- Triple Negative Breast Cancer

Breast Cancer – Epidemiology

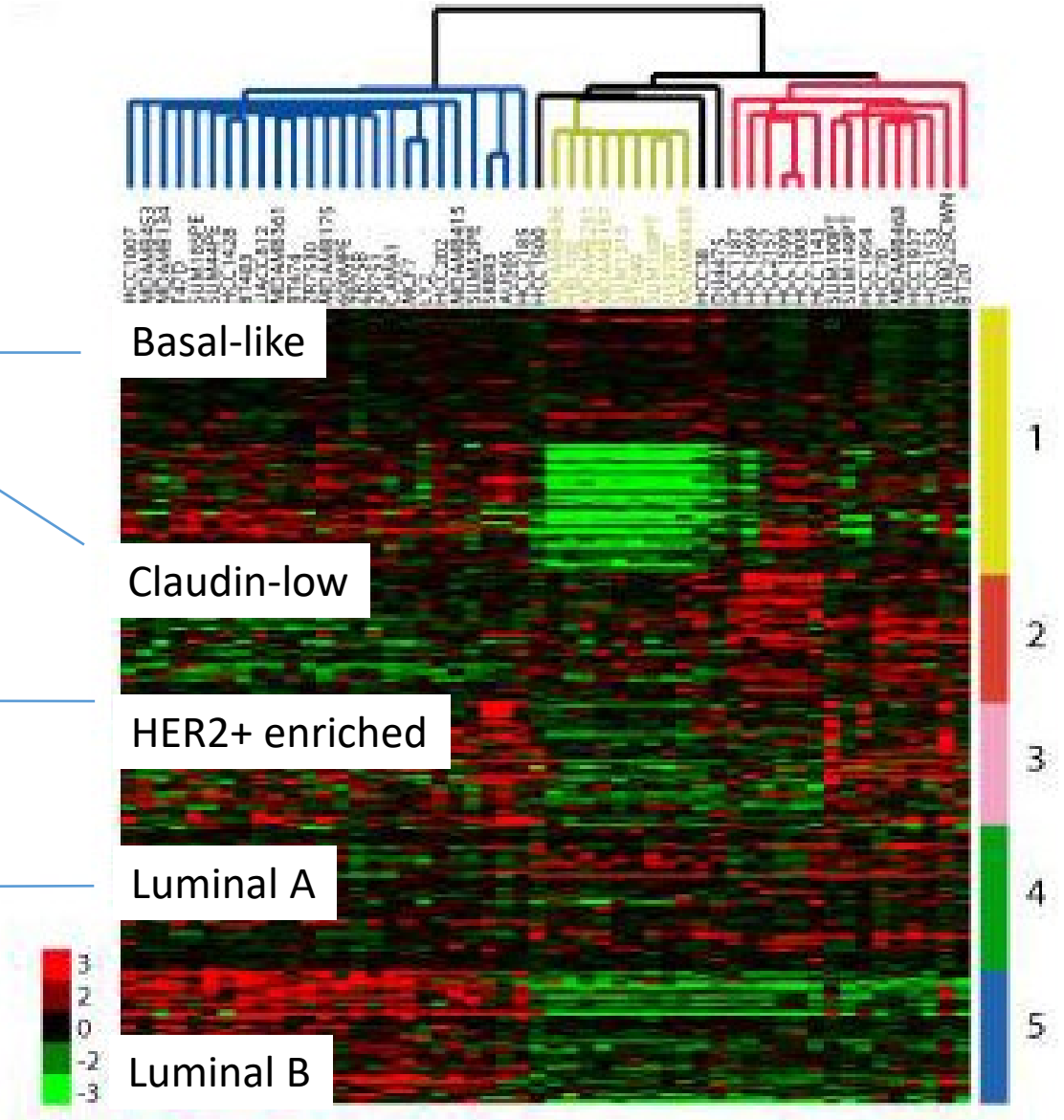
- Most common cancer in women and 2nd leading cause of cancer death in the US
- It is estimated that 287,850 individuals were diagnosed and 43,250 died of breast cancer in 2022
- 5 year Overall Survival 91%



American Cancer Society. Breast Cancer Facts & Figures 2023 at www.cancer.org.
CA A Cancer J Clinicians, Volume: 74, Issue: 1, January 2024, DOI

Breast Cancer Subtypes

- Triple Negative Breast Cancer (TNBC)
  - Estrogen Receptor (ER),Progesterone receptor (PR), and HER2 negative
  - Tx: Chemotherapy +/- Immunotherapy
- HER2 Positive Breast Cancer
  - HER2 overexpressing or amplified
  - Tx: Chemotherapy + HER2 therapy
- Hormone Receptor Positive BCa
  - Estrogen Receptor (ER) and / or Progesterone receptor (PR) positive
  - Tx: Anti-estrogen, +/- Chemotherapy

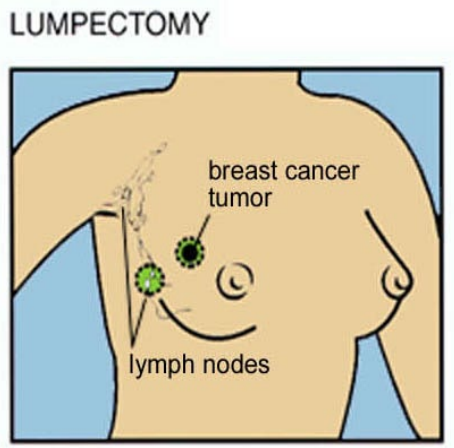


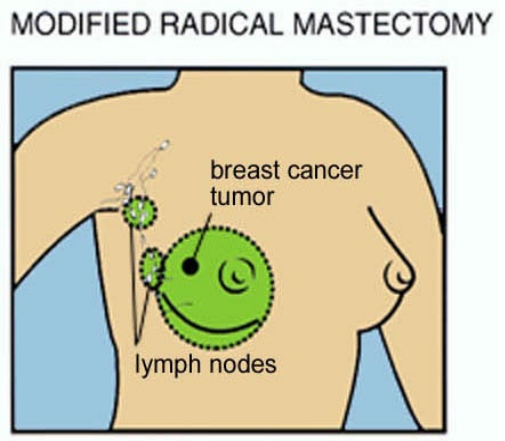
Prat A, et al. Breast Cancer Res. 2010

Breast Cancer – Local Therapy

- Lumpectomy + Radiation (BCT) vs Mod Rad Mastectomy
  - 6 randomized trials
  - No survival difference

- Contraindications to breast conservation therapy (BCT)
  - Prior radiation
  - Multifocal disease*
  - Ongoing pregnancy
  - Poor cosmetic outcome
  - Connective tissue disease involving the skin





Breast Cancer – Local Therapy

- Sentinel lymph node localization or Axillary LN dissection (AXLND)
  - Randomized trials confirmed utility of sentinel LN localization
- Is completion axillary LN dissection required for +SLN?
- ACOSOG Z0011 (Z11) Trial
  - Enrolled pts with clinically node negative w T1/T2 primary but <3+ LNs on SLN localization
  - Randomized to: Completion AXLND + XRT vs XRT alone
  - Results: No difference in DFS or OS at 10 yrs. follow-up

Giuliano AE, et al. JAMA. 2017

Adjuvant Anti-Estrogen Therapy ER/PR+ Breast Cancer

Adjuvant Therapy – ER/PR+ disease

- Foundation of adjuvant therapy – Anti-estrogen therapy
- Chemotherapy is not need in all cases
- Chemotherapy is always needed for:
  - T4 tumors
  - ≥4+ axillary LNs
  - High Oncotype RS (≥ 26)
  - High Risk Mammaprint (Clinically High Risk)
  - Inflammatory breast cancer

How Effective is Adjuvant Tamoxifen?

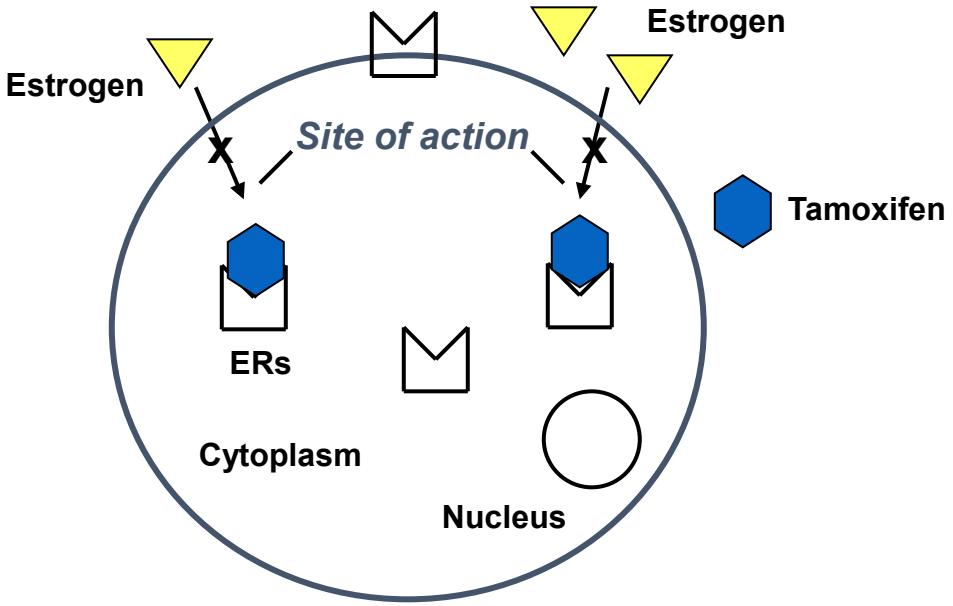
ER/PR+ Breast Cancer

Tamoxifen

- Selective estrogen receptor modulator (SERM)
  - Agonist: bone, liver, uterus
  - Antagonist: breast, CNS
- Effective in pre- and post-menopausal states
- Side effects:
  - Hot flashes
  - Mood alterations
  - Hair Thinning
  - Endometrial carcinoma (rare)
  - DVT/PE (rare)

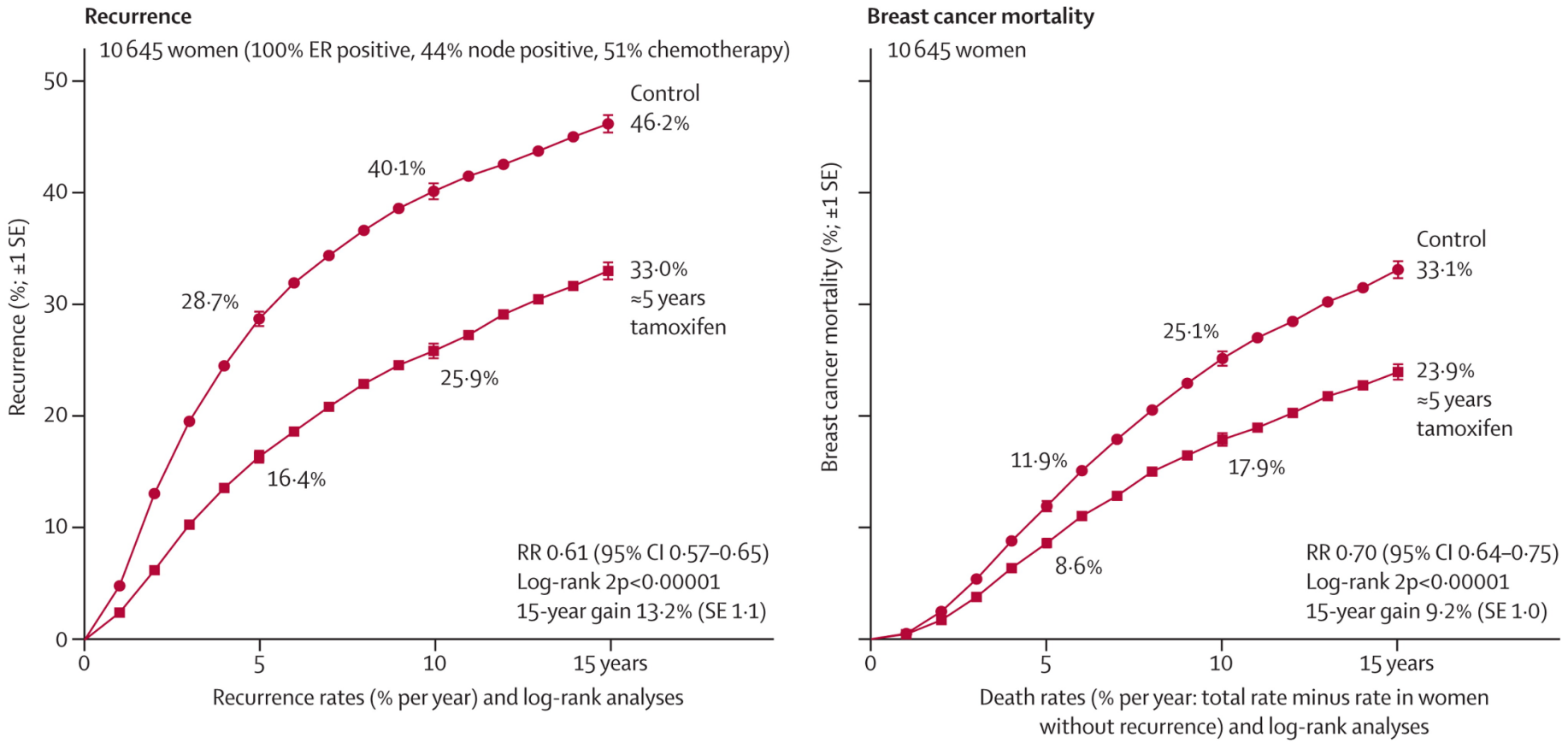
Estrogen Receptor Antagonists

- Compete with estrogen binding to receptor[1]



1. Gradishar WJ, Jordan VC. *Hematol Oncol Clin North Am*. 1999

Benefits of Adjuvant Tamoxifen (5 yrs., ER+)



Davies et al. EBCTCG, Lancet. Sept 2011

Post-menopausal women: Are Aromatase Inhibitors (AIs) Better Than Tamoxifen?

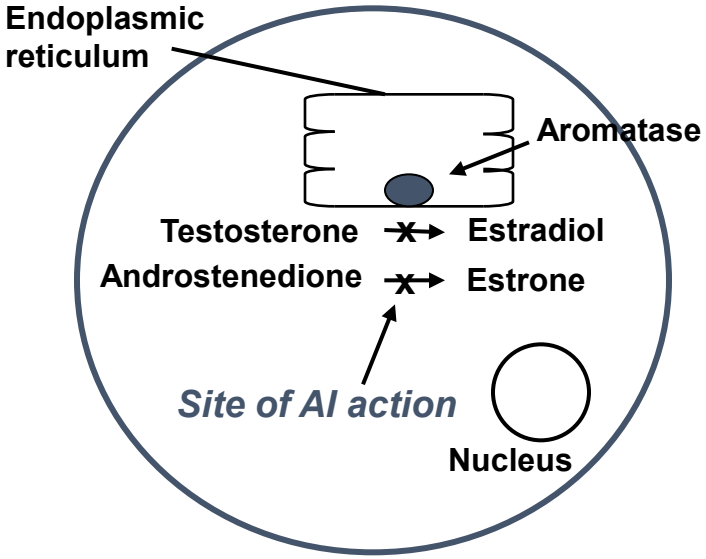
ER/PR+ Breast Cancer

Aromatase inhibitor (AI)

- Blocks aromatase, that converts androgens to estrogens
  - Aromatase is the main source of estrogen in post-menopausal women
  - Steroidal and non-steroidal AIs
- Side effects that of estrogen loss:
  - Hot flashes
  - Mood disturbances
  - Hair thinning
  - Accelerated loss of bone mineral density
  - Musculoskeletal pain and stiffness

Aromatase Inhibitors

- Inhibit synthesis of estrogens[1,2]



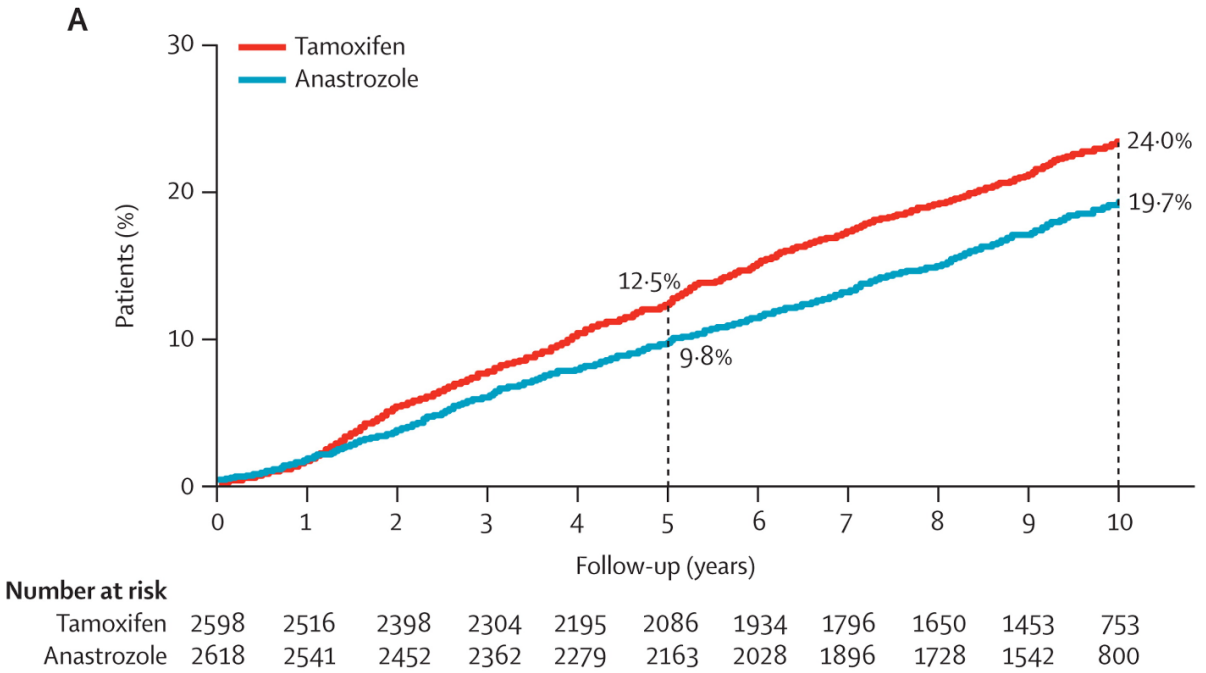
1. Gradishar WJ, Jordan VC. *Hematol Oncol Clin North Am*. 1999; 2. Goldhirsch A, Gelber RD. *Semin Oncol*. 1996.

