Hormone receptor positive breast cancer

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Trials Save Lives
breastcancertrials.org.au

Disclosures

Advisory board: Lilly, Eisai, Astra Zeneca, MSD, Novartis, Gilead, Roche, Menarini

Honorarium: Roche, Pfizer, Eisai, Amgen, Gilead, Novartis, Lilly, Astra Zeneca, MSD, Daiichi Sankyo

Research funding (institutional): Pfizer, Roche, GSK, Novartis, BMS, Astra Zeneca

Education funding: Roche, Novartis, Pfizer, Lilly

Stock: Nil

Agenda – Hormone receptor positive breast cancer
An update for 2025

Early stage disease

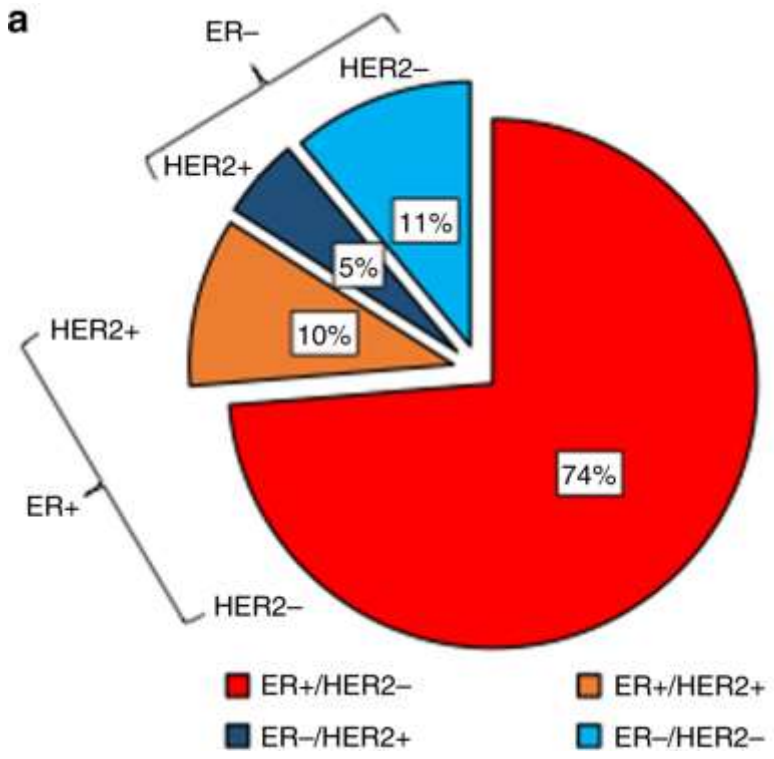
1. Re-thinking definitions of HR-positive
2. Chemotherapy – who really needs it?
3. Endocrine therapy – what and for how long?
4. CDK 4/6 inhibitors – thresholds for treatment

Metastatic disease

1. First line endocrine and (other) targeted therapy
2. Options for second line and beyond

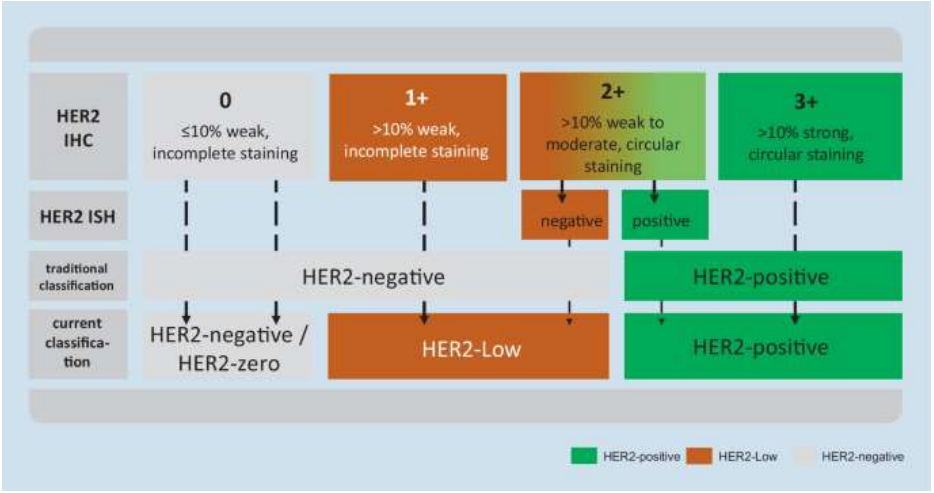
Early stage hormone receptor positive (HER2 negative) breast cancer

Definitions



Evolution of HER2-low

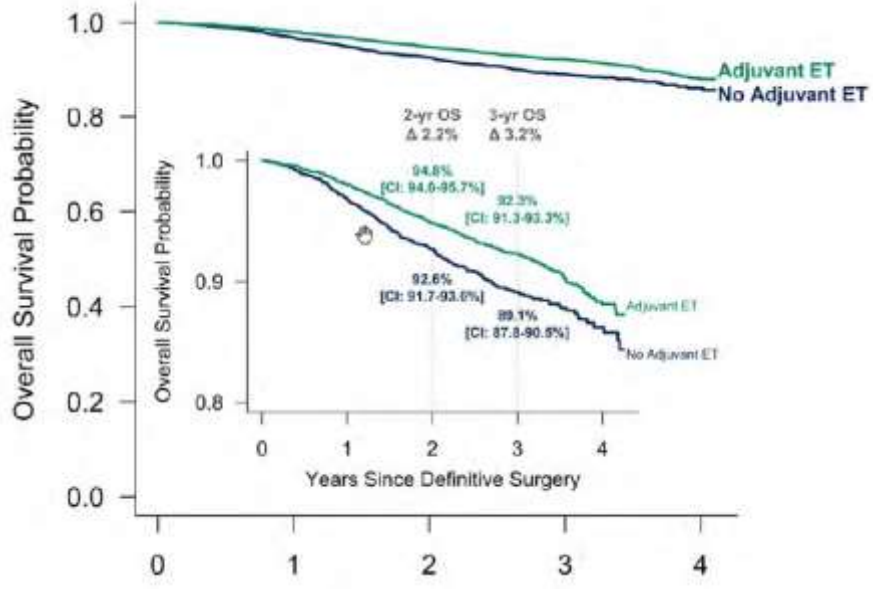
- 50% of breast cancers
- HER2 IHC 1+ or 2+, and ISH negative



BREAST CANCER TRIALS

Oestrogen receptor low (positive) 1-10% IHC staining

- Behave similarly to ER-negative
- Endocrine therapy is indicated
- Early stage – less endocrine sensitive
- Consider (neo)adjuvant chemotherapy
- Immunotherapy: KN-756 (pCR benefit in ER-low group)
- Trials may exclude in both ER+ and TNBC definition

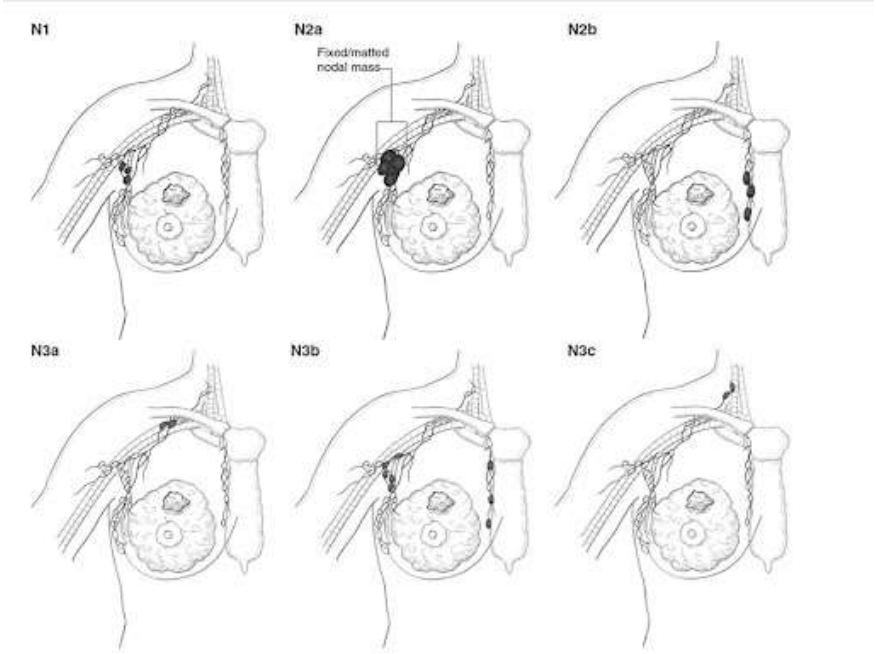


NCDB analysis, retrospective

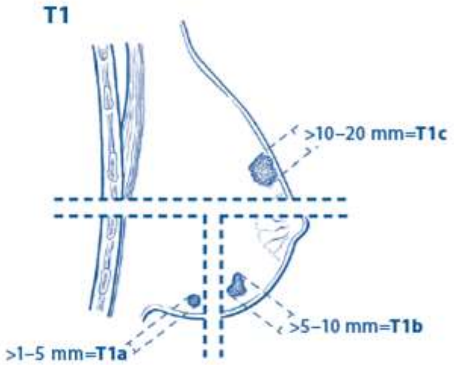
Caveats: no ET duration data, type of chemotherapy, recurrence data

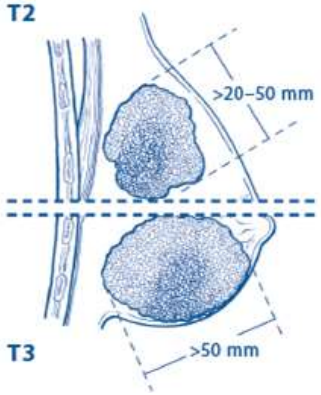
ASCO-CAP, JCO 2020; Choong, ASCO AM 2024

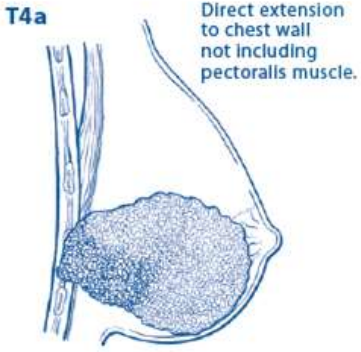
Staging: AJCC anatomical TNM
Remains the strongest prognostic factor



