Endocrine options for ER+, Hi-risk EBC

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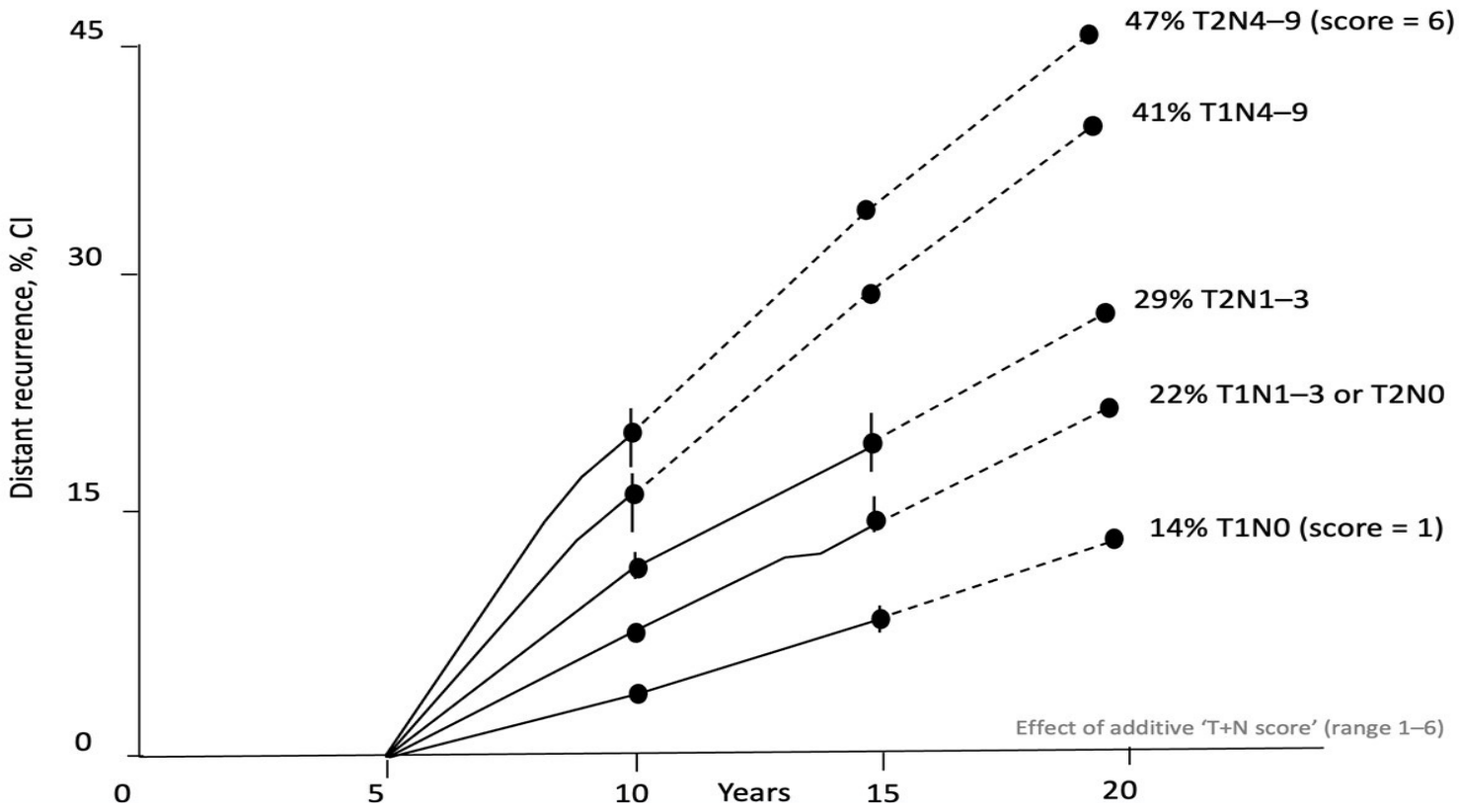
PRIMO 2024

EBCTCG main findings: Long-term risk

After 5 years' endocrine therapy, recurrences continue steadily to at least year 20