ATAC: Adjuvant Anastrazole vs Tamoxifen

- 10 year follow-up of Anastrazole vs Tamoxifen in post-menopausal women

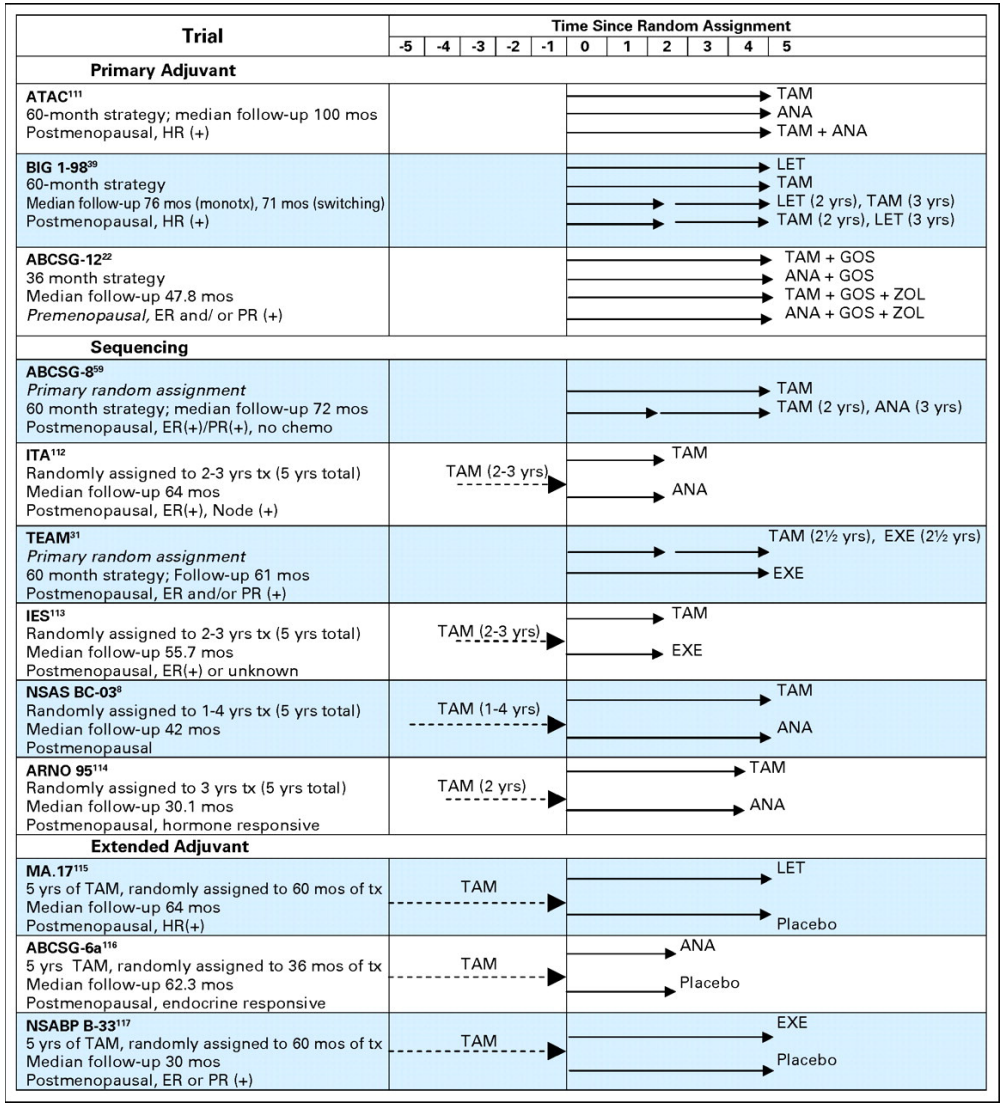
- Anastrazole significantly improved:
  - Time to recurrence
  - Disease-free survival
  - Time to distant recurrence

Time to recurrence



Cuzick et a. Lancet Oncol. 2010 Dec;11(12):1135-41.

Adjuvant Aromatase Inhibitor Trials



Absolute Gain in DFS of AI vs Tam at 3-6 yrs.

AI vs Tamoxifen Primary	2-4%
Tam -> AI Sequential	3-5%
Tam x 5 yrs. -> AI Extended	6%

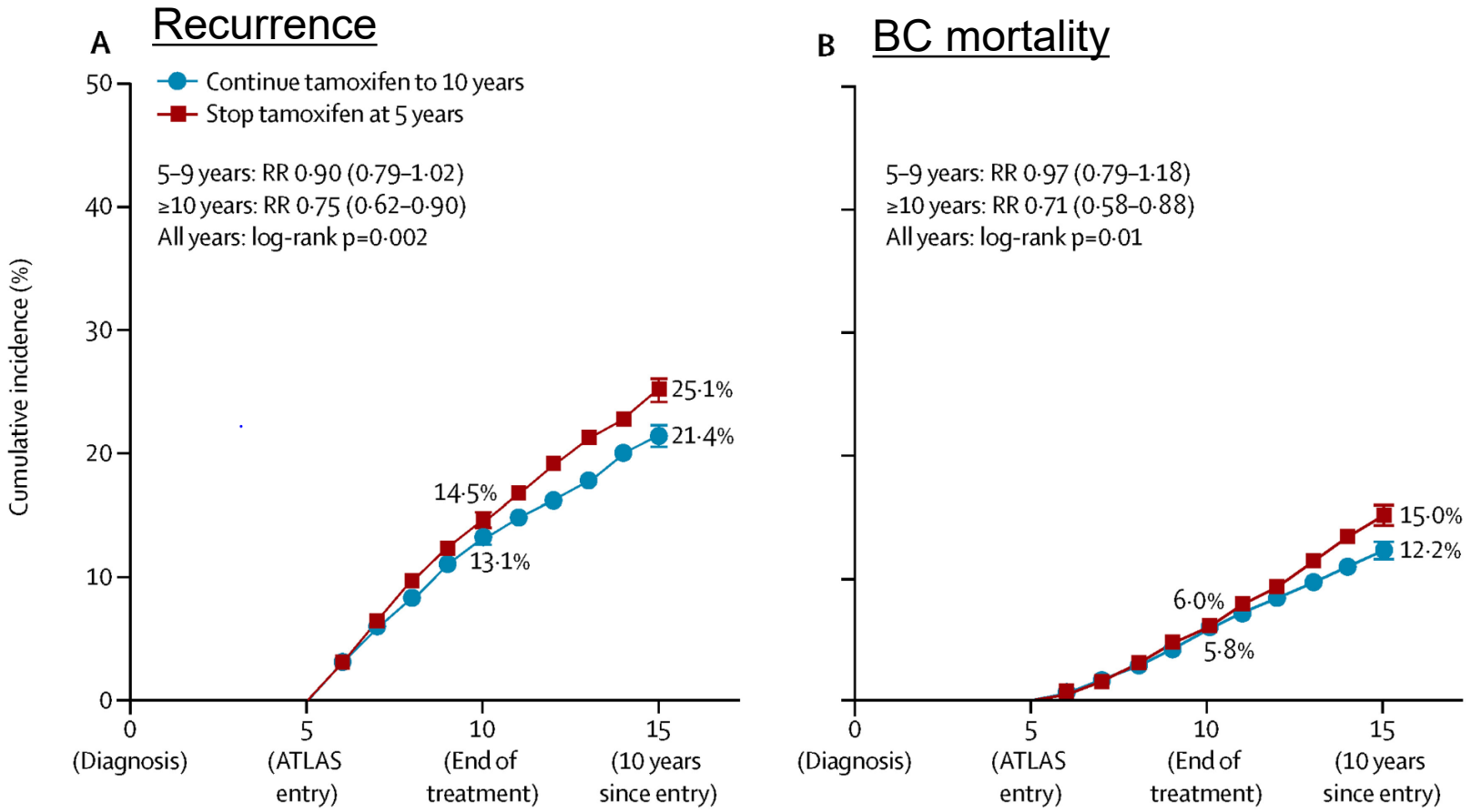
Burstein et al. JCO 2010

Extended Adjuvant Anti-Estrogen Therapy

ER/PR+ Breast Cancer

ATLAS: 5 vs 10 yrs. of Tamoxifen

- N=6,846 who had received 5 yrs. of Tamoxifen
- Randomized to:
  - Additional Tam x 5 yrs.
  - Stopping Tam



- reduced BC mortality (331 *vs* 397 deaths, p=0·01)
- reduced overall mortality (639 *vs* 722 deaths, p=0·01)

Davies et al. Lancet. 2013 Mar 9.

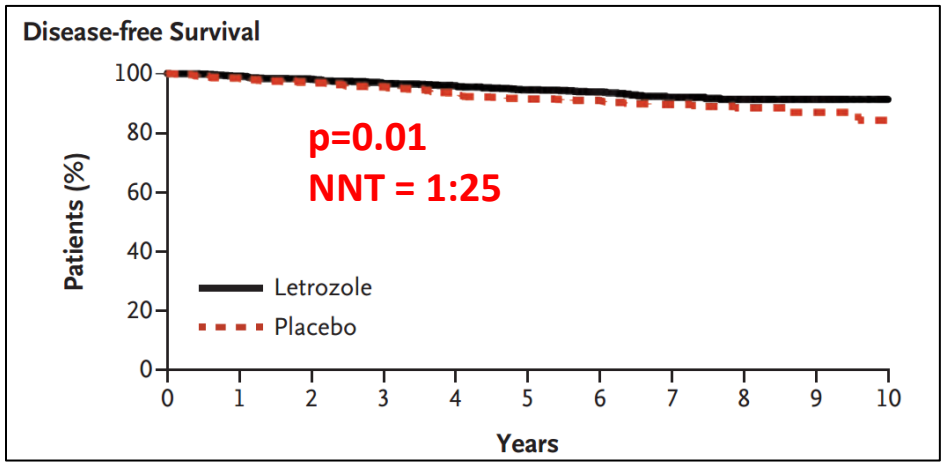
ATLAS: Adverse Events

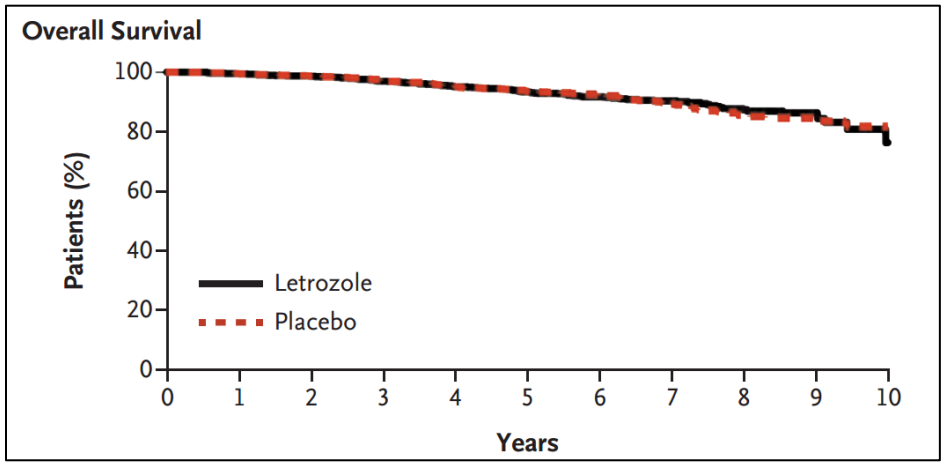
Death without recurrence			
Vascular death			
Stroke	1·03 (0·72–1·46)	0·89	
Pulmonary embolus	1·21 (0·48–3·04)	0·69	
Heart disease§	0·85 (0·69–1·03)	0·10	
Neoplastic death			
Endometrial cancer¶	1·49 (0·71–3·13)	0·29	
Other neoplastic disease	1·01 (0·74–1·39)	0·94	
Other death			
Specified cause	1·03 (0·83–1·28)	0·80	
Unspecified cause	1·06 (0·86–1·32)	0·58	
Second cancer incidence			
Contralateral breast cancer	0·88 (0·77–1·00)	0·05	
Endometrial cancer¶	1·74 (1·30–2·34)	0·0002	**+53 cases**
Primary liver cancer	0·99 (0·20–4·90)	0·99	
Colorectal cancer	0·86 (0·58–1·27)	0·44	
Unspecified site	0·99 (0·83–1·18)	0·91	
Non-neoplastic disease (ever hospitalised or died)			
Stroke	1·06 (0·83–1·36)	0·63	
Pulmonary embolus	1·87 (1·13–3·07)	0·01	**+20 cases**
Ischaemic heart disease	0·76 (0·60–0·95)	0·02	
Gallstones	1·11 (0·80–1·54)	0·54	
Cataract	1·11 (0·79–1·56)	0·54	
Bone fracture	0·86 (0·61–1·21)	0·39	

Davies et al. Lancet. 2013 Mar 9.

MA.17R: Extended Adjuvant with AI

- Breast cancer pts who had completed 5 yrs. of adjuvant anti-estrogen therapy
  - Extended Adj with 5 yrs. of Letrozole vs placebo
- 5-year disease-free survival rate:
  - Letrozole - 95%
  - Placebo - 91%
- No significant difference in overall survival





Goss et al, NEJM 2016

MA.17R: +10 years AI?