AJCC 2016

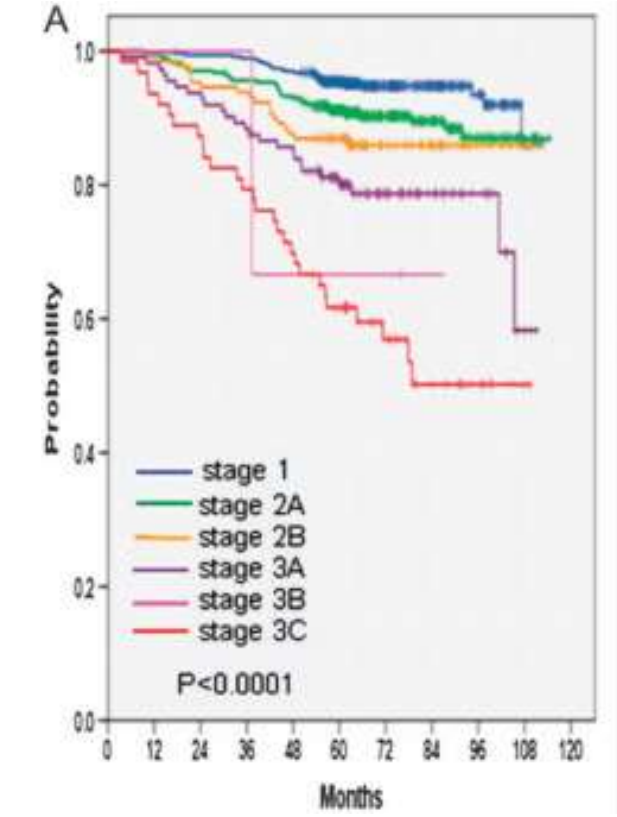




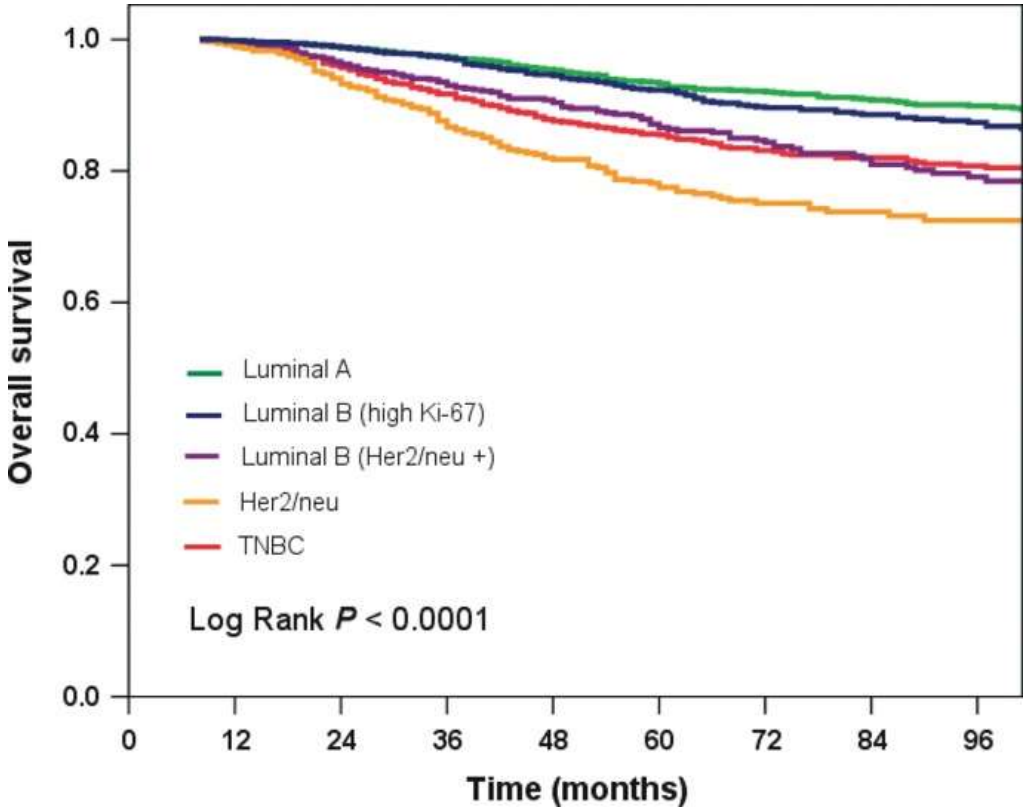


BREAST CANCER TRIALS

Prognosis by stage (ER+)

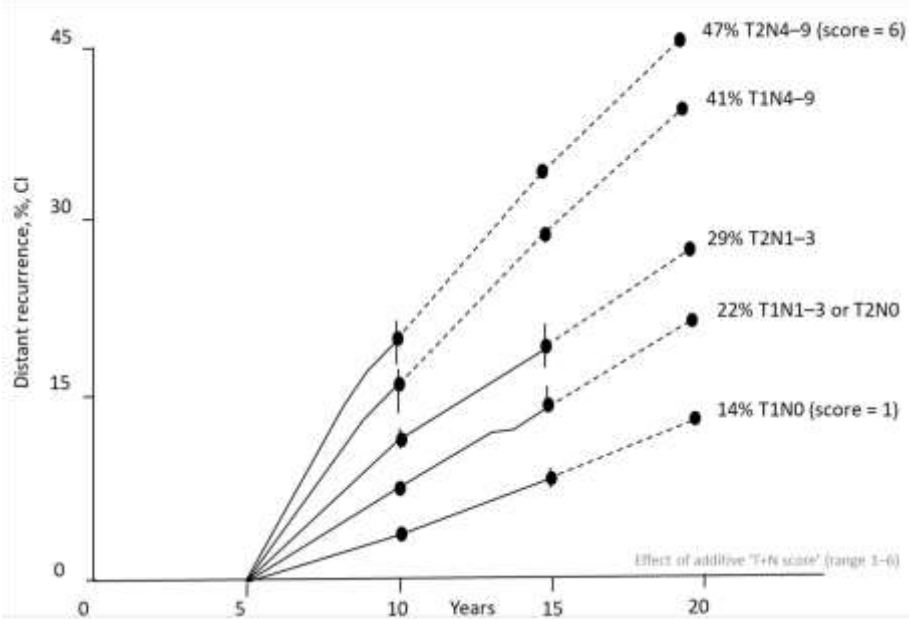


Prognosis by subtype



BREAST CANCER TRIALS

Long term recurrence risk

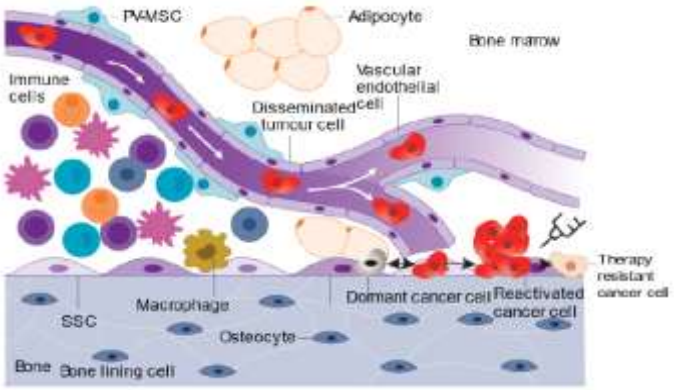


Pan NEJM 2017

ER positive breast cancer has an ongoing late recurrence risk

- Suppressive effect of endocrine therapy
- Tumour cell dormancy

This is true even for low risk T1N0 primary cancers



BREAST CANCER TRIALS

Determining recurrence risk

Clinical risk

- Tumour size
- Nodes
- Grade

Genomic risk

- Intermediate clinical risk
- All comers
- High clinical risk

Predict calculator

Treatment	Additional Benefit	Overall Survival %
Surgery only	-	71%
+ Hormone therapy	7.1% (4.2% – 8.9%)	78%
+ Chemotherapy	3.6% (2.0% – 4.9%)	82%

If death from breast cancer were excluded, 96% would survive at least 10 years, and 4% would die of other causes

predict breast cancer

BREAST CANCER TRIALS

Determining treatment sensitivity

Prognostication vs prediction

Oncotype: TailorX (21 gene RS)

Predictive/prognostic

MINDACT: Mammaprint

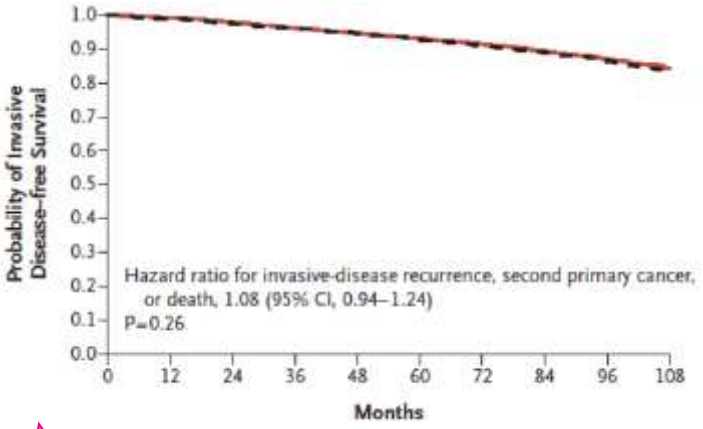
Predictive?/prognostic

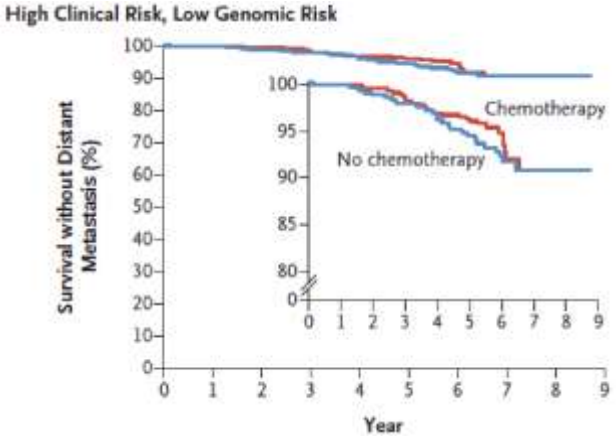
PAM50 ROR

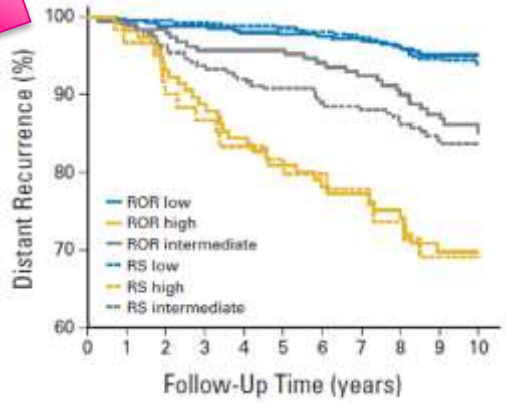
Prognostic/subtype

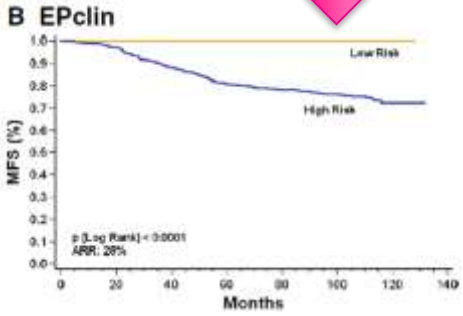
Endopredict

Prognostic







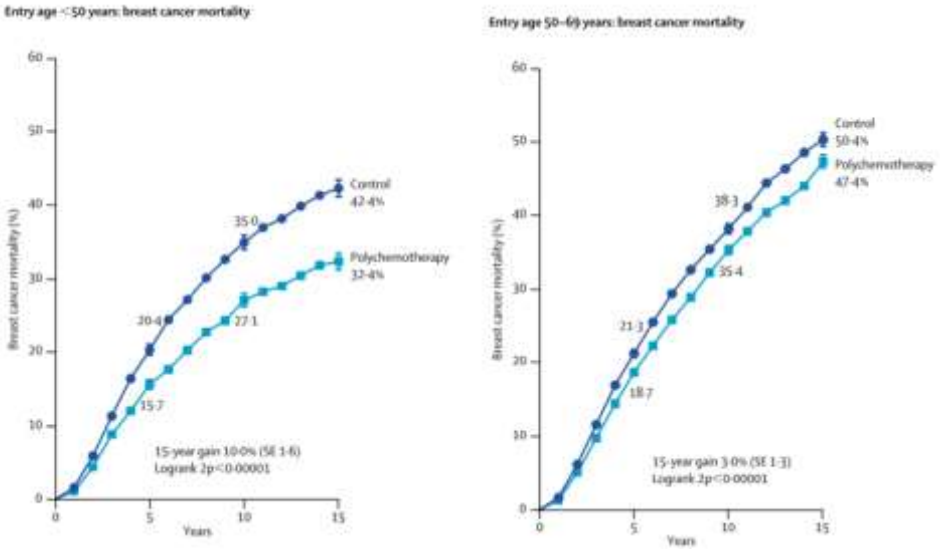


BREAST CANCER TRIALS

Predictive strategies – adjuvant chemotherapy for ER+
Which patients should be given chemotherapy?