Absolute recurrence risk in years 5–20 is appreciable even for T1N0 disease



Pan H et al, N Engl J Med 2017; 377: 1836-46

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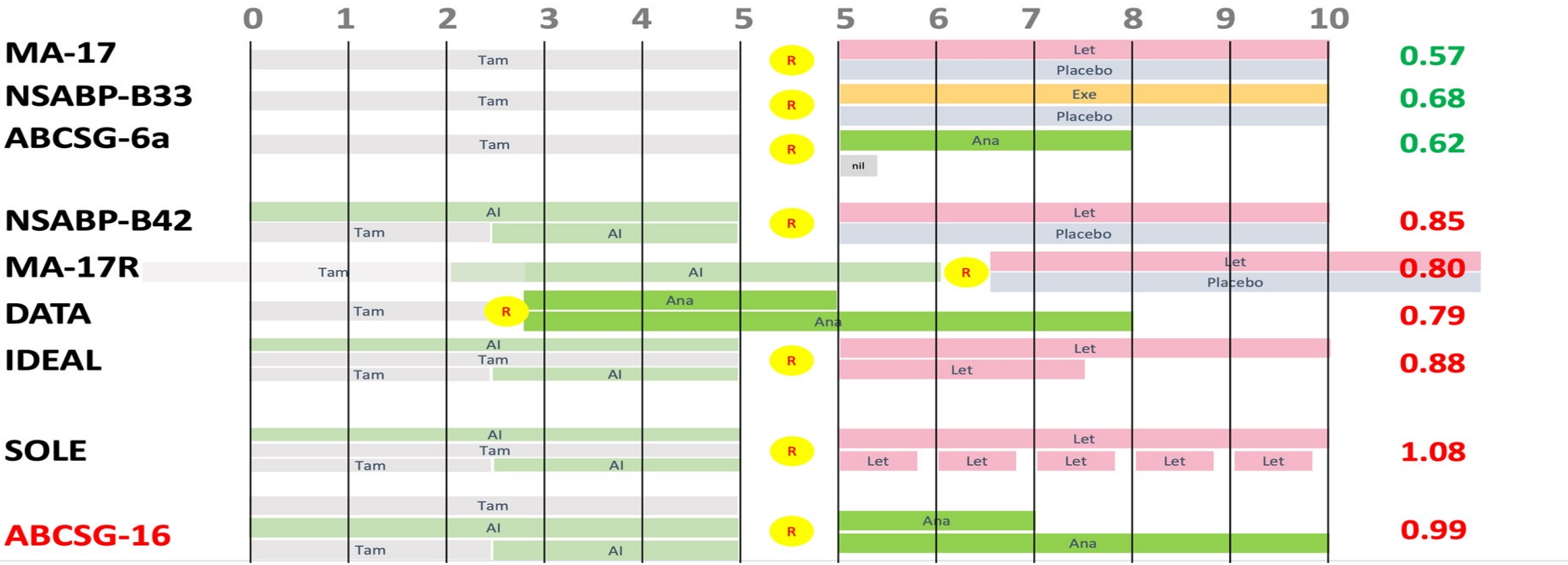
Extending Adjuvant AIs beyond 5 years



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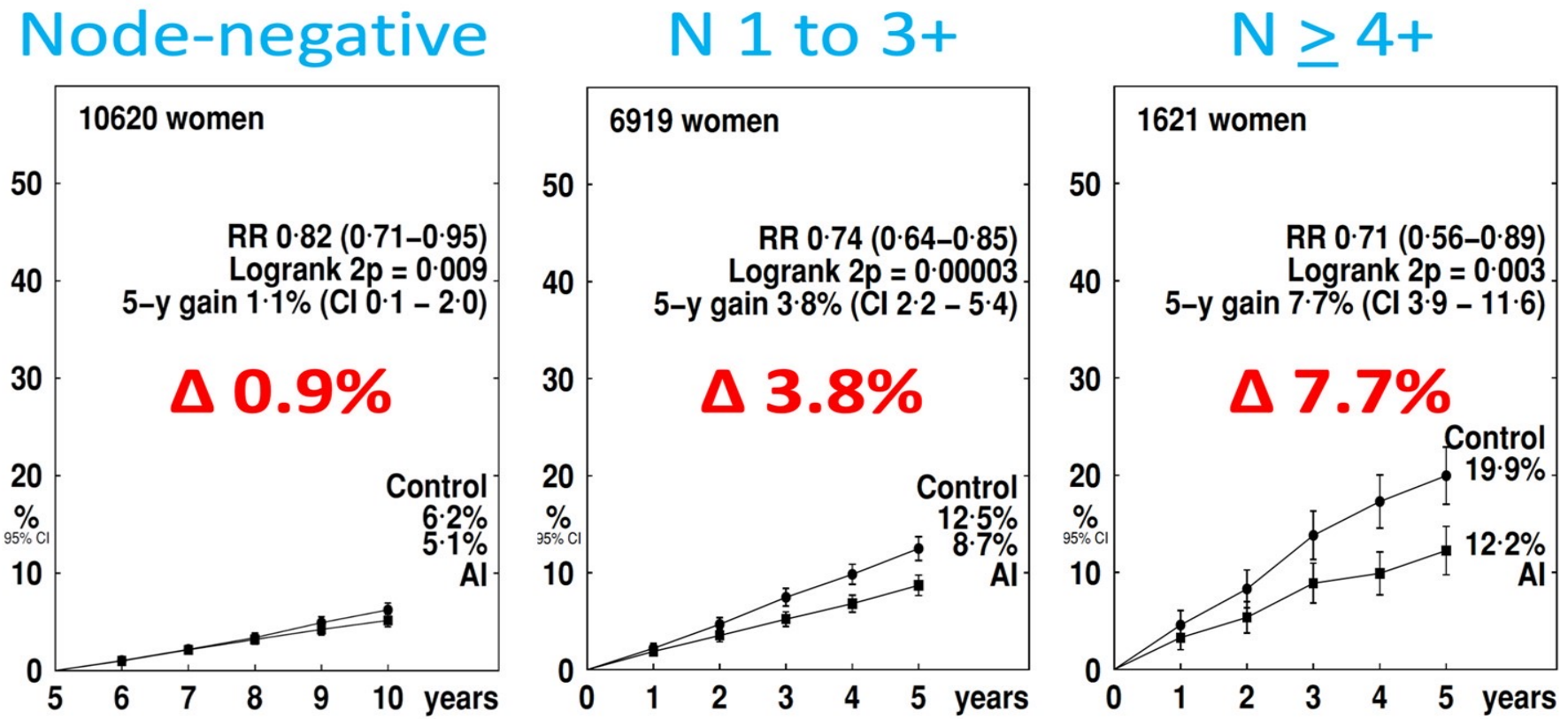
EBCTCG: Extended Therapy Benefit by N stage