Variable	Letrozole (N=959)	Placebo (N=959)
	number (percent)	
Patients with a recurrence of the primary cancer or with contralateral breast cancer	67 (7.0)	98 (10.2)
Recurrence*†	55 (5.7)	68 (7.1)
Local breast	8 (0.8)	10 (1.0)
Local chest wall	6 (0.6)	7 (0.7)
Regional	5 (0.5)	13 (1.4)
Distant	42 (4.4)	53 (5.5)
Contralateral breast cancer†	13 (1.4)	31 (3.2)

NNT = Distant Mets1:100

NNH =

1. Fracture, 1:20 (14% v 9%, p=0.001)
2. New osteoporosis, 1:20 (11% v 6%, p<0.001)

Goss et al, NEJM 2016

Pre-menopausal women and adjuvant anti-estrogen therapy

ER/PR+ Breast Cancer

Adjuvant ovarian suppression

- In pre-menopausal women ovarian suppression:
  - Further decreases risk of recurrence
  - Enables use of Aromatase Inhibitors

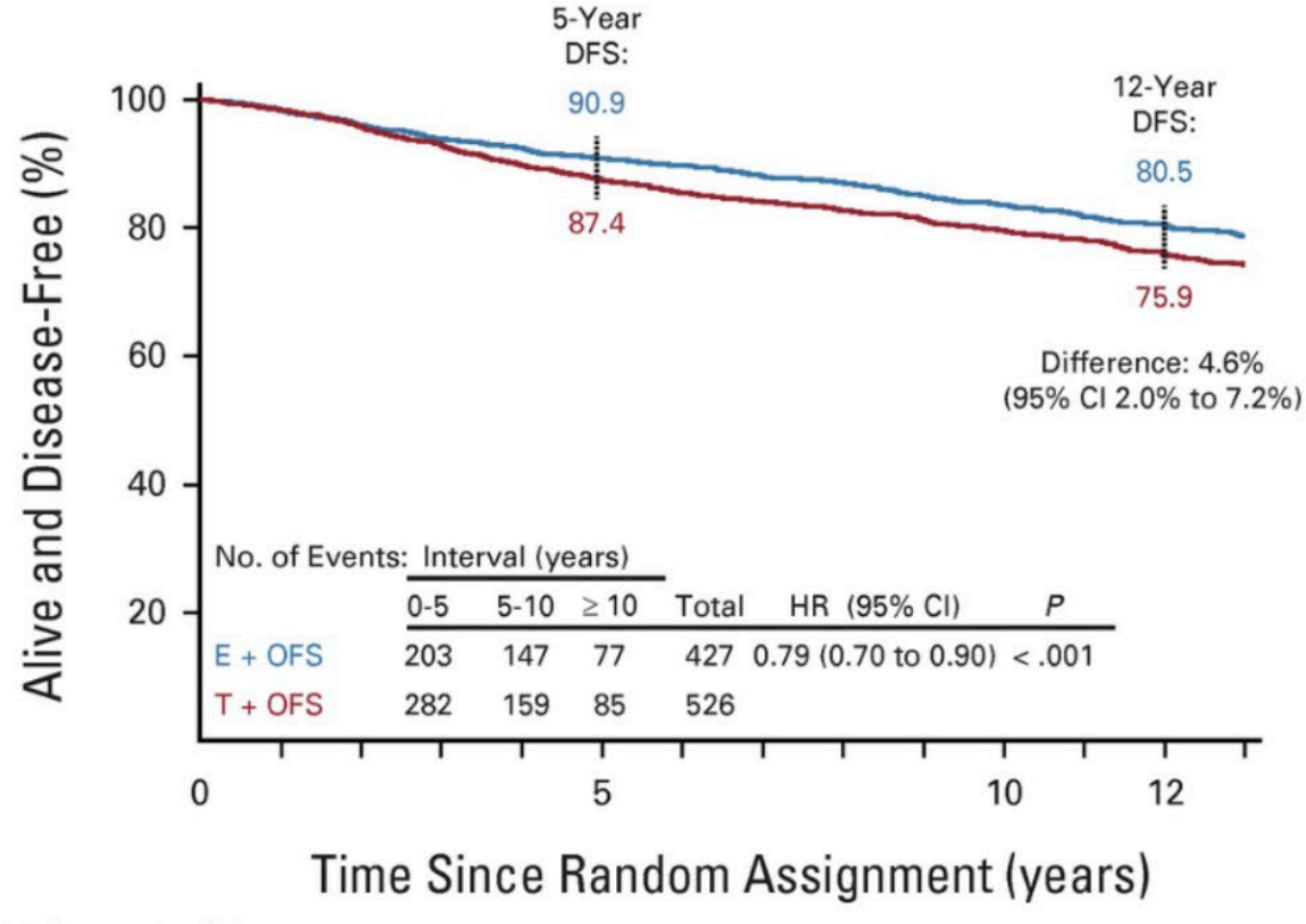
- Direct
  - Medical: GnRH analogues
    - Goserelin, Leuprolide
  - Surgical: oophorectomy
  - Radiation

- Indirect:
  - Chemotherapy-induced

SOFT and TEXT Trial – Pre-menopausal

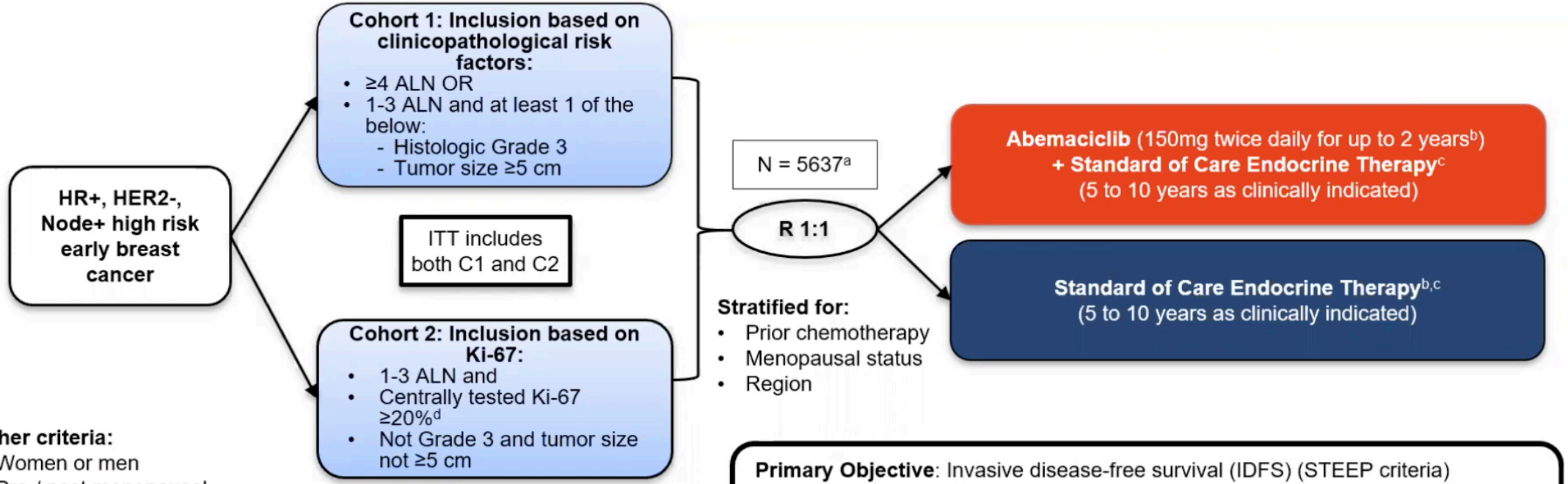
- Pre-menopausal women Combined analysis of:
  - Tamoxifen
  - OS + Tamoxifen
  - OS + AI
- OS + AI significantly reduced recurrence

- Clinical application:
  - Most pre-menopausal women only need Tam
  - Consider OS + AI with high-risk features
    - <35yo
    - Received chemotherapy



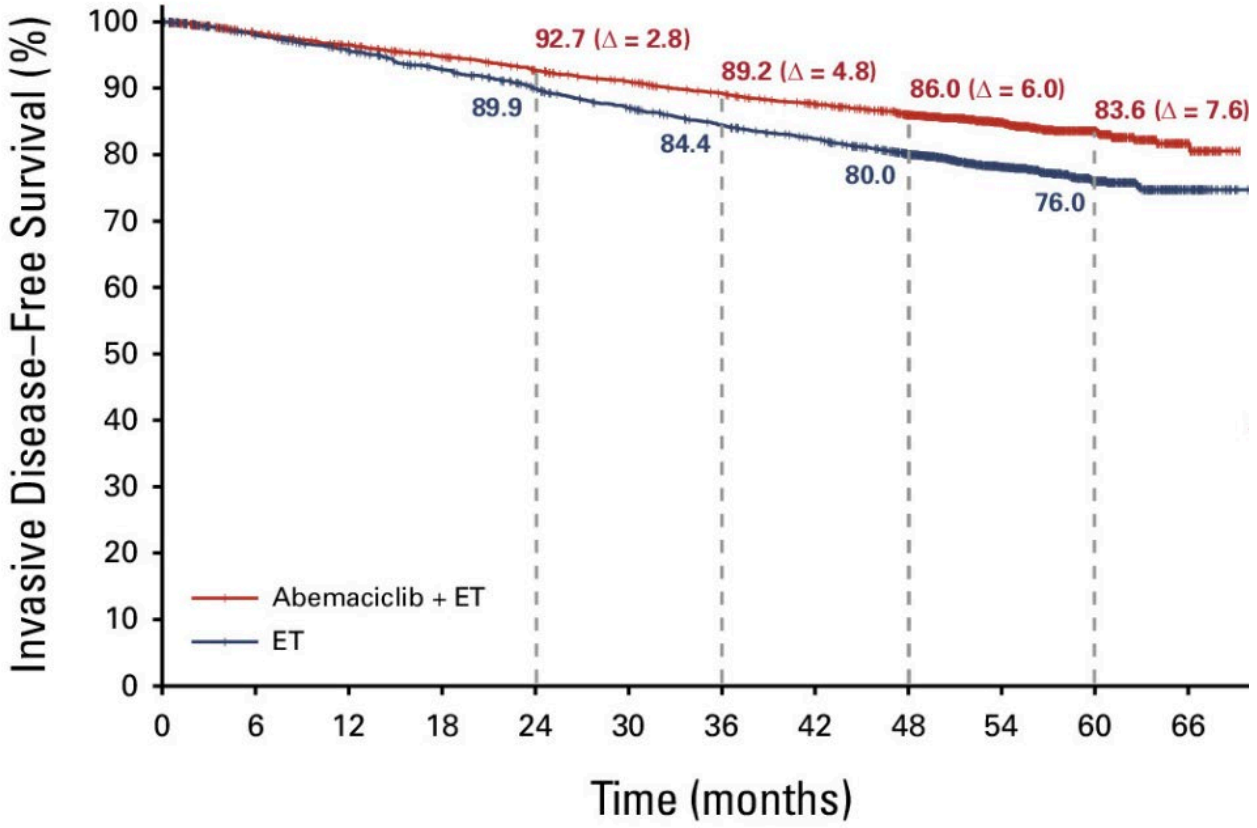
PA Francis et al. N Engl J Med 2018. Pagani O, et al. JCO 2023

MonarchE Study Design



MonarchE Trial – JCO 2024

- Median 4 years of follow-up
  - 2 yrs after completion of Abema
- 4-year IDFS rates:
  - 83.6.8% in Abemaciclib + ET
  - 76.0% in ET alone
- Adverse events: Abema + ET
  - Diarrhea, Fatigue, Neutropenia
  - Rare - VTE (2.4%), ILD (2.9%)



Rastogi P, et al. JCO 2024

Which ER/PR+ Patients Need Chemotherapy

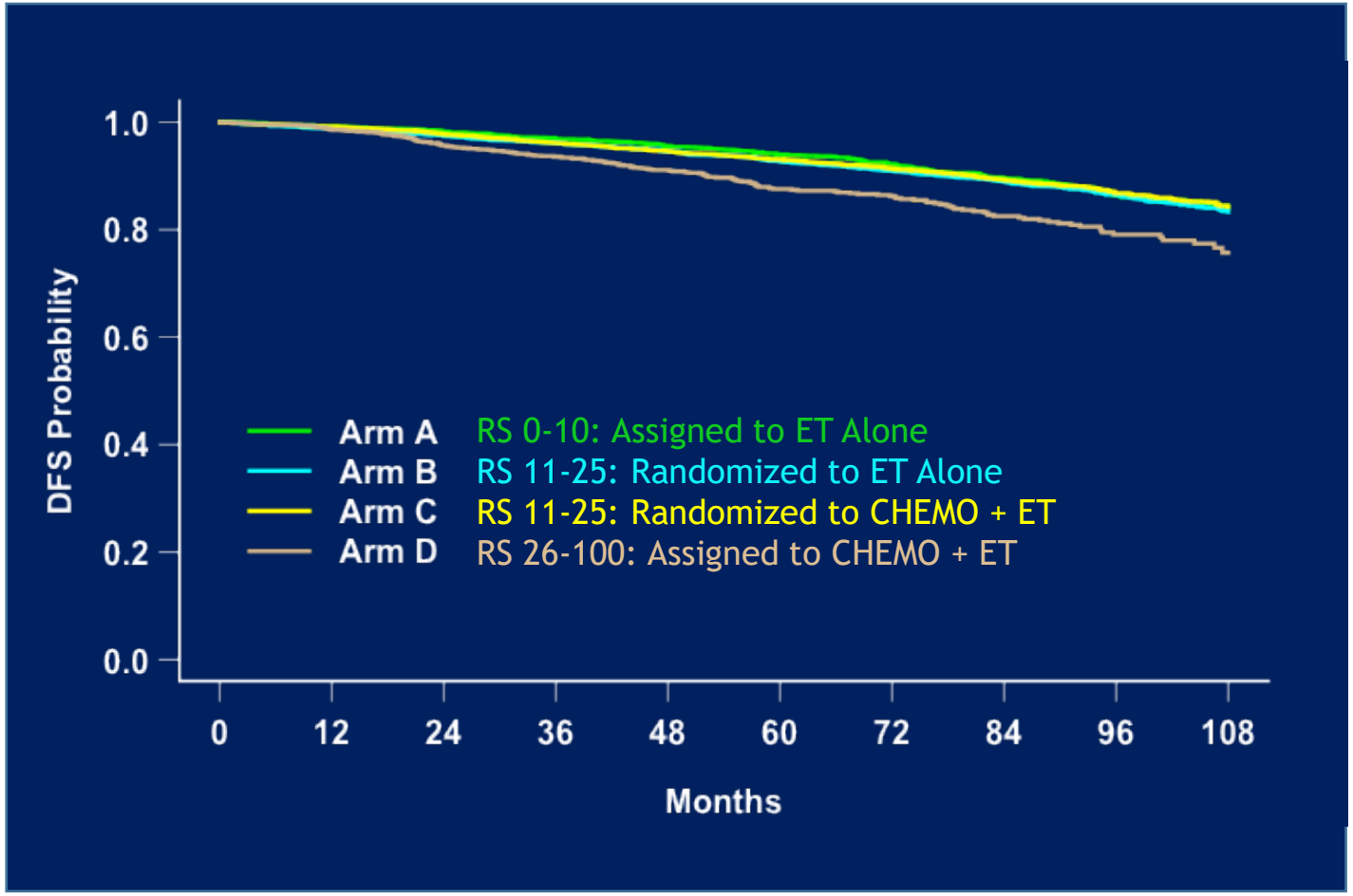
ER/PR+ Breast Cancer

Oncotype Dx: Indications for assay

Criteria:

- Invasive breast cancer
- Hormone receptor positive (ER+ and/or PR+)
- HER2 negative (IHC 0-1+ or FISH/ISH non-amplified)
- pT1b (>0.5cm to 1.0cm) AND histologic grade 2 or 3, LVI
- pT1c, pT2, pT3

TAILORx: Prospective Validation for Oncotype Dx, 9-yr event rates



Arm A: ET alone (RS 0-10)
3% Distant recurrence rate

Arms B & C: Randomized (RS 11-25)
5% Distant recurrence rate overall

Arm D: Chemo + endocrine (RS 26-100)
13% Distant recurrence rate despite chemotherapy + endocrine therapy