Factors should not be taken in isolation

- NST/ductal > lobular
- Luminal B: high grade, Ki67>20%, PR<30%
- Node positive
- Younger/premenopausal
  - Impact of ovarian ablation
- High genomic risk



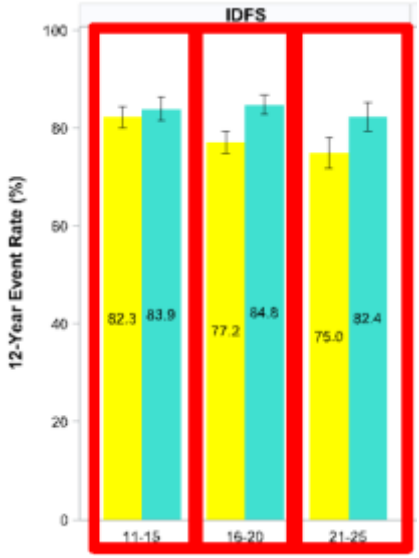
EBCTCG 2005

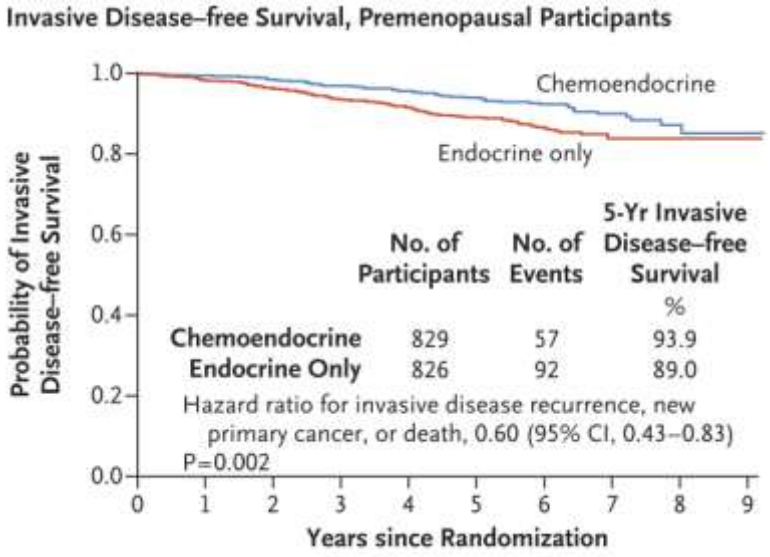
BREAST CANCER TRIALS

Oncotype in premenopausal

Node negative:
TailorX

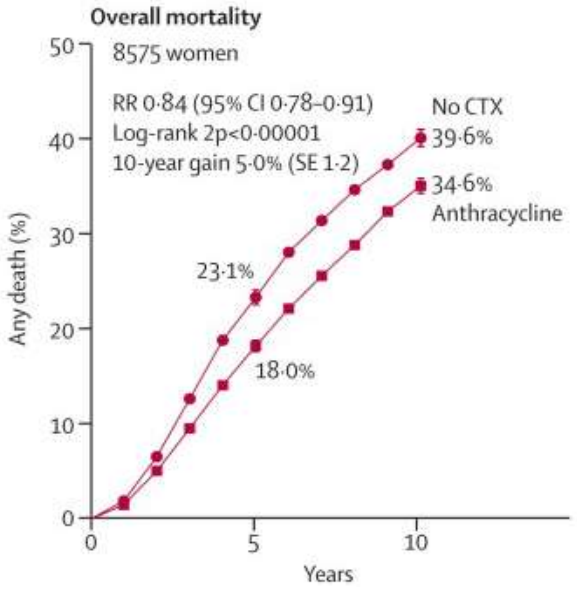
- No chemo benefit for RS 11-15
- Marginal benefit for RS 16-20
- Evident benefit for RS 21-25

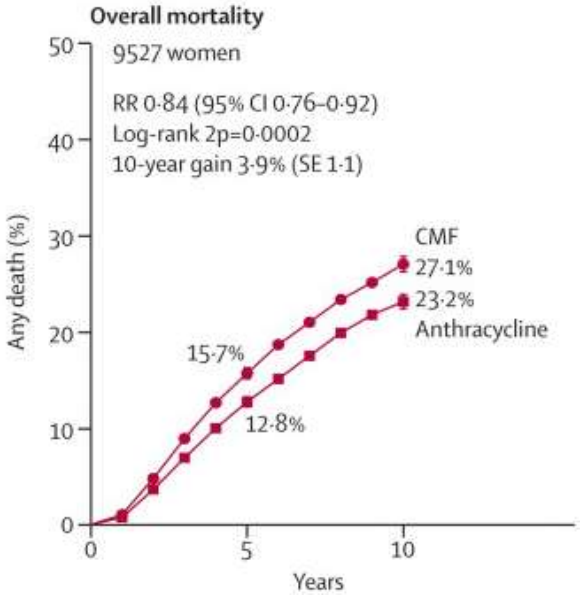


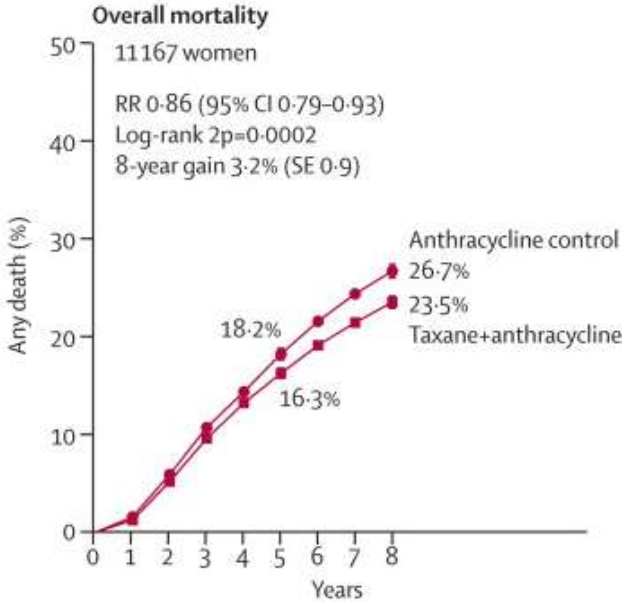


Kalinsky NEJM 2021; Sparano SABCS 2023

Impact of chemotherapy







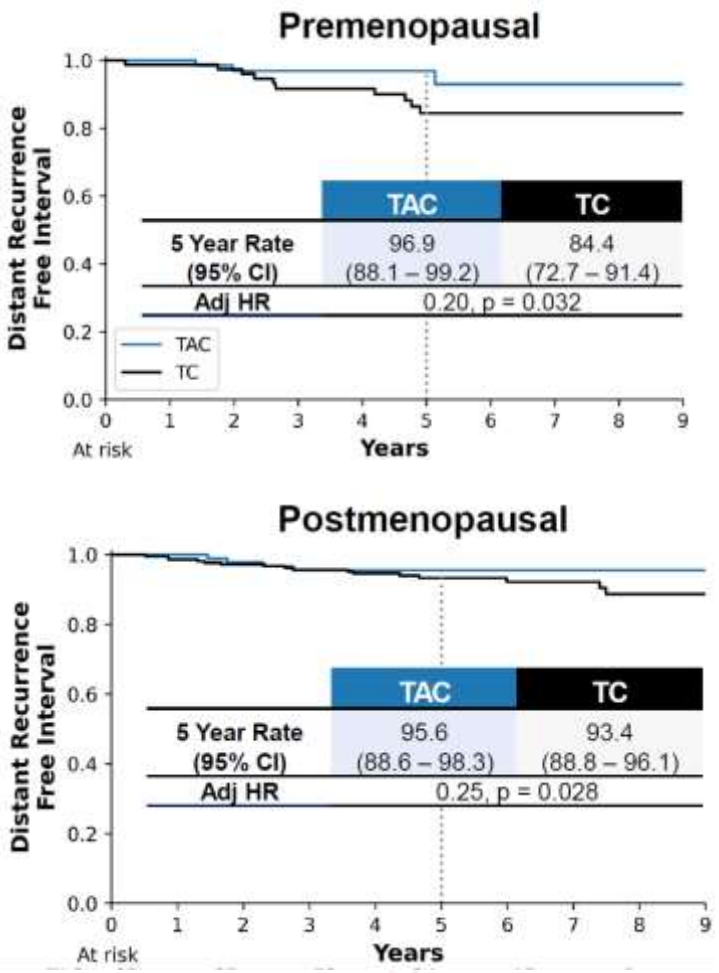
EBCTCG 2012

Which chemotherapy regimen?

Consider: risk-benefit balance

- Low risk chemo candidate: 4xTC
- Intermediate: ECx3-Dx3
- High risk: dose dense ACx4-P(x4 or x12)
- Avoiding anthracycline or taxane?

