Role of Endocrine Therapy in Breast Cancer

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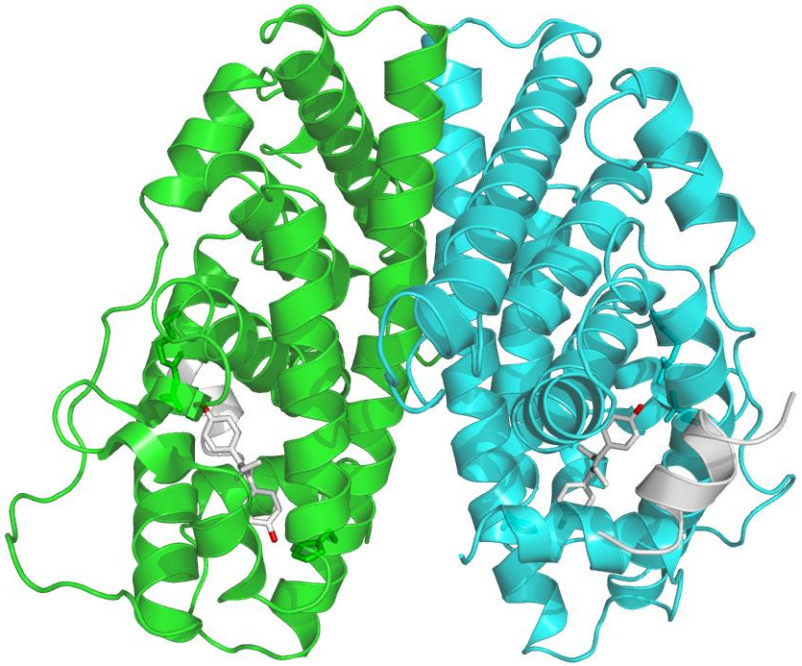
32nd AROI ICRO Teaching Course on Breast Cancer, 27th of July 2019

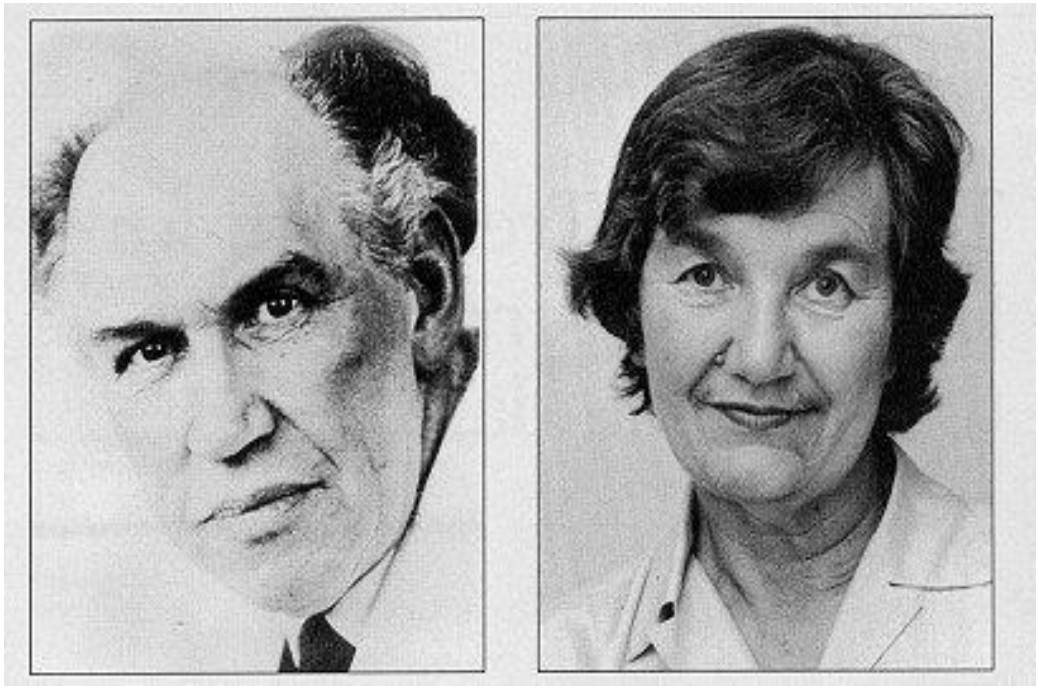


WHY ENDOCRINE THERAPY IN BREAST CANCER?

Evolution

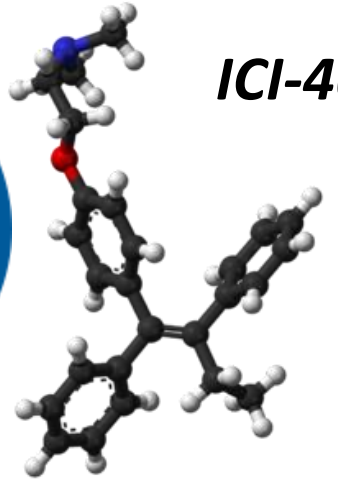
- "Removal of ovaries reduces size of primary breast cancer"
  - **George Beatson (1896)**
- Stilbestrol
  - **Haddow ~ 1930s**
- Adrenalectomy
  - **Huggins ~ 1940s**
- Androgenic steroids
  - **1950s**
- Hypophysectomy or ablation
  - **Forest ~ 1960s**
- **TAMOXIFEN 1970s**
- Aminoglutethimide and Goserelin
  - **1980s**
- **AROMATASE INHIBITORS 1990s**
- **FULVESTRANT / EVEROLIMUS / CDK4/6 inhibitors**

Early days



On Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases.

Beatson G.W. Lancet 1896



ICI-46,474

A NEW ANTI-OESTROGENIC AGENT IN LATE BREAST CANCER
AN EARLY CLINICAL APPRAISAL OF ICI46474

M. P. COLE, C. T. A. JONES AND I. D. H. TODD

From the Christie Hospital and Holt Radium Institute, Manchester M20 9BX

Received for publication April 7, 1971

SUMMARY.—An introductory clinical trial of the anti-oestrogenic agent ICI46474 in late or recurrent carcinoma of the breast is described.

Forty-six patients have been treated, of whom 10 have shown a good response. This is of the same order as that seen with oestrogens and androgens.

The particular advantage of this drug is the low incidence of troublesome side effects.

Early days..

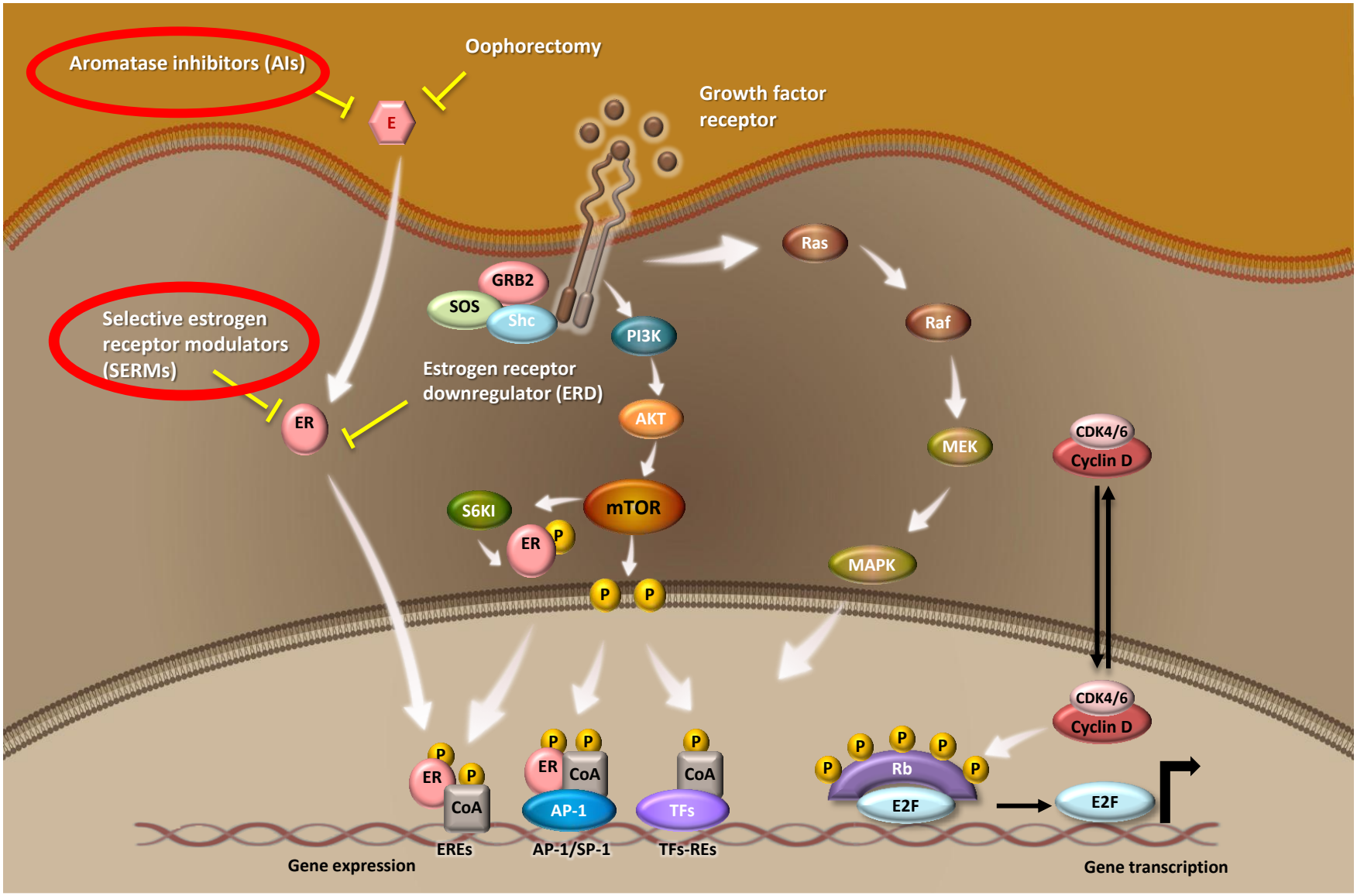
Anti-oestrogen Therapy for Breast Cancer: A Trial of Tamoxifen at Two Dose Levels

H. W. C. WARD

PRELIMINARY TRIAL OF AMINOGLUTETHIMIDE IN BREAST CANCER

C. THOMAS GRIFFITHS, MD,* THOMAS C. HALL, MD,† ZEINA SABA, MD,‡ JOSEPH J. BARLOW, MD,§ AND HANS B. NEVINNY, MD‖

Targets and pathways for Endocrine Therapy in Breast Cancer



Adapted from Yardley DA, et al. ASCO BC 2011. Abstract 268; Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; Yamnik RL, et al. *J Biol Chem.* 2009;284:6361-6369.

Hormone Therapy in Breast Ca : Major determining factors.

- **ER**
- **PR**
- **HER 2 neu**

Ki 67

PI3KCA mutations

- **Menstrual Status**
  - *Not a predeterminant for necessity of Hormone therapy.*
  - *Just a factor for the choice of Hormone.*

Definition of Menopause

EUSOMA Guidelines

- Amenorrhea > 12mo
  Irrespective
- Amen
  A
- 12
- h
- ,
  Le
  opausal

NCCN Guidelines v 2.2019

ation of menses which

se in ovarian

⇨ *In women who have become amennorhic during chemotherapy or the menopausal status is unsure,* ***serial serum Estradiol & FSH*** *measurements are necessary to establish Menopausal Status.*

WHO ARE THE CANDIDATES FOR HORMONE THERAPY IN BREAST CANCER ?

- LCIS (**ER +ve**)
- DCIS (**ER +ve**)
- Invasive Cancer
  - All **ER +ve** pts.
  - A subset of these patients may be candidates for ET alone
    - Age > 70 yrs
    - Micro-invasive or pT < 0.6 cm pN0
    - Low grade, no LVSI, strongly ER+
- In ER *unknown* – Tamoxifen???

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

M. Elizabeth H. Hammond, Daniel F. Hayes, Mitch Dowsett, D. Craig Allred, Karen L. Hagerty, Sunil Badve,

VOLUME 28 · NUMBER 16 · JUNE 1 2010

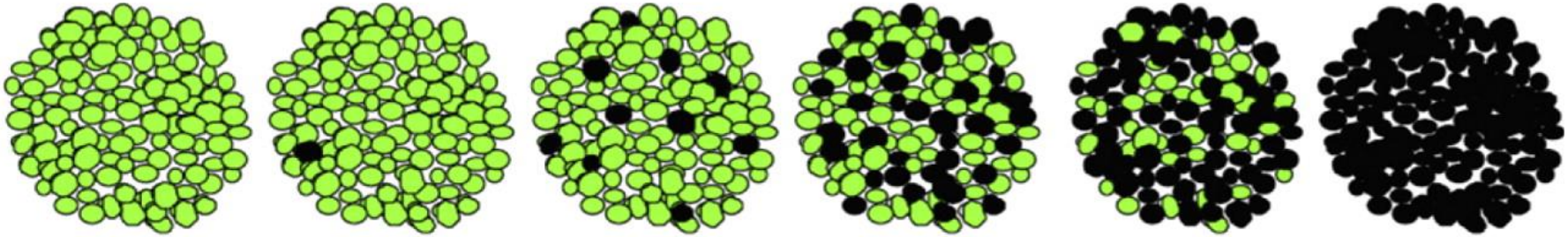
JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

	Recommendation
Optimal algorithm for ER/PgR testing	Positive for ER or PgR if finding of ≥ 1% of tumor cell nuclei are immunoreactive. Negative for ER or PgR if finding of < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen). Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.

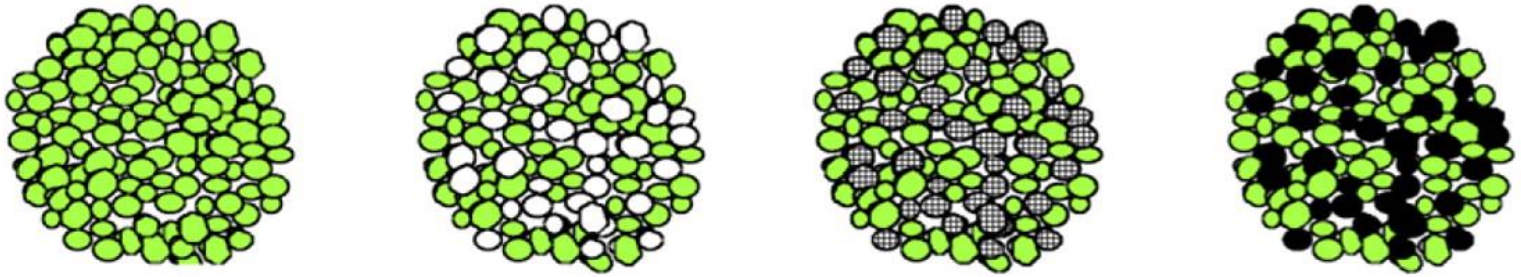
Allred Scoring

A Proportion Score (PS)



0 1→1/100 2 →1/10 3 →1/3 4 →2/3 5 →1

B Intensity Score (IS)



0 = negative 1 = weak 2 = intermed 3 = strong

Allred Score = PS + IS (range 0-8)

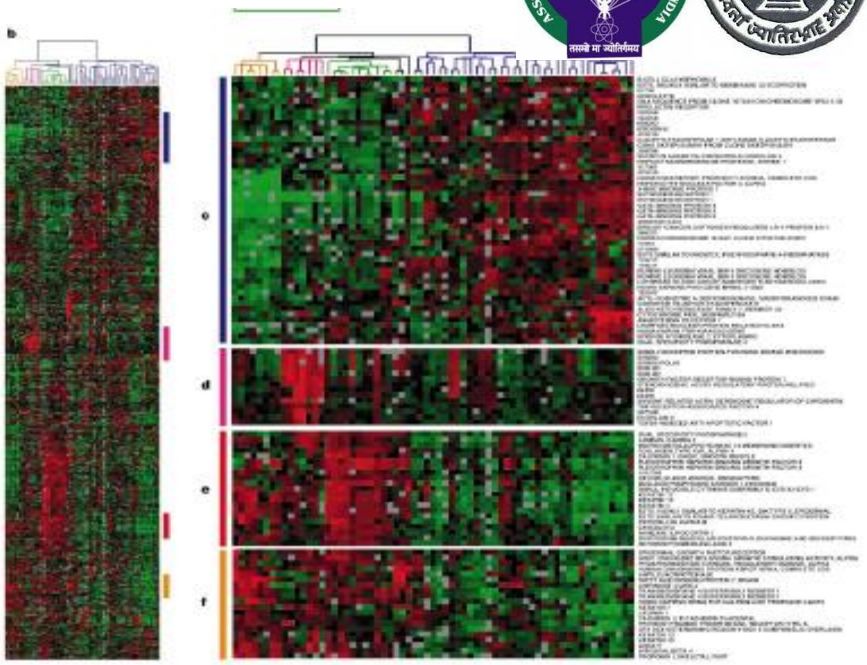
BREAST CANCER - *ONE* DISEASE ?

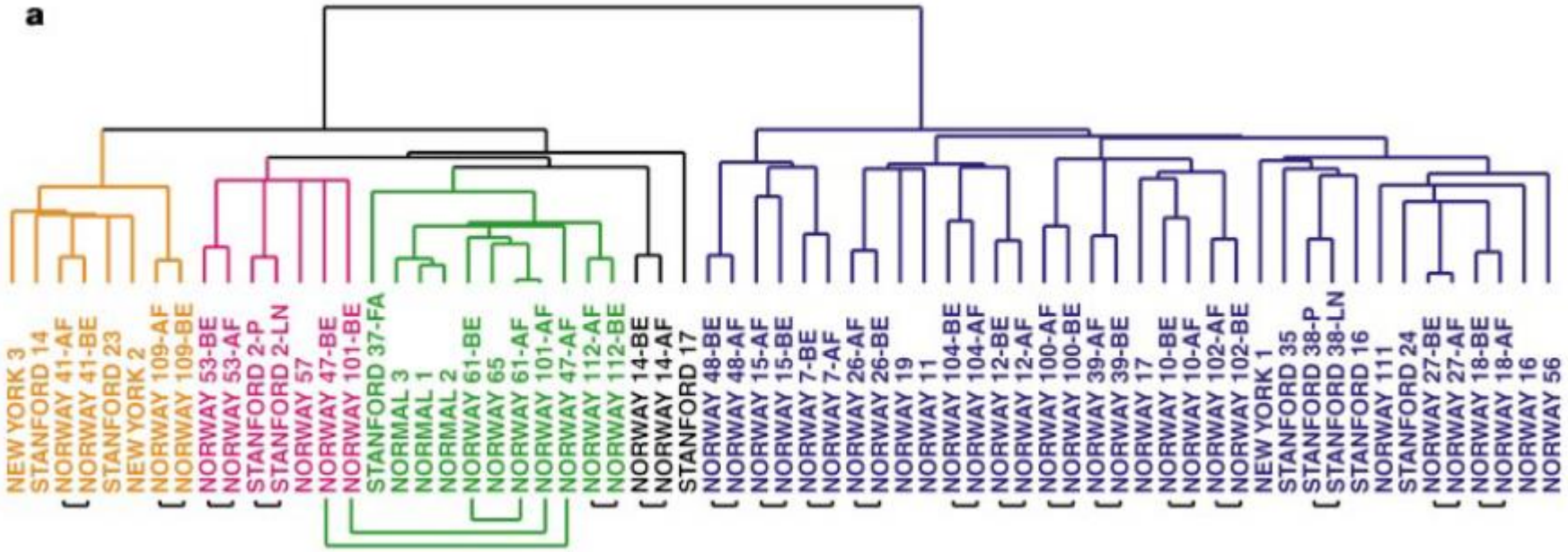
Intrinsic subtypes

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein***

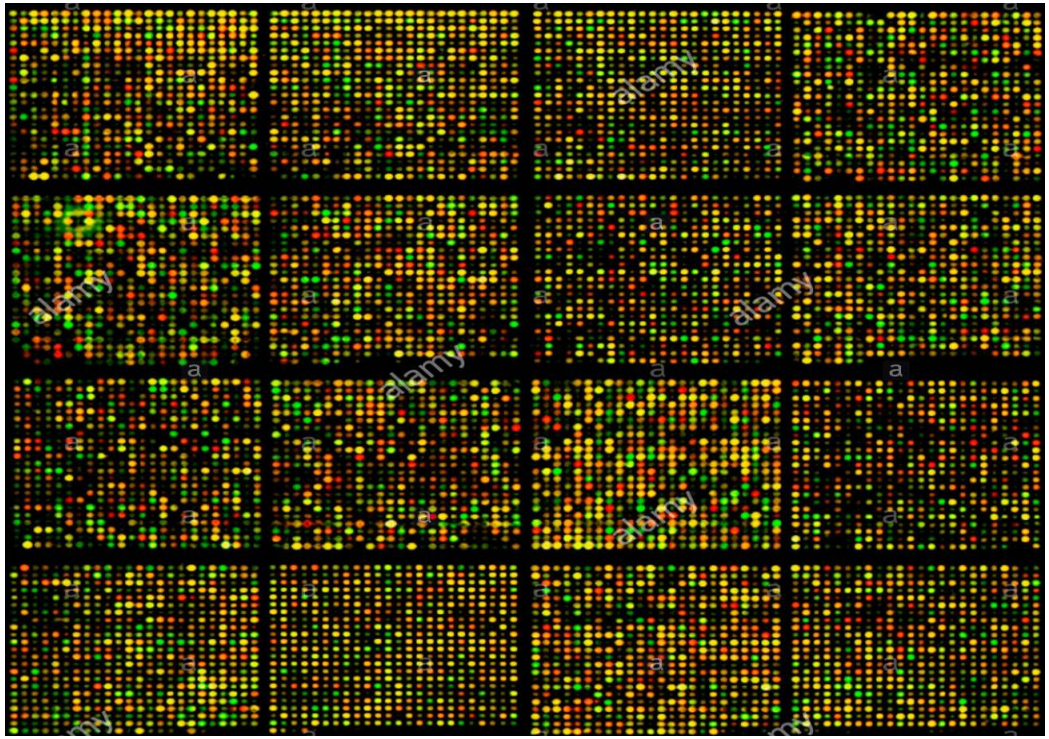
** Department of Genetics, Stanford University School of Medicine, Stanford, California 94305, USA*
‡ Department of Genetics, The Norwegian Radium Hospital, N-0310 Montebello Oslo, Norway





Intrinsic Subtype	Characteristics
Luminal A	ER+ PR high Her2 neu – Ki 67 low Recurrence risk low
Luminal B	ER+ PR low Her2 neu – Ki 67 high Recurrence risk high
	ER+ PR any Her2 neu + Ki 67 any Recurrence risk any
Her 2 overexpressed	Her2 neu overexpressed / amplified ER and PR absent
Basal	ER– PR– Her 2 neu – Triple Negative

The threshold for cut-off of PR high and low is typically taken as 20% and for Ki 67 as 14% respectively.



CAN WE BETTER PREDICT WHO WILL BENEFIT MOST FROM ENDOCRINE THERAPY?

Tools to better predict candidates for ET alone

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, E.A. Perez, J.A. Olson, Jr., J.A. Zujewski, T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.N. Atkins, J.L. Berenberg, and G.W. Sledge

Tools to better predict responsiveness to ET

EndoPredict®

start · new · breast cancer · EndoPredict · provider

start page • EndoPredict • principle of operation

principle of operation
late metastasis
Publications
development
Frequently Asked questions

principle of operation

OF TUMOR BIOLOGY THERAPY DECISION IN THREE STEPS

The EndoPredict animation illustrates the operating principle of gene expression tests. The test result is composed of the "molecular fingerprint" of a tumor in combination with the established prognostic parameters nodal status and tumor size. This EPclin score provides information on the individual clinical course of a patient and supports the specialists among others in deciding whether chemotherapy is necessary or not.

Laden im App Store

The EndoPredict animation answers the following questions:

1. How do the different genes in the tumor, the prognosis?
2. What is the interplay of the clinical data tumor size and nodal status with the gene expression?
3. What benefit can expect a patient from chemotherapy?

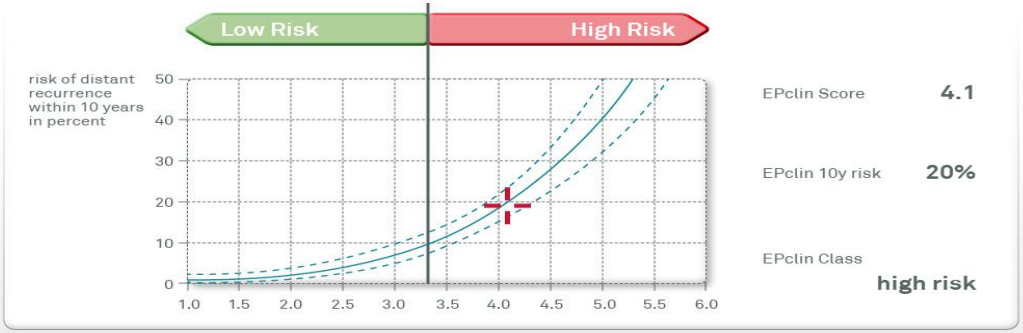
Chemotherapy
Yes or no?