Sparano J et al, N Engl J Med 2018

TAILORx: Benefit of Chemotherapy in Women ≤50yo

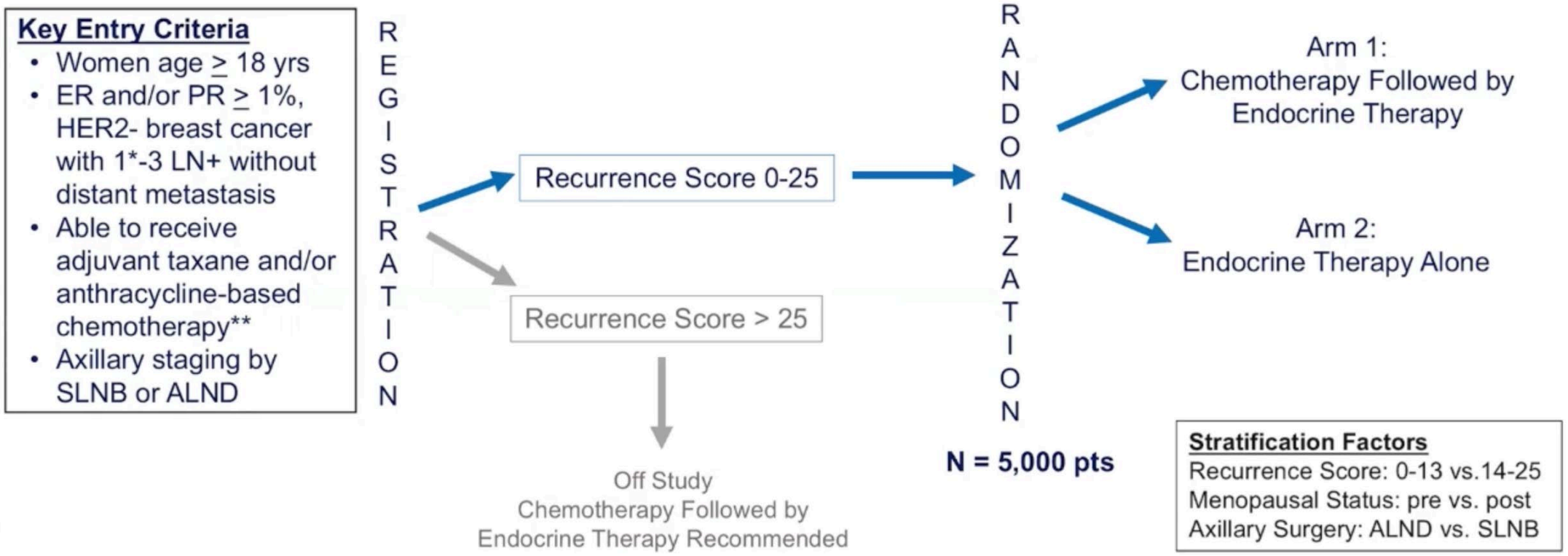
- Interaction between Age – Recurrence Score – Chemotherapy
  - Some chemotherapy benefit in women ≤ 50yo with a RS of 16-25
  - Greatest impact on distant recurrence with RS 21-25

Subgroup Age ≤50 years				
RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
No CT Benefit	No CT Benefit	~1.5% CT Benefit	~7% CT Benefit	Large CT Benefit

Sparano J et al, N Engl J Med 2018

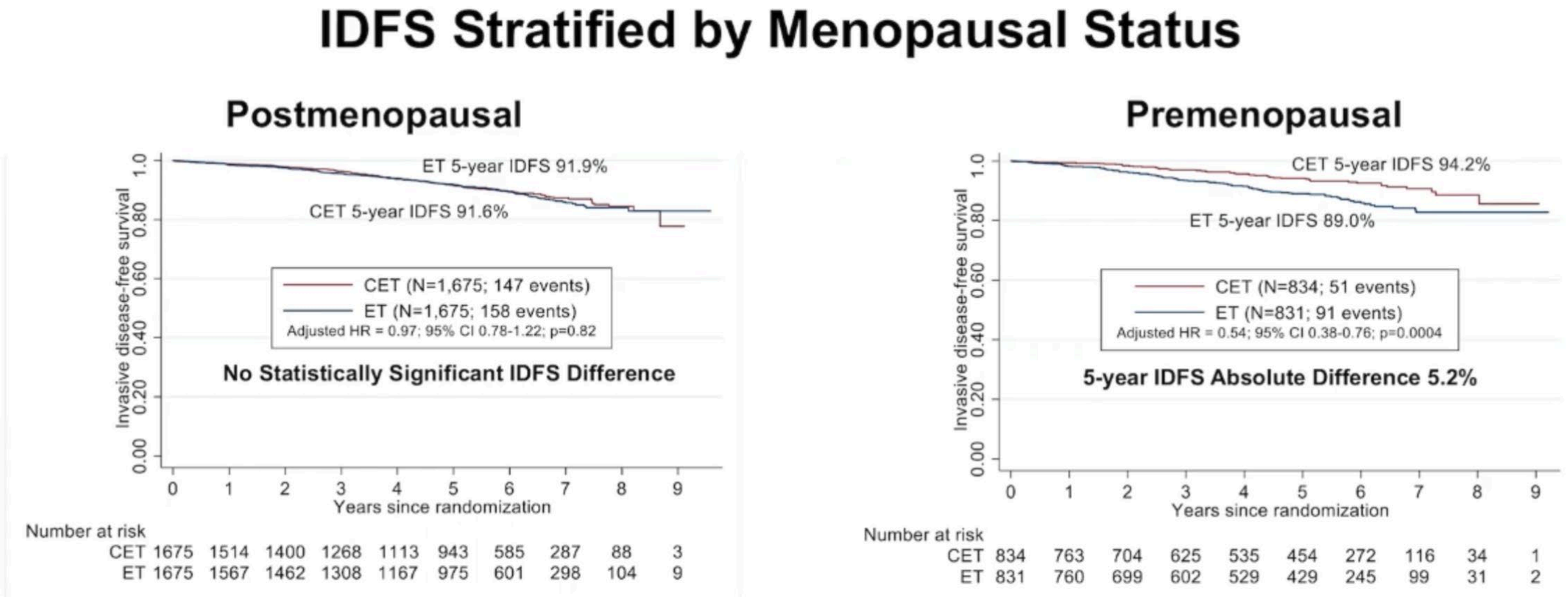
Genomic Assays: HR+ and Lymph Node Positive

RxPonder – Oncotype RS in 1-3+ LNs



Primary objective: invasive disease free survival (IDFS) in pts w/ 1-3 nodes and RS of 25 or less.

RxPonder: Chemo and Menopausal status



Postmenopausal women w/ 1-3+ nodes w/ RS 0-25 can safely forego adjuvant chemo

Premenopausal women w/ 1-3 pos nodes w/ RS 0-25 may benefit from chemo.

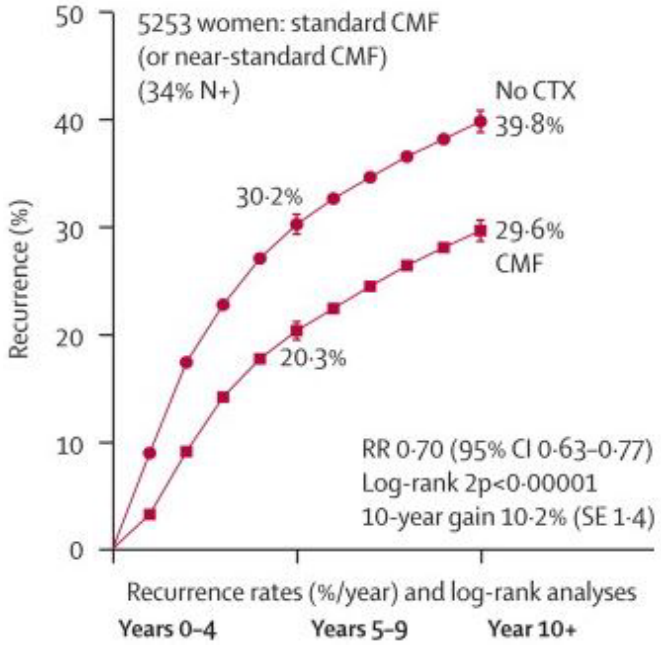
Kalinisky K,. SABCS 2020. Abstr GS3-00.

Chemotherapy regimens

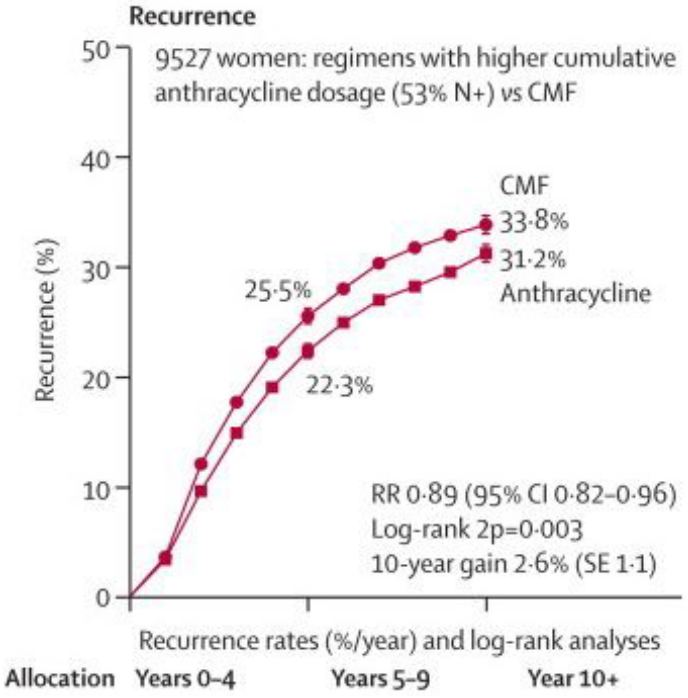
Localized or locally advanced breast cancer

Benefits of Adjuvant Chemotherapy

- Polychemo. vs No Chemo, results in:
  - Decreased risk of recurrence
  - Decreased breast cancer mortality
  - Improved OS



- CMF vs Anthracycline Based chemotherapy

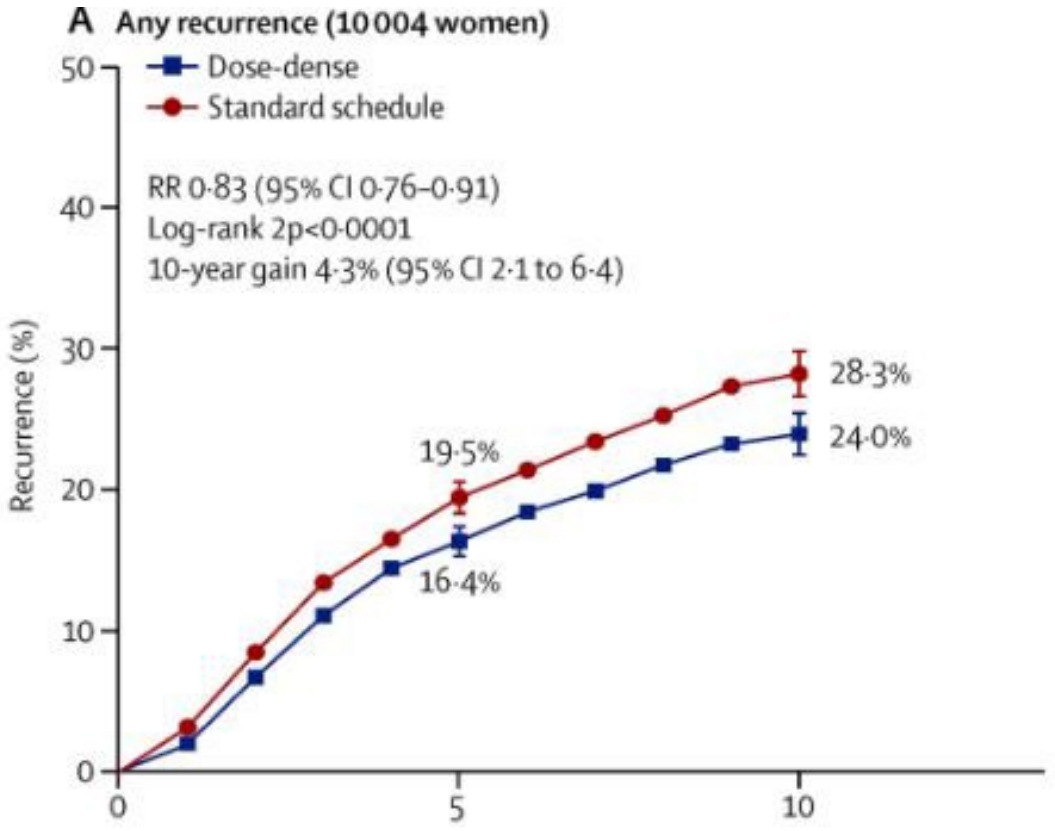


EBCTCG, Lancet. 2012

Dose Density – Q2 vs 3 weekly Anthracycline

- Meta-analysis of 26 studies adjuvant chemo trials

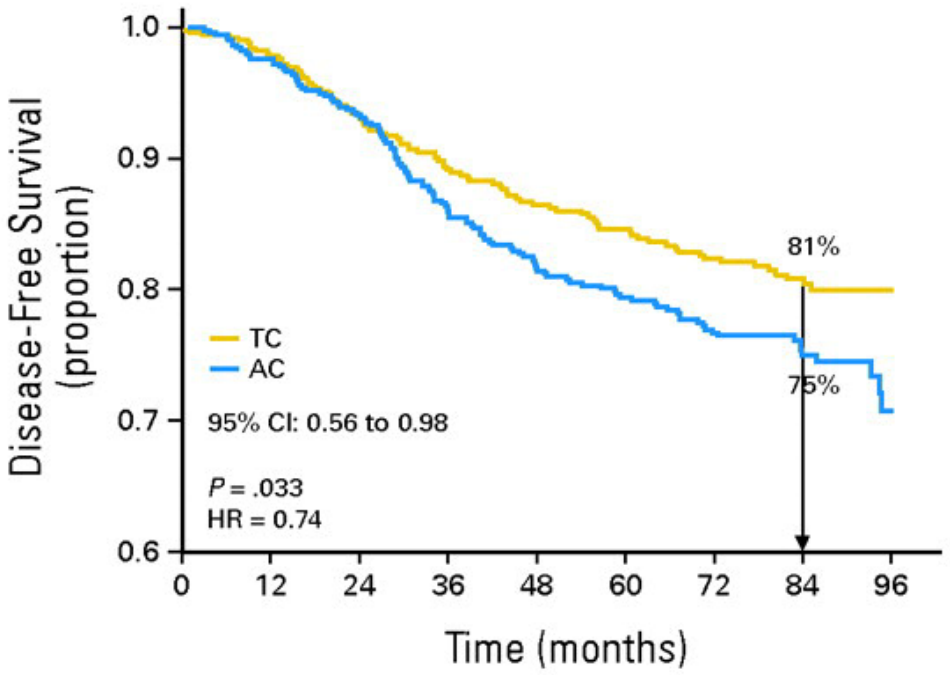
- Dose Dense Q2 weekly chemo is superior to Q3 weekly chemo in reducing:
  - Risk of recurrence
  - Breast cancer mortality



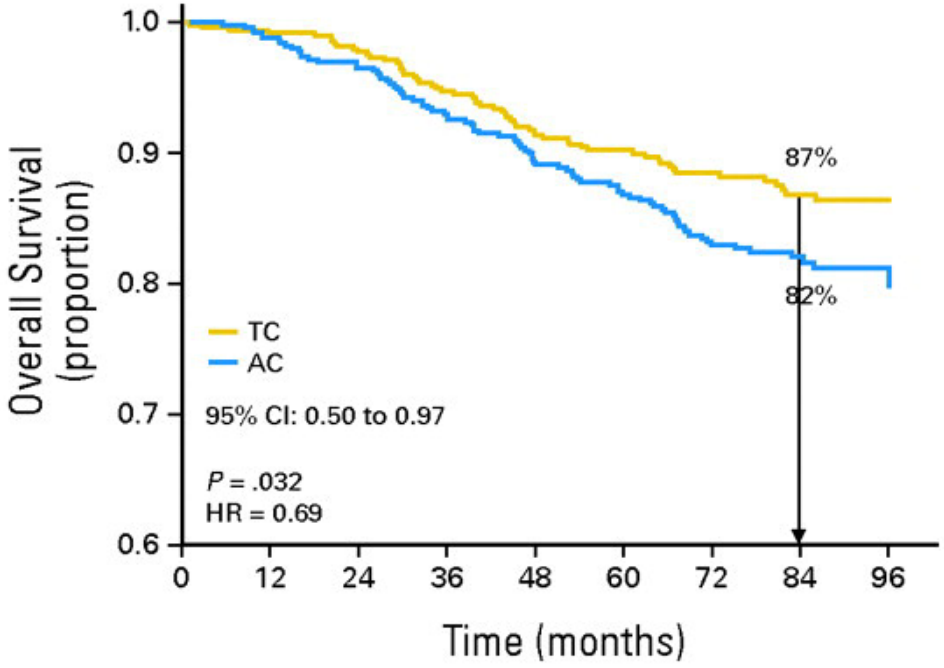
EBCTCG, Lancet 2019

Adjuvant Taxane vs Anthracycline Chemo

- TC associated with improved DFS compared to Q3 wk. AC



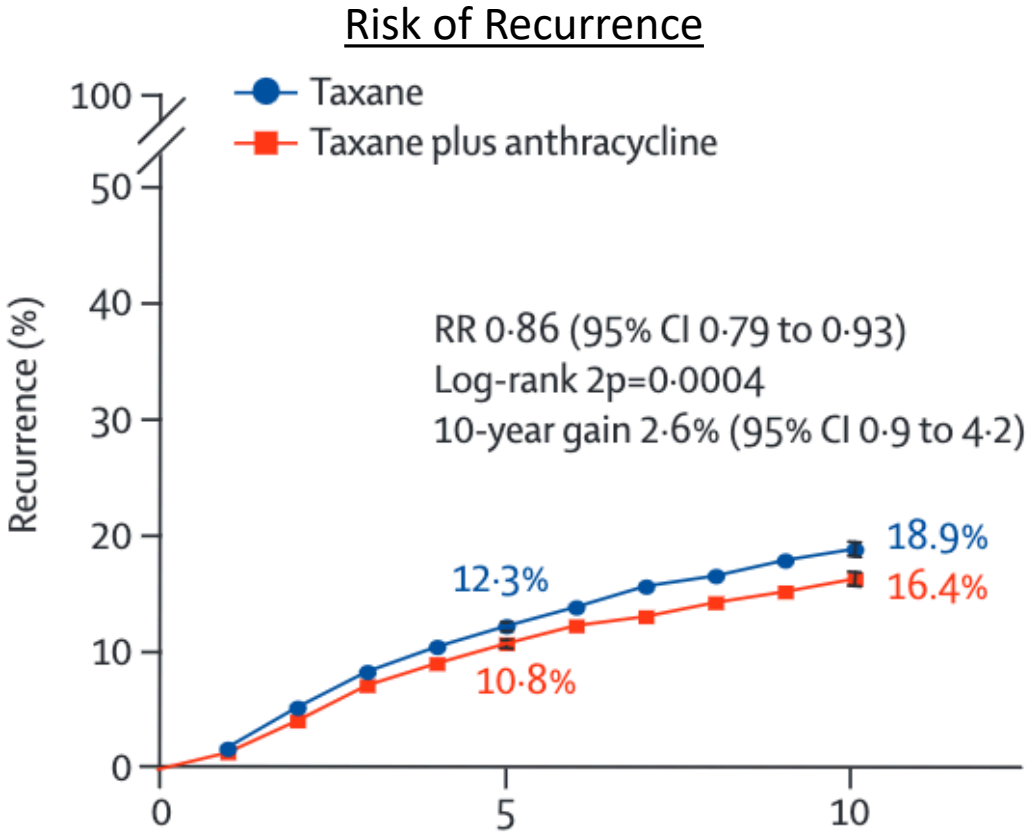
- TC associated with improved OS compared to Q3 wk. AC