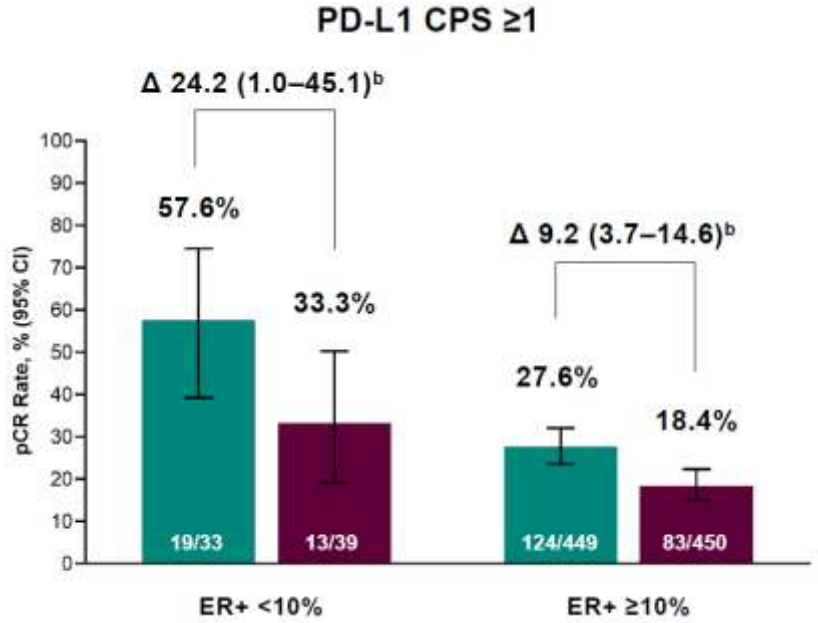
- Recurrence score ≥31 suggests anthracycline benefit



Chen SABCS 2024

Neoadjuvant chemotherapy and immunotherapy
HR-positive

KEYNOTE-756



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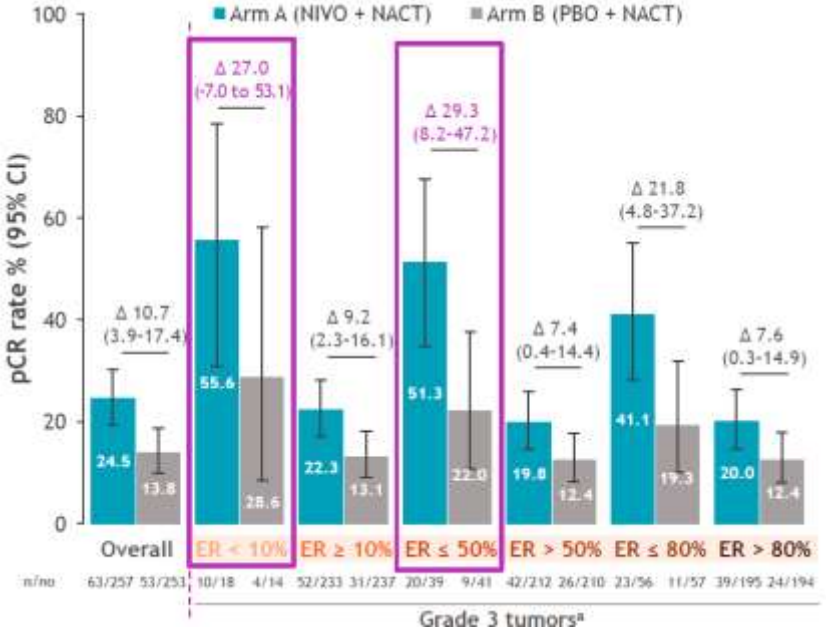
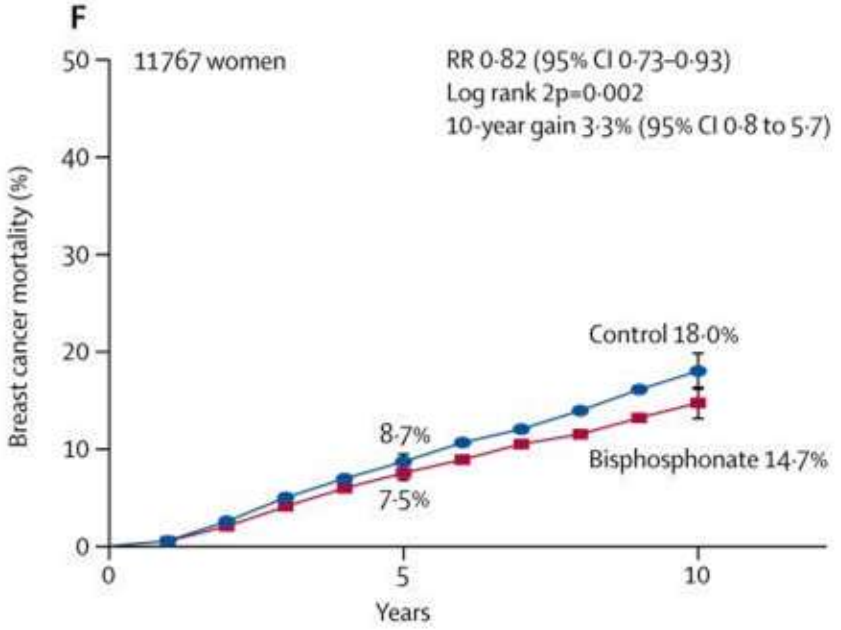


Loi SABCS 2023; Cardoso SABCS 2023

Adjuvant zoledronic acid

- Benefit restricted to postmenopausal
- Visceral and bone metastasis prevention
- 6 doses, given every 6 months = 3 years
- 4mg IVI
- Fracture risk reduction for patients on AI
- Dental review suggested
  - Osteonecrosis of the jaw



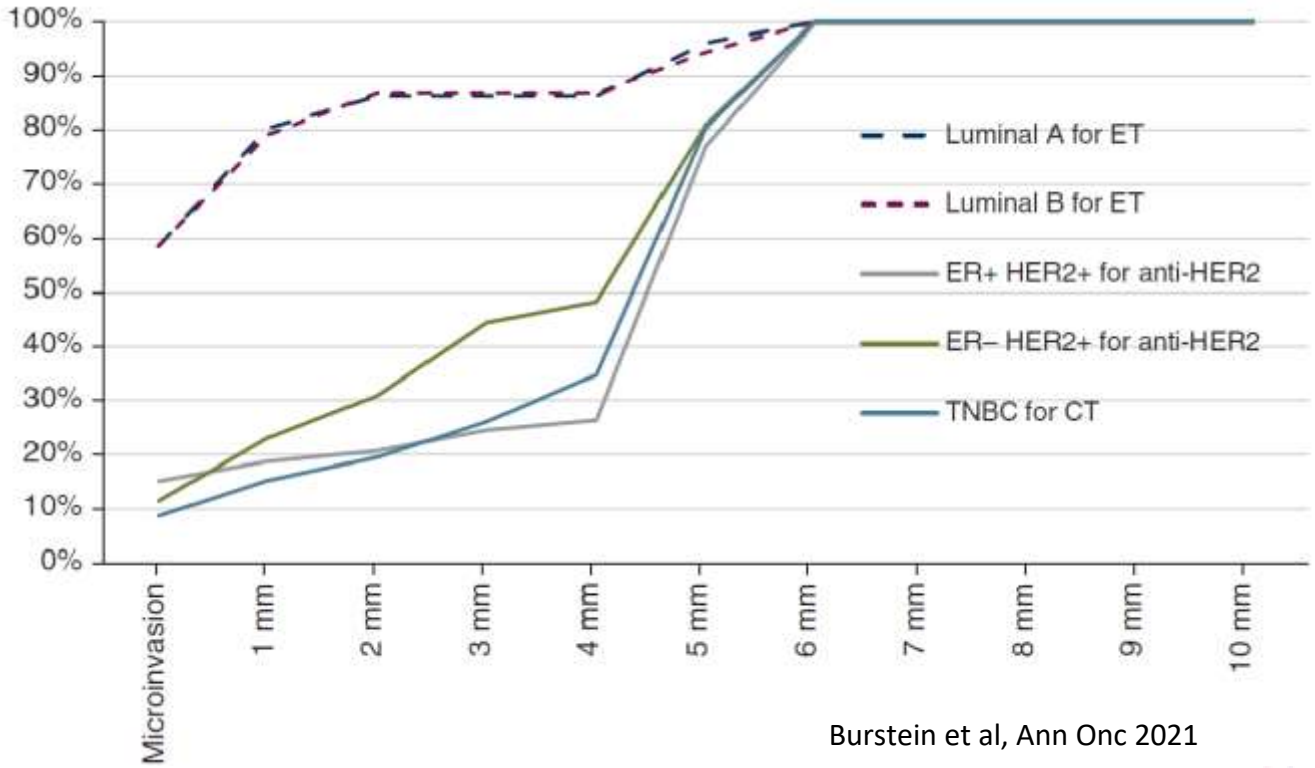
Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·56 (1·41–1·72)	1·57 (1·30–1·84)	1·30 (0·34–2·26)
Control	1·74 (1·58–1·91)	2·04 (1·74–2·35)	2·73 (1·30–4·16)
Rate ratio (95% CI)	0·86 (0·72–0·99)	0·76 (0·55–0·97)	0·52 (0·18–1·44)
from (O–E)/V	−27·1/174·9	−18·0/65·0	−2·4/3·6

BREAST CANCER TRIALS

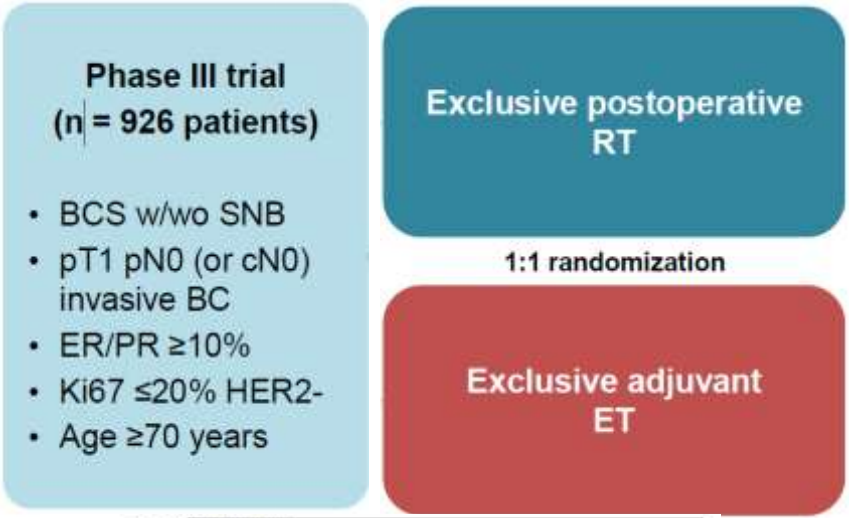
Who (not) to give adjuvant endocrine therapy?