Wiss. Publications
About EndoPredict

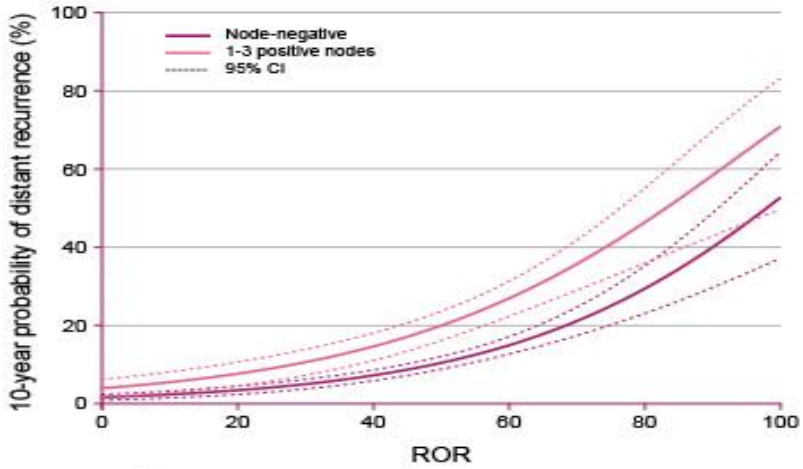
Contact

EPclin Score

Molecular fingerprint in context with classical parameters



10-year rate of distant recurrence by nodal status[1]



Adapted from Prosigna Package Insert, 2013.

The PAM50 intrinsic subtypes help you provide an individualized risk assessment[1]

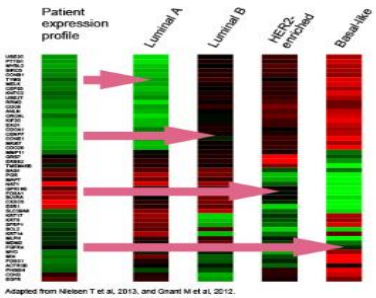
Intrinsic subtypes | **Prosigna algorithm** | Prognostic info

Use Prosigna to predict your patient's Risk of Recurrence (ROR)*

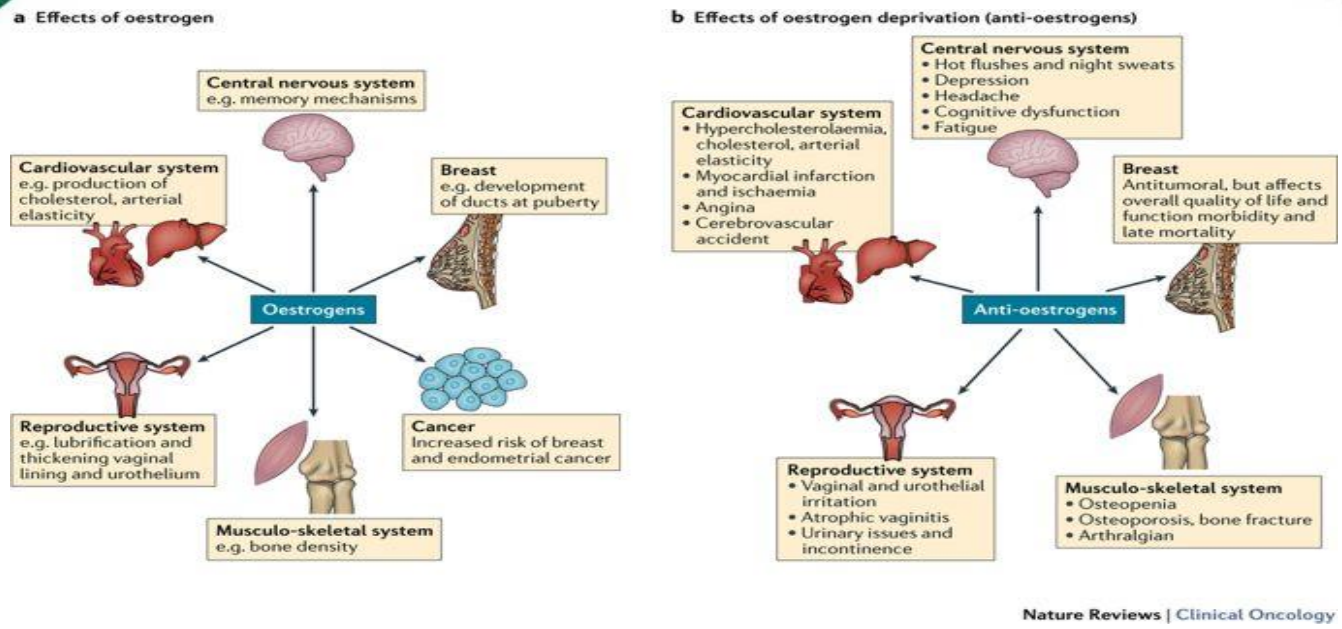
Prosigna generates ROR from a proprietary algorithm[1]

- Intrinsic subtypes are biologically and clinically distinct types of breast cancer that are characterized by different PAM50 gene expression signatures[2,3]
- ROR is derived from a proprietary algorithm based on the PAM50 gene signature, intrinsic subtype, tumor size, nodal status, and proliferation score[1]
- The gene expression profile of a patient's tumor is compared to each of the defined intrinsic subtype gene signatures to determine the degree of similarity[1]
- Proliferation score is determined by evaluating multiple genes within the proliferation pathway[4]
- ROR is provided as a numerical score on a 0-to-100 scale that estimates the probability of distant recurrence over 10 years[1]

Compare patient profile to intrinsic subtypes[5,6]

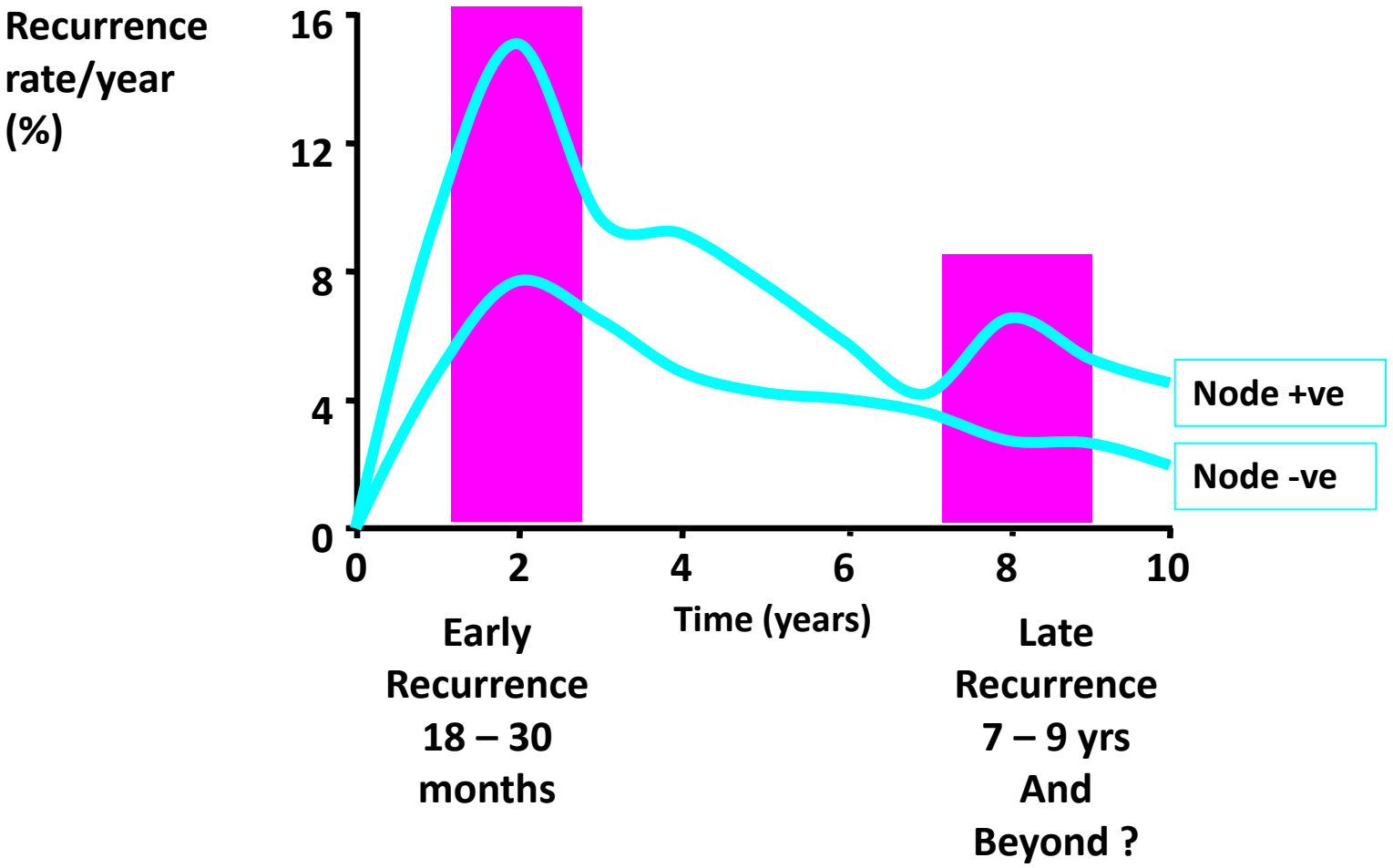


Adapted from Nielsen T et al, 2013, and Gnant M et al, 2012.



ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER.

Timing ET: newly diagnosed women



Endocrine therapy is generally not given along with Chemotherapy but can be used concomitant with Radiotherapy and Her 2 directed therapy.

EBCTCG Lancet 1998;352:930-942.

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2005; 365: 1687–1717

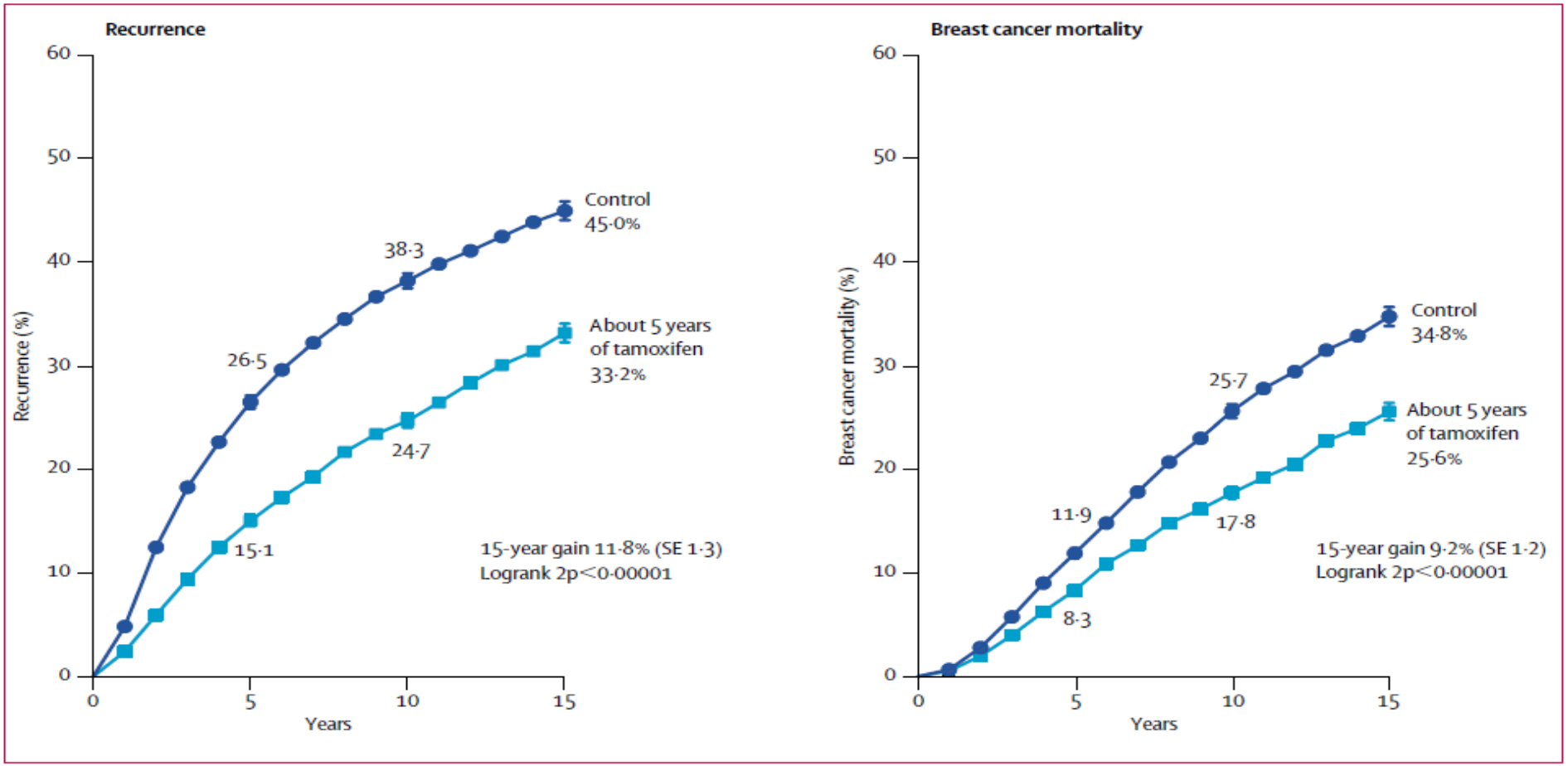


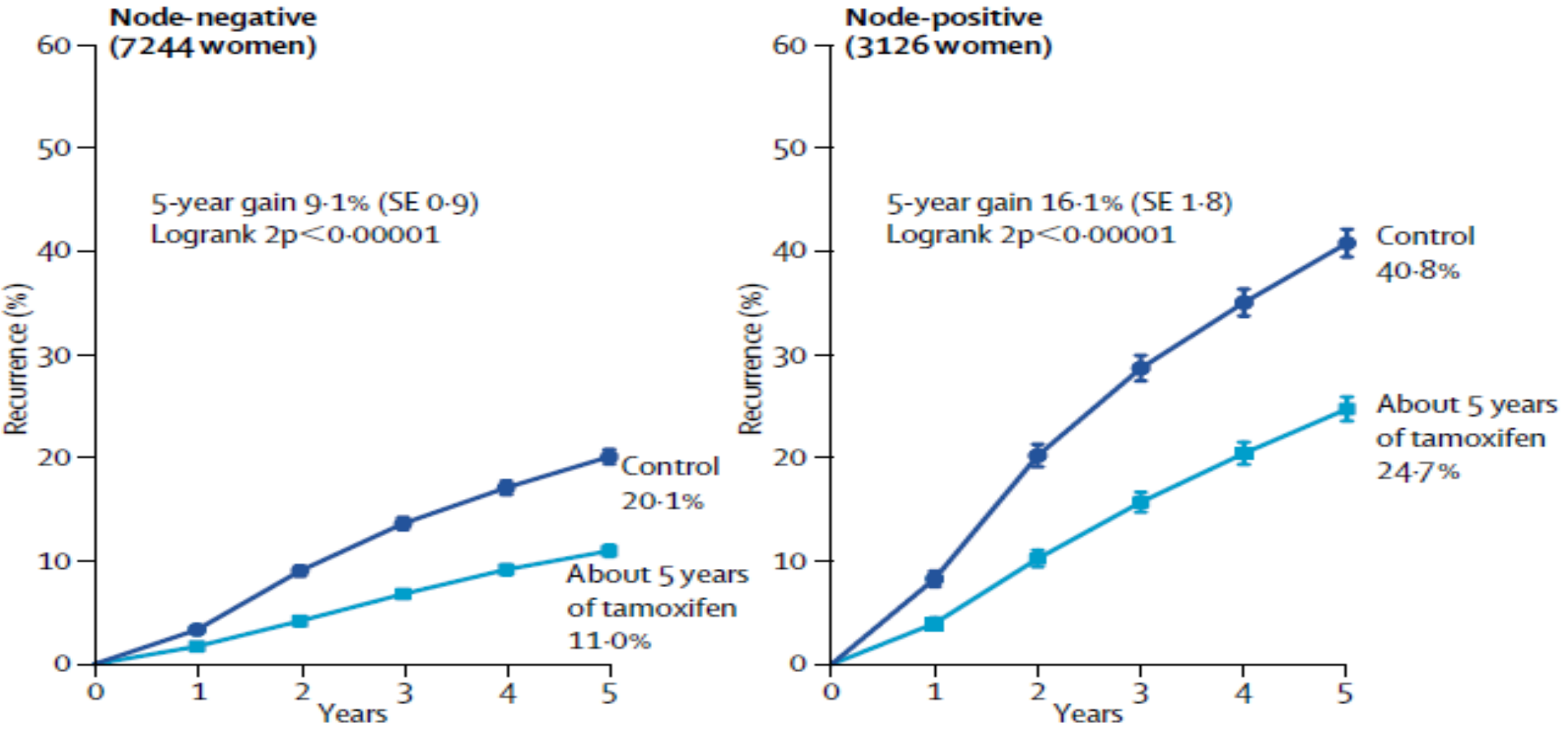
Figure 8: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality**
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

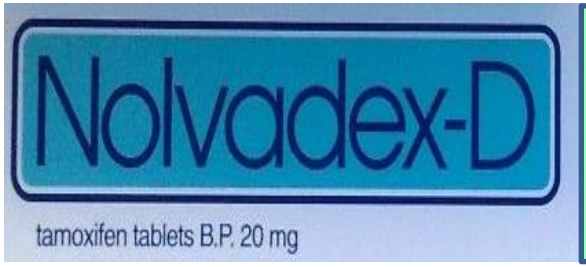
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2005; 365: 1687–1717

Nodal status



Which drug to choose ?



- SERM, Prodrug, CYP2D6
- Hot flushes, thromboembolic events
- Endometrial hyperplasia – a concern

- Most mature data yet available
- Long carryover effect
- BMD reduction more; CVS problems less

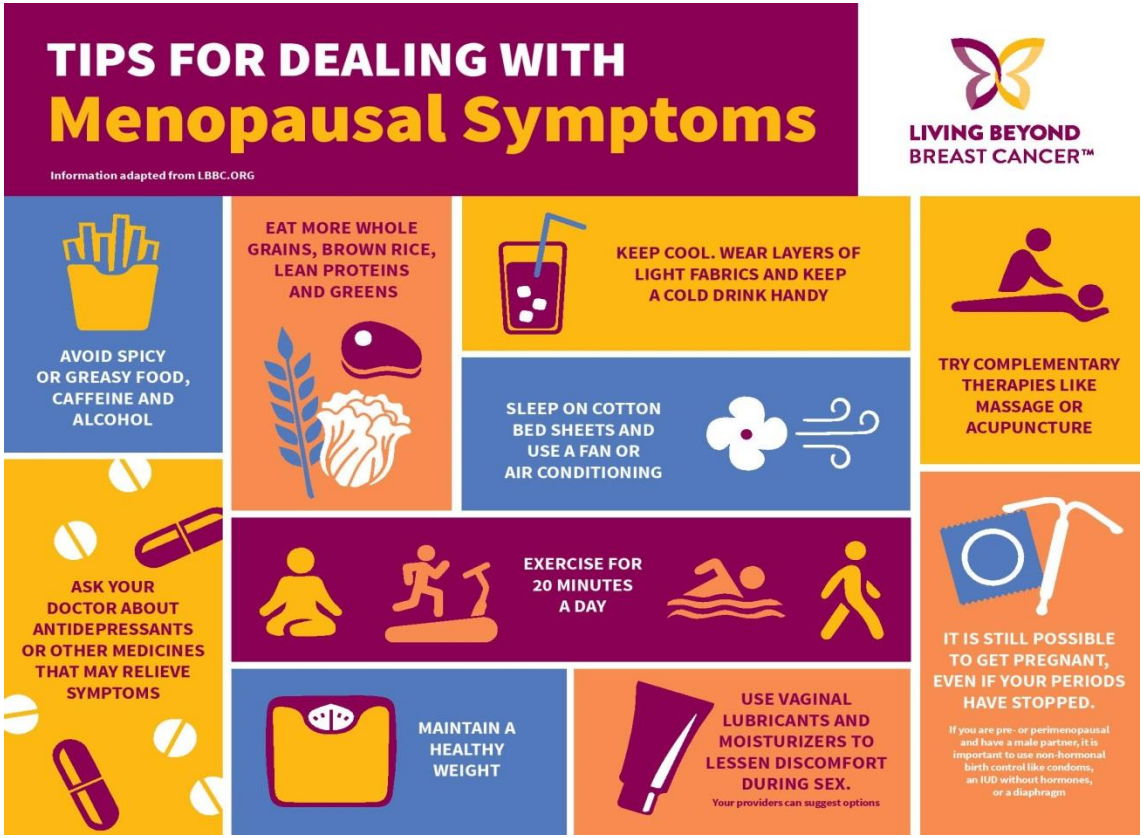
- Max suppression of estradiol
- ↑OS in node+
- CVS, Thromboembolic events more

- Better in pts. with low BMD & impaired lipid profile

The broad guidelines

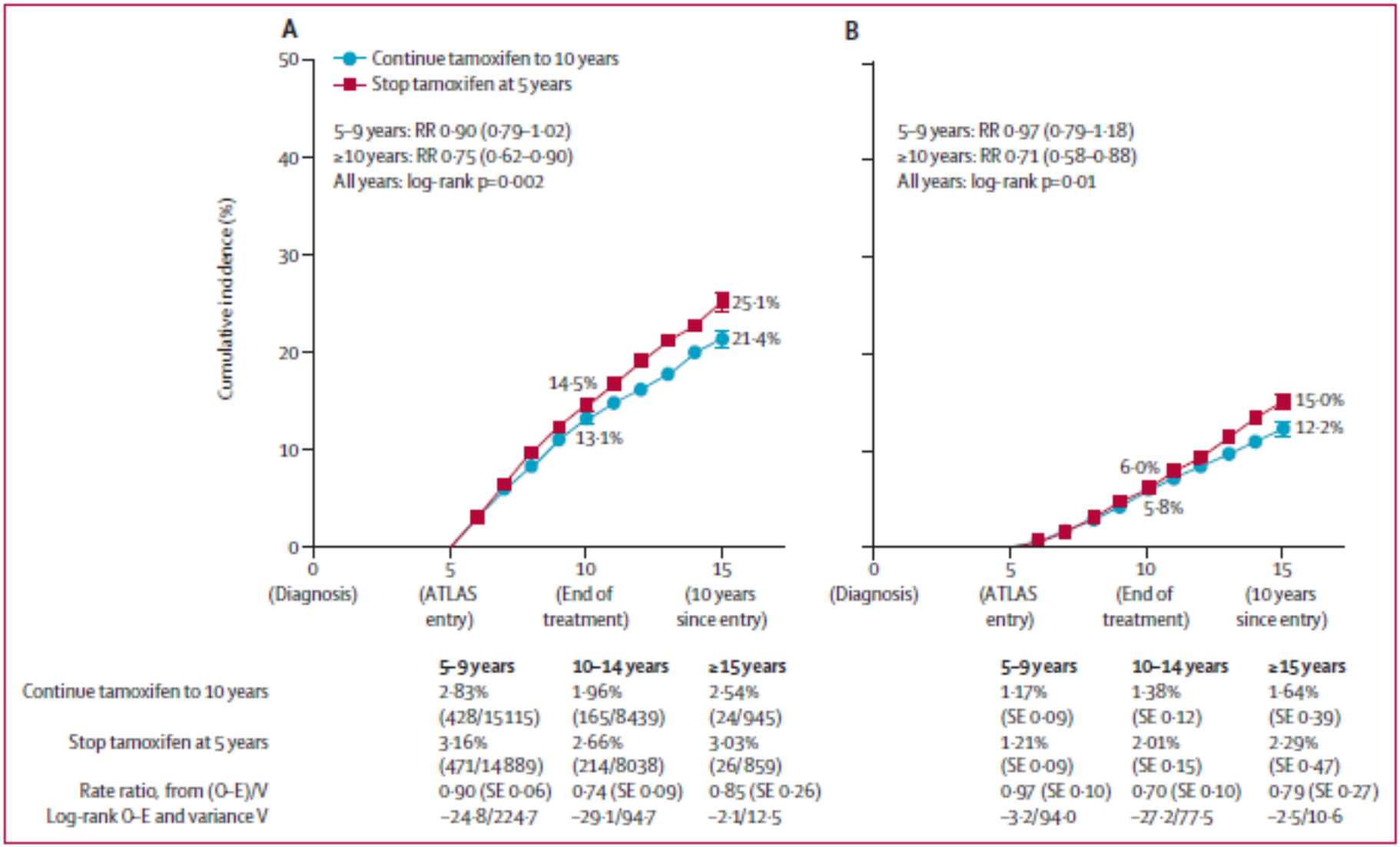
- Premenopausal
  - Tamoxifen 20 mg OD for at least 5 years.