Jones JCO 2009

Adjuvant chemotherapy: Taxane + Anthracycline

- Addition of Taxane chemotherapy to Anthracycline resulted in:
  - Decreased risk of recurrence
  - Decreased breast cancer mortality
  - Improved overall survival



Recurrence rates per year (%[events per women-year]) and log-rank analysis

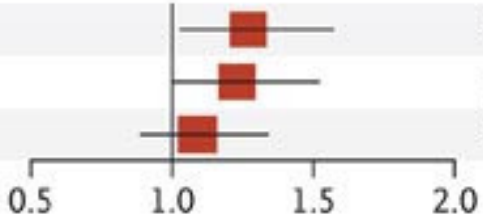
EBCTCG, Lancet. 2023

The NEW ENGLAND JOURNAL of MEDICINE

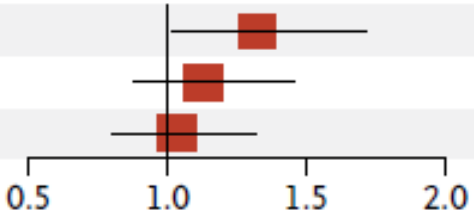
Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer

What is the optimal Taxane and schedule?

Treatment Group	No. of Patients	Hazard Ratio for Disease-free Survival (98.3% CI)	P Value
Weekly paclitaxel	2484	1.27 (1.03–1.57)	0.006
Docetaxel every 3 wk	2489	1.23 (1.00–1.52)	0.02
Weekly docetaxel	2483	1.09 (0.89–1.34)	0.29



Treatment Group	No. of Patients	Hazard Ratio for Overall Survival (98.3% CI)	P Value
Weekly paclitaxel	2484	1.32 (1.02–1.72)	0.01
Docetaxel every 3 wk	2489	1.13 (0.88–1.46)	0.25
Weekly docetaxel	2483	1.02 (0.80–1.32)	0.80



Sparano et al, NEJM. 2008

Cochrane Database of Systematic Reviews

Preoperative chemotherapy for women with operable breast cancer

- Meta-analysis of 14 trials
- Neoadjuvant vs Adjuvant Chemotherapy
  - Equivalent OS rates (HR 0.98, 95% CI, 0.87 to 1.09)
  - Equivalent DFS rates (HR 0.97, 95% CI 0.89-1.07)
- Neoadjuvant associated with improved breast conservation rates
- Pathologic complete response associated w/ significant improvements in:
  - OS (HR 0.48, 95% CI 0.33-0.69)
  - DFS (HR 0.48, 95% CI 0.37-0.63)

Mieog et al. Cochrane Database Syst Rev.2007

Neoadjuvant and Adjuvant chemotherapy regimens

- Preferred Regimens (NCCN)
  - Dose-Dense AC followed by Paclitaxel wkly
  - Dose-Dense AC followed by Paclitaxel Q2 wkly
  - TC (Docetaxel/Cyclophos) Q3 wkly

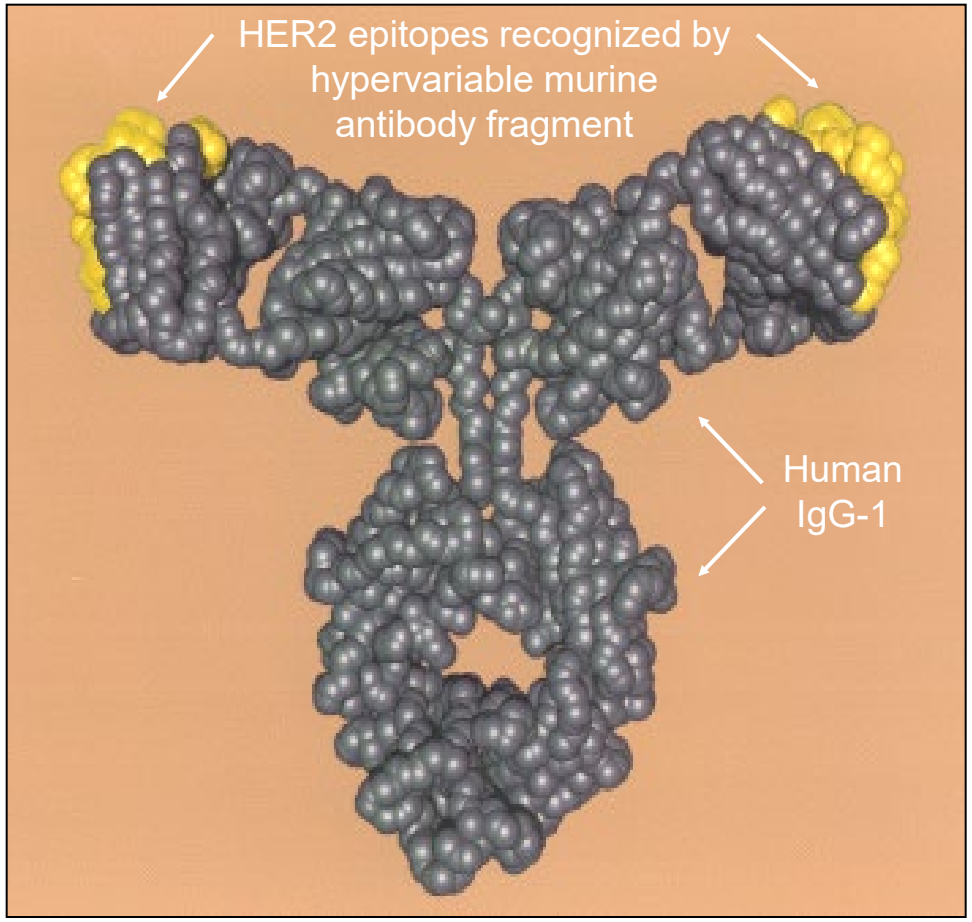
- Additional Regimens (NCCN)
  - Dose dense AC (Doxorubicin/Cyclophos)
  - AC Q3 wkly
  - CMF
  - AC Q3 wkly followed by Paclitaxel wkly

HER2+ Breast Cancer: Neoadjuvant and Adjuvant Therapy

HER2 Positive Breast Cancer

- 25–30% of breast cancers
- Human epidermal growth factor receptor 2 (HER2) important in cell signaling and proliferation
- Overexpression of HER2 correlates with a more aggressive breast cancer
- HER2+ disease diagnosed by immunohistochemistry (IHC) or gene amplification by fluorescence *in-situ* hybridization (FISH)
  - ASCO/CAP updated guidelines - 2018

Trastuzumab (Herceptin): humanized anti-HER2 antibody



- Targets HER2 protein's ECD
- High affinity and specificity
- 95% human, 5% murine
  - Increases potential for recruiting immune effector mechanisms
- Fc portion recruits and interacts with immune effector cells
- Extensively investigated mechanisms of action

Pivotal adjuvant trastuzumab trials: patient characteristics

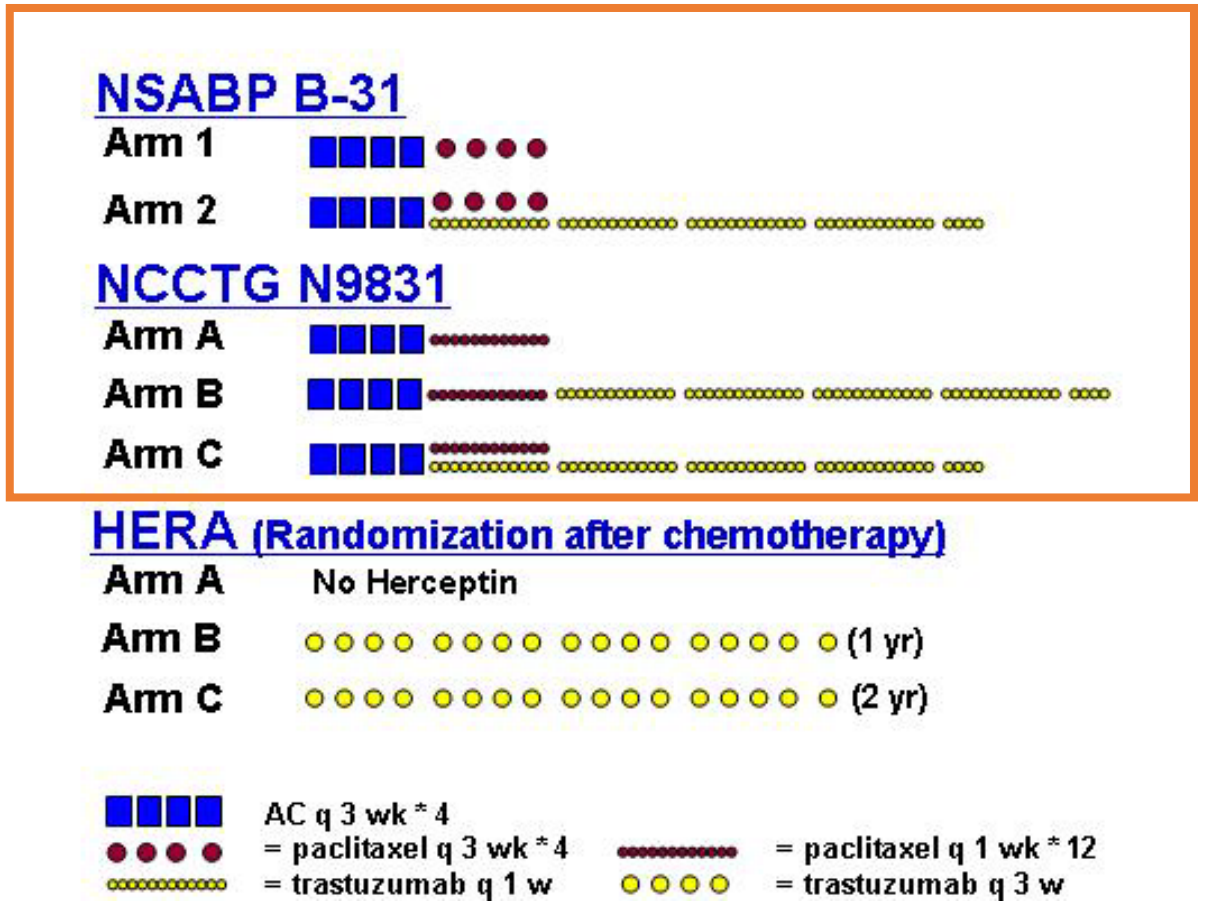
- HER2 positive (IHC 3+ or FISH amplified) invasive breast cancer, post lumpectomy/mastectomy

- Nodal status
  - Node positive (NSABP B-31)
  - Node positive or high-risk node negative (NCCTG N9831, HERA, BCIRG 006)

- No previous or current cardiac disease

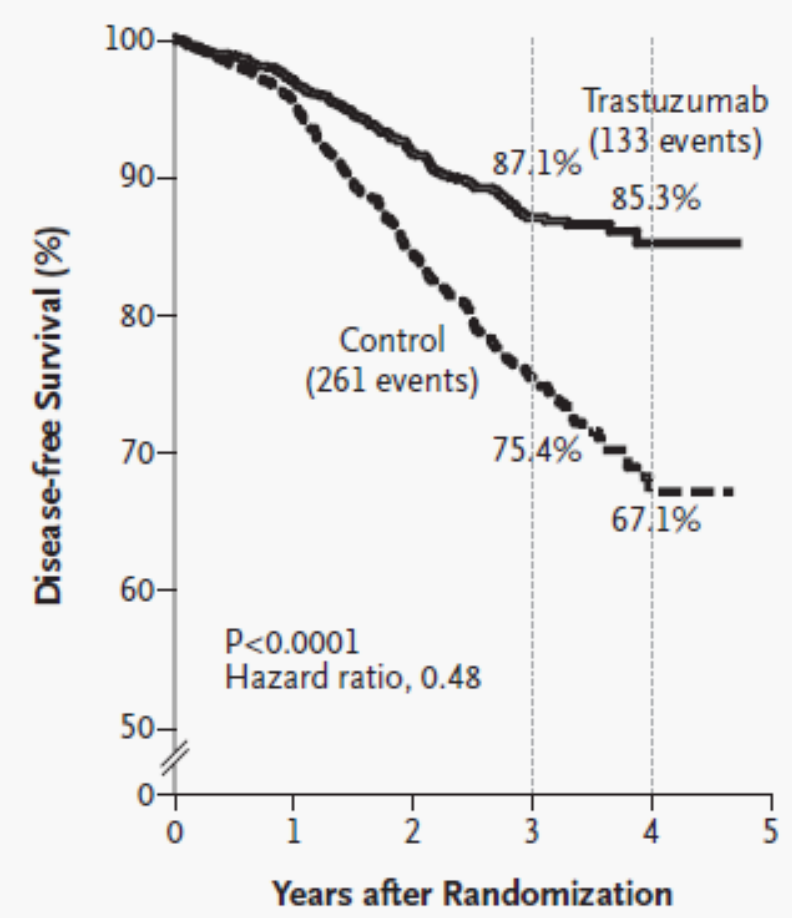
HER2+ Randomized Phase III Trials

- HER2 positive:
  - IHC 3+ or FISH amplified
  - post lumpectomy/mastectomy
- Nodal status
  - Node positive (NSABP B-31)
  - Node positive or high-risk node negative (NCCTG N9831, HERA, BCIRG 006)
- No previous or current cardiac disease