Size criteria – St Gallen panel



Burstein et al, Ann Onc 2021

EUROPA Trial



RT: Hypofractionated WBI or PBI

ET: 5-10 years AI or tamoxifen

Interim analysis of a subset of the full cohort (N=207)

Co-primary endpoint with ipsilateral breast tumour recurrence – no local recurrences at 24m mFU

Better quality of life with radiotherapy alone vs ET alone

Limited follow-up for breast cancer outcomes

Meattini SABCS 2024

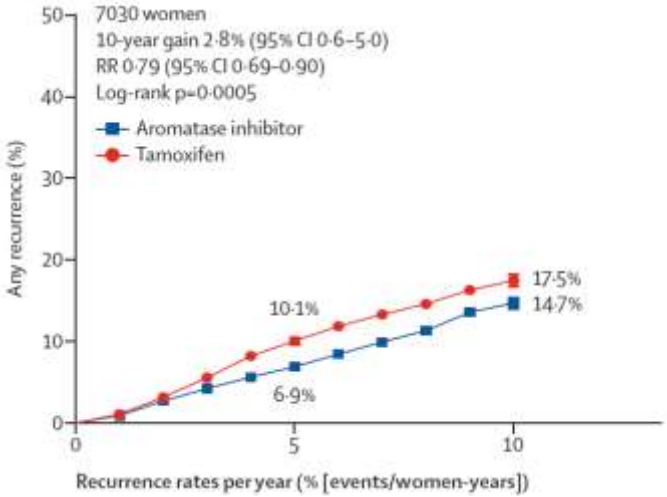
Endocrine therapy – premenopausal

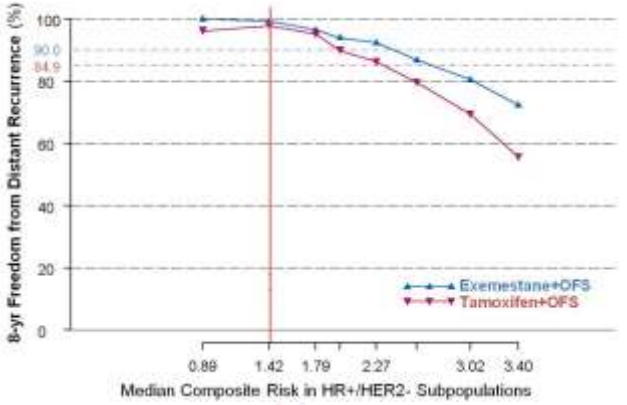
SOFT: Tamoxifen, or tamoxifen + OFS, or exemestane + OFS

TEXT: OFS + tamoxifen, or OFS + exemestane

Benefits of OFS depend on underlying recurrence risk:

- Chemotherapy candidates
- Node positive
- High grade and 2cm+ primary





EBCTCG Lancet Oncology 2022; Regan ASCO 2018

BREAST CANCER TRIALS

Endocrine therapy - postmenopausal

Years 0-5 (start during/after RT)

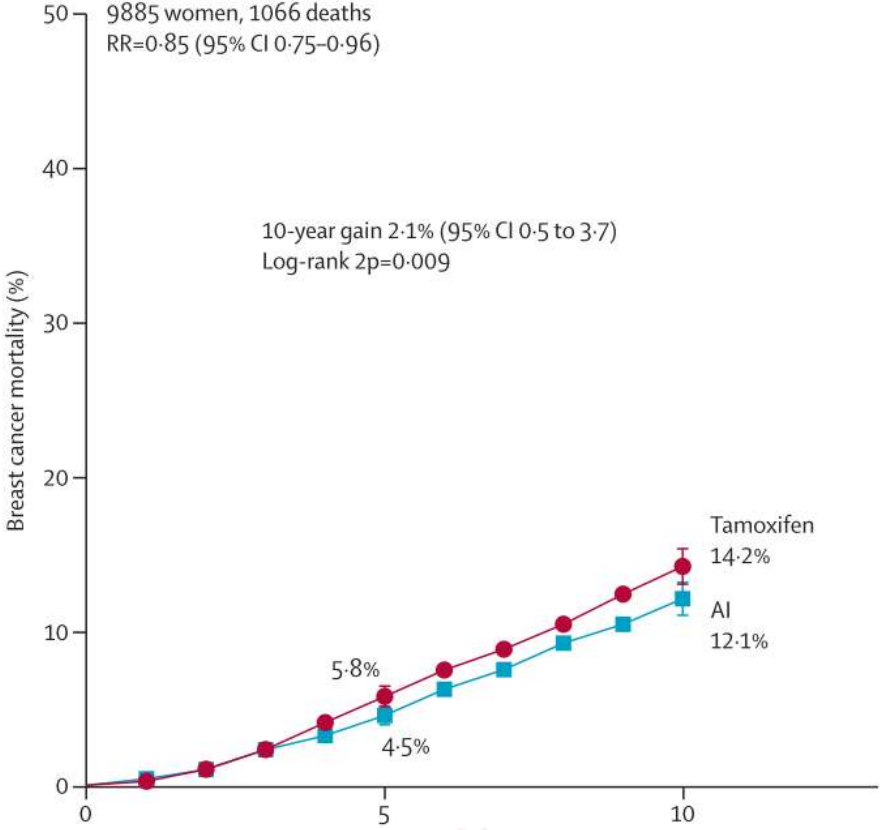
Reduced breast cancer mortality and all-cause mortality with AI over tamoxifen

Sequential tamoxifen-AI has similar benefits over tamoxifen alone

Difference is small

Treatment decision often made based on toxicity (constant rate):

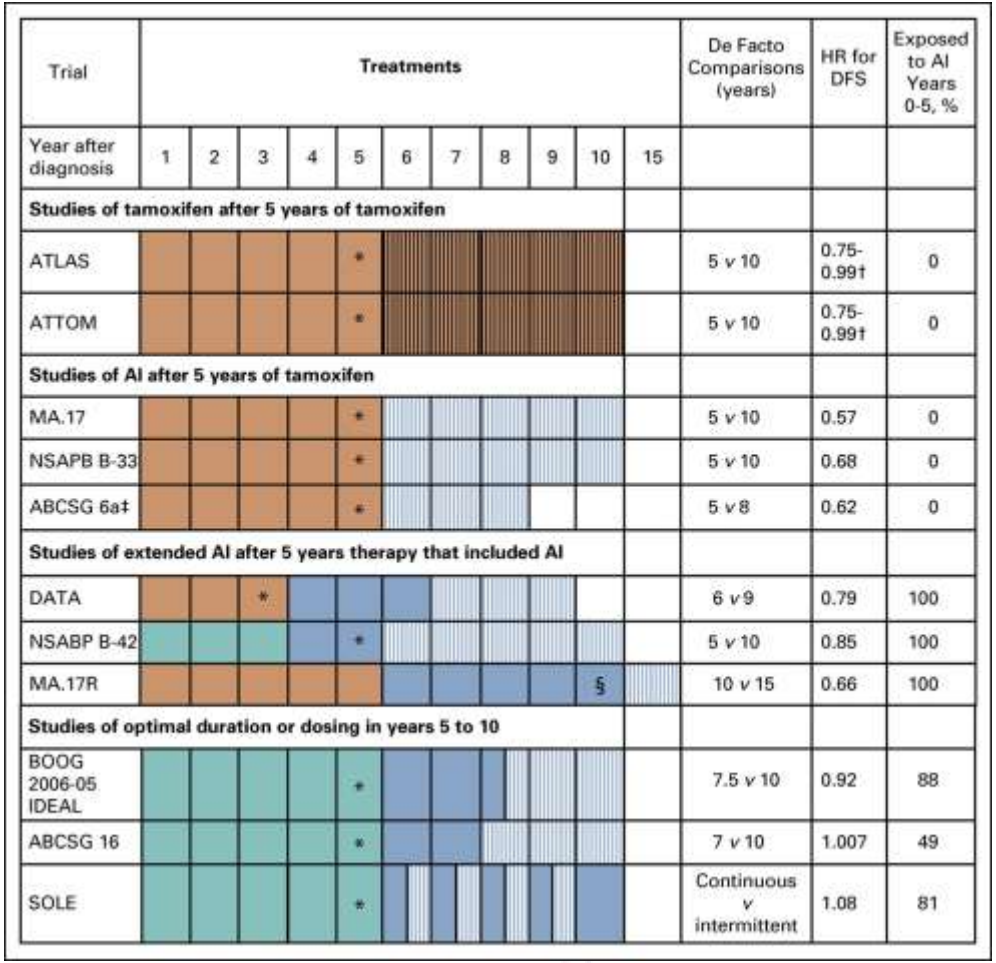
- AI: Fractures, arthralgia
- Tamoxifen: VTE, endometrial cancer



BREAST CANCER TRIALS

Duration of endocrine therapy

- Greatest benefit in first 5 years
- Tamoxifen: 10>5 years
  - N+ or ≥T2
- AI: 7-10 years in N+
- AI after 5 years: SOLE
  - 9 on, 3 off same as 12 on
- Indefinite therapy?
- Patients will often have a view on duration (toxicity and FOCR)



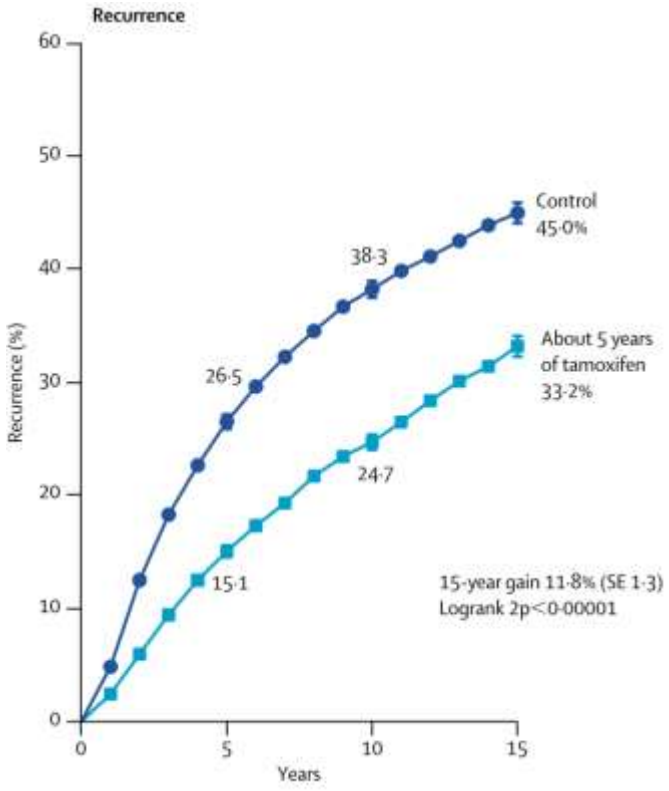
Carry-over effect after completion of endocrine therapy

Long term benefits of 5 years of endocrine therapy

Includes new primary breast cancers

- These are typically found at a very early stage
- Minimal mortality risk if found on annual follow-up imaging
- Prevention remains worthwhile

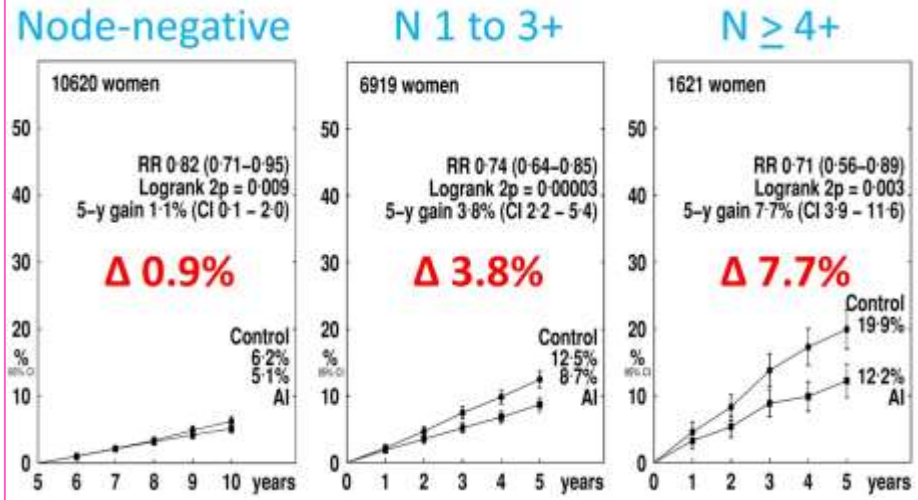
Toxicity resolves soon after ET cessation