- Postmenopausal
  - An AI should be incorporated into the adjuvant endocrine therapy of these women at some point of time.
  - Bisphosphonates should be incorporated into the treatment paradigm of these patients to prevent / reverse AI induced BMD derangements.



ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER : PREMENOPAUSAL

Adjuvant Tamoxifen 10 vs 5 yrs?



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

***Figure 3*: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease**

Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate– rate in women without recurrence) are percentage per year (SE). ATLAS=Adjuvant Tamoxifen: Longer Against Shorter.

Adjuvant AI + GnRH in Premenopausal women

The TEXT & SOFT trials

TEXT

- Premenopausal, HR+ BC
- ≤ 12 wks after surgery
- N = 2672

Tamoxifen 20 mg/day + OFS* (n = 1338)

Exemestane 25 mg/day + OFS* (n = 1334)

SOFT

- Premenopausal HR+ BC ≤ 12 wks after surgery (if no chemo) *or*
- ≤ 8 mos after chemo if premen status confirmed
- N = 3066

Tamoxifen 20 mg/day + OFS* (n = 1024)

Exemestane 25 mg/day + OFS* (n = 1021)

Tamoxifen 20 mg/day

Joint Analysis

Tamoxifen + OFS*

N = 2344

- Median follow up: 68 months
- 42% N+
- Neo/Adjuvant chemotherapy: 58%

Exemestane+ OFS*

N = 2346

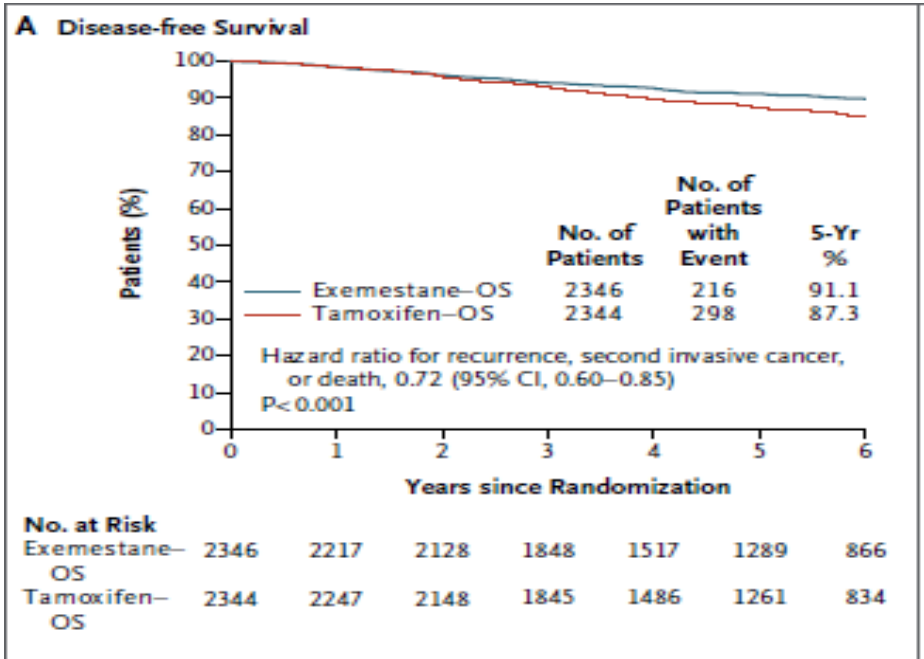
*OFS

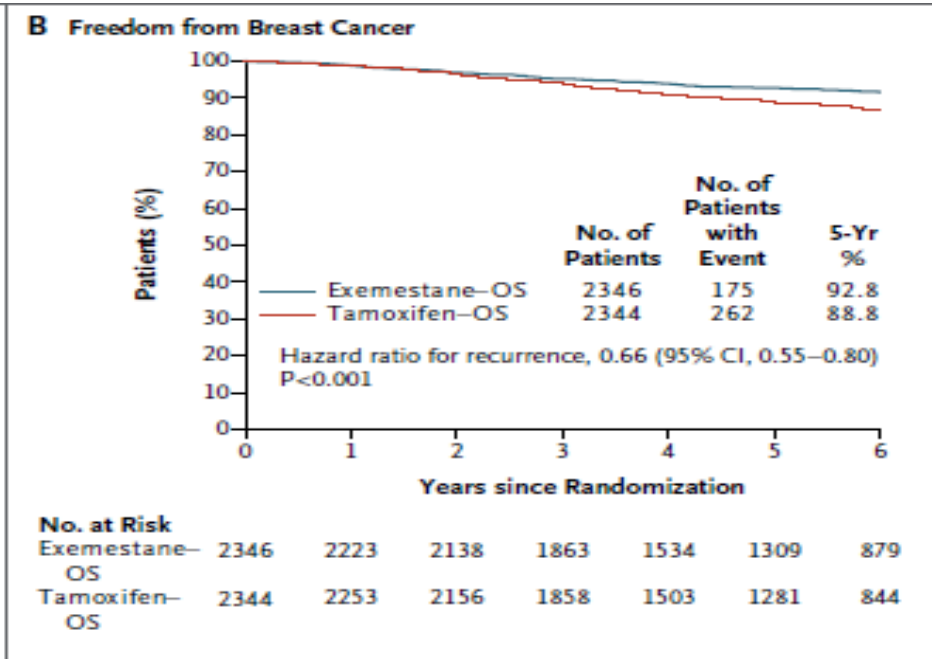
- TEXT: **Inj. Triptorelin 3.75 mg IM every 28 days** for 6-8 weeks prior to initiation of HT or concurrently with chemotherapy.
- SOFT: triptorelin, bilateral oophorectomy or Ovarian irradiation

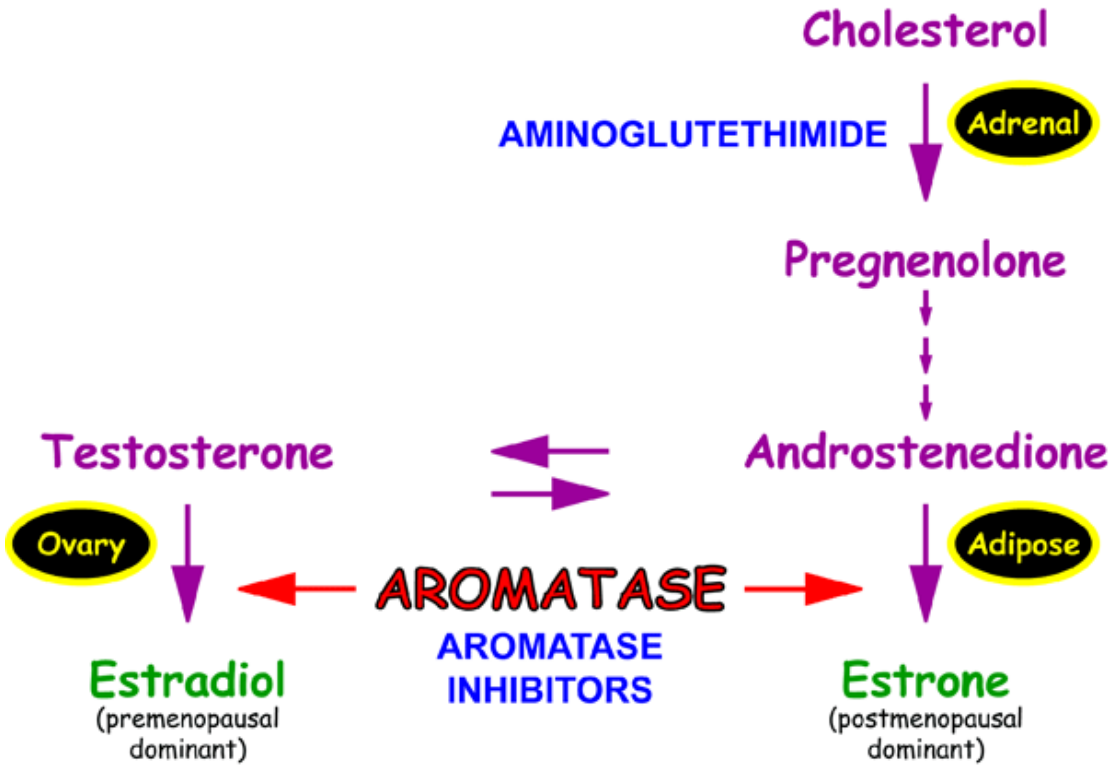
Pagani O, et al. N Engl J Med 2014;371:107-18.

TEXT & SOFT : Results

In premenopausal women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane (an AI) plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence rates. The impact on overall survival was not significantly different.







ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER : POSTMENOPAUSAL

Aromatase inhibitors as Adjuvant ET in EBC

Two strategies, both superior to tamoxifen alone

I. AI x 5 years — Upfront

II. Tamoxifen x 2 to 3 years → AI x 2 to 5 years — Switching

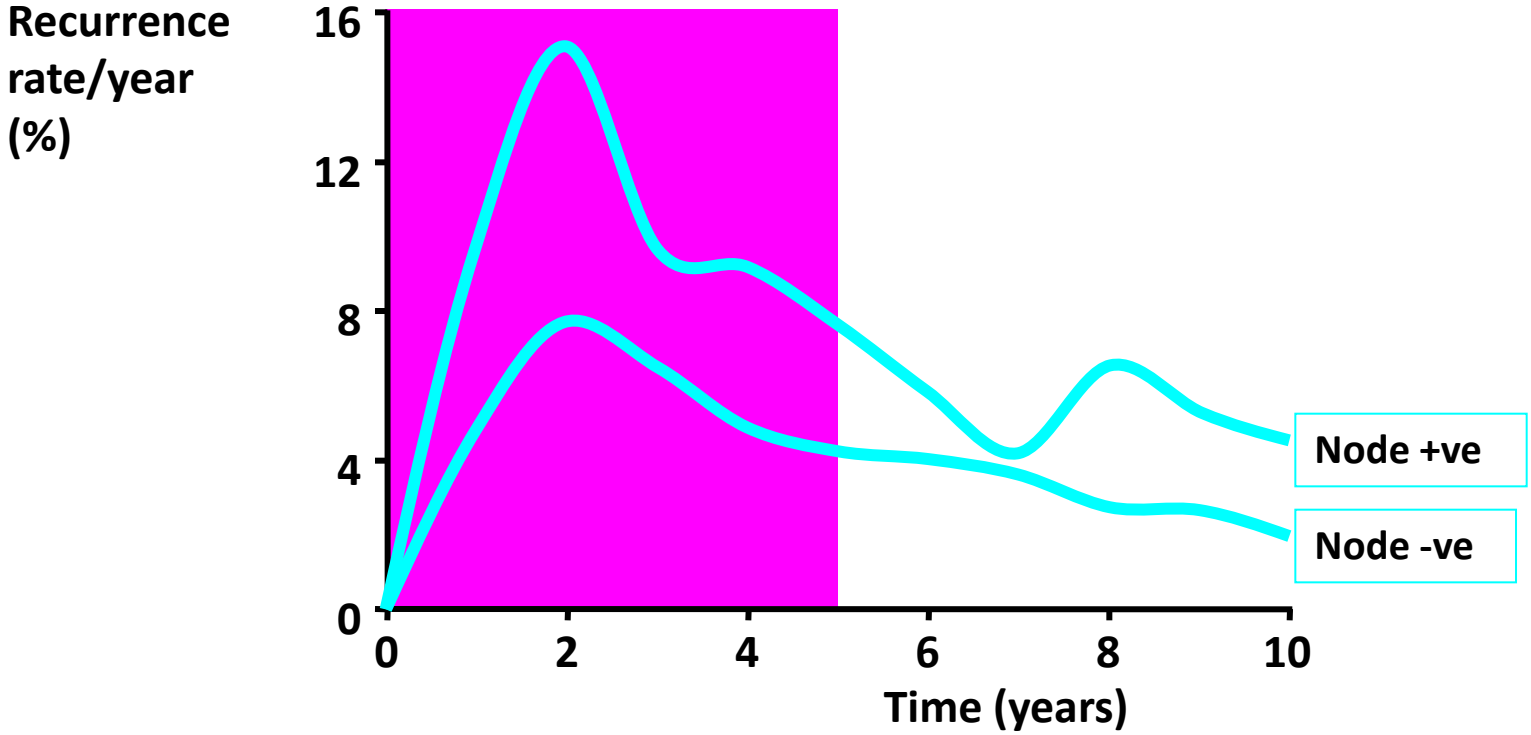
A third strategy looks good as well

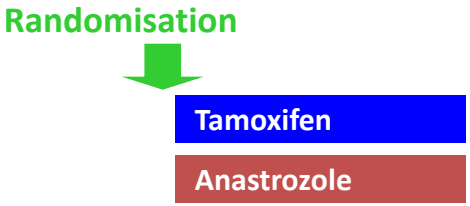
III. Tamoxifen x 5 years → AI x 5 years

A fourth strategy tested but not robust enough

IV. AI x 2 years → Tamoxifen x 3 years

Women on adjuvant ET 5 yrs of Tamoxifen vs AI : **The Upfront Trials**



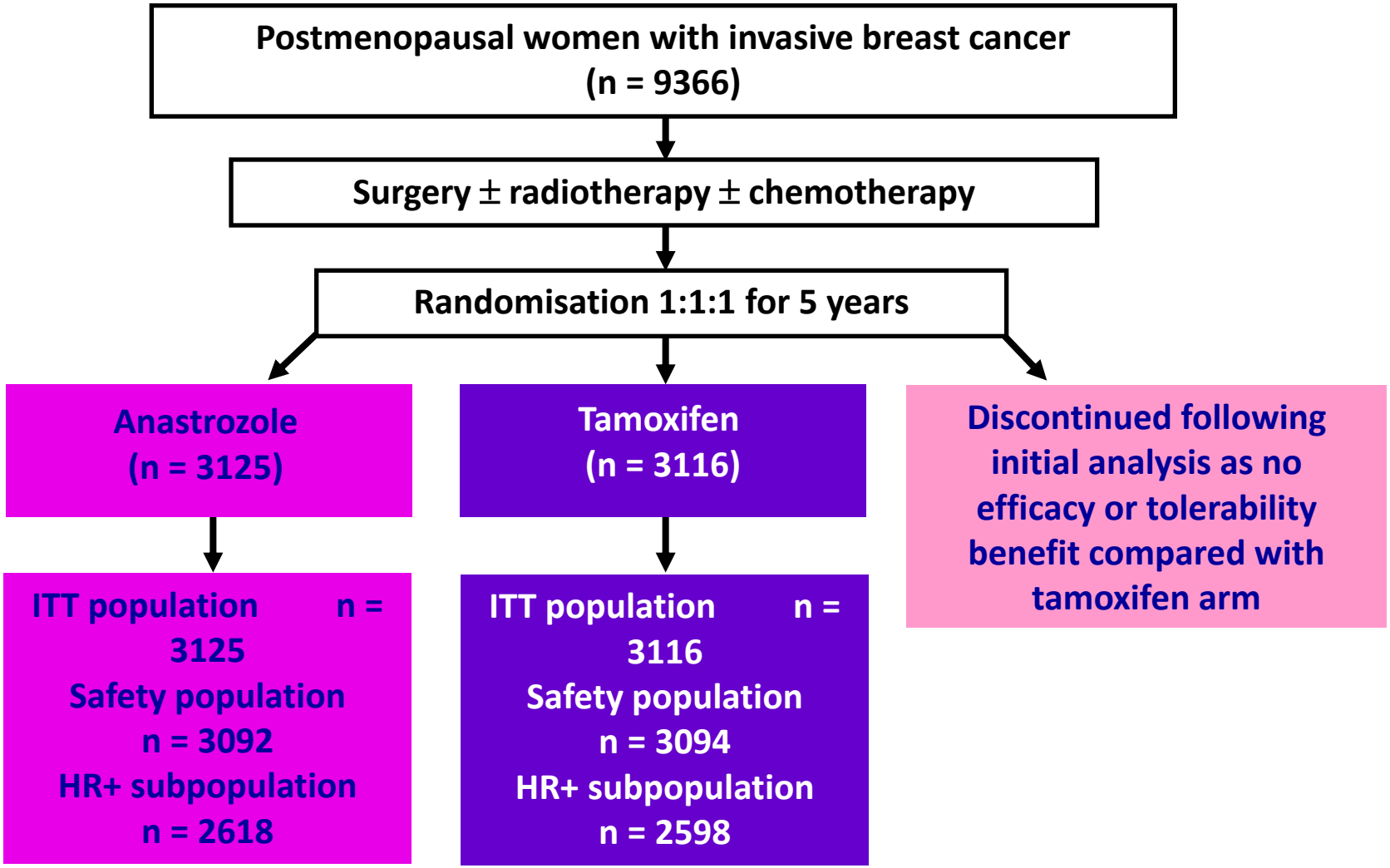


Arimidex and Tamoxifen Alone or in Combination (ATAC)

Breast International Group 1-98 (BIG 1-98)

Adapted from EBCTCG. Lancet 1998;352:930-942

The *Arimidex*™ Alone or in Combination ATAC trial : 10-year analysis



ITT, intent-to-treat; HR+, hormone receptor-positive

Cuzick et al, Lancet Oncol 2010;11:1135 - 1141

ATAC 10 years Efficacy Summary

Arimidex, as com… (i.e. HR+ve patients), signifi…

- …

The absolute differences in time to recurrence between anastrozole and tamoxifen ***increased over time*** *(2˙7% at 5 years and 4˙3% at 10 years)*

Cuzick et al, Lancet Oncol 2010;11:1135 - 1141

- we… with anastro…

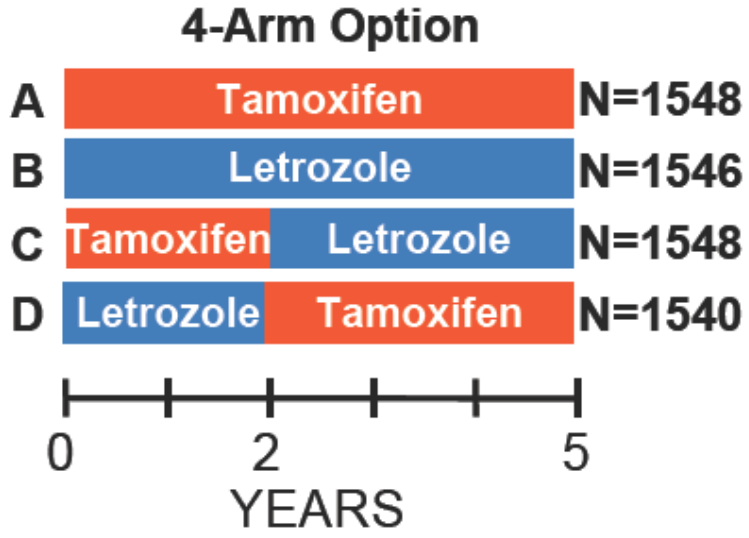
BIG 1-98 Overall Design

SURGERY

Stratify

- Institution
- CT (Adjuvant/ Neoadjuvant)
  - -Prior
  - -None
  - -Concurrent

RANDOMIZE



N=6,182 Enrolled 1999-2003

N=8,010*

*ITT: excludes 18 patients who withdrew consent and did not receive study treatment

Previous Analyses:

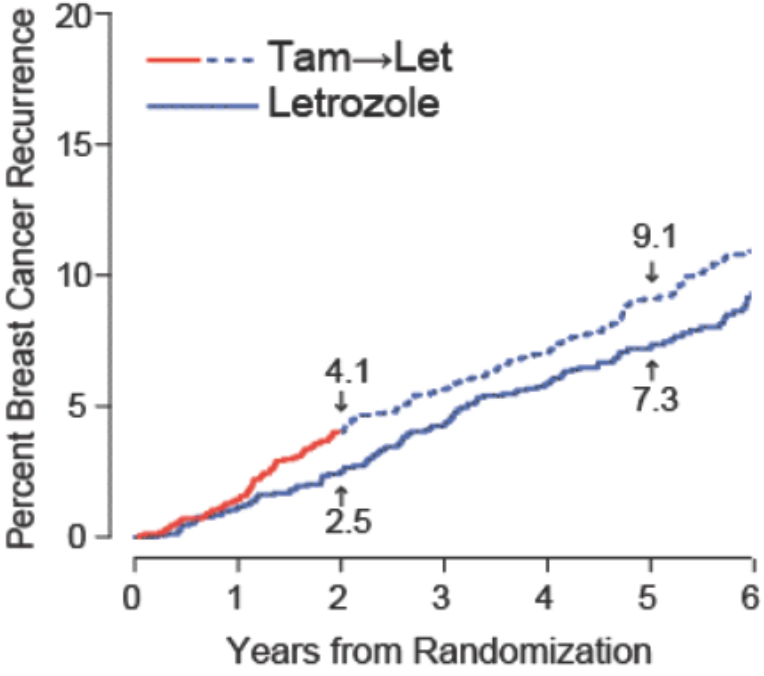
Is 5 years Let superior to 5 years Tam as initial therapy?

- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months

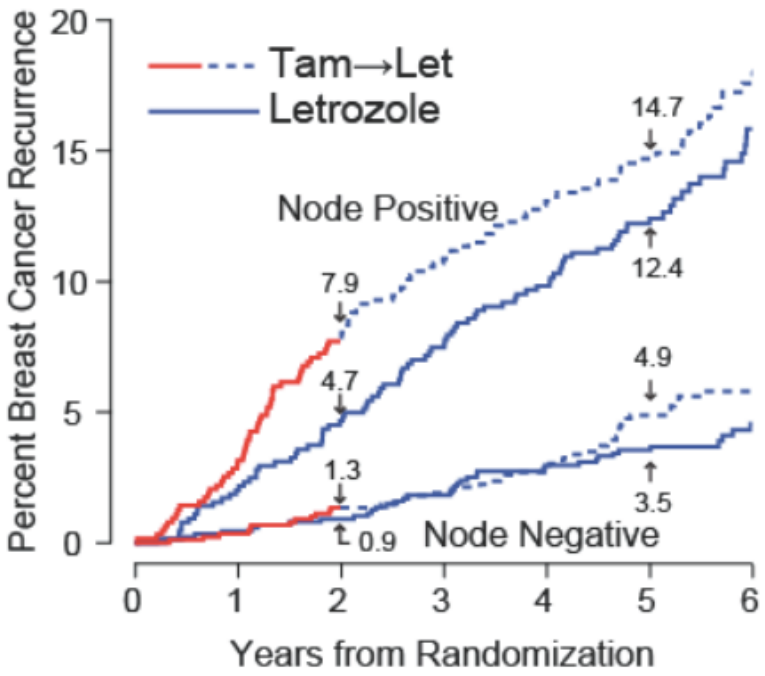
Breast Cancer Events

Tam→Let vs. Let

Overall



By Nodal Status*

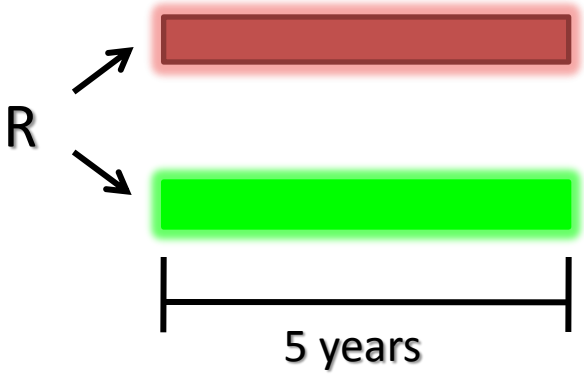


*42% of the population is node positive; 58% node negative

International Breast Cancer Study Group
IBCSG SABCS 2008

BIG
BREASTINTERNATIONALGROUP

UPFRONT AI TRIALS: COMBINED ANALYSIS



Trials
• ATAC • BIG 1-98

TAM AI

Upfront adjuvant AIs decrease the recurrence and improve the DFS. Impact on OS uncertain.