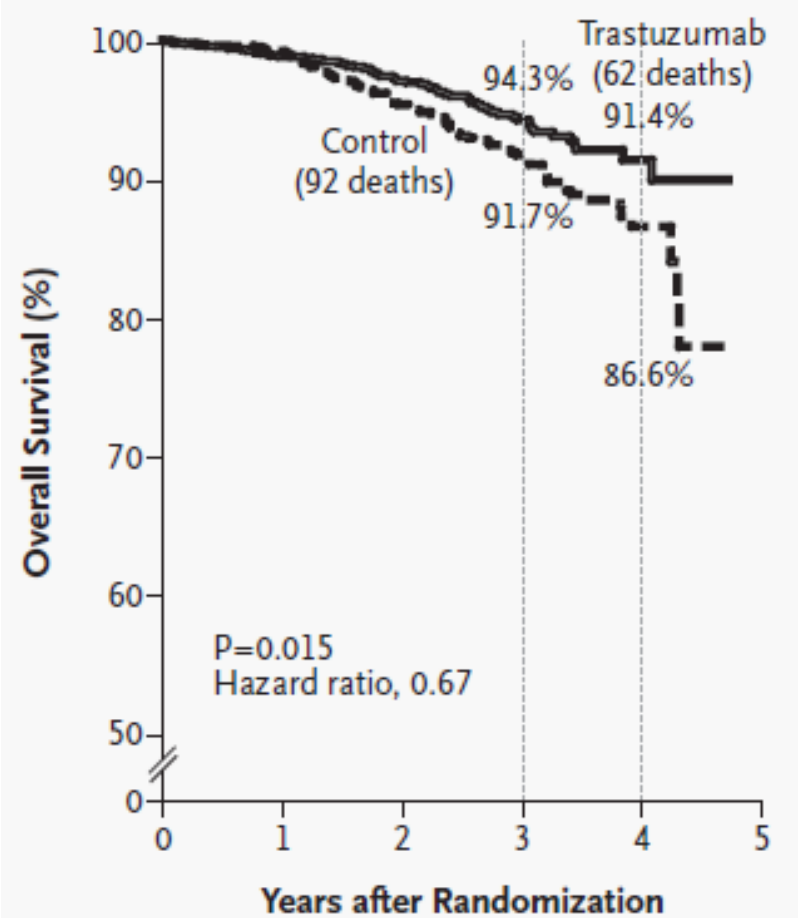


Combined Analysis of B-31 and N9831

- Trastuzumab improved DFS



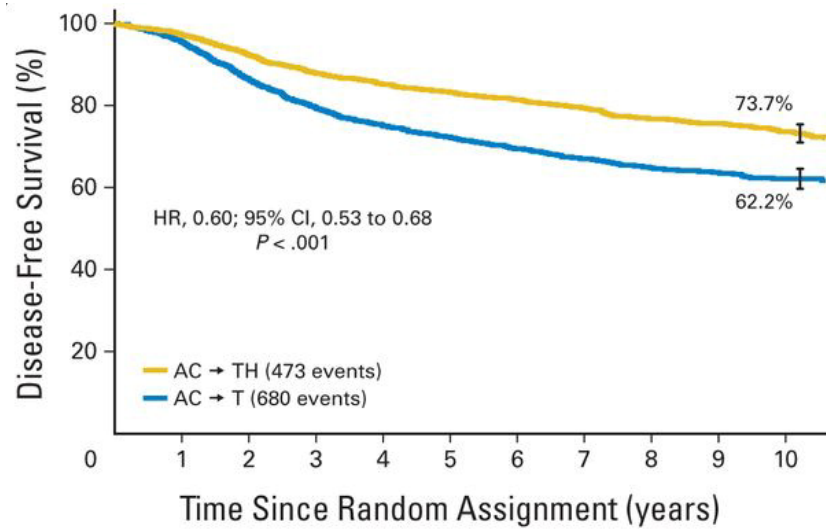
- Trastuzumab improved OS

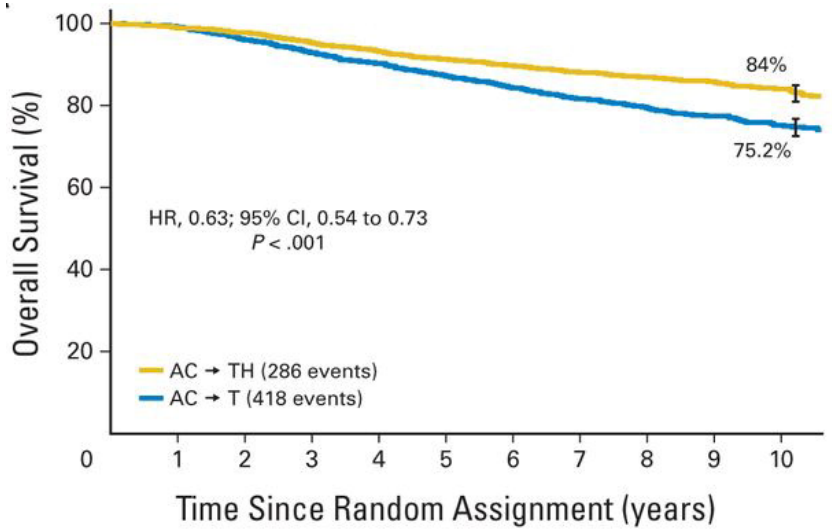


Romond et al; NEJM 2005

Combined analysis of B31 and N9831 – 10 yr.

- Adding Trastuzumab to chemotherapy resulted in:
  - Improved DFS – 40%
  - Improved OS – 37%
- Acceptable toxicity
  - Cardiac events – 3%





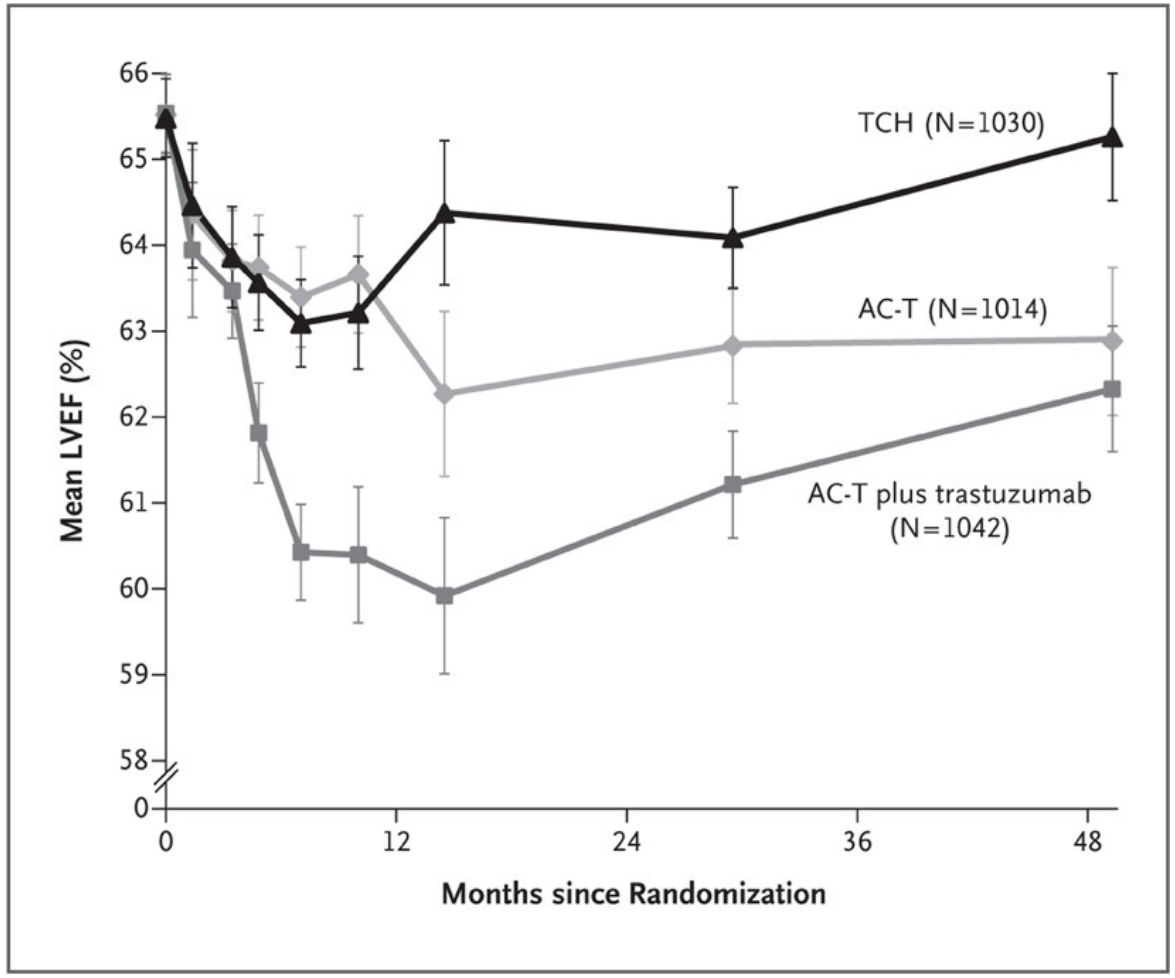
Perez et al. JCO. 2014

CV Risk: Trastuzumab and Anthracyclines

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

CV side effects w/ Anthracycline and Trastuz:

- 15% will have clinically sign. decrease in EF
- 1-3% w/ symptomatic CHF



Slamon et al. NEJM, 2011

Duration of Trastuzumab (HER2 therapy)

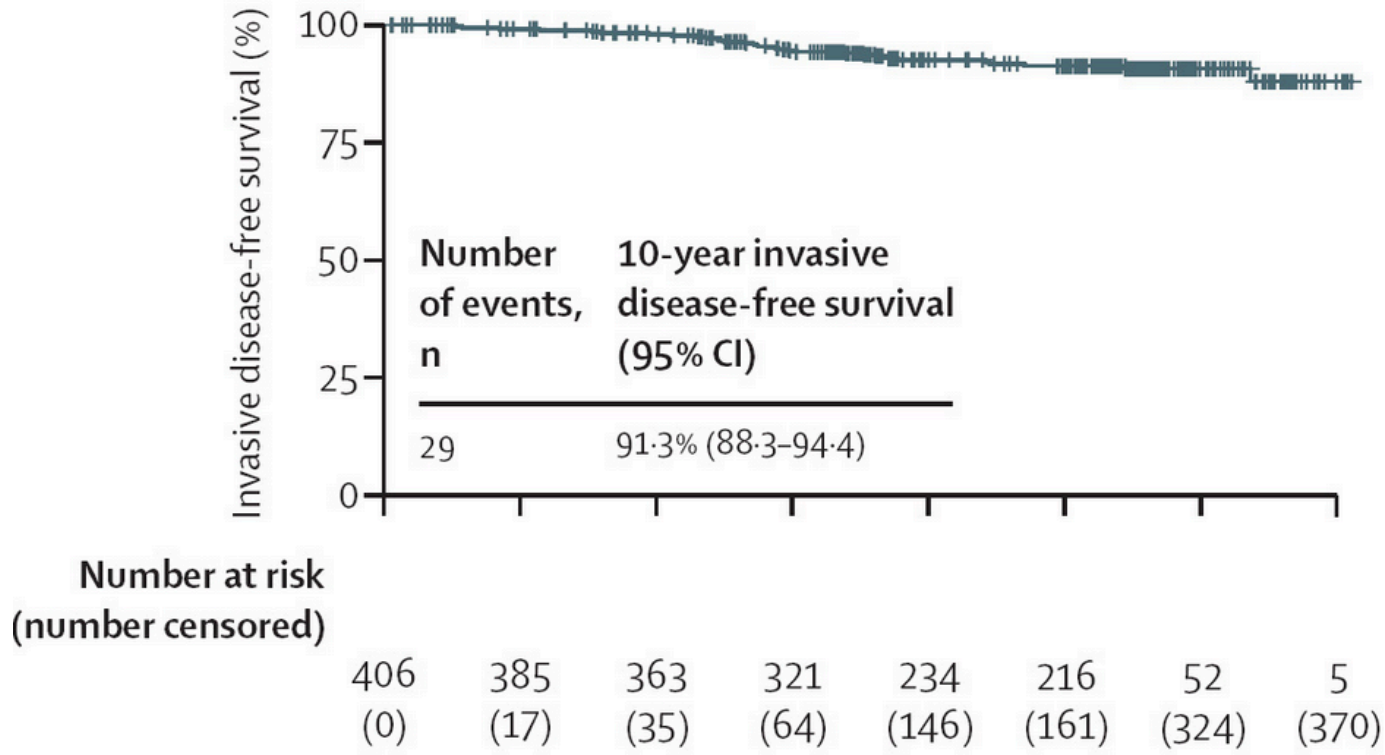
- HERA Trial: 1 year vs 2 years of Trastuzumab
  - No difference between 2-year vs 1-year for DFS (HR, 0.99, 95% CI, 0.85-1.14; *P*=0.86)
  - OS was also similar between both groups (HR, 1.05, 95% CI, 0.86-1.28; *P*=0.63)
  - Asymptomatic cardiac dysfunction was higher after 2 years of trastuzumab (7.2% vs. 4.1%)

- PHARE Trial: 6 months vs 1 year of Trastuzumab
  - HR for DFS in the study was 1.28 (95% CI: 1.05-1.56; p=0.29).
  - The non-inferiority of 6 months of trastuzumab compared to 12 months could not be demonstrated
  - Could not prove noninferiority of 6 months

Gelber RD et al. 2012 ESMO 2012, Abstract LBA6.
Pivot X et al. ESMO 2012, Abstract

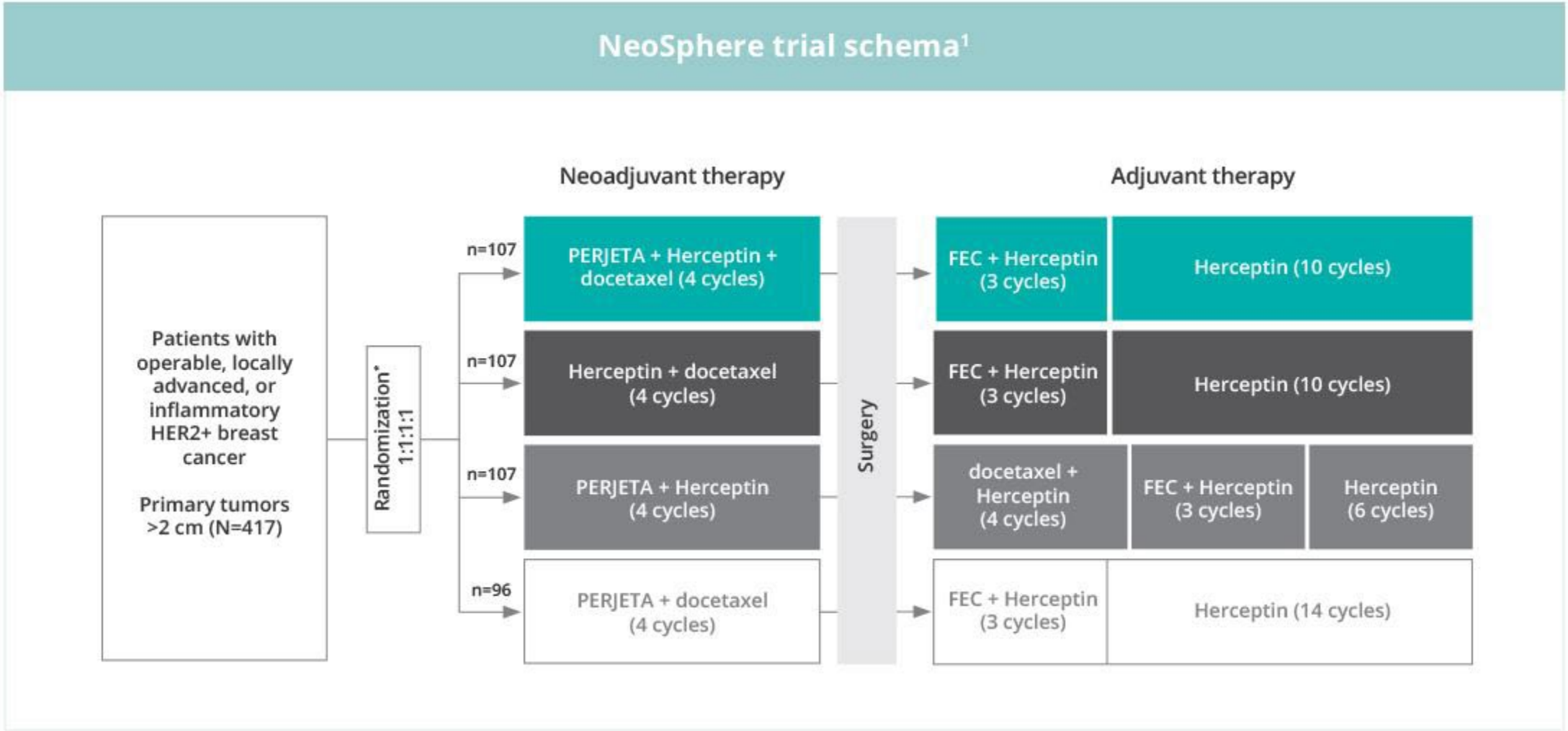
Stage I HER2+ breast cancers: APT Trial

- APT Trial
  - Multicenter, Single-Arm Trial
  - Paclitaxel + Trastuzumab
- Eligibility:
  - HER2+ (3+ or FISH>2.0)
  - Primary tumor ≤ 3cm
- Results:
  - 10 yr. inv. disease free survival:
    - 91.3% at 10 yrs.
  - DFS by HR status:
    - HR positive: 91.6%
    - HR negative: 90.6%