BREAST CANCER TRIALS

Benefit of extended ET increases with higher nodal burden

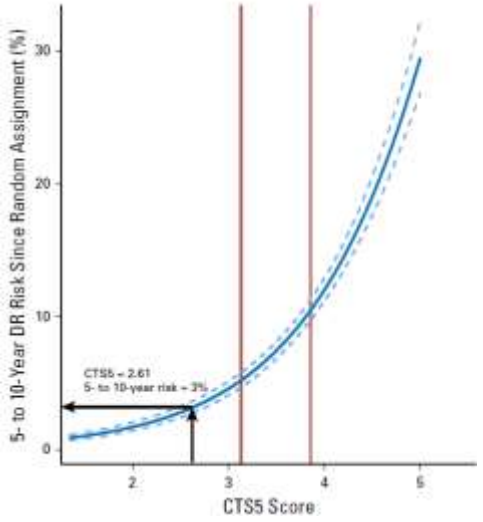
Meta-analysis of extended endocrine therapy trials



Gray SABCS 2018; Dowsett JCO 2018

CTS-5 score: online calculator for distant recurrence years 5-10

Age, tumour size, nodes, grade



BREAST CANCER TRIALS

Adjuvant abemaciclib: MonarchE

High risk early breast cancer: 4+ nodes, or 1-3 nodes and G3 or 5+cm

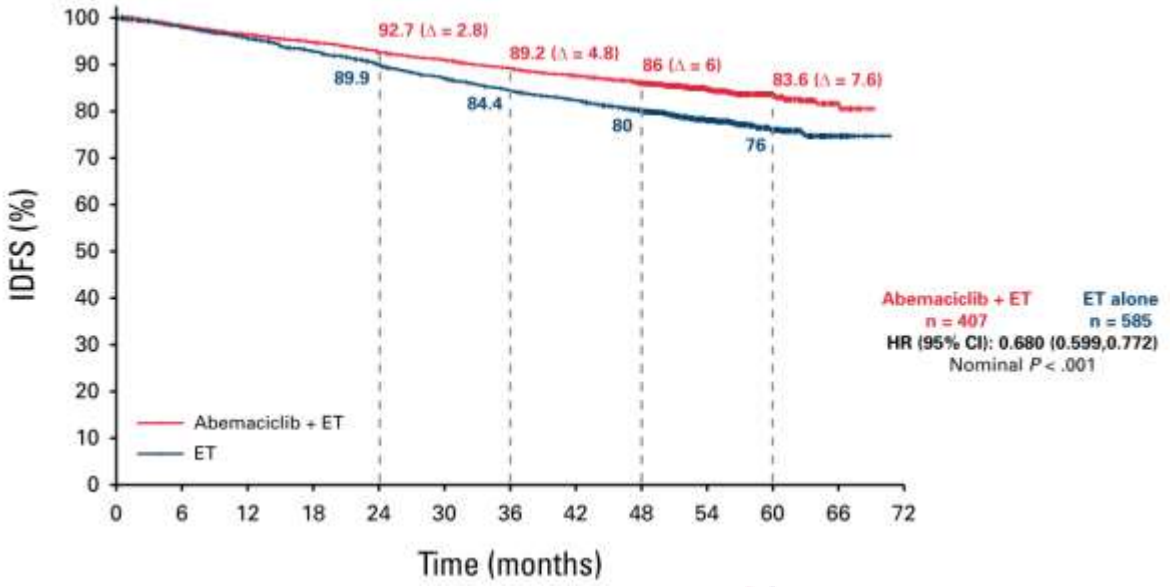
2 years of abemaciclib 150mg bd with AI or tamoxifen -> ongoing ET 5+ years

IDFS benefit 7.6% at 5 years

No overall survival difference
(data immature)

Stable across subgroups

Ki67 prognostic,
not predictive



Rastogi JCO 2024

Adjuvant ribociclib: NATALEE

Intermediate to high risk: Stage IIA-III within 12 months of starting ET

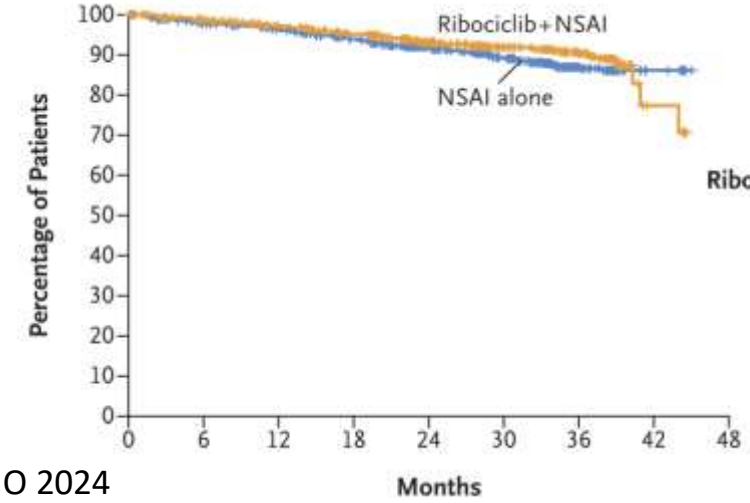
Ribociclib 400mg daily, 3 weeks on, 1 week off for 3 years, with NSAI for 5+ years

IDFS benefit at 27.7m Δ3.3% (90.4 vs 87.1%)

Update: 4-year f/u IDFS Δ4.9% (88.5% vs 83.6%), similar across node + vs -

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 or
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]



	No. of Patients with Event/ Total No. (%)	3-Yr Invasive Disease–free Survival
		percent
Ribociclib+NSAI	189/2549 (7.4)	90.4
NSAI alone	237/2552 (9.3)	87.1

Hazard ratio for invasive disease, recurrence, or death, 0.75 (95% CI, 0.62–0.91)
Two-sided P=0.003

Median follow-up for invasive disease–free survival, 27.7 mo

Slamon NEJM 2024; Fasching ESMO 2024

Comparison of eligibility: NATALEE vs MonarchE

N0 not allowed in monarchE

AJCC Anatomical Staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IIA	T0N1	✓	Only if grade 3 or Ki-67 ≥20%
	T1N1	✓	Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if G3 or G2 with Ki-67 ≥20% or high genomic risk[a]	✗
Stage IIB	T2N1	✓	Only if grade 3 or Ki-67 ≥20%
	T3N0	✓	✗
Stage IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	✓	✗
	T4N1	✓	Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2	✓	✓
Stage IIIC	Any TN3	✓	✓

In monarchE, relatively few patients with stage II were allowed:
- N1 allowed only if grade 3 or Ki-67 ≥20%

In monarchE, within stage III,
- N0 not allowed (in IIIB)
- N1 (whether in IIIA or IIIB) allowed only if tumor size ≥5 cm, grade 3, or Ki-67 ≥20%

Comparison of toxicity: NATALEE vs MonarchE

Abemaciclib:

- Diarrhoea/abdominal pain – tends to improve with dose reduction
- VTE and pneumonitis - uncommon
- Less cytopenias

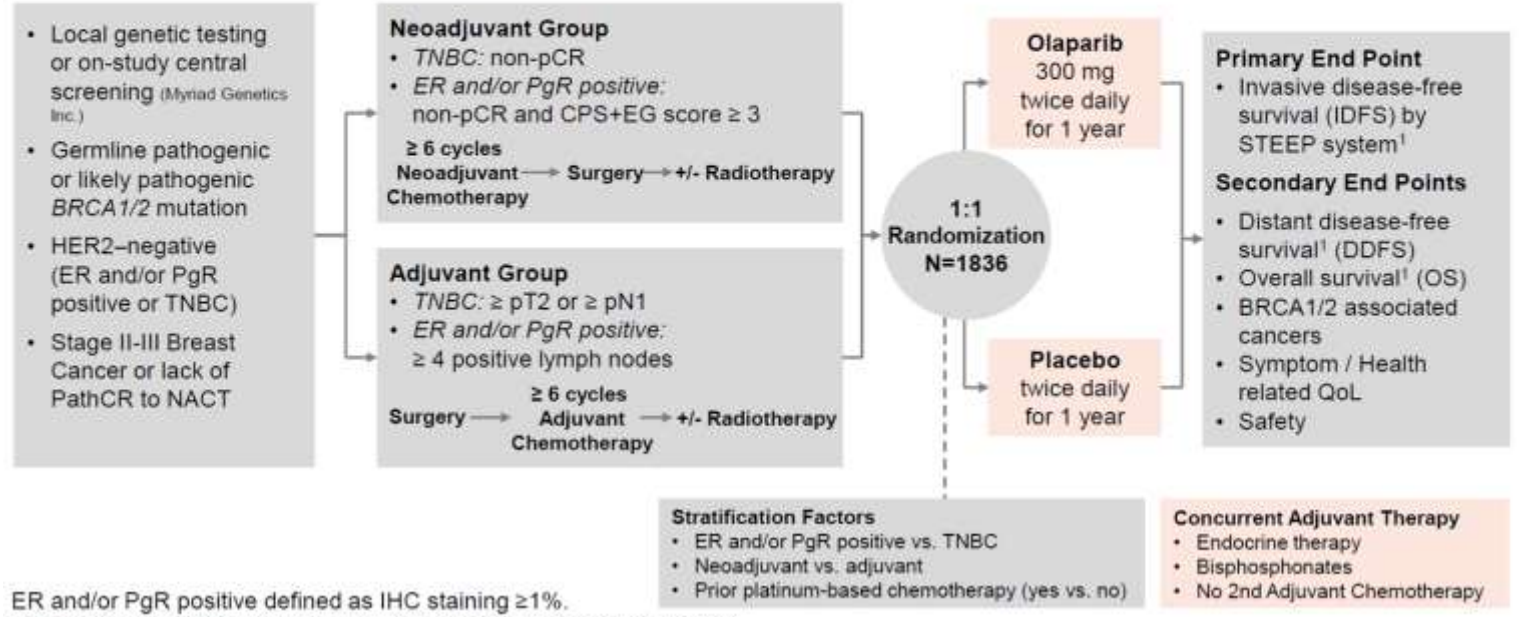
Ribociclib:

- Cytopenia – neutropenia, reversible, not associated with severe infection
- QTc prolongation (avoid tamoxifen)
- Transaminitis

Efficacy appears to be maintained even with dose reduction

Germline BRCA1/2 mutation

OlympiA: Trial schema



ER and/or PgR positive defined as IHC staining ≥1%.
Triple Negative defined as ER and PgR negative (IHC staining < 1%)

Garber SABCS 2024

OLYMPIA: ER positive population (N=325, 18%)