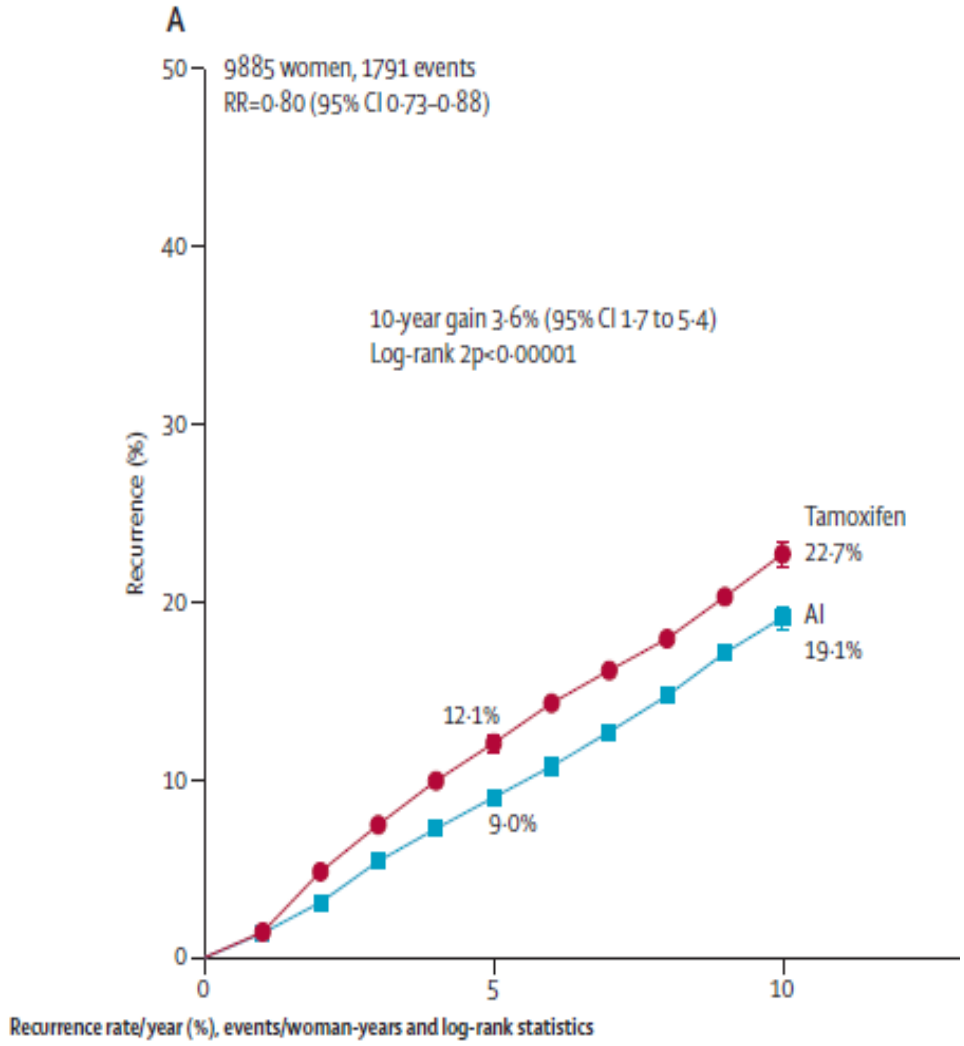
** As first event, heterogeneity,* p = *0.08*

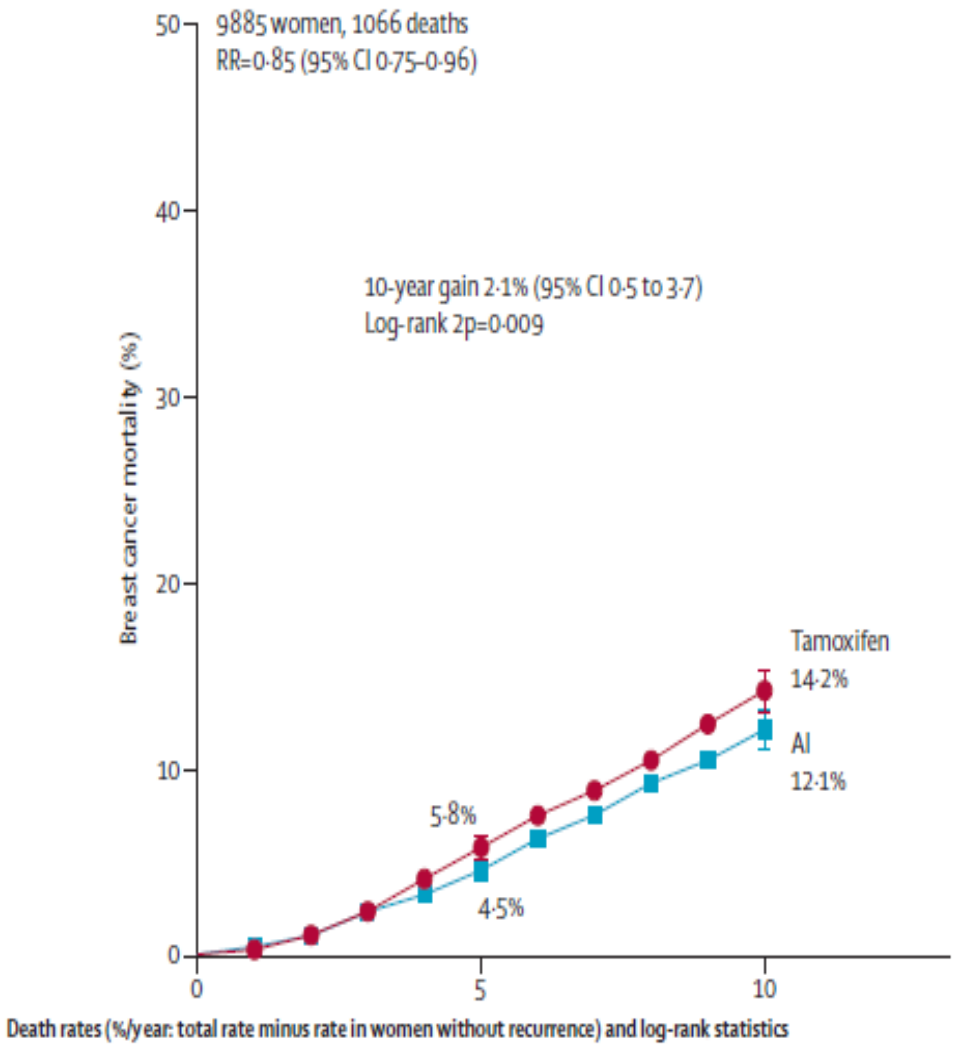
Dowsett M et al JCO 2009

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2015; 386: 1341–52





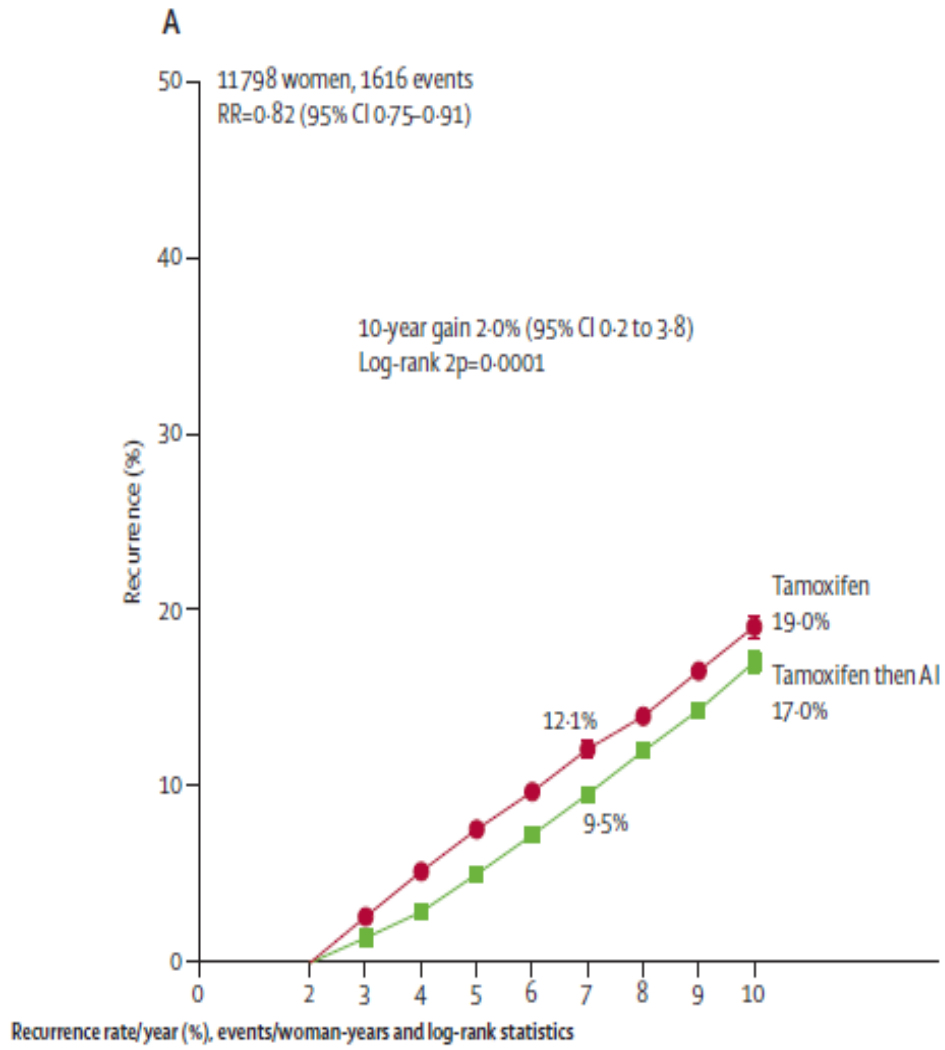
Recurrence

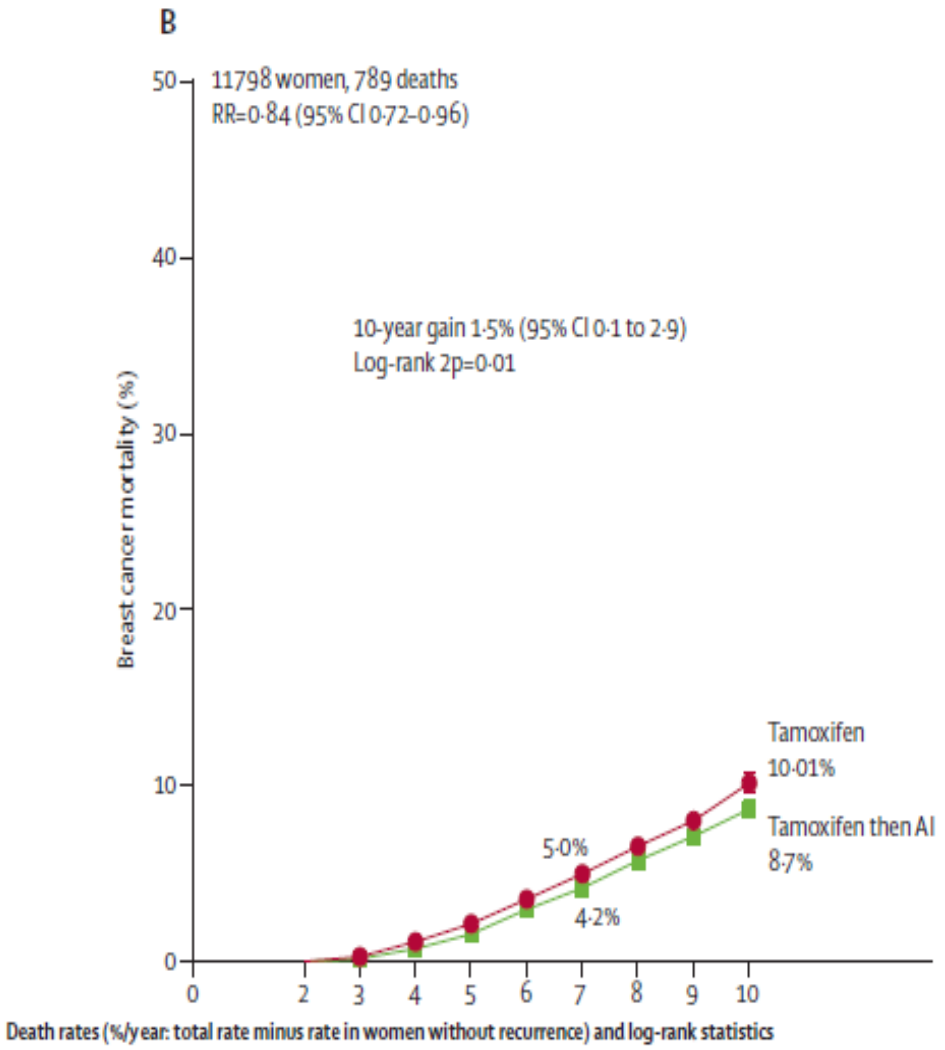
Breast cancer mortality

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Lancet 2015; 386: 1341–52

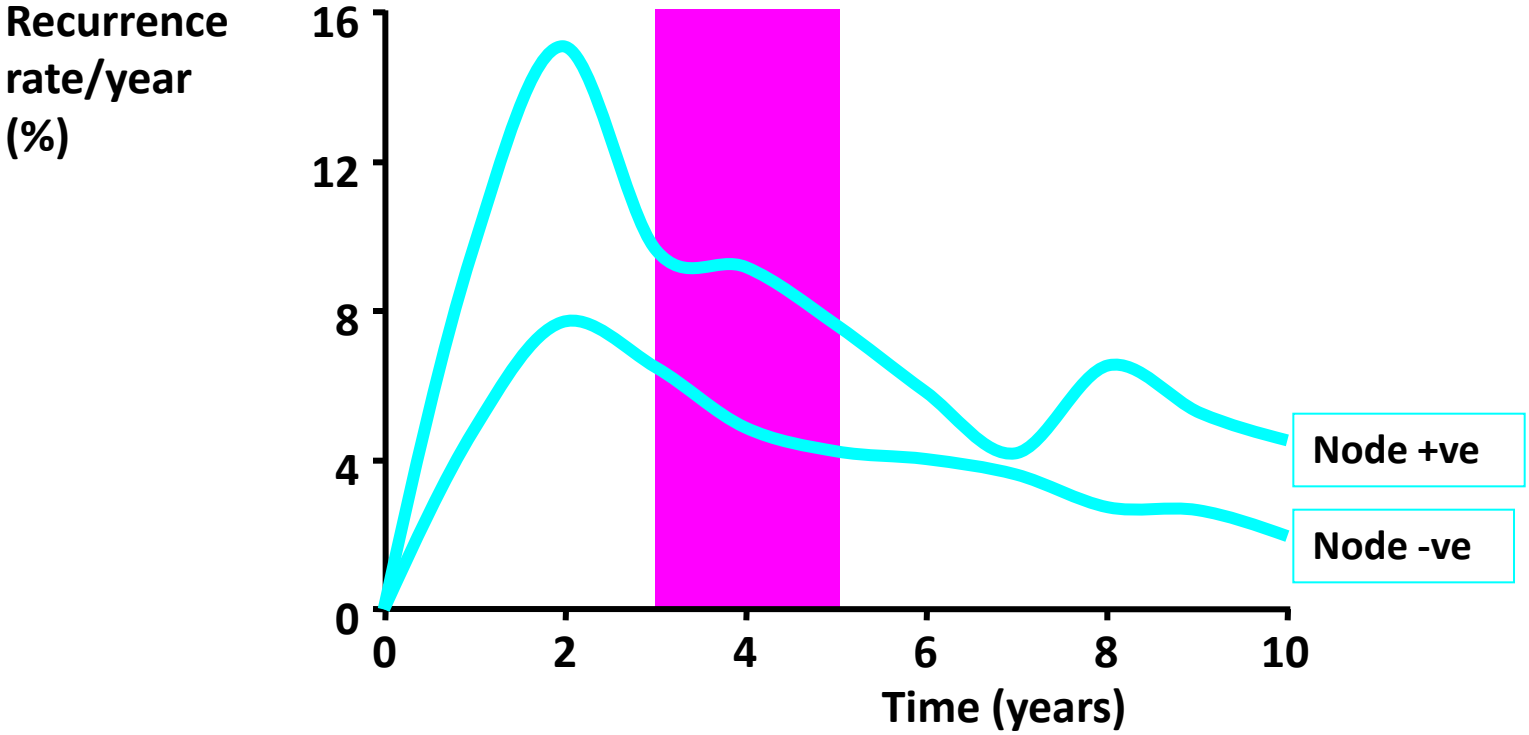


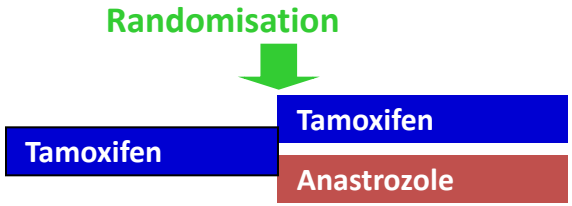


Recurrence

Breast cancer mortality

Women already on adjuvant ET : Tam for 2-3 yrs : **The Switching Trials**

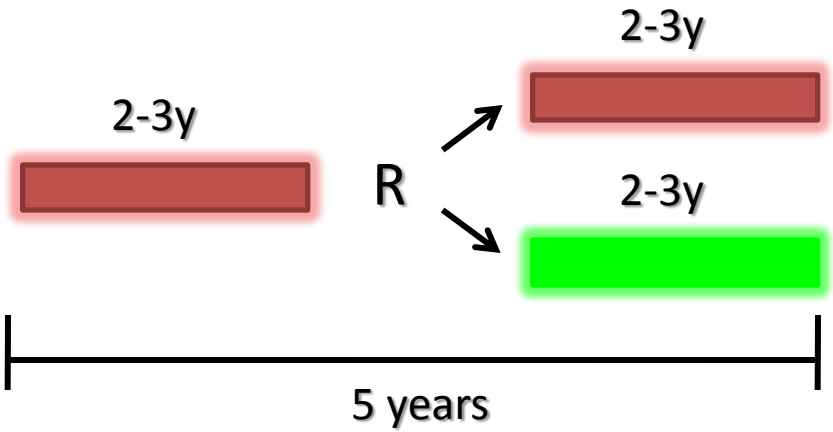




Intergroup Exemestane Study (IES)
Italian Tamoxifen Anastrozole (ITA); Austrian Breast & Colorectal Cancer Study Group (ABCSG) 8 / Arimidex-Nolvadex (ARNO) 95

Adapted from EBCTCG. Lancet 1998;352:930-942

SWITCHING TRIALS: COMBINED ANALYSIS



Trials

- **IES**
- **ABCSG VIII**
- **ARNO**
- **ITA**

TAM AI

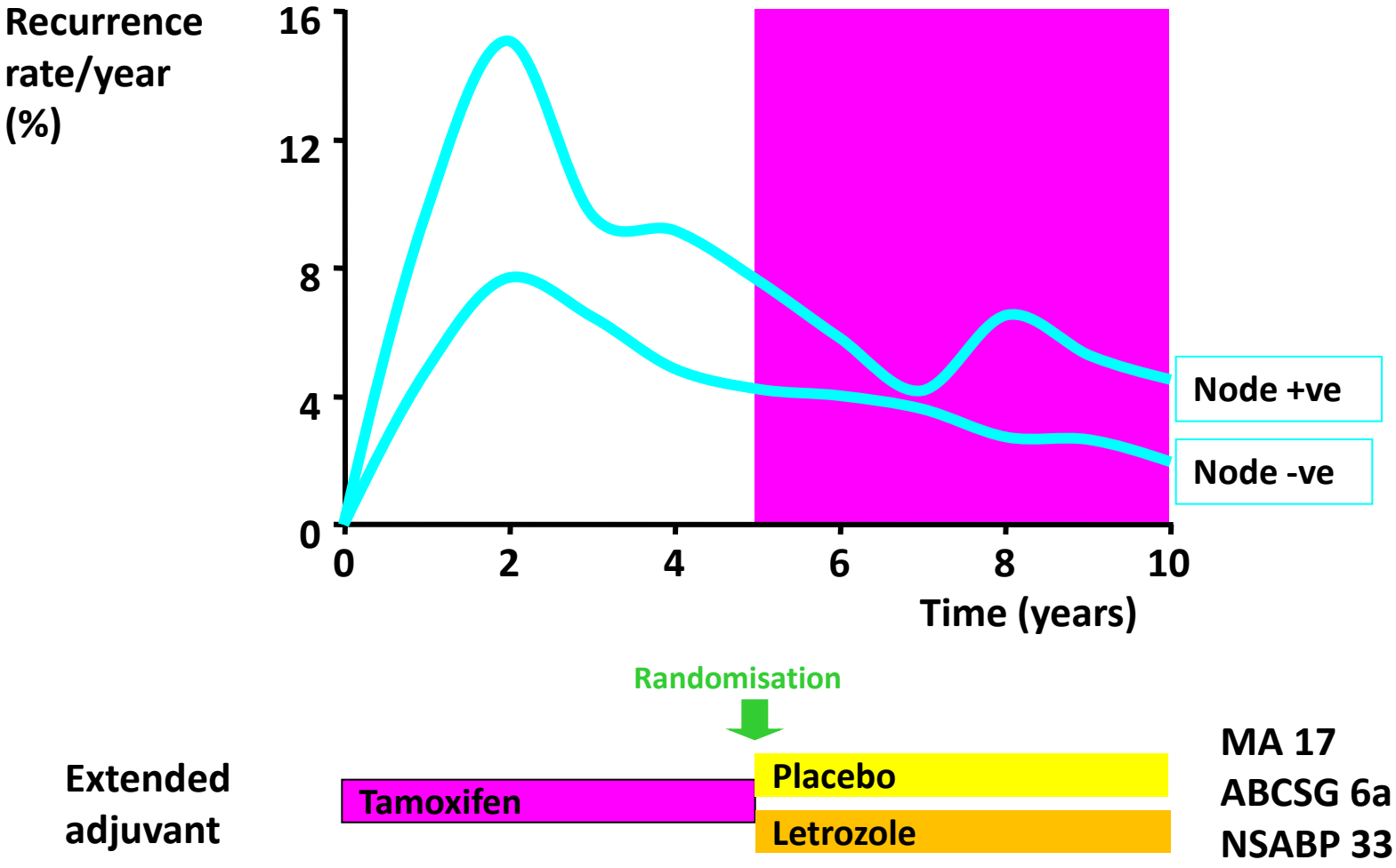
Switching to AIs decreases the recurrence rate and improves the DFS. Impact on OS uncertain.