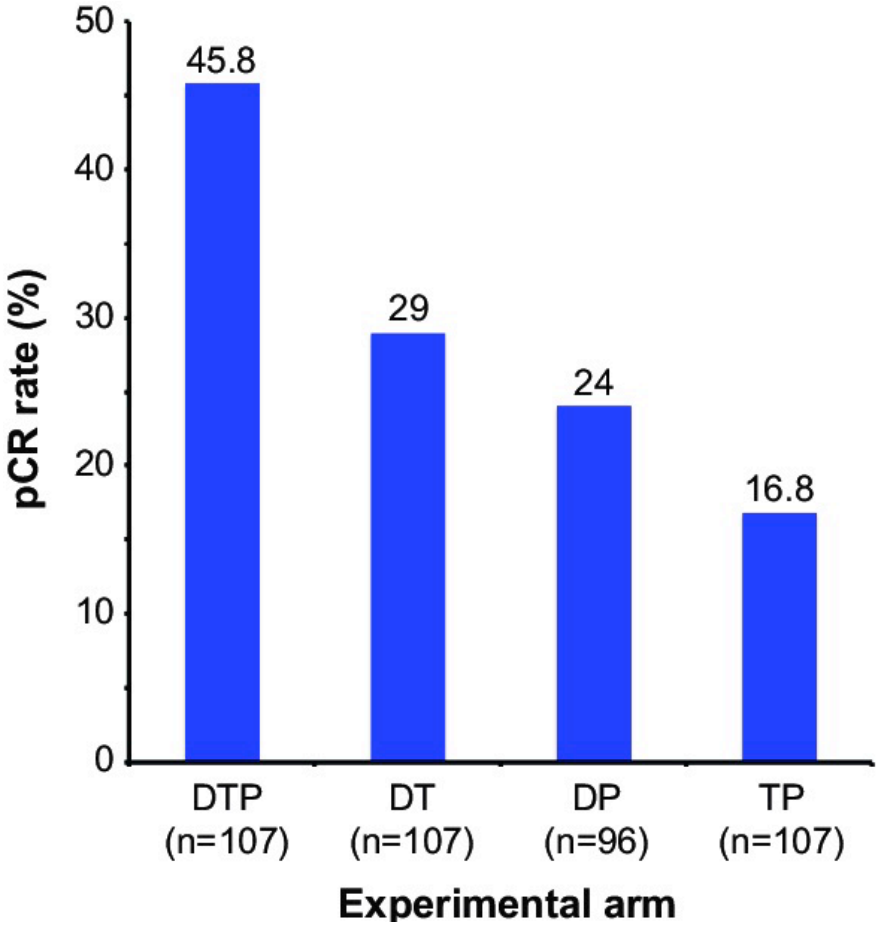
Tolaney EM, et al. The Lancet Oncology 2023

Neosphere Trial: Neoadjuvant Pertuzumab



Neosphere Trial: Path complete response

- Highest pathologic CR rate in the Pertuzumab + Trastuzumab + Docetaxel arm
  - 45.8% (95% CI 36.1-55.7)
- Most common grade ≥3 AEs:
  - Neutropenia
  - Febrile neutropenia
  - Leukopenia

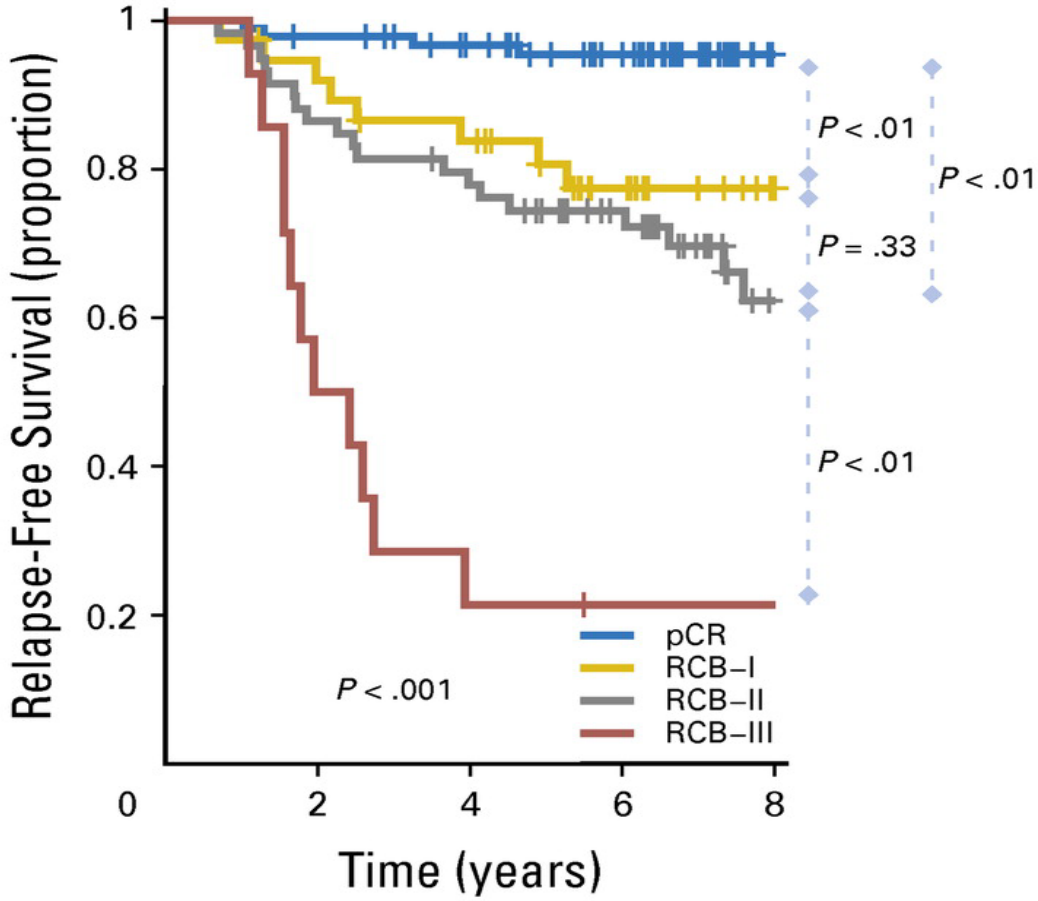


Gollamudi J, et al. Cancer Management and Research. 2016

Residual disease after neoadjuvant therapy

Residual Cancer Burden (RCB) - Prognostic

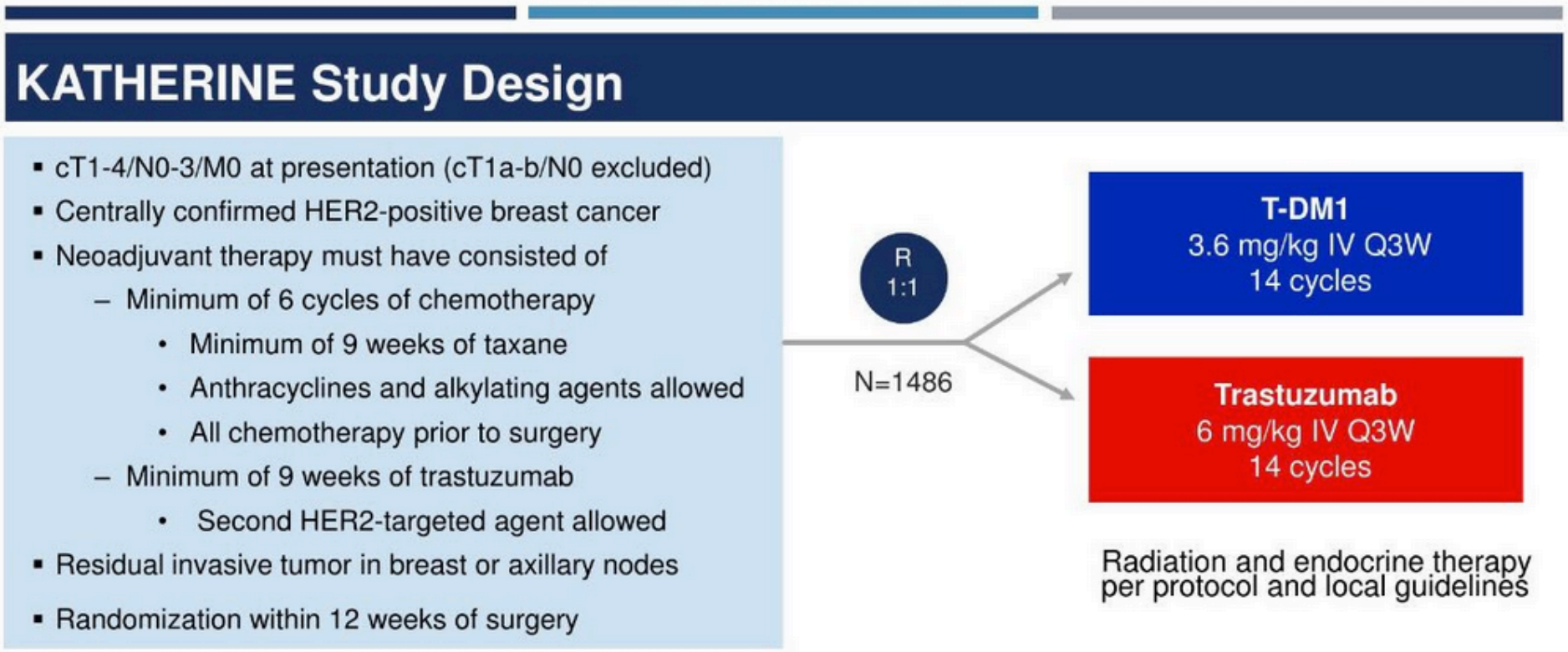
- pCR had RFS of 95% - 5 yrs. and 10 yrs.)
- RCB-I (RFS of 81% - 5 yrs., 77% - 10 yrs.)
- RCB-II (RFS of 74% - 5 yrs., 47% - 10 yrs.)
- RCB-III (RFS of 21% - 5 yrs. and 10 yrs.)



* Additional Therapies Needed

Symmans et al JCO 2017

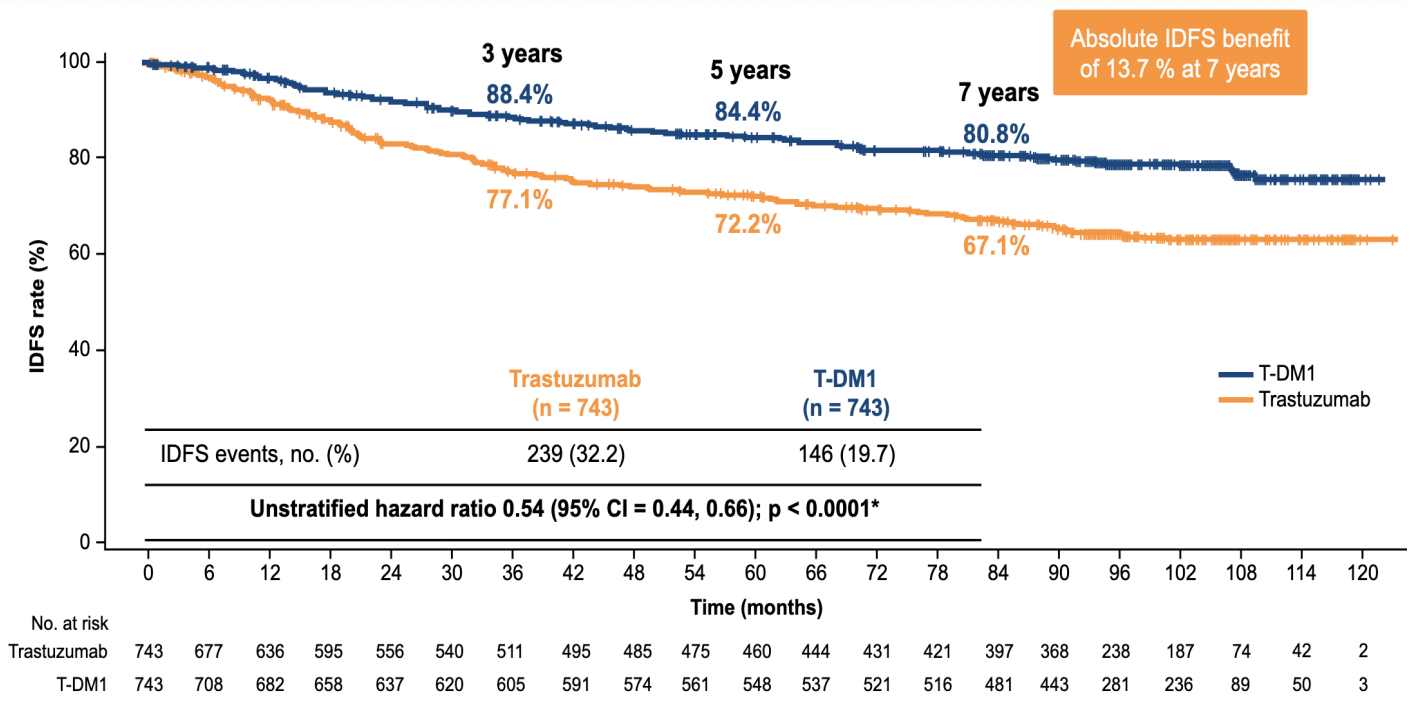
KATHERINE Study – Adjuvant TDM-1



Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

KATHERINE – IDFS, Median 7yrs



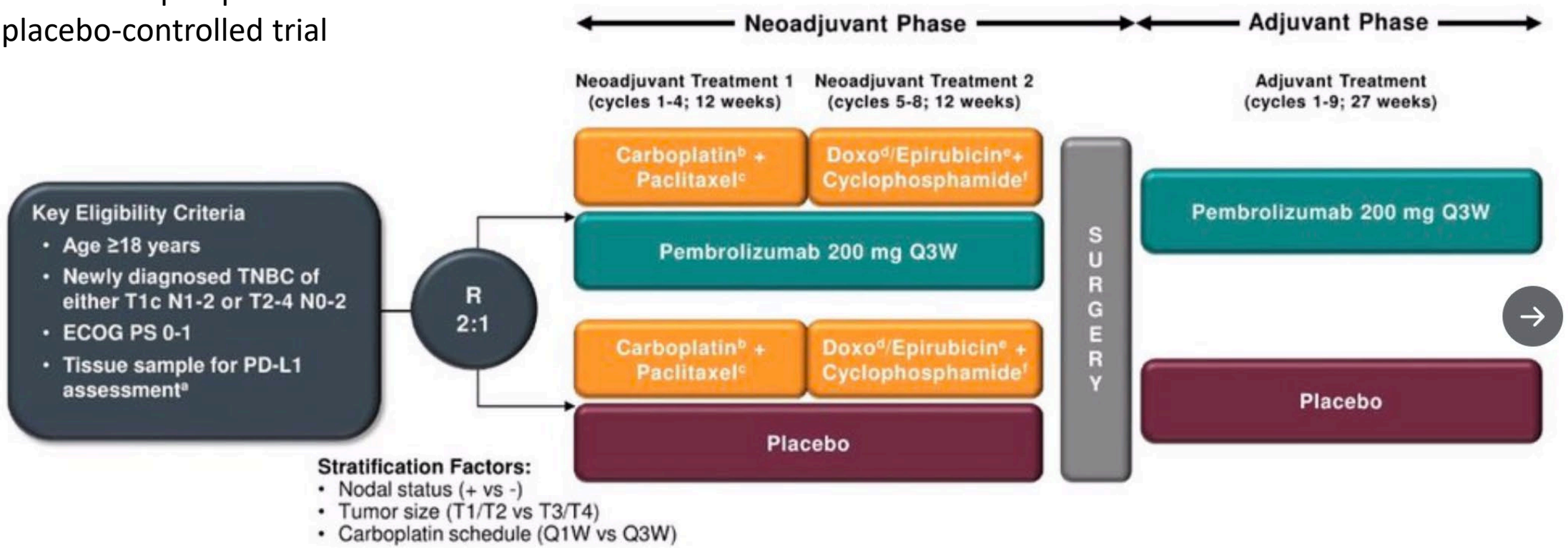
- Inv. Disease-Free Survival:
  - TDM-1: 80.8%
  - Trastuzumab: 67.1% (HR 0.54, p<0.0001)
- 2nd interim Overall Survival:
  - TDM-1: 89.1%
  - Trastuzumab: 84.4% (HR 0.66, p=0.0027)