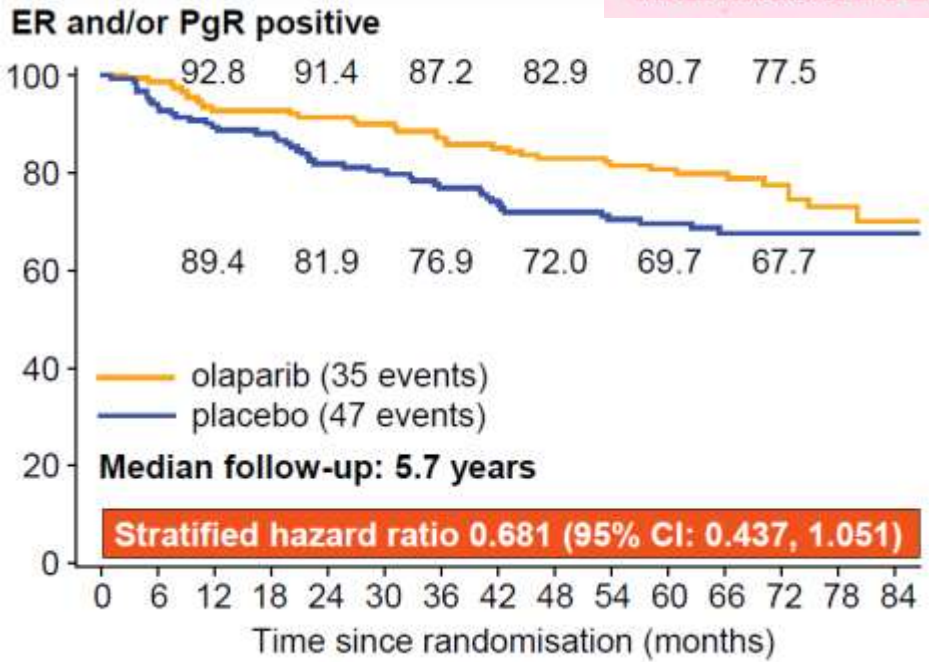
IDFS/OS benefit at 6 years follow-up in ITT and ER+

ITT: 4.4% difference in OS

9.4% difference IDFS

Low toxicity, no excess MDS/AML or pneumonitis

Lower second primary malignancy rate



Garber SABCS 2024

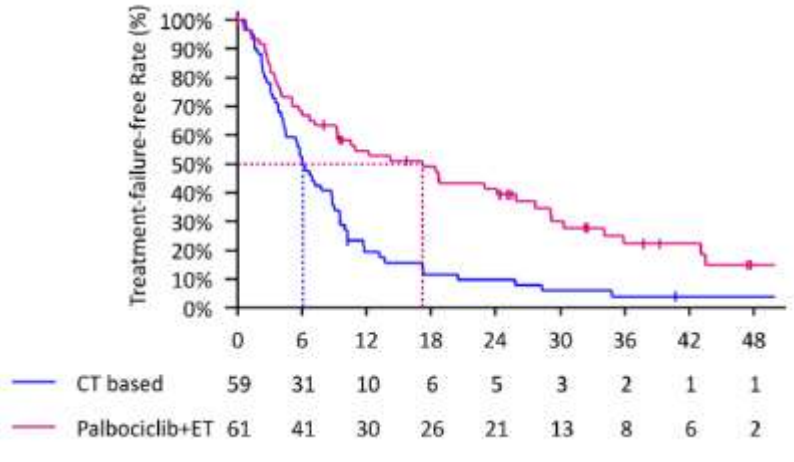
Future directions and guidance for early stage disease

- Neoadjuvant chemotherapy +/- immunotherapy for appropriately selected patients

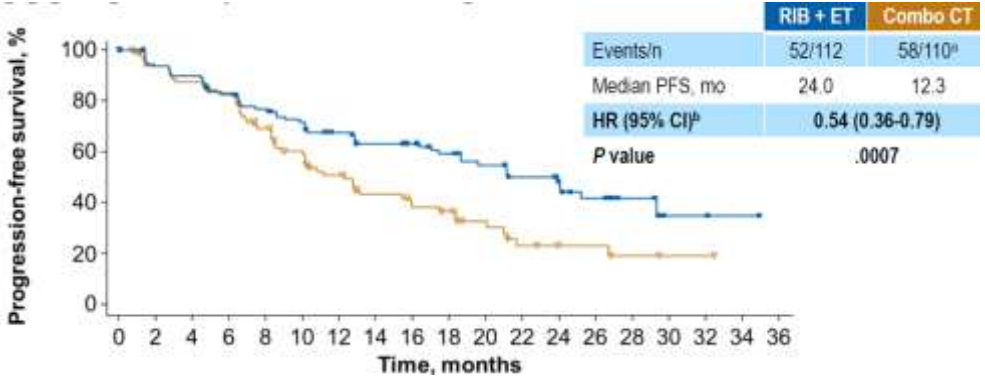
  Grade 3, mammaprint high 2, ER-low (1-10%)
- Neoadjuvant endocrine therapy to determine sensitivity (? Avoid chemo)
- Less chemotherapy (OPTIMA trial)
- Adaptive treatment (genomic and/or imaging guided)
- Less endocrine therapy for those at very low risk of recurrence

Metastatic hormone receptor positive breast cancer

First line treatment choices: Chemo vs ET + CDKi



	Palbociclib + ET	CT
TTF events, N (%)	45 (73.8)	55 (93.2)
Median TTF months	17.2	6.1
HR 0.46: 95% CI (0.31-0.69), p<0.001 (log-rank)		



- ET + CDK 4/6i is the standard first line treatment for ER+ MBC
- Benefit across subgroups: age, visceral disease, disease-free interval, de novo vs recurrent

Loibl SABCS 2024; Lu SABCS 2022

BREAST CANCER TRIALS

First line treatment choices
Endocrine therapy +/- CDK 4/6i

Endocrine sensitive: AI (or tamoxifen)

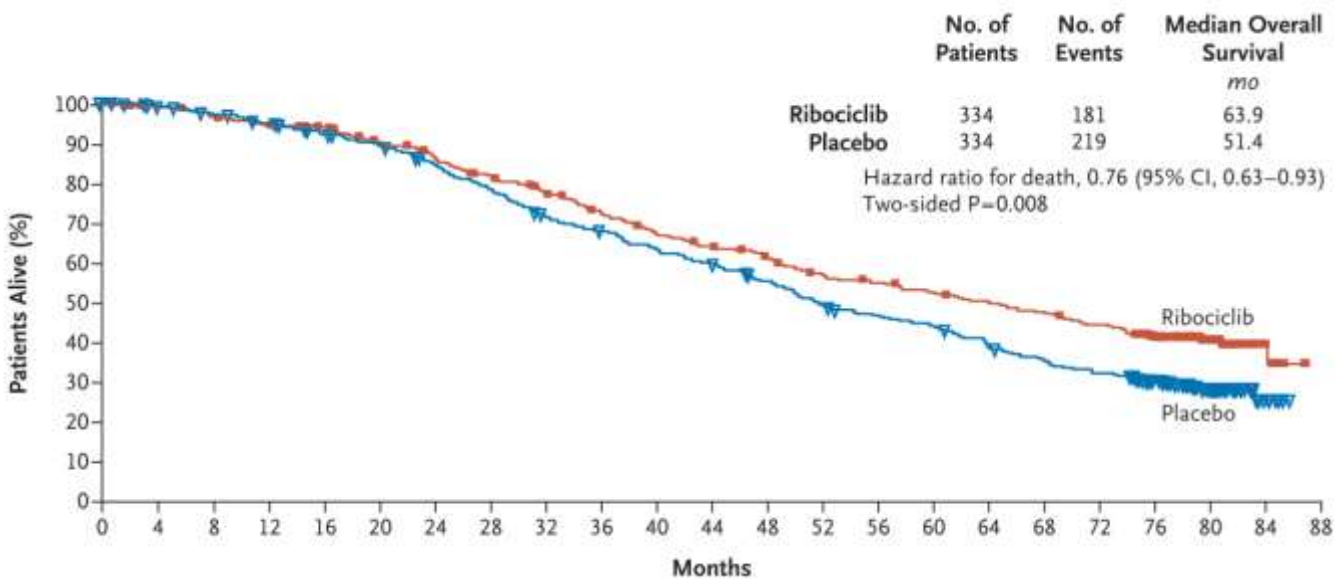
Endocrine resistant: consider SERD

MONALEESA-2

Letrozole +/-

Ribociclib

12.5m OS benefit



Hortobagyi NEJM 2022

First line abemaciclib with endocrine therapy MONARCH-3

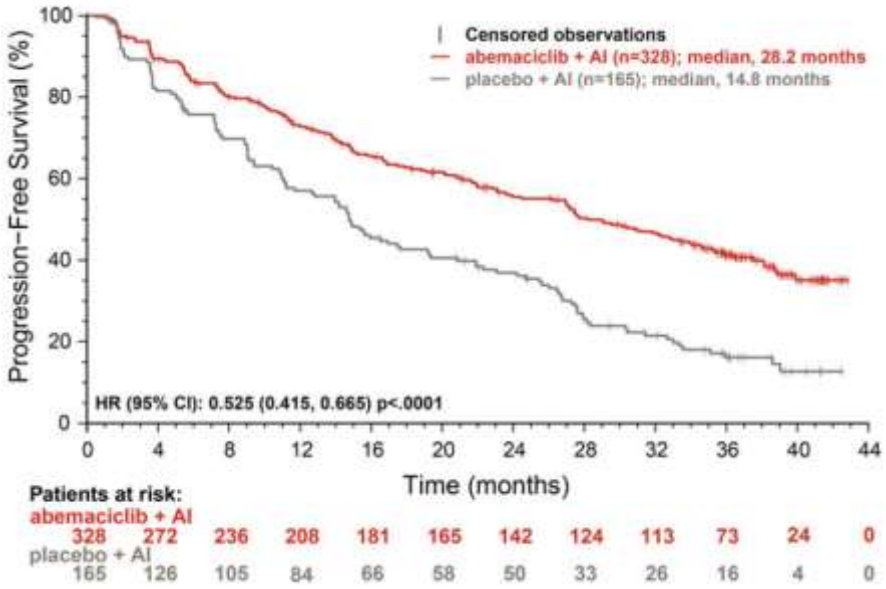
N=493

Median follow up 39 months

Ongoing PFS benefit ~Δ14 months

Consistent benefit, including high grade, liver metastases, TFI, PR negative

PFS2 37m vs 26m



Real world comparison of CDK4/6i

N=1850, Italy

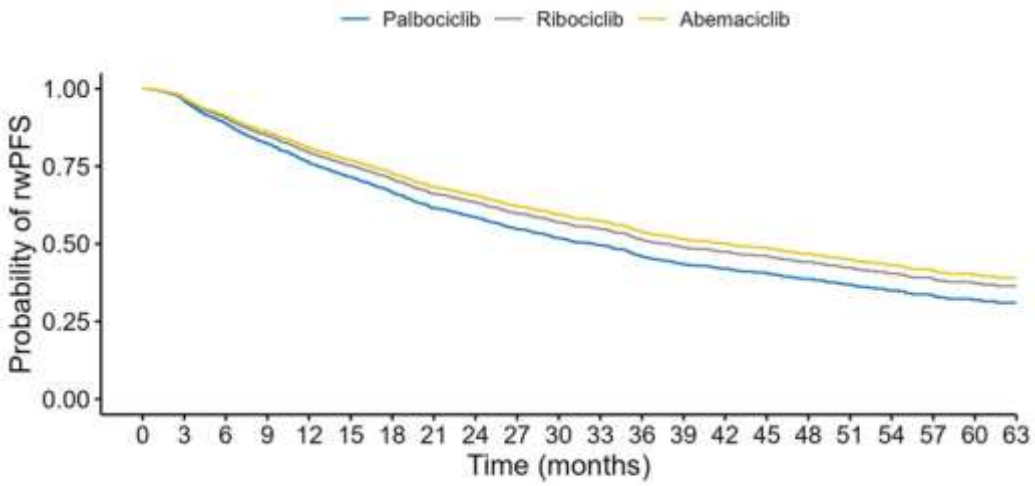
Abemaciclib and ribociclib better than palbociclib