** As first event, heterogeneity,* p = *0.4*

Dowsett M et al JCO 2009

Women who have completed 5 years of Tam

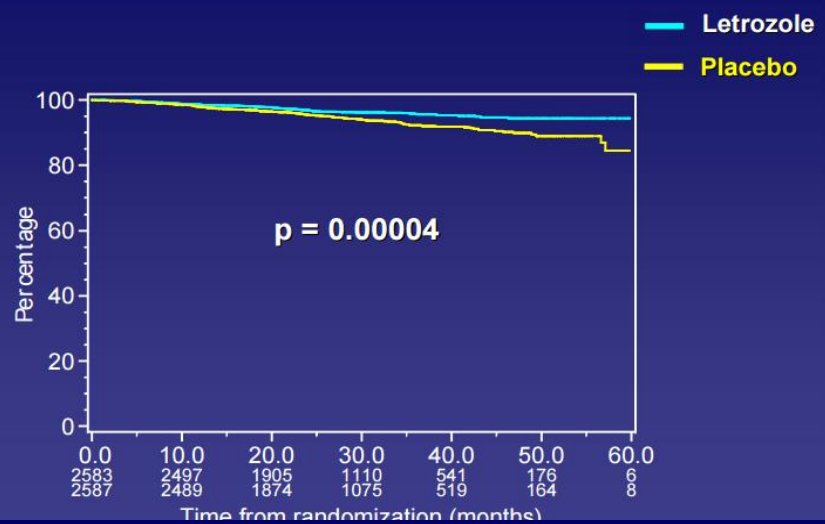
The Extended Adjuvant Trials



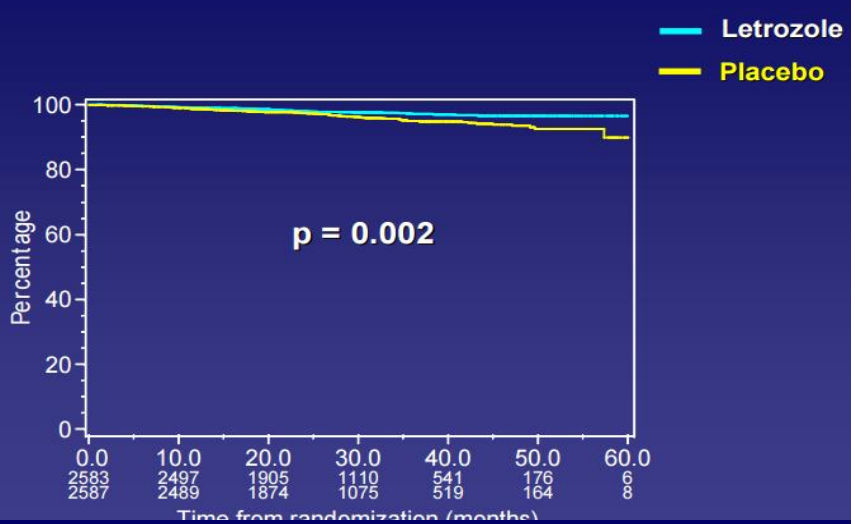
Adapted from EBCTCG. Lancet 1998;352:930-942

MA 17 Trial

Disease Free Survival – All Patients

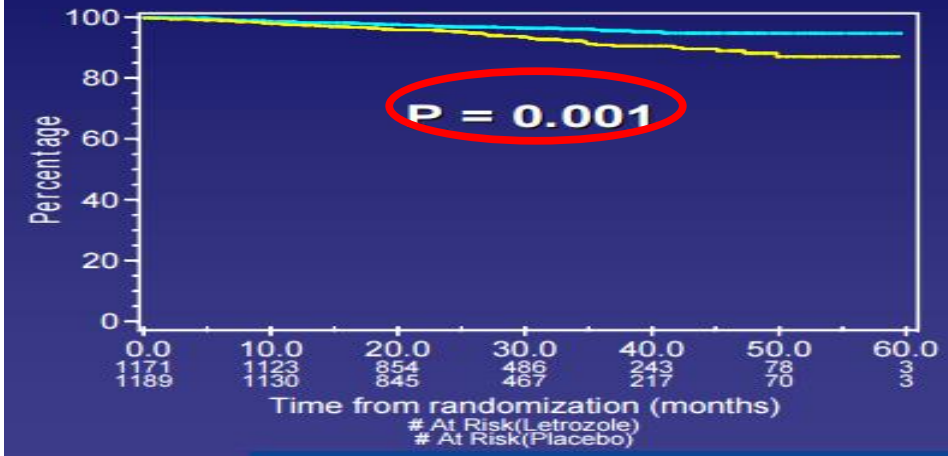


Distant DFS – All Patients

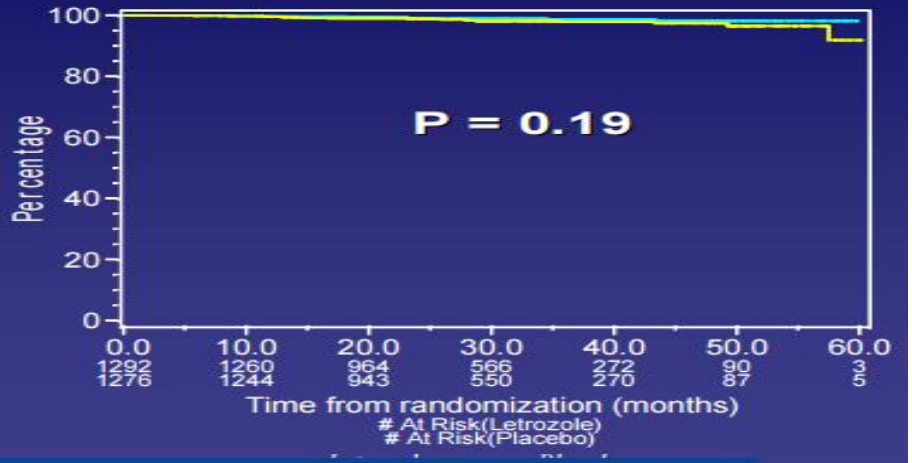


Distant DFS

Node Positive



Node Negative



Letrozole Placebo

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Harold J. Burstein, MD, PhD[1]; Christina Lacchetti, MHSc[2]; Holly Anderson, RN[3]; Thomas A. Buchholz, MD[4]; Nancy E. Davidson, MD[5];

J Clin Oncol 37:423-438. © 2018 by American Society of Clinical Oncology

Focused Update Recommendations

Recommendation 1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

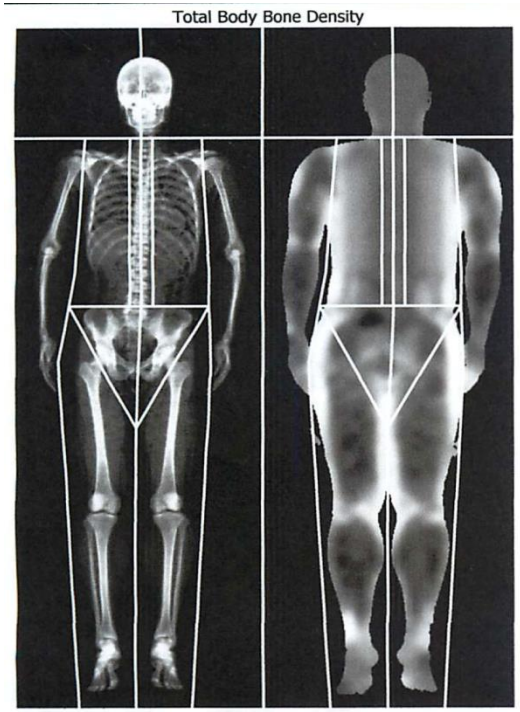
Recommendation 2. Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

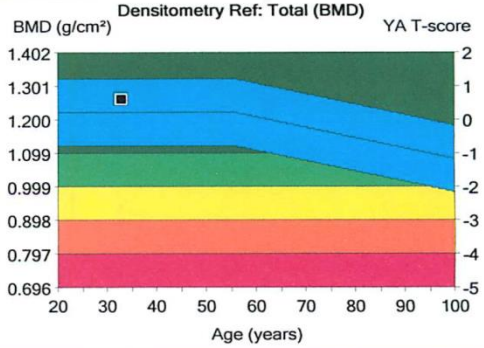
Recommendation 3. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.

Recommendation 4. As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

Recommendation 5. Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

Qualifying Statement. To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.





Region	[1] BMD (g/cm²)	[2] Young-Adult T-score	[3] Age-Matched Z-score
Head	2.002	-	-
Arms	1.064	-	-
Legs	1.333	-	-
Trunk	1.075	-	-
Ribs	0.998	-	-
Pelvis	1.076	-	-
Spine	1.199	-	-
Total	1.264	0.6	0.4

BONE HEALTH WITH AIS IN BREAST CANCER : ROLE OF BISPHOSPHONATES

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2015; 386: 1353–61

- 18,766 women with mFU of 5·6 woman-years.

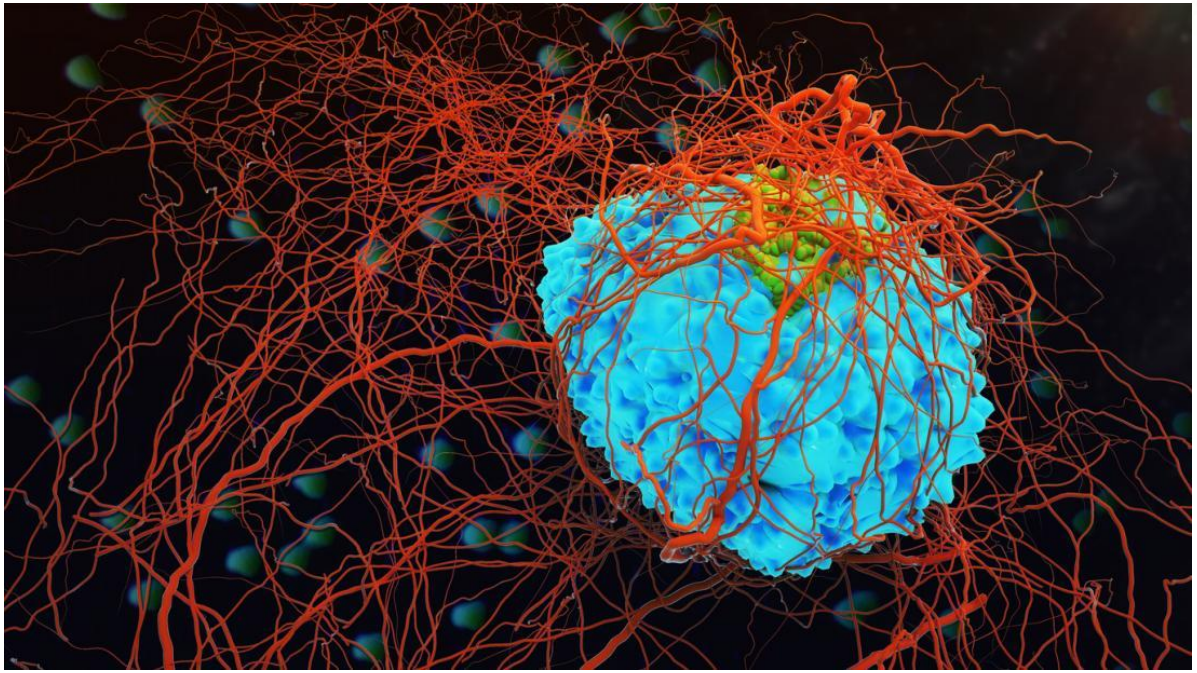
- Adjuvant bisphosphonates (Zoledronate, Ibandronate, Alendronate, Pamidronate, Clodronate) :
  - Reduced the rates of breast cancer recurrence in the bone. (RR 0.84)
  - Definite benefit only in women who were postmenopausal when treatment began.
  - Reductions in recurrence (RR 0·86), distant recurrence (0·82), bone recurrence (0·72) and breast cancer mortality (0·82, 0·73–0·93) in postmenopausal women.

VOLUME 35 · NUMBER 18 · JUNE 20, 2017
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

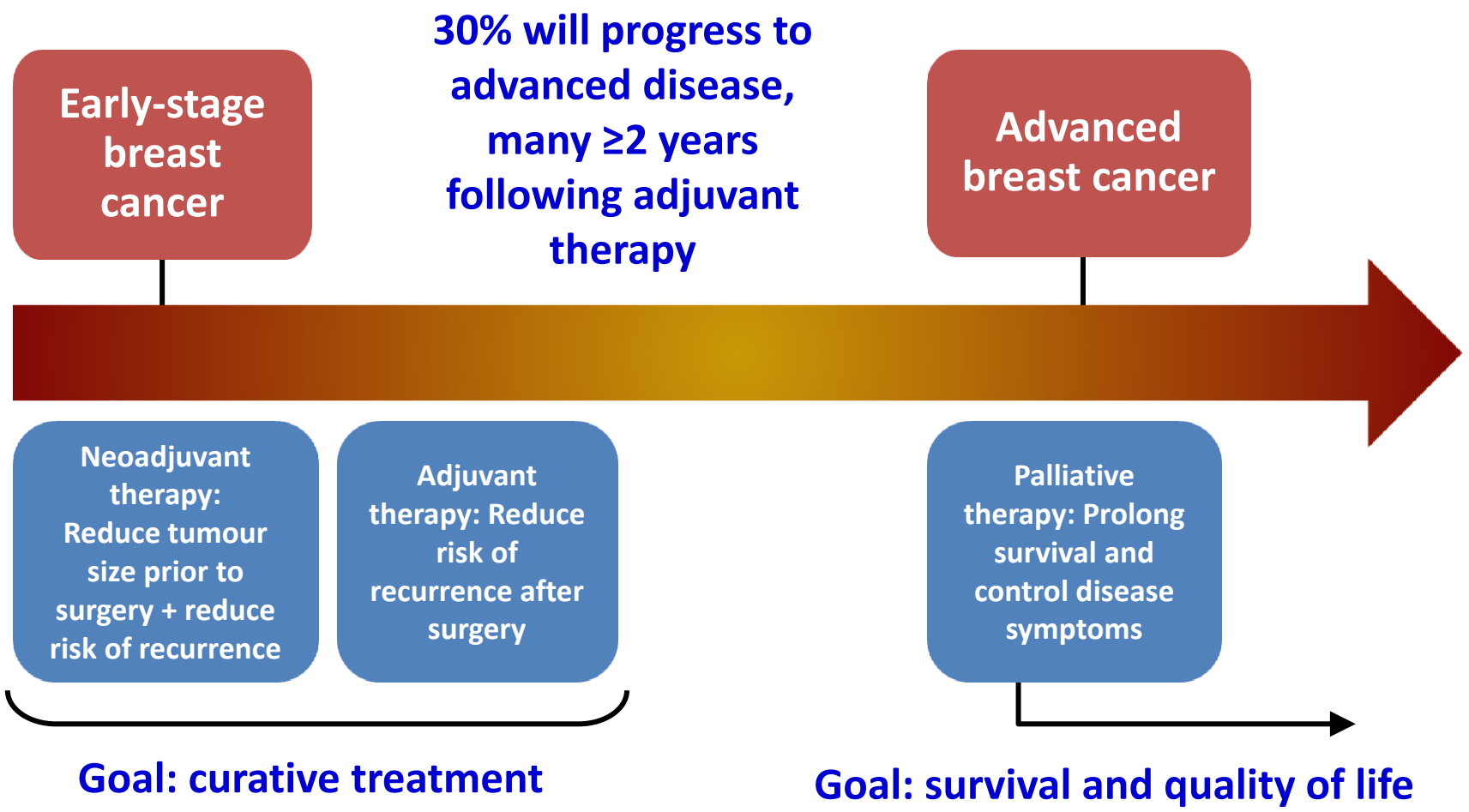
Sukhbinder Dhesy-Thind, Glenn G. Fletcher, Phillip S. Blanchette, Mark J. Clemons, Melissa S. Dillmon, Elizabeth

- Bisphosphonates should be considered as adjuvant therapy for *all* postmenopausal patients with breast cancer.
- Zoledronic acid (*4mg IV over 15 mins q 6 months for 3 – 5 years*) and Clodronate (1600 mg/day for 2-3 years) are the recommended bisphosphonates.
- While results for adjuvant Denosumab look promising, data are insufficient at this time to make a recommendation.
- The optimal timing to start bisphosphonates is unclear; however, most of the clinical trials started it soon after surgery or CT.
- A *dental assessment is recommended*, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible *to prevent BRONJ*.



ENDOCRINE THERAPY IN ADVANCED BREAST CANCER

Evolution of Breast Cancer Treatment



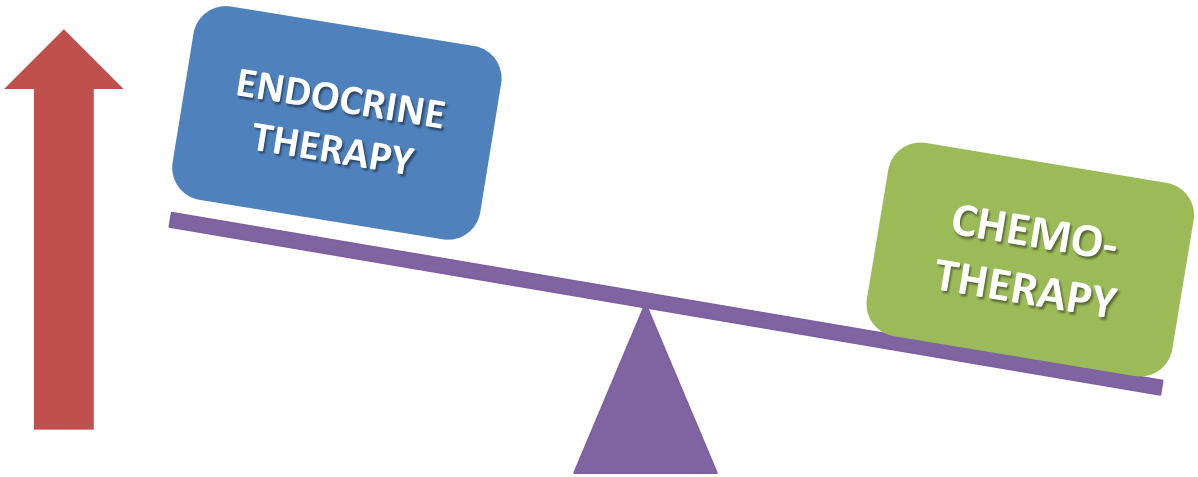
Senkus E, *et al. Ann Oncol* 2015;26 (Suppl. 5):v8–v30;
O'Shaughnessy J. *Oncologist* 2005;10 Suppl. 3:20–29;
Cardoso F, *et al. The Breast* 2014;23:489–502.

International Treatment Guidelines Emphasise Endocrine Therapy for HR+/HER2– ABC

Major treatment guidelines (ABC 4, ASCO, ESMO, NCCN, EUSOMA recommend Endocrine therapy over Chemotherapy for Advanced Breast Cancer with HR+ Her2neu- disease).

✓Less toxic

✓Better QoL



1. Partridge AH, *et al. J Clin Oncol* 2014;32:3307–3329;
2. Cardoso F, *et al. The Breast* 2014;23:489–502; 3. NCCN Guidelines: Breast Cancer. Version 2.2016.

Treatment of “Rapidly Progressive Disease”

VISCERAL CRISIS[1] is defined as **severe organ dysfunction** as assessed by signs and symptoms, laboratory studies, **and rapid progression of disease**. Visceral crisis is **not the mere presence of visceral metastases** but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible. **(LoE: Expert opinion)**.

ET is the preferred option for HR-positive disease, **even in the presence of visceral disease, unless there is visceral crisis** or concern/proof of endocrine resistance. **(LoE I/A).**

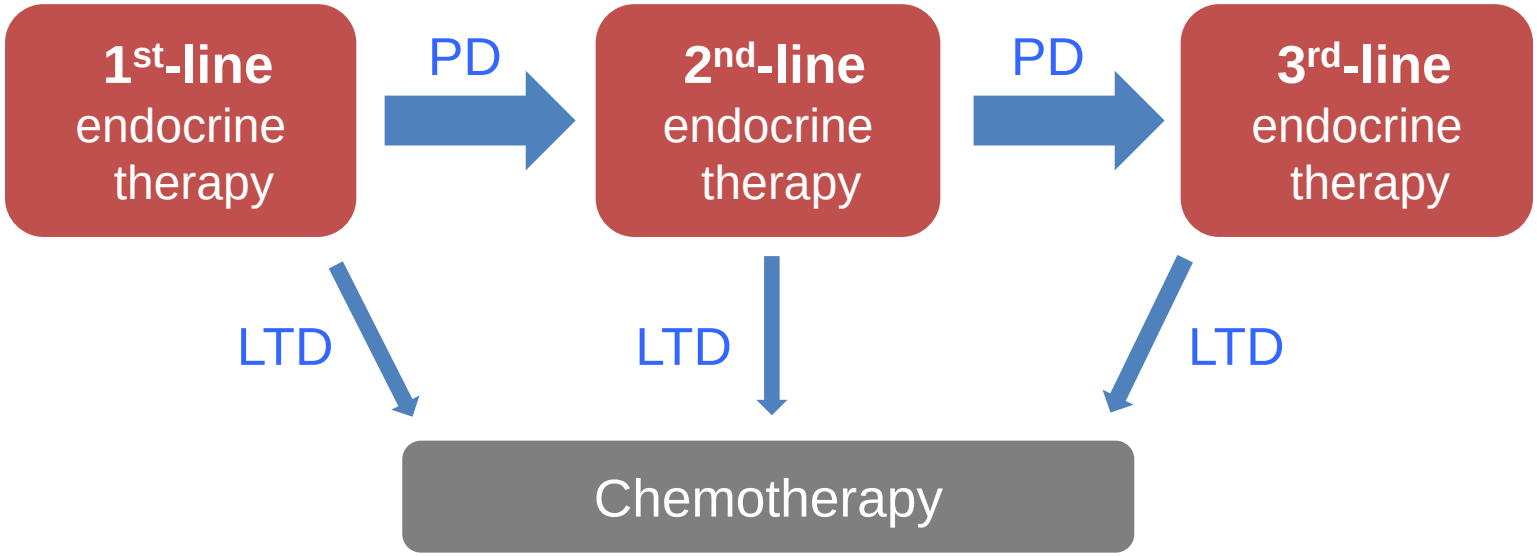
For pre-menopausal women, for whom ET was decided, **OFS/OFA combined with additional ET** is the preferred choice. **(LoE I/A).**

1. Cardoso F, *et al. The Breast* 2014;23:489–502.
2. Cardoso F, *et al.* Ann Oncol 2018;29: 1634–1657

When to Switch from ET to CT

"Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine-resistance." – ESMO/ABC2 guidelines[1]

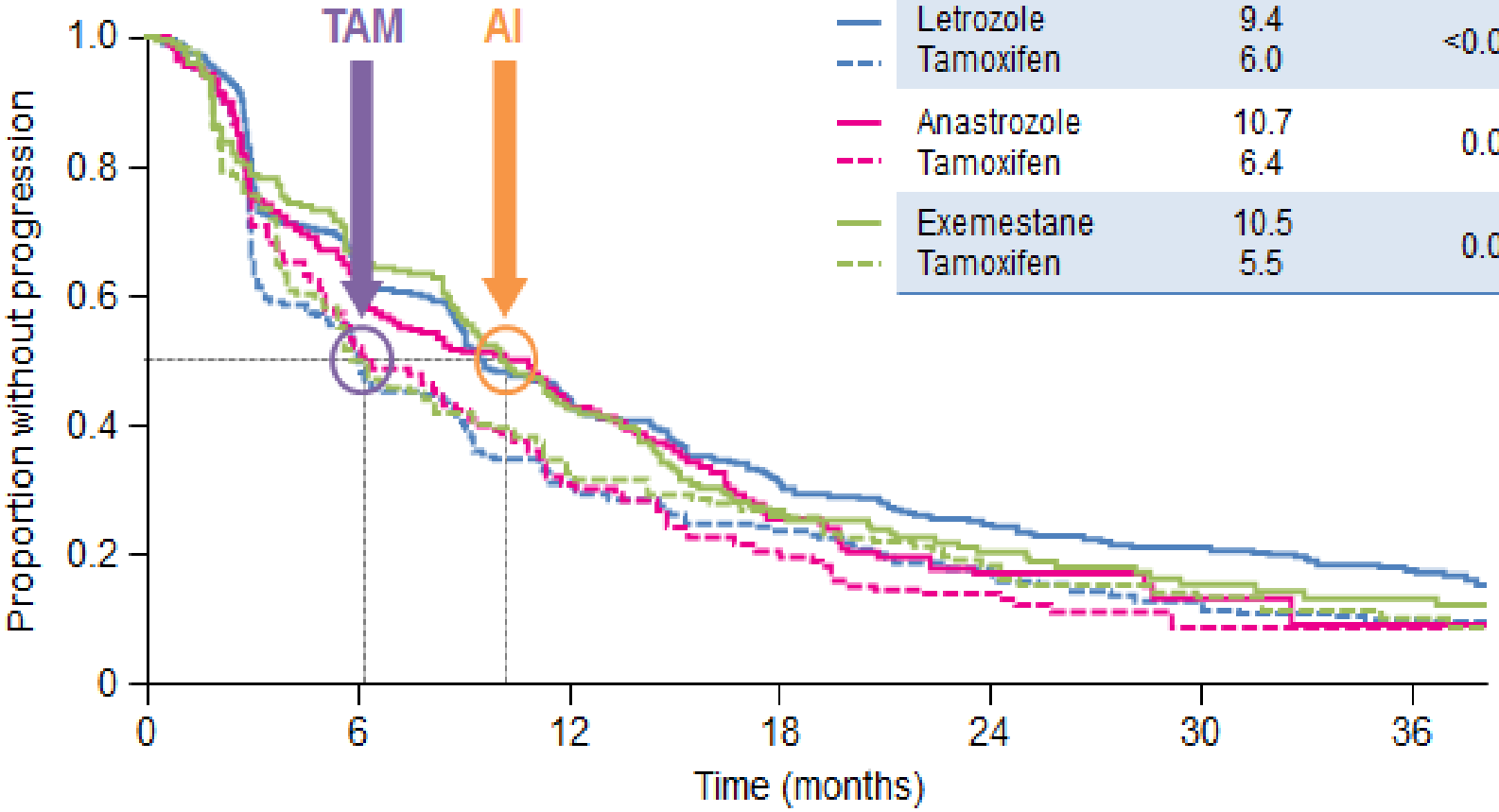
"Endocrine therapy, rather than chemotherapy… except for immediately life threatening disease or if there is concern regarding endocrine resistance." – ASCO guidelines[2]



LTD, life threatening disease;
PD, progressive disease.

1. Cardoso F, *et al*. *The Breast* 2014;23:489–502;
2. Partridge AH, *et al*. *J Clin Oncol* 2014;32:3307–3329.

AIs better than Tam in Postmenopausal



	TTP (months)	P
Letrozole	9.4	<0.0001
Tamoxifen	6.0	
Anastrozole	10.7	0.022
Tamoxifen	6.4	
Exemestane	10.5	0.028
Tamoxifen	5.5	

AI, aromatase inhibitor; TAM, tamoxifen.