Loibl, S et al. SABCS 2023

Triple Negative Breast Cancer

KEYNOTE-522: Neoadjuvant anti-PD-1

- Phase 3 prospective randomized placebo-controlled trial



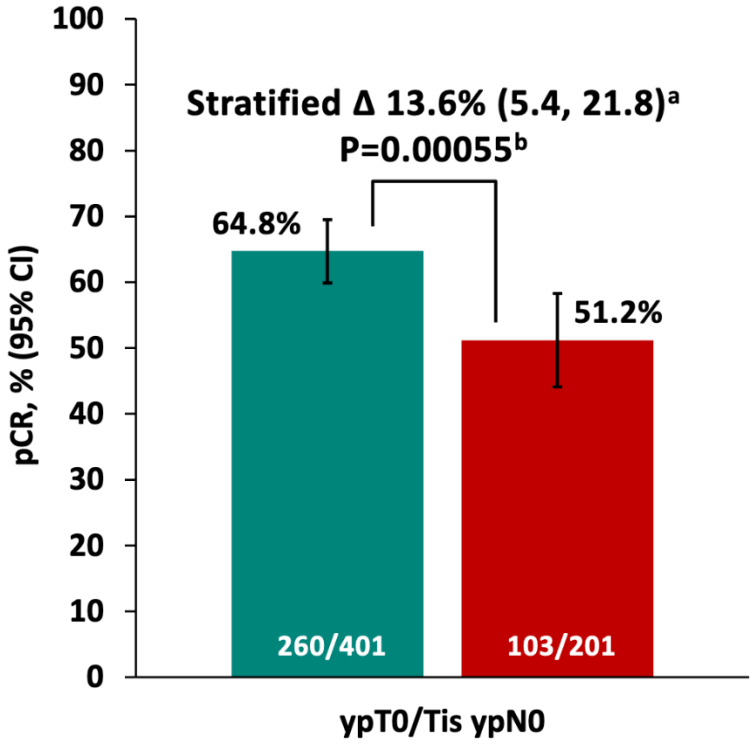
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

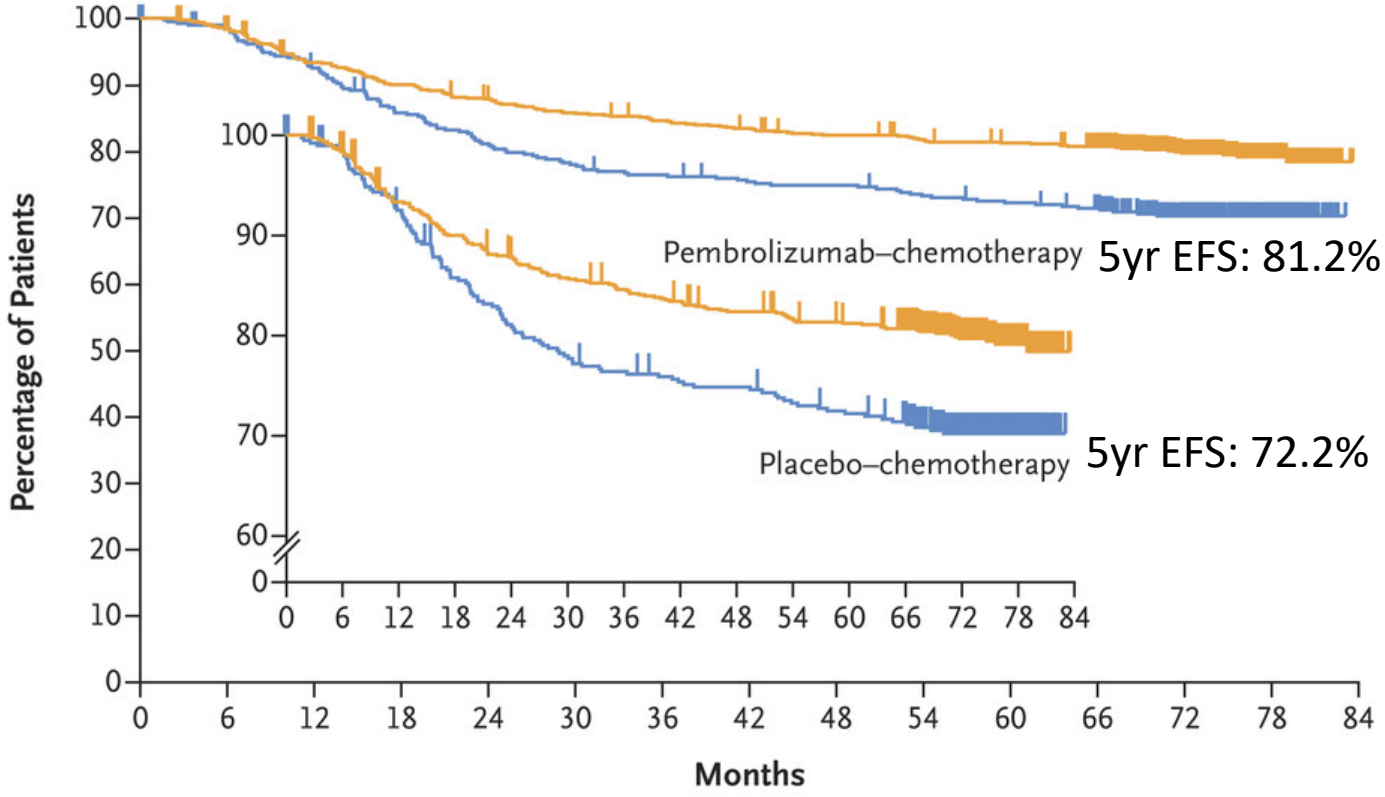
Schmid P , et al. ESMO, 2019

KEYNOTE-522: Primary Endpoint pCR and EFS

Pathologic CR



Event Free Survival



5yr EFS: 81.2%

5yr EFS: 72.2%

Overall Survival – 5yrs:

- Pembro-chemo: 86.6%
- Placebo-chemo: 81.7%

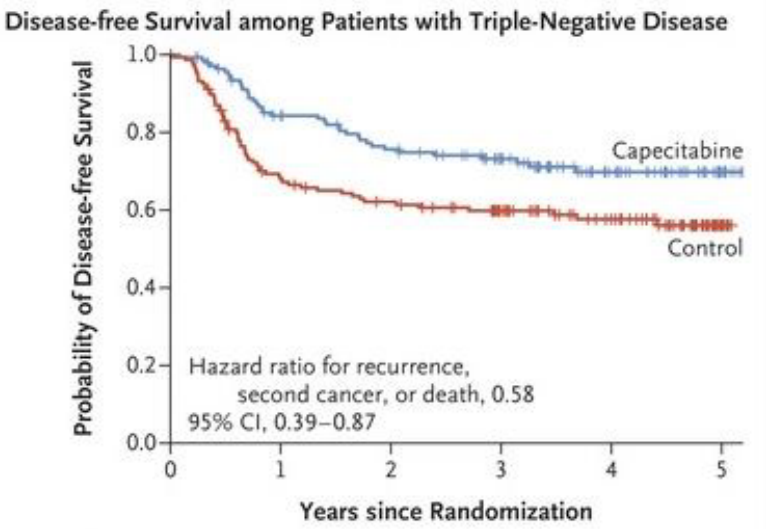
Schmid P, et al. ESMO, 2019
Schmid P, et al. NEJM, Sept. 2024

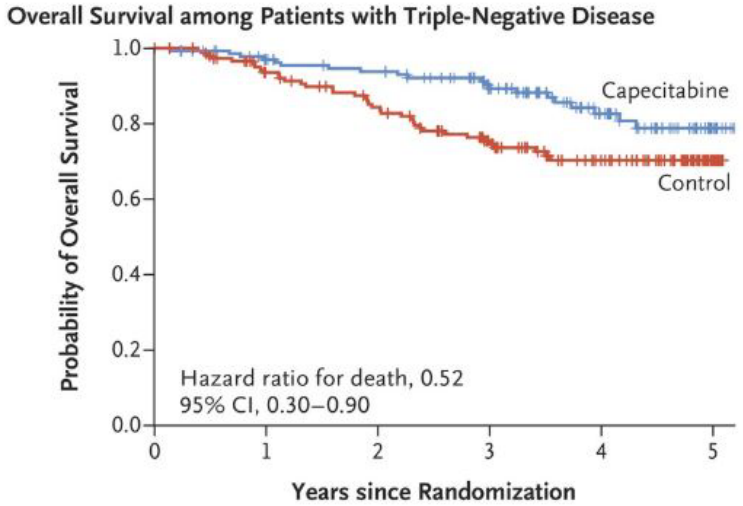
The NEW ENGLAND JOURNAL of MEDICINE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

- HR+ and TNBC patients with residual disease after neoadjuvant chemo

- In TNBC patients adjuvant Capecitabine improved:
  - Disease-free survival
  - Overall Survival





Masuda N, et al. NEJM. 2017

OlympiA Trial – Adjuvant Olaparib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr.,

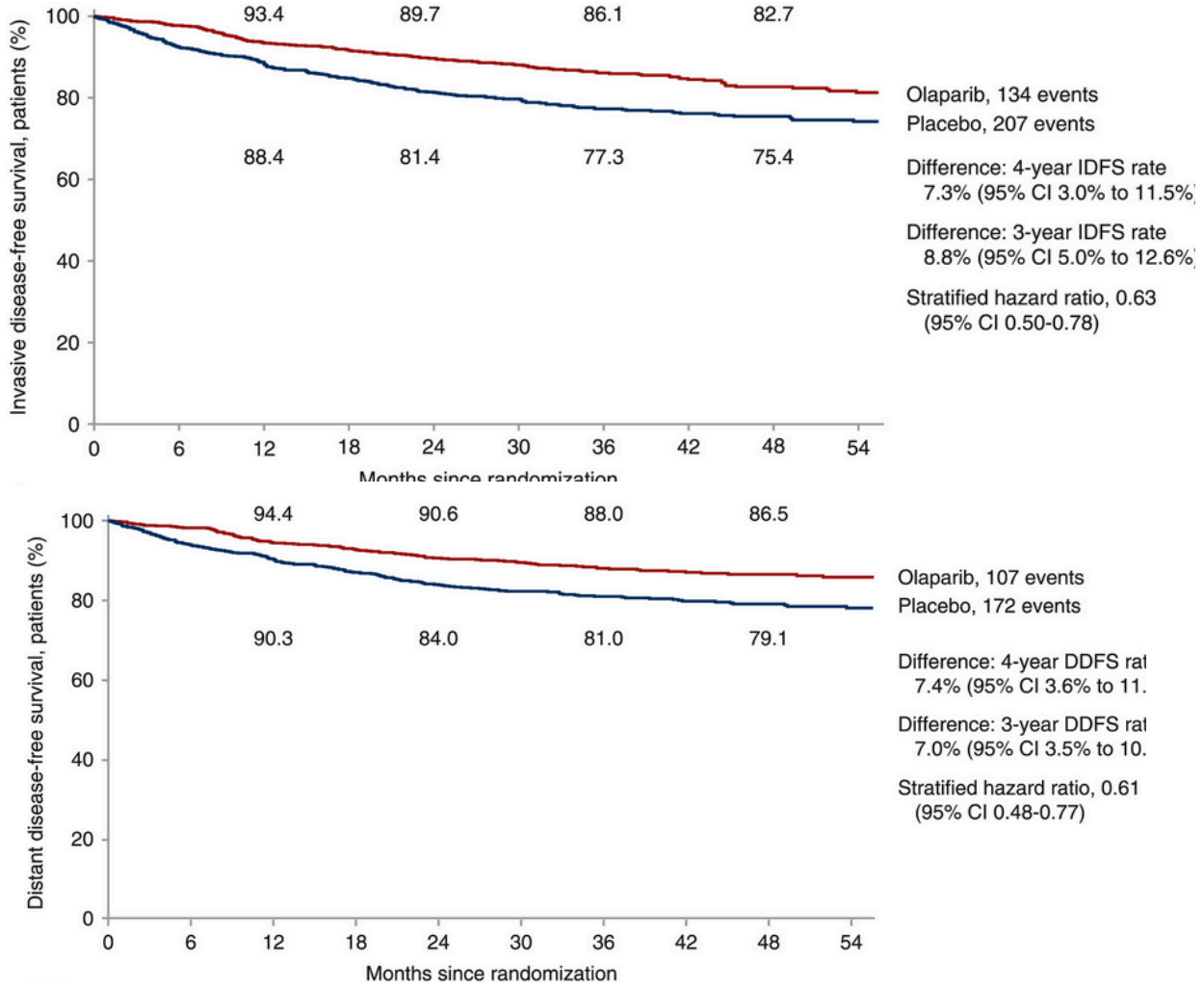
Tutt AN, et al. N Engl J Med 2021

OlympiA Trial – Adjuvant Olaparib

- Eligibility, TNBC or HR+
  - TNBC:
    - Adjuvant chemo and LN+
    - Residual disease post neoadjuvant
  - HR+:
    - Adjuvant chemo and 4+ LN
    - Residual disease post neoadjuvant

- 4-year IDFS
  - 82.7% in the olaparib group
  - 75.4% in the placebo group

- 4-year distant DFS
  - 86.5% in the olaparib group
  - 79.1% in the placebo group

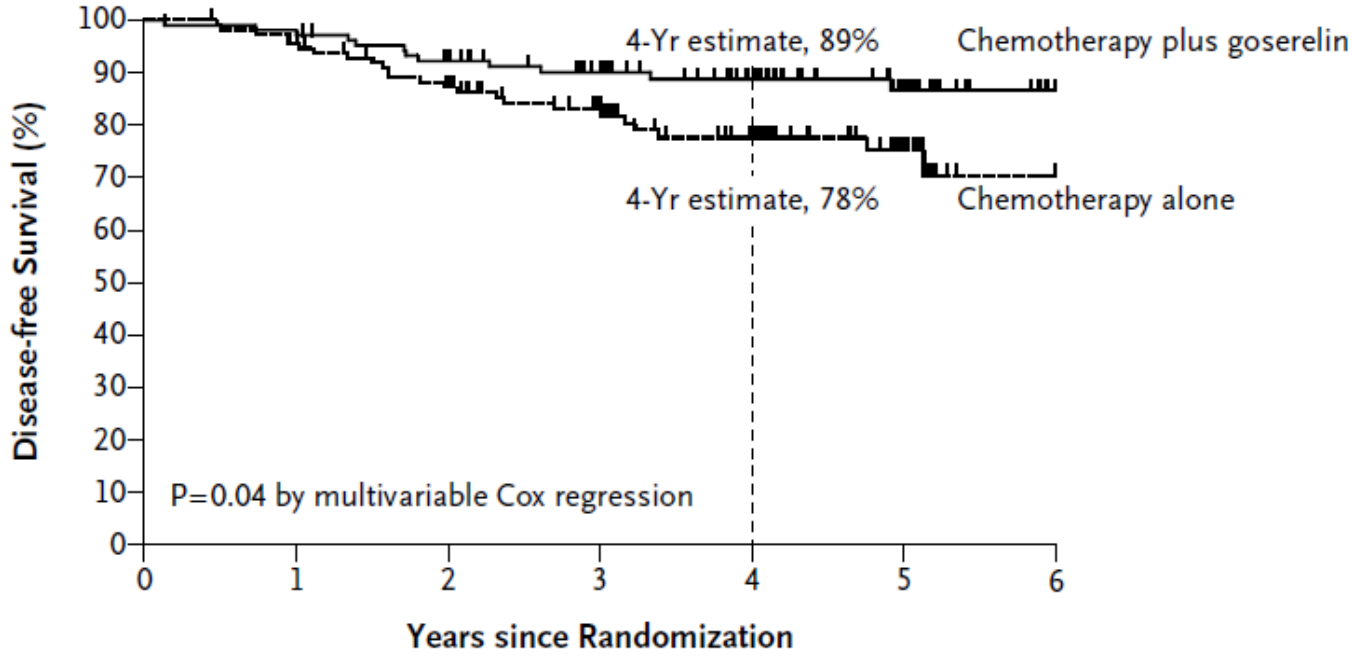


Geyer CE, et al. Annals of Oncology, 2022

The NEW ENGLAND JOURNAL of MEDICINE

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

- Pre-menopausal undergoing adjuvant chemo assigned to:
  - Goserelin + chemotherapy
  - Chemotherapy alone
- Goserelin associated with:
  - Less ovarian failure
  - More pregnancies (21% vs 11%)
  - Improved DFS and OS



Moore, NEJM 2015

Thank You