No difference between ribociclib and abemaciclib

PFS 34.7m

OS 66.6m

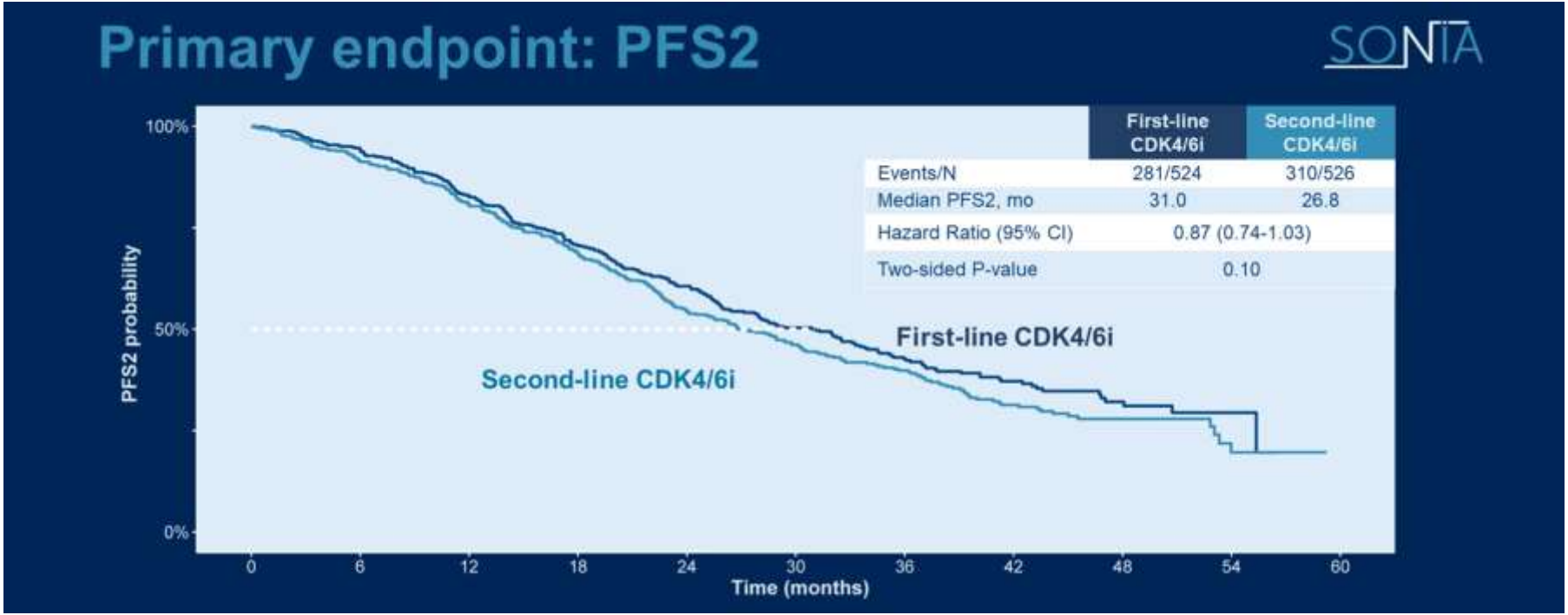
OS comparison immature



- **Abemaciclib vs. palbociclib: aHR 0.71 (95% CI: 0.56-0.90; p=0.005)**
- **Ribociclib vs. palbociclib: aHR 0.81 (95% CI: 0.65-0.99; p=0.048)**
- Abemaciclib vs. ribociclib: aHR 0.91 (95% CI: 0.70-1.19; p=0.505)

Vernieri ASCO 2024

SONIA: ET + CDK 4/6i in first or second line MBC
No difference in PFS2 or OS, much lower cost

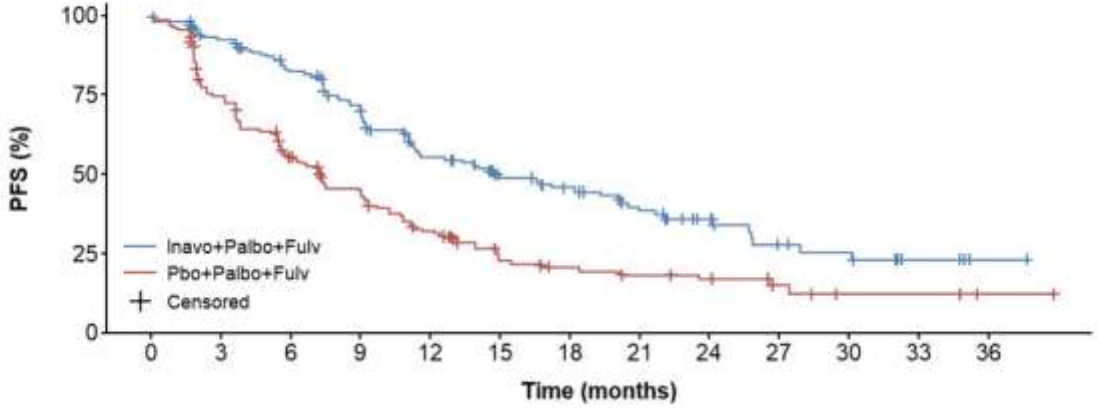


Sonke, ASCO 2023

Adding agents in first line (PIK3CA mutated)

INAVO120 primary analysis results

- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC who recurred on or within 12 months of adjuvant endocrine therapy
- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]



Juric, ASCO 2024

Beyond first line – Endocrine therapy

SOLAR-1: alpelisib and fulvestrant (PIK3CA mutation)

EMERALD: Elacestrant (ESR1 mutation)

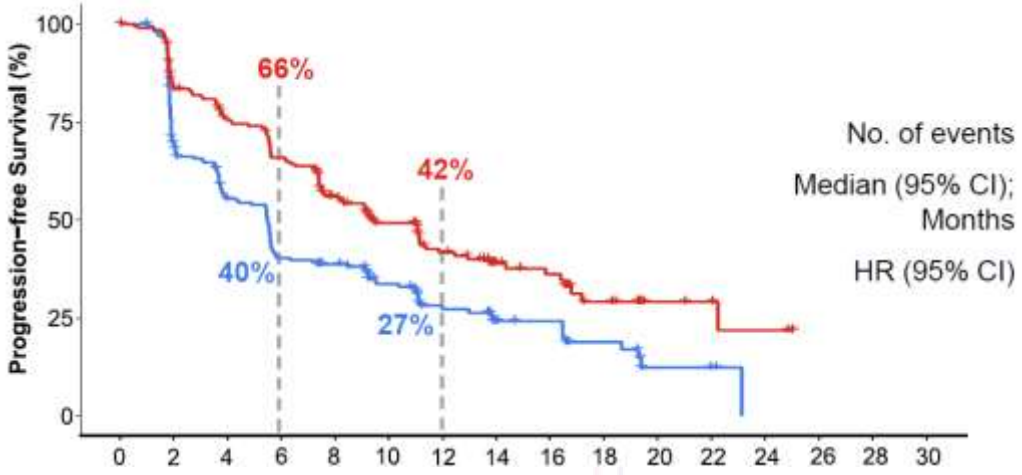
CAPITELLO-291: Ipatasertib and fulvestrant (AKT altered>overall pop.)

BOLERO-2: Exemestane and everolimus (all)

EMBER-3: Imlunestrant and abemaciclib > imlunestrant (all) despite prior CDKi

Imlunestrant > fulvestrant (ESR1m)

	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5-11.9)	**5.5** (3.8-5.6)
HR (95% CI)	**0.57 (0.44-0.73)** *p*-value <0.001	



Jhaveri, SABCS 2024

Beyond first line – Chemotherapy for ER+

Shared decision-making at this time can help guide treatment

Capecitabine, especially in lobular disease

Can consider 1500mg, 7 days on, 7 days off (X-7/7)

Eribulin 2l – active in ER+ vs TPC

TROPICS-O2: Sacituzumab govitecan, mOS 14 vs 11m (TPC)

Taxane, anthracycline, cyclophosphamide/methotrexate, carboplatin +/- gemcitabine, vinorelbine

Rugo SABCS 2022; Khan ASCO 2023; Pivot Ann Onc 2016

DESTINY Breast-04: HER2 low Metastatic endocrine refractory

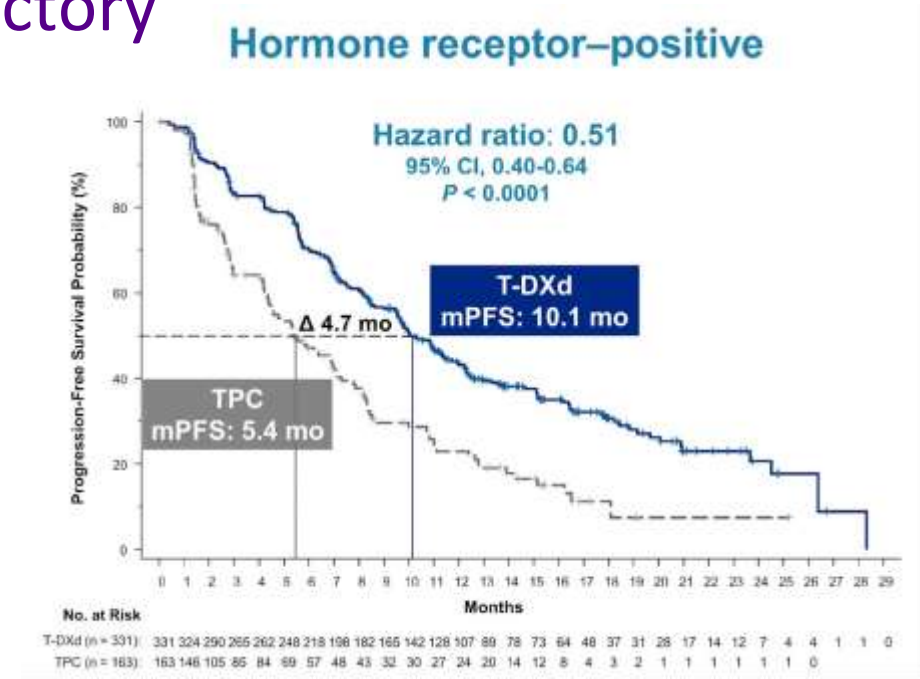
N=480 ER+ patients

Trastuzumab deruxtecan vs treatment of physician's choice

Eribulin 51%, Capecitabine 20%, Nab-paclitaxel 10%, gemcitabine 10%, Paclitaxel 8%

2/3 had 3 or more prior lines of Rx

Toxicity: Nausea, fatigue, alopecia, ILD



Modi, ASCO 2022

Summary – Metastatic ER+ breast cancer

Consider endocrine sensitivity

Endocrine therapy whilst sensitive

Second line

- ESR1m: elacestrant
- PI3K inhibitors, AKT inhibitors

Then sequential single agent chemotherapy

Surgery to breast primary only in select cases – progressive breast disease despite radiotherapy, for local control

Primary endocrine resistance is defined as relapse while on the first 2 years of adjuvant ET, or PD within the first 6 months of first-line ET for ABC, while on ET.

Secondary 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 ABC, while on ET.

BREAST CANCER TRIALS

5TH BBCC
BANGLADESH BREAST CANCER CONFERENCE 2025

Thank you

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