Mouridsen, *et al. Oncologist* 2004;4:489–496;
Bonneterre, *et al. Cancer* 2001;92:2247–2258;
Paridaens, *et al. J Clin Oncol* 2008;26:4883.

On progression to frontline Therapy

Primary Endocrine Resistance is defined as:[1]

- Relapse while on the first 2 years of adjuvant ET, or
- PD within first 6 mos of initiating 1st-line ET for MBC, while on ET

Secondary (Acquired) Endocrine Resistance is defined as:

- Relapse while on adjuvant ET but after the first 2 years, or
- Relapse within 12 months of completing adjuvant ET, or
- PD ≥6 months after initiating ET for MBC, while on ET

ET resistance is a "progressive, step-wise process, and the underlying mechanism remains unclear."[2]

1. Cardoso F, *et al. The Breast* 2014;23:489–502;
2. Fan W, *et al. Future Med Chem* 2015;12:1511–1519.

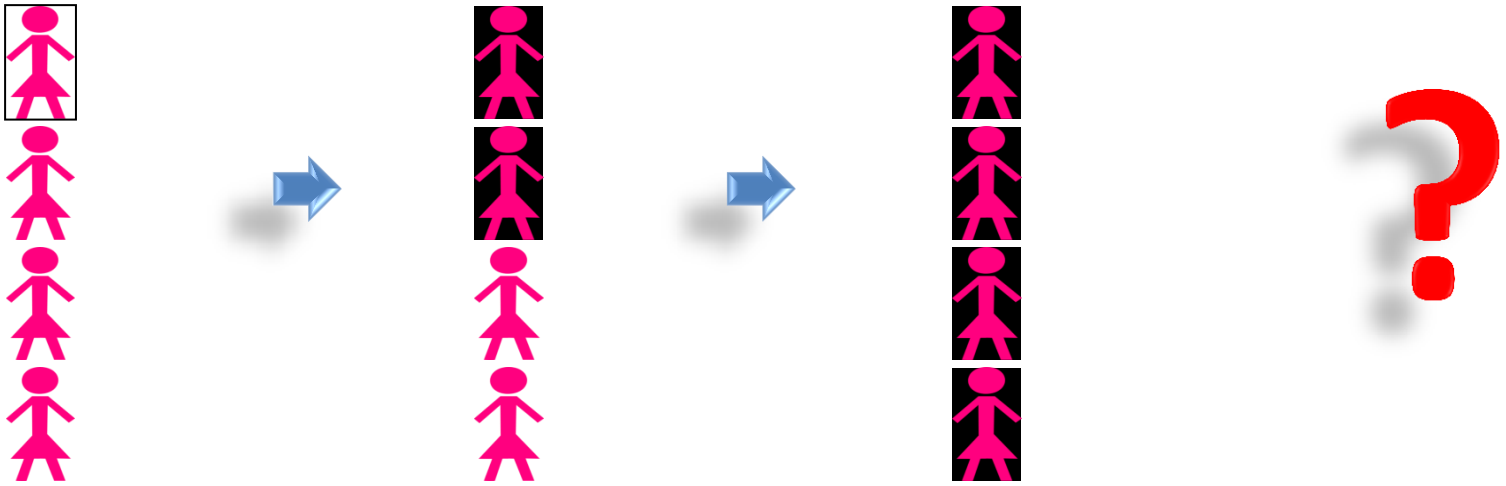
Progression on AIs – Treatment?

Aromatase inhibitors are first-line endocrine therapy for postmenopausal patients

Approximately 50% of ER+ patients do NOT respond to initial treatment

Even those who do respond to initial treatment will eventually progress

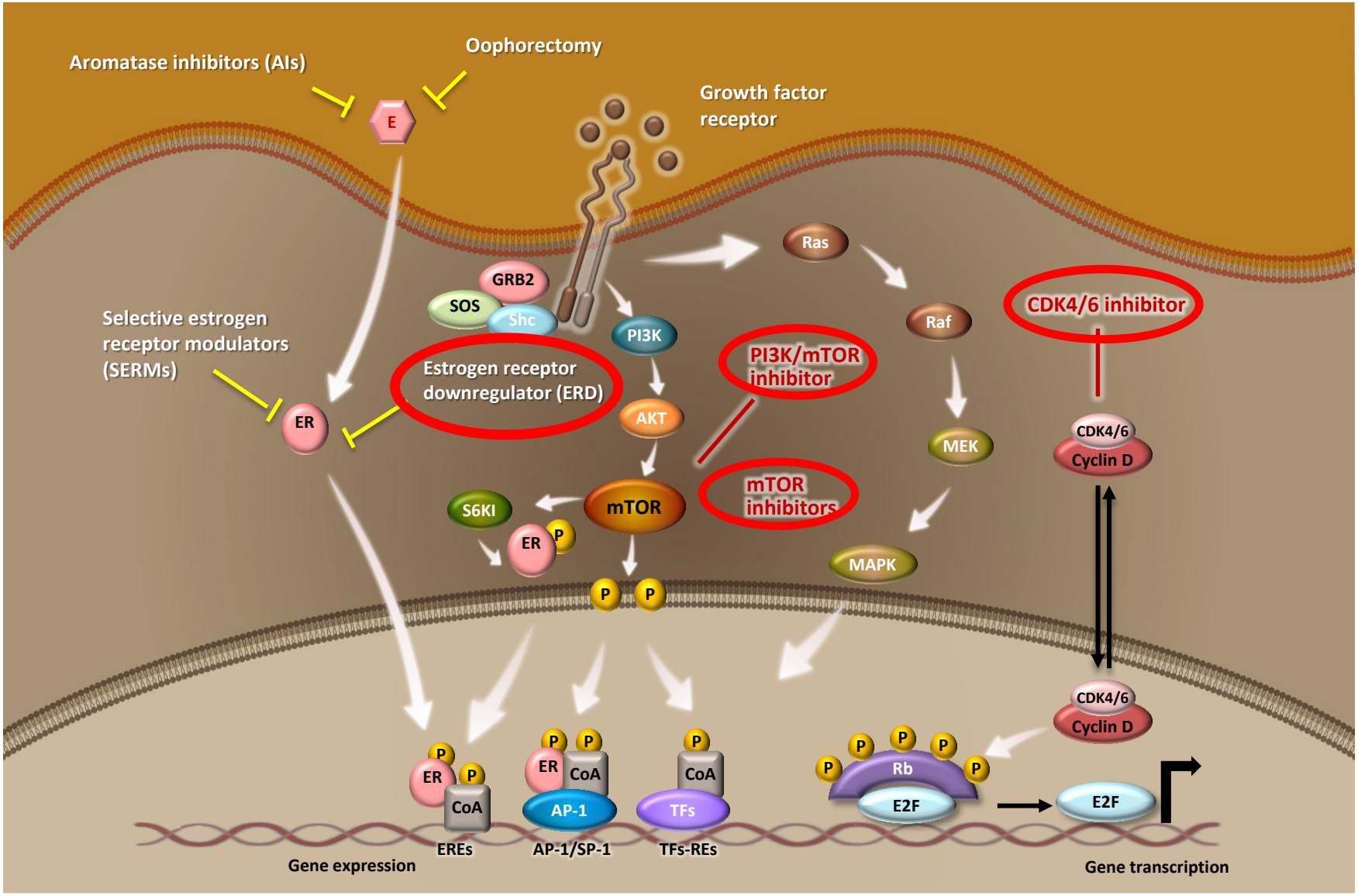
"Optimal post-aromatase inhibitor treatment is uncertain"



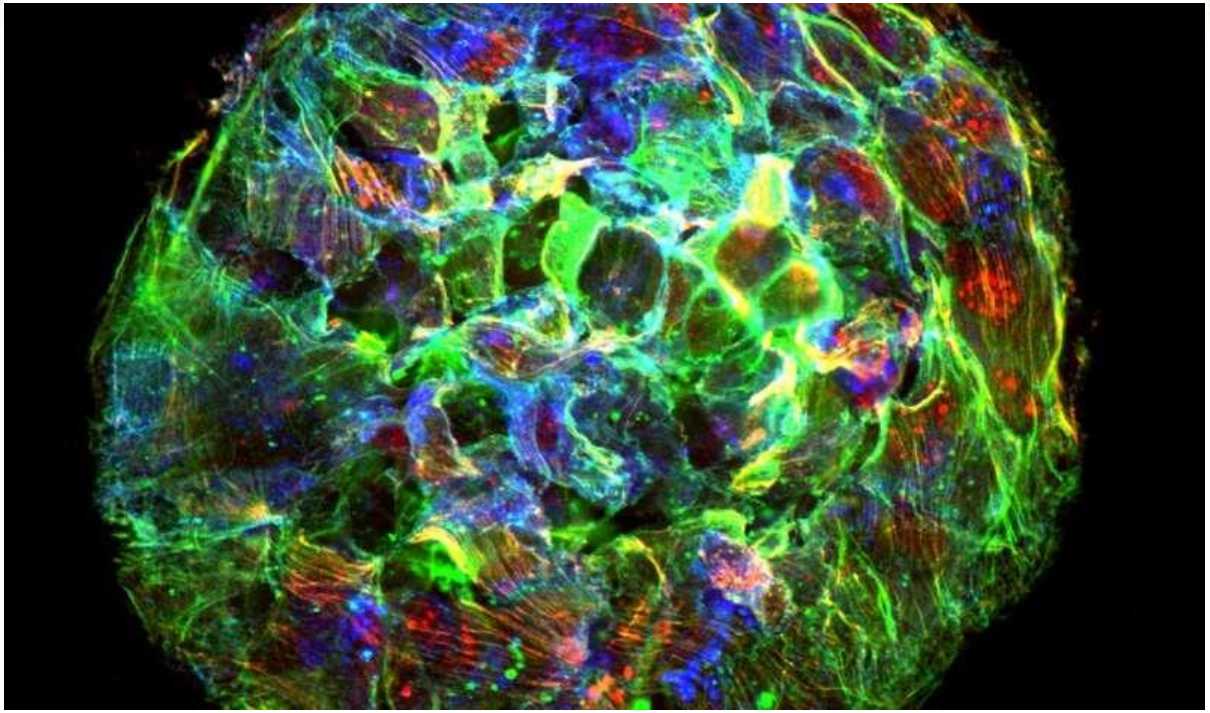
ER+, estrogen receptor positive

Normanno N, et al. *Endocr Rel Cancer.* 2005;12:721-747; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V.2012. NICE, CG81 Advanced breast cancer: Diagnosis and treatment. 2009 Available at http://publications.nice.org.uk/advanced-breast-cancer-cg81 Cardoso F, et al. *Ann Oncol.* 2010;21(suppl 5): v15-v19 ; Cardoso F, et al. *Breast.* 2012;24:242-252.

Targets and pathways for Endocrine Therapy in Breast Cancer



Adapted from Yardley DA, et al. ASCO BC 2011. Abstract 268; Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; Yamnik RL, et al. *J Biol Chem.* 2009;284:6361-6369.



OPTIONS FOR ENDOCRINE THERAPY IN ADVANCED BREAST CANCER

Options for 1st line / progression beyond 1st line in Advanced Breast Cancer

- Progestins
  - Megestrol acetate
  - Medroxyprogesterone acetate

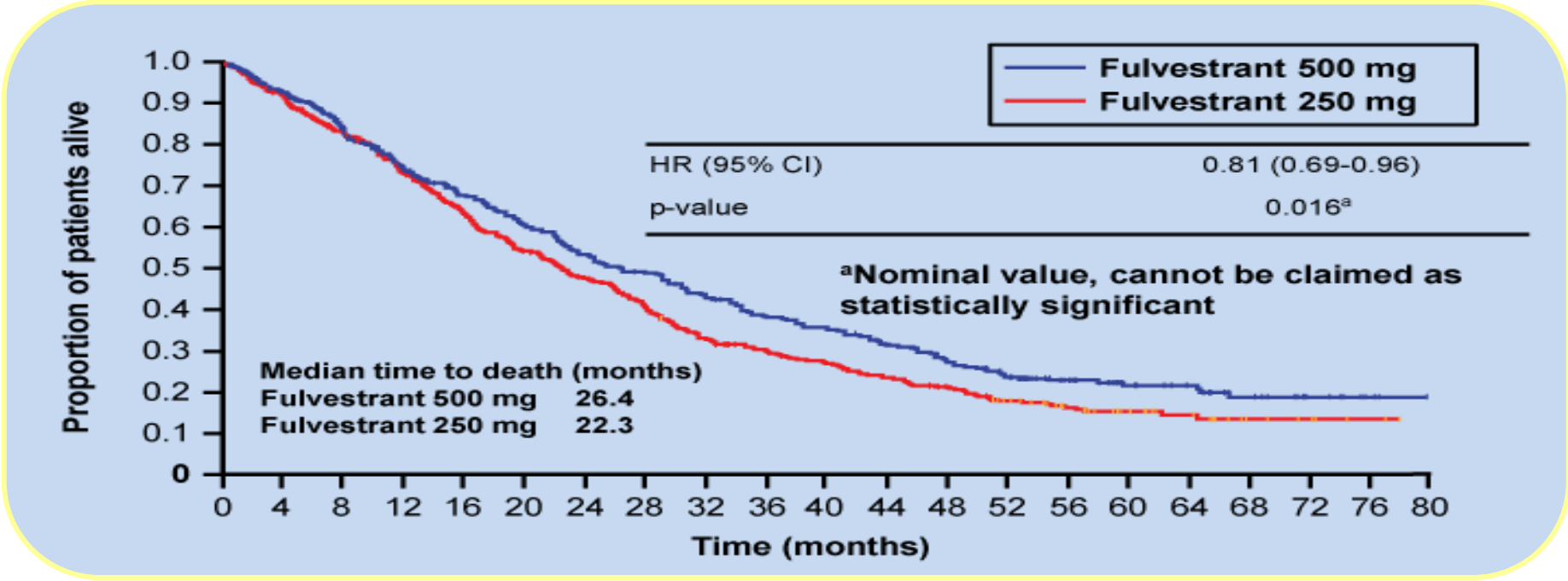
- CDK4 / 6 inhibitors
  - **Palbociclib**
  - **Ribociclib**
  - Abemaciclib

- PI3K inhibitors
  - Buparlisib
  - Alpelisib
  - Taselisib

Fulvestrant

- Is an injectable selective estrogen receptor downregulator that binds, blocks &↑ degradation / apoptosis of the ER.
- First studies in advanced disease showed similar efficacy to anastrozole, exemestane and tamoxifen, but doses and schedules were sub-optimal (250 and no loading doses).
- Greater antitumor activity CONFIRMed with the high dose schedule (500 mg with loading dose).
- Toxicities : GI disturbances, hot flashes, asthenia, injection site reactions.

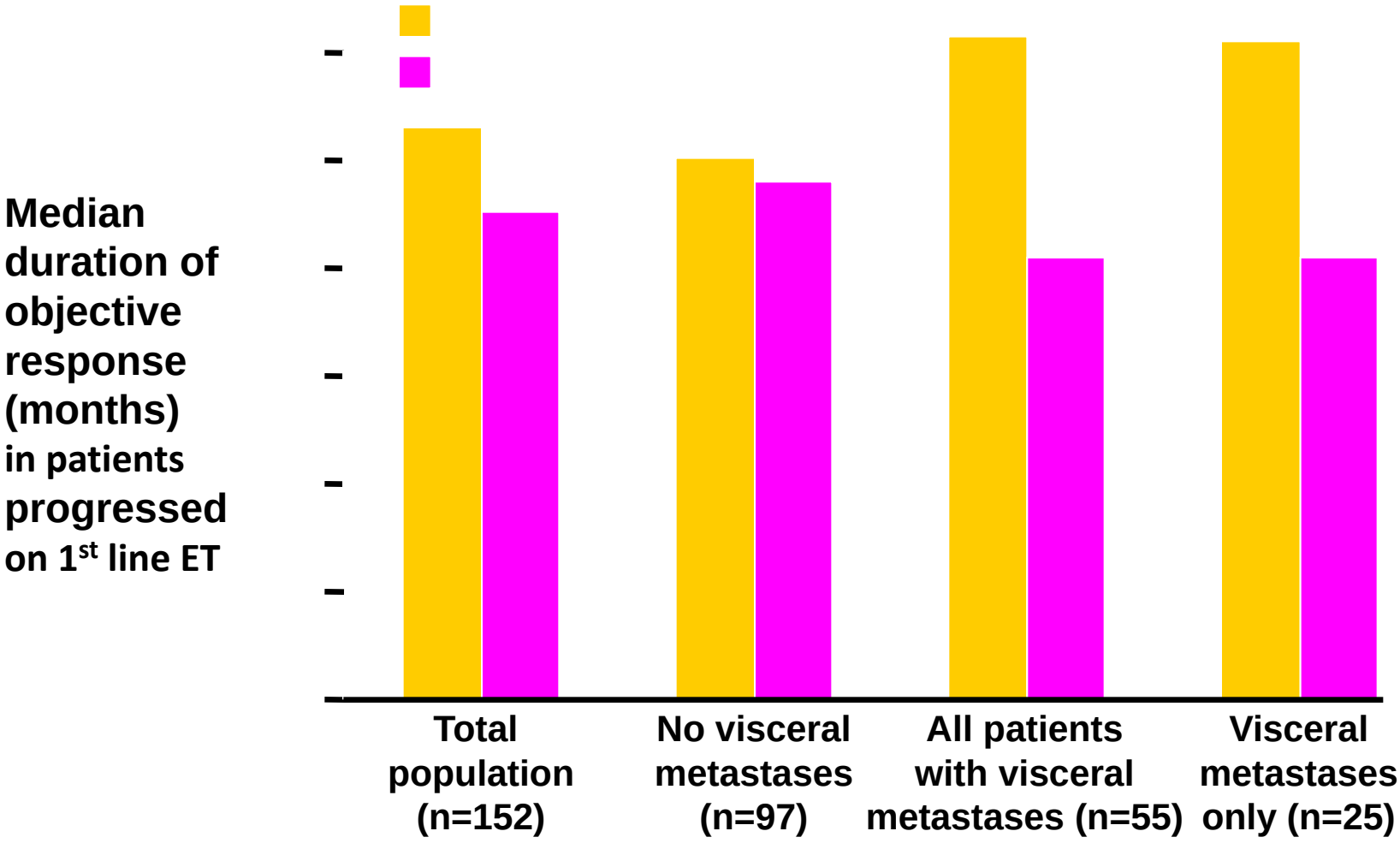
CONFIRM
Fulvestrant HD 500 mg vs AD 250 mg



PFS, OS, TTP, ORR, CBR and DoCB improved with Fulvestrant HD, *toxicities similar*.

DiLeo et al. *J Clin Oncol* 2013

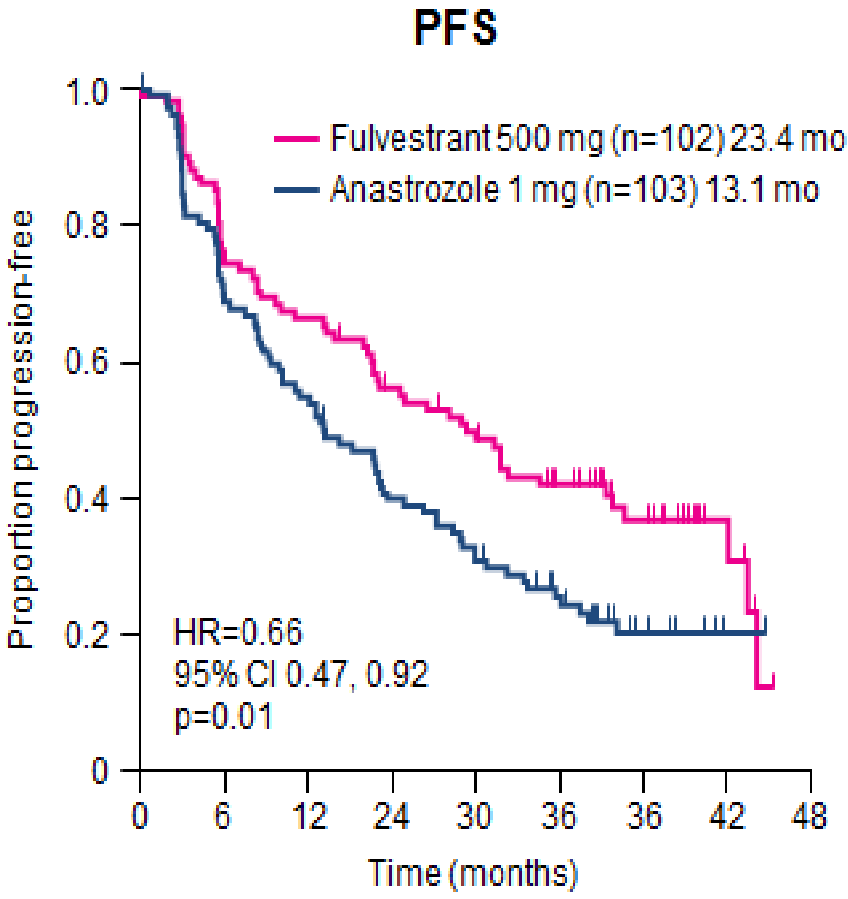
Median Duration of Response in pts with or without visceral metastases

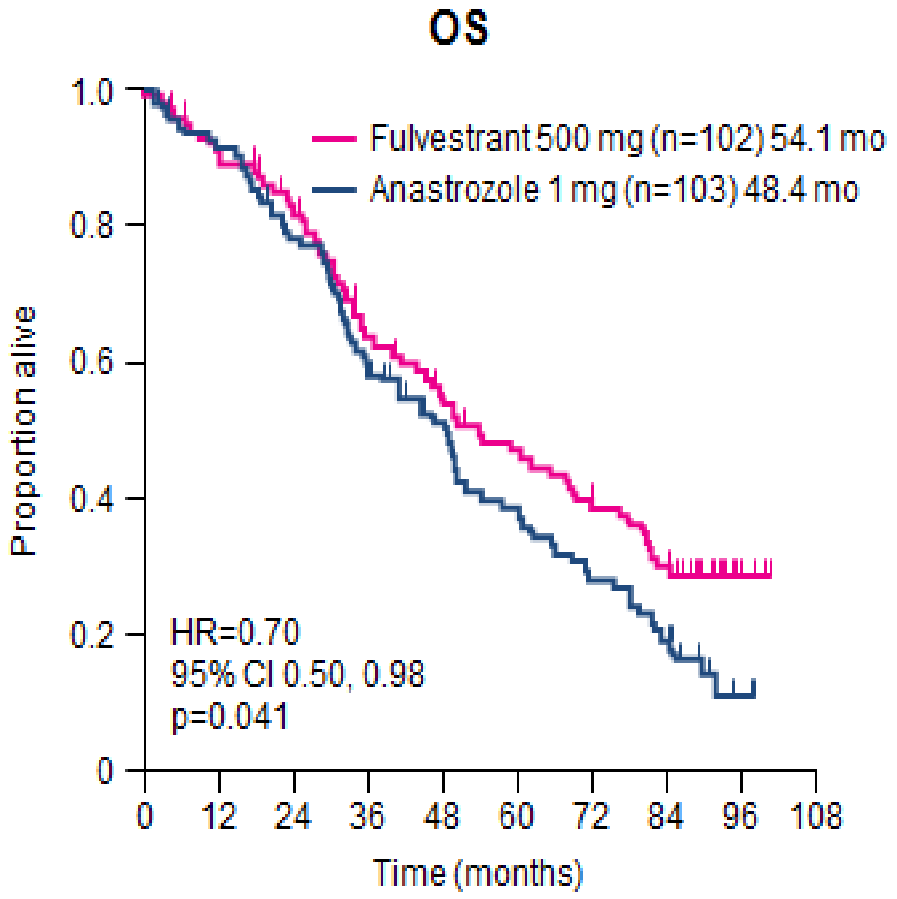


Mauriac et al. Eur J Cancer 2003; 39: 1228–1233

Fulvestrant HD vs AI : **Phase II FIRST Study**

Postmenopausal patients with Stage IIIB or IV, ER/PR+ HER2–
Primary Objective: CB (no differences)





CB, clinical benefit; HD, high dose.

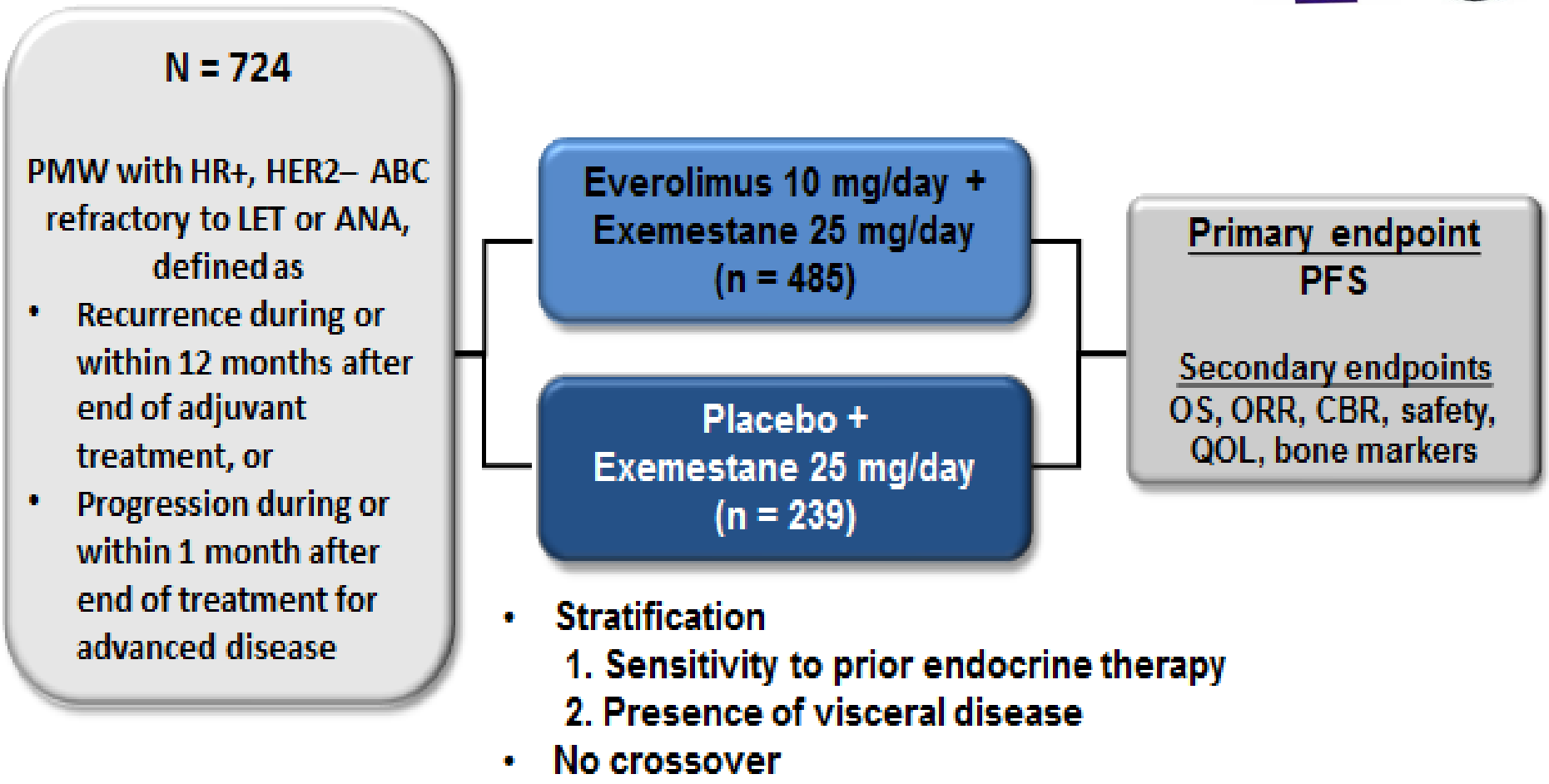
Bergh J, *et al. J Clin Oncol* 2012;30:1919–1925.

Everolimus

- Is an oral mTOR inhibitor used for 2nd line ABC, mRCC and aPNET .
- Compared to Exemestane alone after progression on NSAI in 2nd line setting.
- Starting dose of 10 mg / day, can be titrated in 2.5 mg steps .
- Toxicities : Stomatitis, diarrhoea, rash, fatigue.

  Hyperglycaemia, dyslipidaemia, pneumonitis.

BOLERO 2 Everolimus + Exe in 2nd line ABC

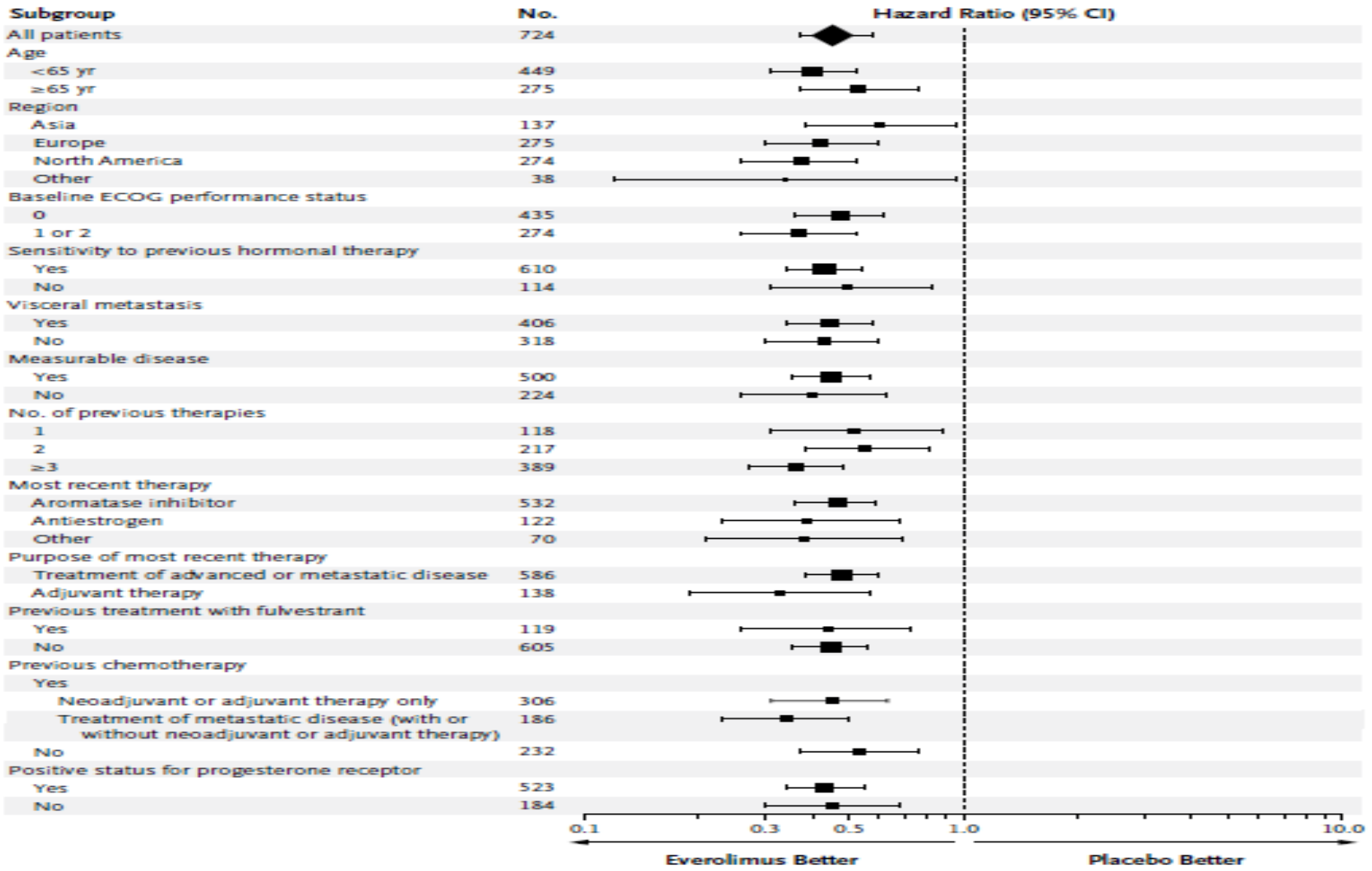


ANA, anastrozole; LET, letrozole.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO 2 – Results in ITT

post NSAI resistance



EVE, everolimus; EXE, exemestane.

Baselga J, *et al. N Engl J Med* 2012:366;36:520–529.

Palbociclib

- Is an oral CDK 4 / 6 inhibitor that targets the G1/S cell cycle checkpoint dependent on Cyclin & CDK 4 / 6.
- Starting dose of 125 mg / day, 3/1 schedule.
- Toxicities : Predominantly hematological, nausea, fatigue.
  - Grade 3 and 4 leucopenia, neutropenia, thrombocytopenia, anemia.
  - Febrile neutropenia low.
  - Treatment compliance not majorly affected.

PALOMA 2

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D.,

- **HR+, HER2– ABC**
- **Postmenopausal**
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

2:1

RANDOMIZATION

Palbociclib 125 mg (3 weeks on 1 week off) plus letrozole: 2.5 mg QD until PD

Placebo (3 weeks on 1 week off)

plus

letrozole: 2.5 mg QD until PD

Primary endpoint:

Investigator-assessed PFS

Secondary endpoint:

OS, Response rates, Safety

Stratification factors:

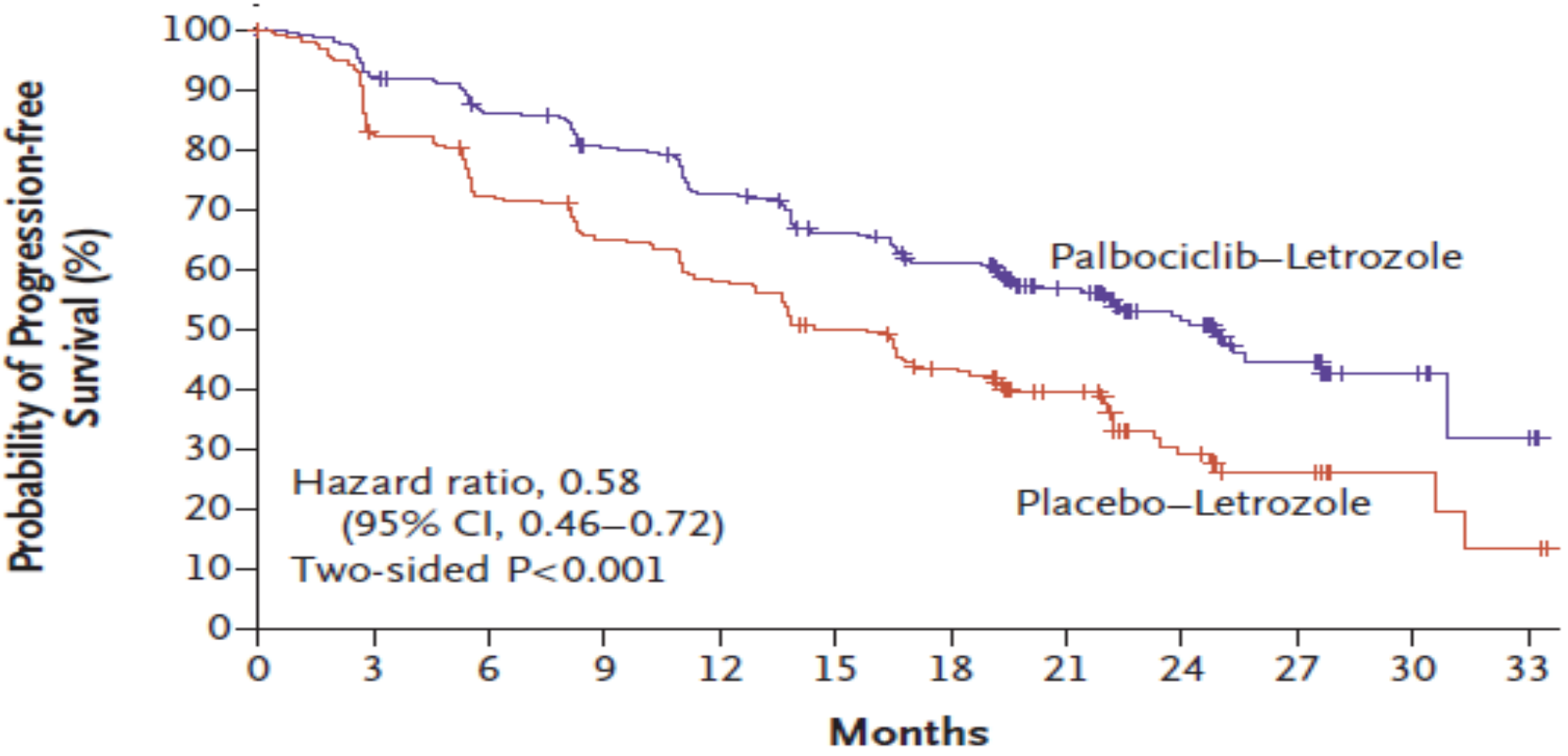
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

PALOMA 2

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D.,

A Investigator Assessment



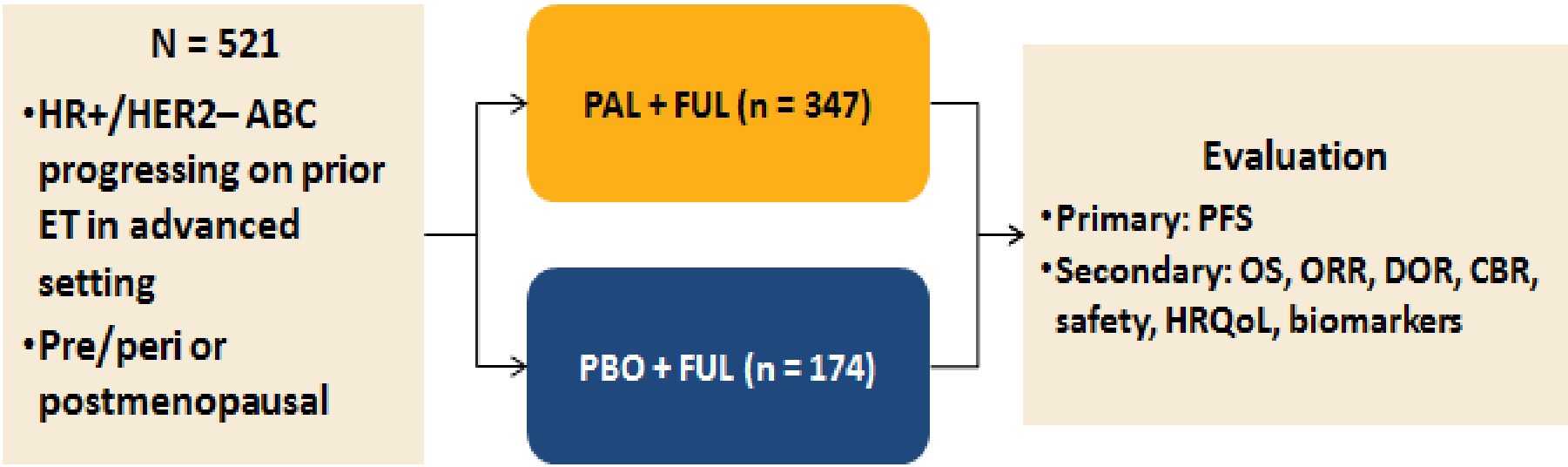
No. at Risk												
Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

PALOMA-3 : 2nd line FUL ± PAL in Pre/Postmeno

Objectives

- **To determine efficacy and safety of palbociclib (PAL) plus fulvestrant (FUL) in pts with HR+/HER2– mBC progressing on prior ET**

Methodology

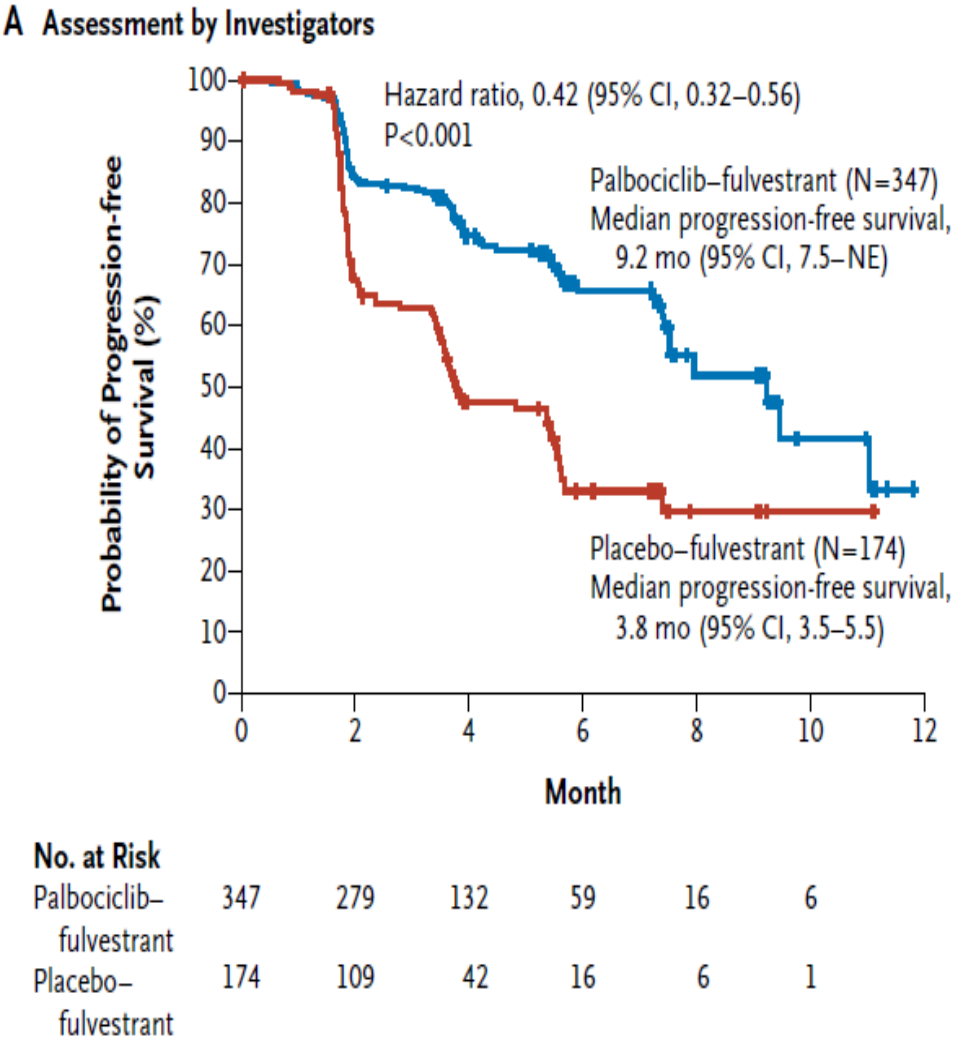


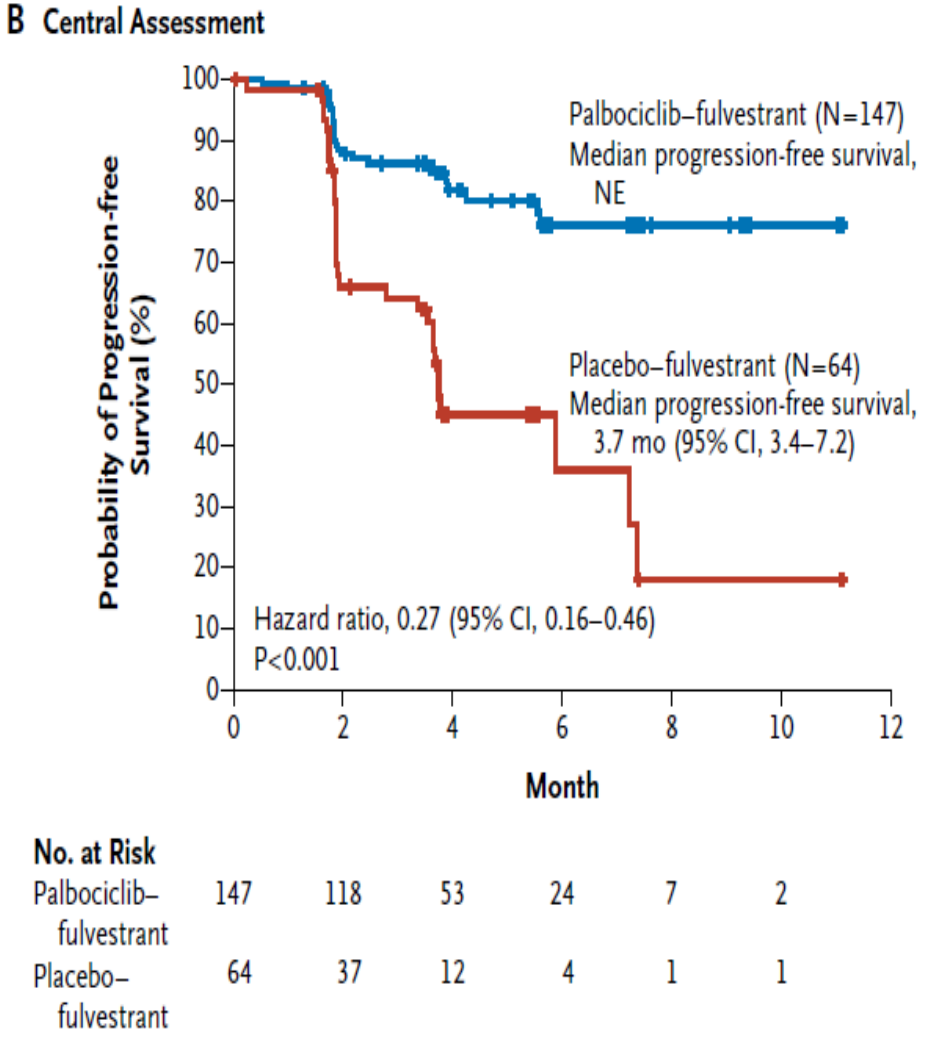
ABC, advanced breast cancer; CBR, clinical benefit rate; DOR, duration of response; ET, endocrine therapy; FUL, fulvestrant; HRQoL, health related quality of life; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression free survival.

Turner NC, *et al. N Engl J Med* 2015;373:209-19.

PALOMA 3 Results in ITT

post ET progression





Turner *et al*. *N Engl J Med* 2015;373:209-19.

Ribociclib

- Is an oral CDK 4 / 6 inhibitor that targets the G1/S cell cycle checkpoint dependent on Cyclin & CDK 4 / 6.

- Starting dose of 600 mg (200 mg x 3)/ day, 3/1 schedule.

- Toxicities : Predominantly nausea, fatigue.
  - Grade 3 and 4 leucopenia, neutropenia, less common.
  - QTc prolongation, especially > 480 ms reported.
  - Liver enzyme elevation reported.

MONALEESA-2: A Phase III, Double-blind, Placebo-Controlled Study of Ribociclib + Letrozole

- Postmenopausal women with HR+/HER2– advanced breast cancer
- No prior therapy for advanced disease
- N=668

Randomiza
(1:1)

Stratified by
presence/abs
of liver and/o
metastas

Ribociclib (600 mg/day)
3-weeks-on/1-week-off
+
Letrozole (2.5 mg/day)
n=334

Placebo
+
Letrozole (2.5 mg/day)
n=334

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

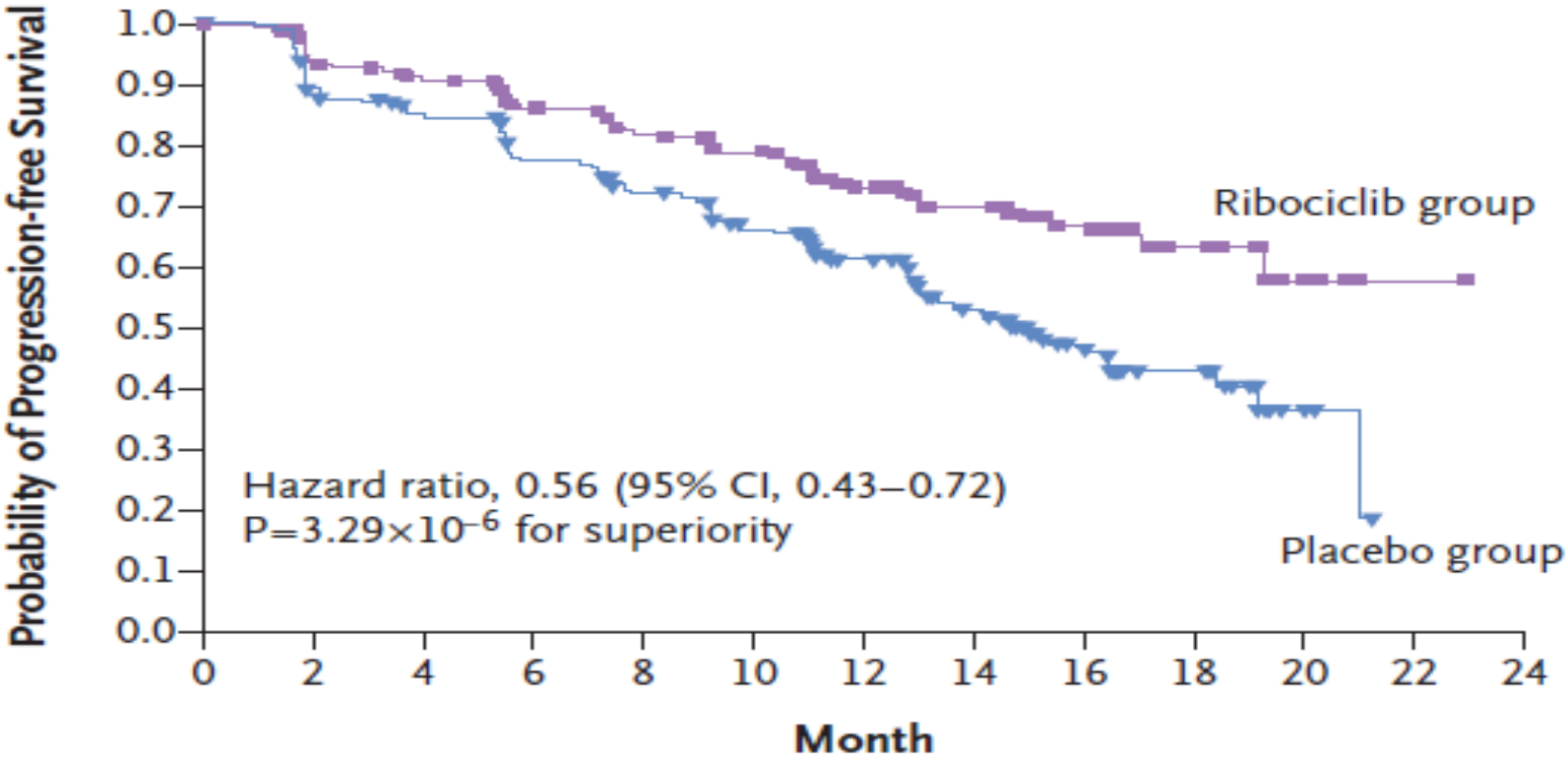
Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio, 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio, ≤0.56 and *P*<0.0000129

PFS, progression-free survival.
MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).
Hortobagyi G, et al. *N Engl J Med.* 2016 October 8 [Epub ahead of print].

Hortobagyi et al; NEJM 2016

MONALEESA-2: A Phase III, Double-blind, Placebo-Controlled Study of Ribociclib + Letrozole



No. at Risk

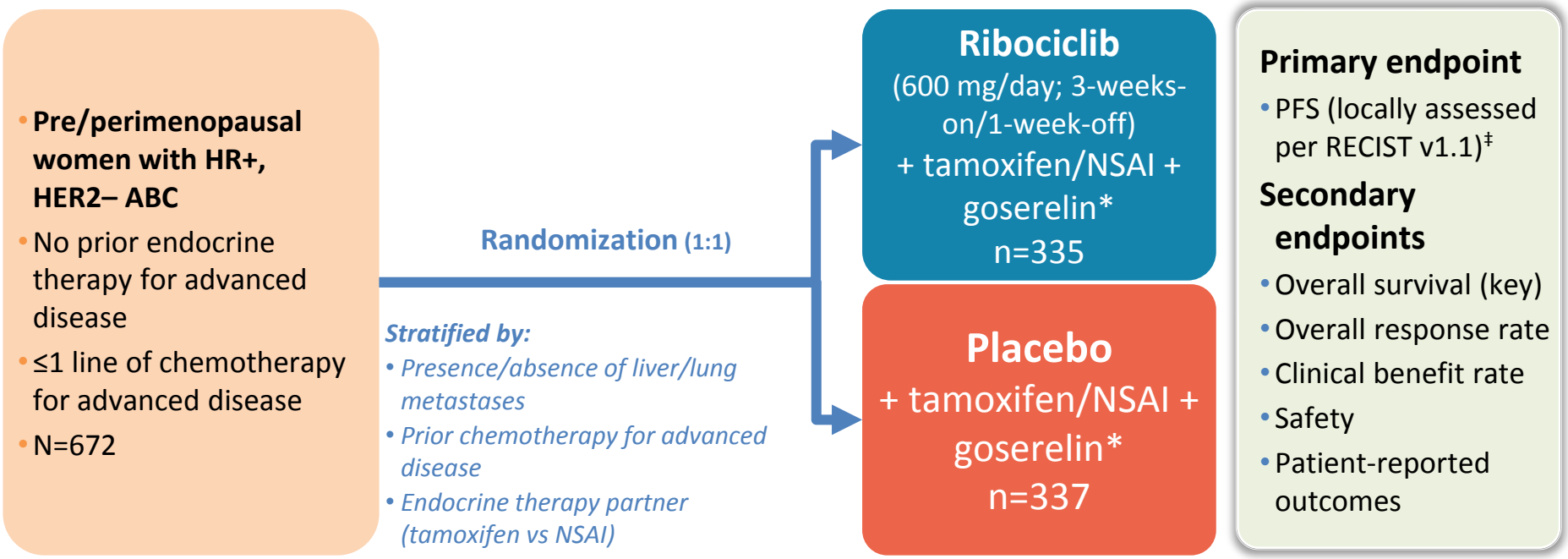
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

Main AEs: QTc prolongation, ALT, AST rise, neutropenia.

Hortobagyi et al; NEJM 2016

MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

Tripathi et al. SABCS 2017



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events

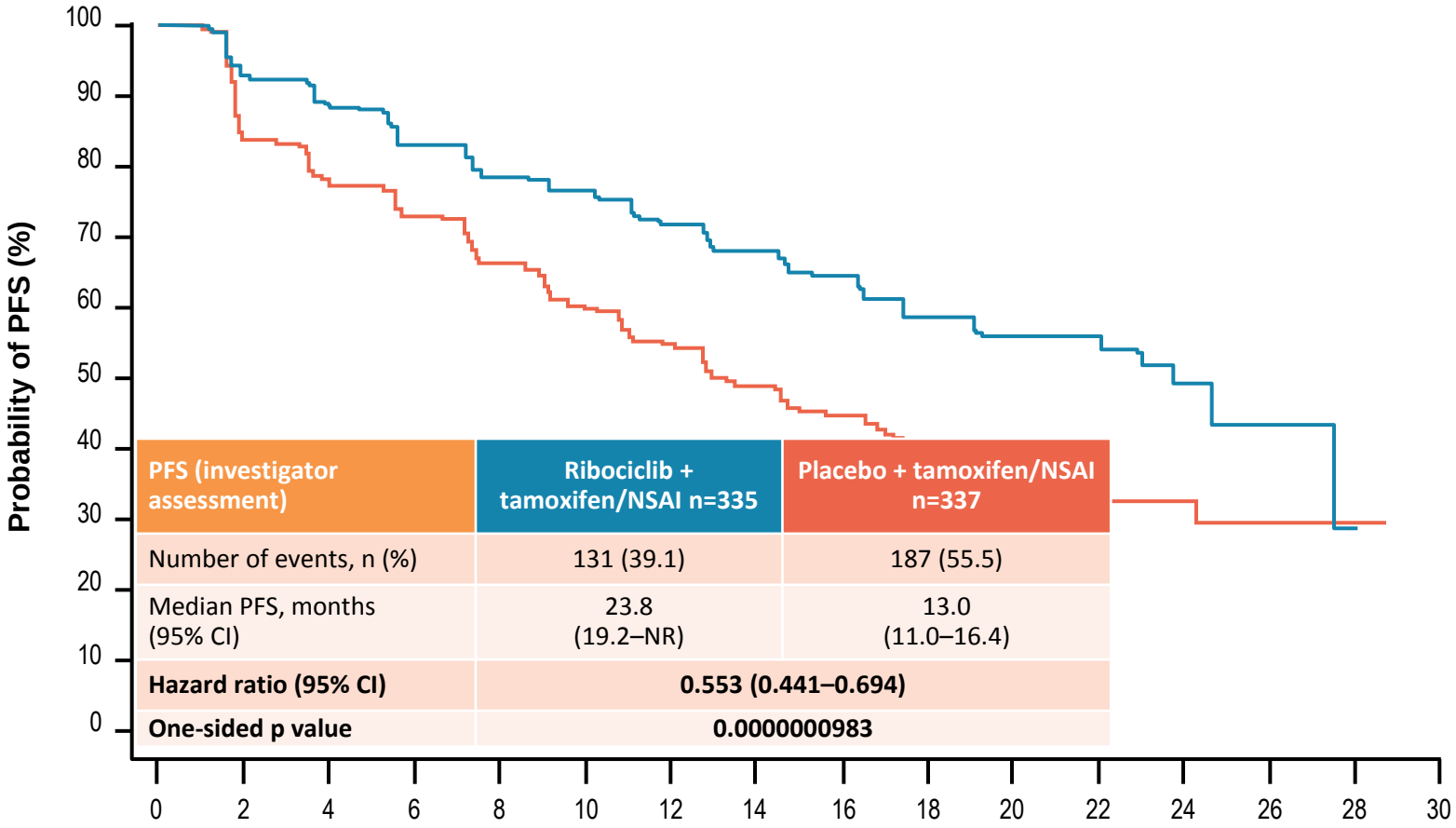
– 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients

- NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
- *Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days; ‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.

1. Klijn JG, *et al*. *J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al*. *J Clin Oncol* 2001;19:2596–2606.

MONALEESA-7 : Primary endpoint: PFS (investigator-assessed)

Tripathi et al. SABCS 2017



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

No. at risk

Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

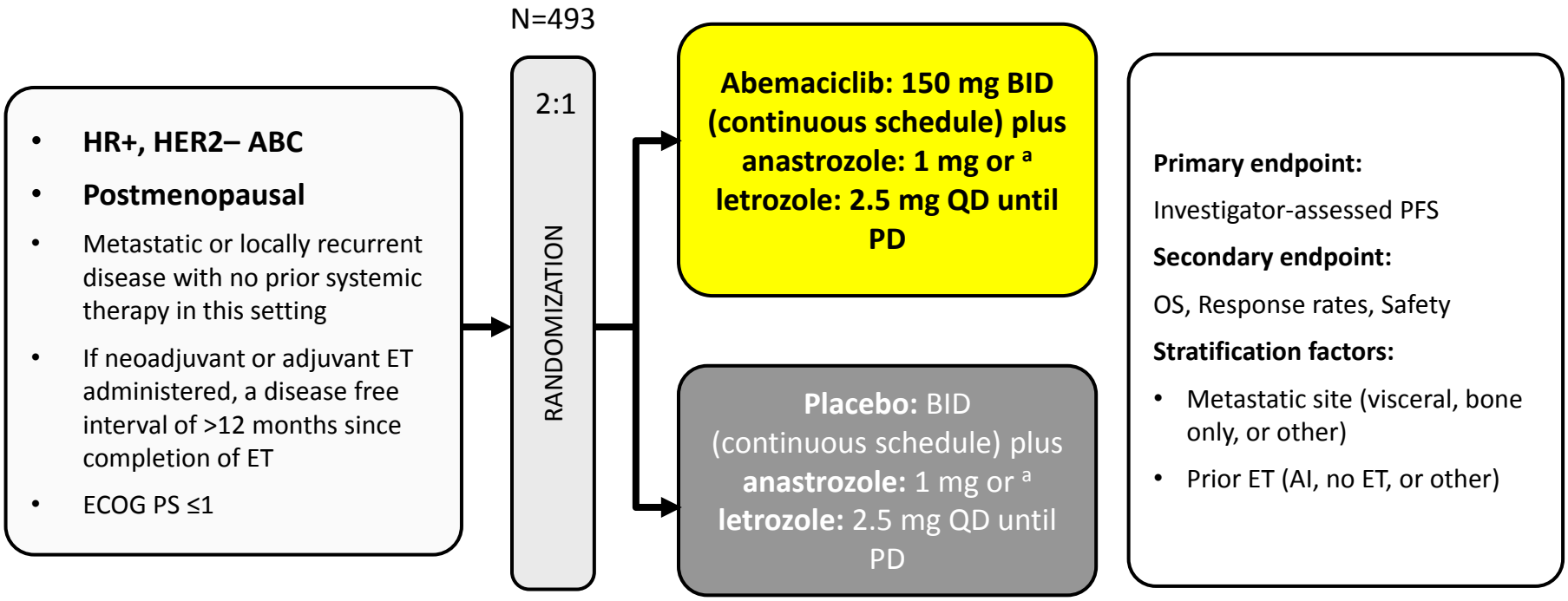
- CI, confidence interval; NR, not reached.
  Goserelin included in all combinations.

PFS by endocrine therapy partner (investigator-assessed)

Tripathi et al. SABCS 2017

PFS (investigator assessment)	Tamoxifen		NSAI	
	Ribociclib arm n=87	Placebo arm n=90	Ribociclib arm n=248	Placebo arm n=247
Number of events, n	39	55	92	132
Median PFS, months (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
Hazard ratio (95% CI)	**0.585 (0.387–0.884)**		**0.569 (0.436–0.743)**	

MONARCH 3: Study Design



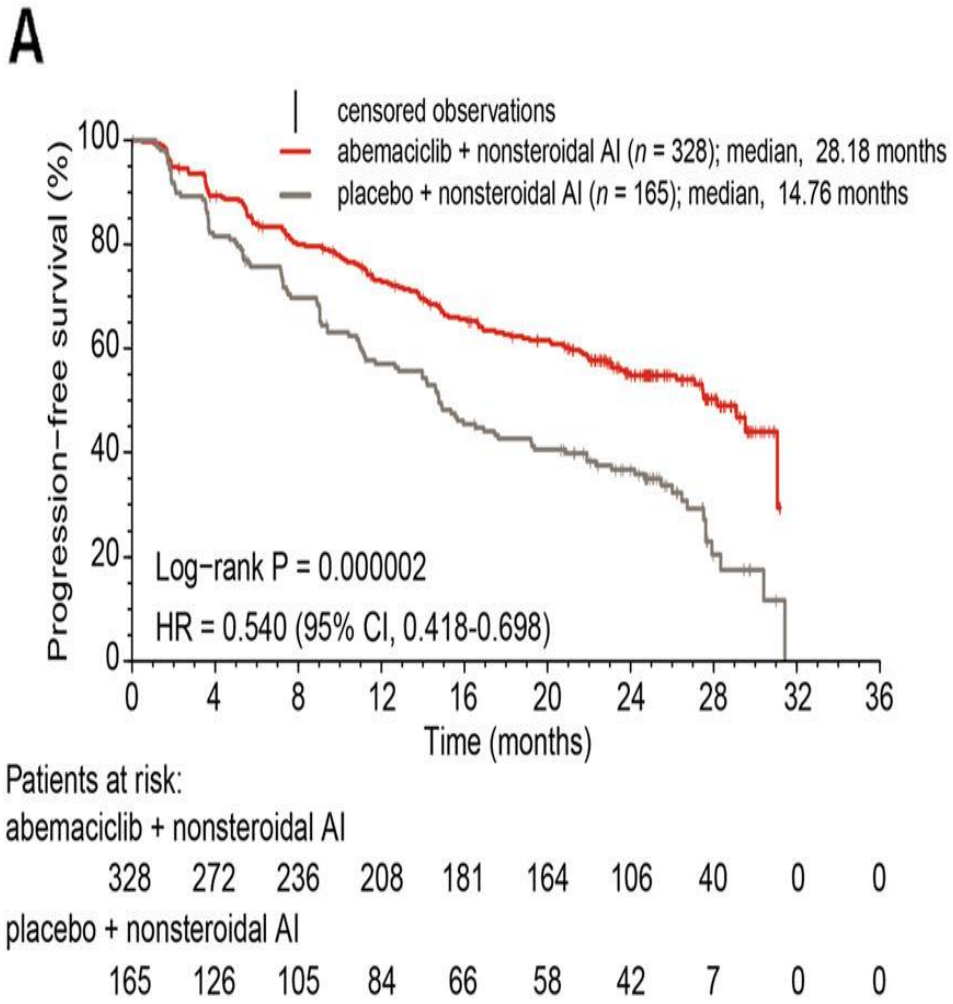
[a] Per physician's choice: 79.1% received letrozole, 19.9% received anastrozole.

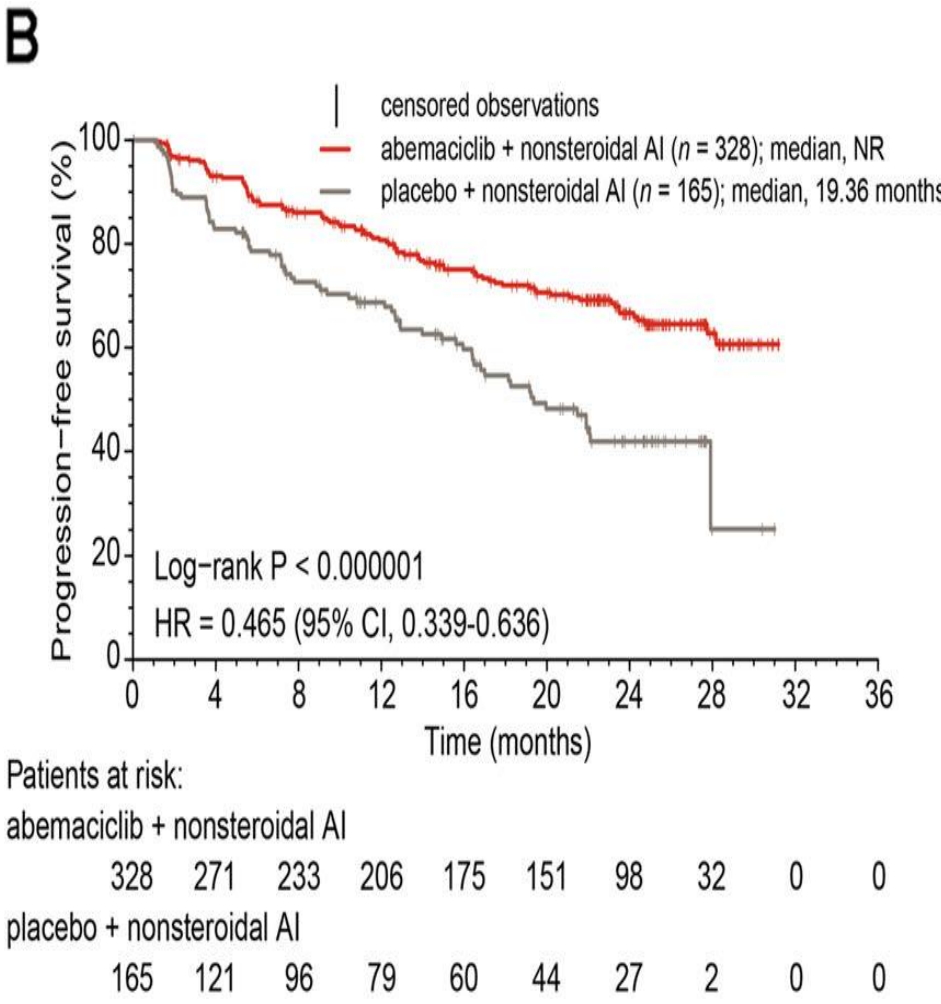
Statistics: Study powered to 80% at one-sided alpha of 0.025 assuming a hazard ratio of 0.67 with analyses at 189 and 240 PFS events. Positive study at the interim required a hazard ratio <0.56 and two-sided p<0.0005

Enrollment: From November 2014 to November 2015 patients enrolled in 158 centers from 22 countries

Median follow-up: 17.8 months (interim analysis)

MONARCH3: Updated results





AEs : neutropenia (21.1% v 1.2%), diarrhea – most common AE (9.5% v 1.2%), and leukopenia (7.6% v 0.6%).

Johnston et al; Nature Breast Cancer 2019

MONARCH 2 Study Design

N= 669

- HR+, HER2- ABC
- Pre/peri-[a] or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS ≤ 1

→ 2:1 Randomization →

abemaciclib: 150 mg[b] BID (continuous schedule) **fulvestrant:** 500 mg[c]

placebo: BID (continuous schedule) **fulvestrant:** 500 mg[c]

Primary endpoint:
Investigator-assessed PFS

Secondary endpoint:
Overall Survival, Response, Clinical Benefit Rate, Safety

Stratification factors:
- Metastatic site (visceral, bone only, or other)
- ET resistance (primary vs secondary)[1,2]

- Patients were enrolled in 142 centers in 19 countries
- Statistics: 378 events for 90% power at one-sided α of .025 assuming a true HR of .703
- 114 pre/peri-menopausal patients were randomized in the study

[a]aged <60 years and have natural menstrual bleeding. Patients were required to receive gonadotropin releasing hormone (GnRH) agonist
[b]dose post-amendment
[c]fulvestrant administered per label

Abbreviations: ABC, advanced breast cancer; BID, twice daily dose; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-; HR, hazard ratio; HR+, hormone receptor+; MBC, metastatic breast cancer; PFS, progression-free survival

1. Cardoso F et al. *Breast*. 2017;31:244-59
2. Cardoso F et al. *Ann Oncol*. 2017;28:16-33

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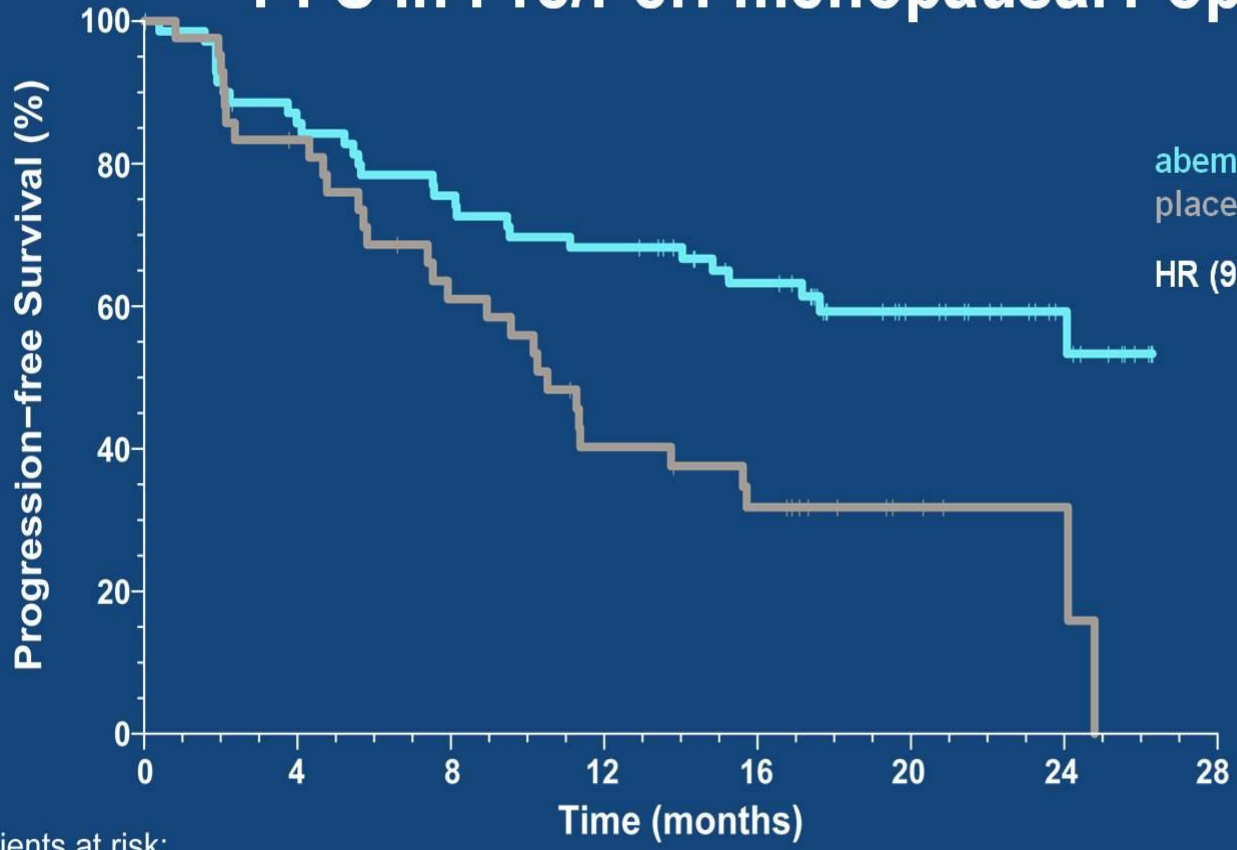
PFS in Pre/Peri-menopausal Population



Median PFS

abemaciclib + fulvestrant: **not reached**

placebo + fulvestrant: **10.5 months**

HR (95% CI): .446 (.264, .754); p=.002

Patients at risk:

abemaciclib	72	59	52	47	36	20	10	0
placebo	42	34	24	15	11	4	2	0

PFS benefit confirmed by blinded independent central review HR: .432; 95% CI: .236, .793; p< .005

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Thank You
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