Gray D, et al. SABCS 2018

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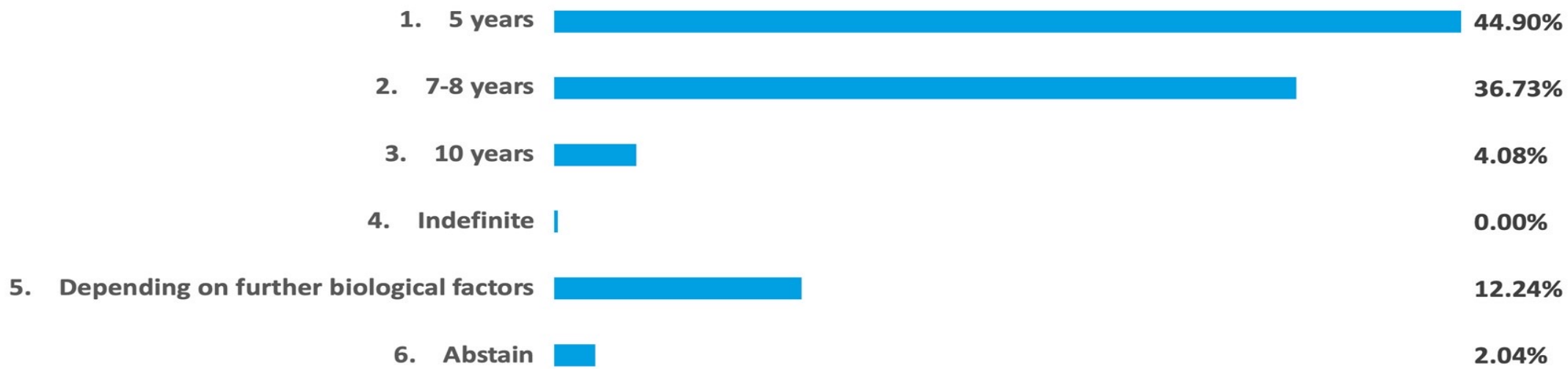
Topic: Adjuvant Endocrine Therapy

Consider a patient with ER positive, HER2 negative breast cancer. The appropriate duration of endocrine therapy for someone with stage 2, node-negative disease is:



Topic: Adjuvant Endocrine Therapy

Consider a patient with ER positive, HER2 negative breast cancer. The appropriate duration of endocrine therapy for someone with stage 2, node positive disease is:

Topic: Adjuvant Endocrine Therapy

Consider a patient with ER positive, HER2 negative breast cancer. The appropriate duration of endocrine therapy for someone with stage 3 disease is:

Adjuvant ovarian function suppression

- **OFS vs No OFS**
- **AI +OFS vs TAM + OFS**

Adjuvant CDK4/6 inhibitors

NCCN Guidelines

Menopause	ODX RS	Recommendations
Pos – M (N0-N1)	<26	ET
	≥26	ChemoET
Pre – M(N0)	<16	ET
	16-25	***Consider*** ChemoET Or OFS + ET
	≥26	ChemoET
Pre - M (N1)	<26	***Consider*** chemoET Or OFS + ET
	≥26	ChemoET

Unclear if chemotherapy benefit was due to the OFS effects promoted by chemotherapy

OFSET Study
designed to answer these questions

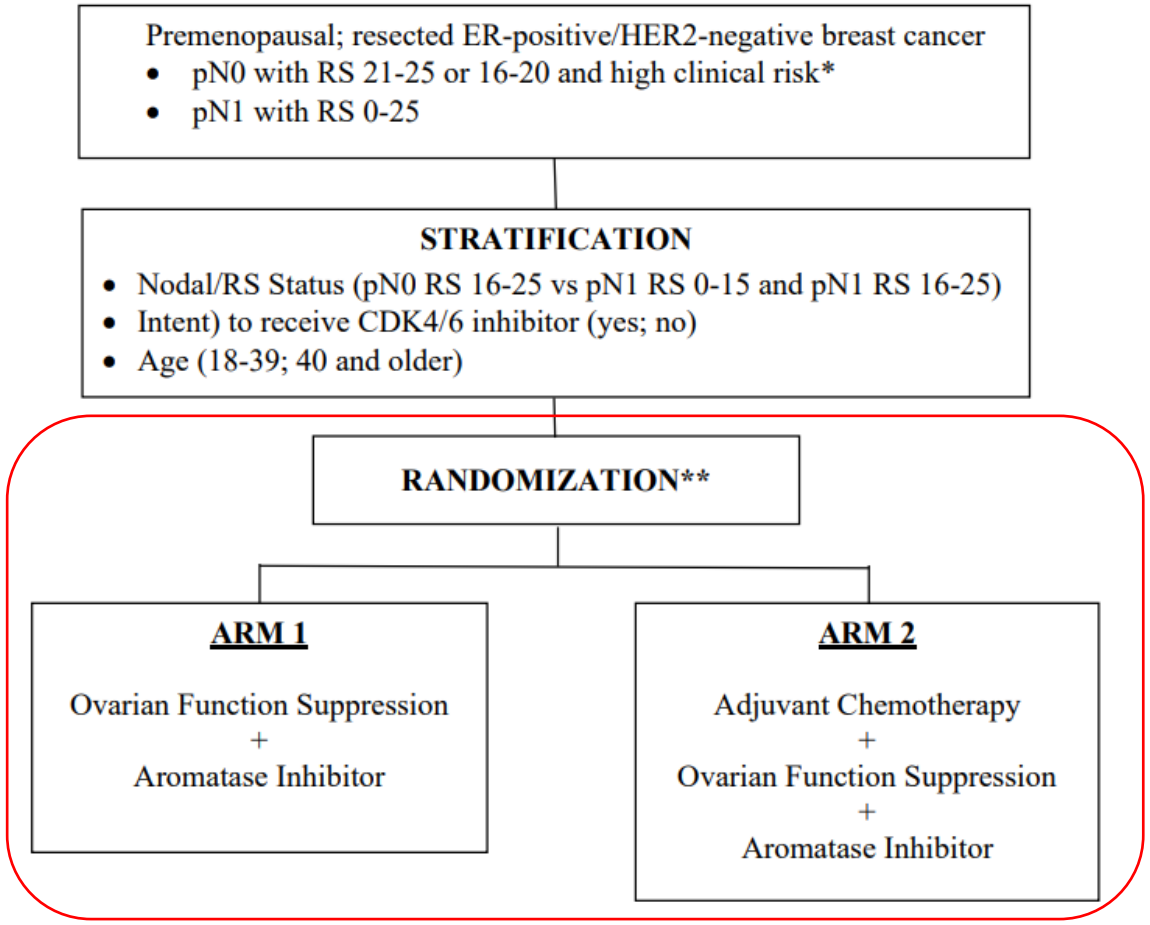
NCCN Guidelines® for Breast Cancer (Version 1.2024).

NRG-BR009 (OFSET)

- Pre-Menopausal
- pT1-T3, pN0-1
- ER+/HER2-
- RS≤25

It's Active

Figure 1. NRG-BR009 Schema



* **High clinical risk defined as:**
1) low histologic grade with primary tumor size > 3 cm, OR
2) intermediate histologic grade with primary tumor size > 2 cm, OR
3) high histologic grade with primary tumor size > 1 cm

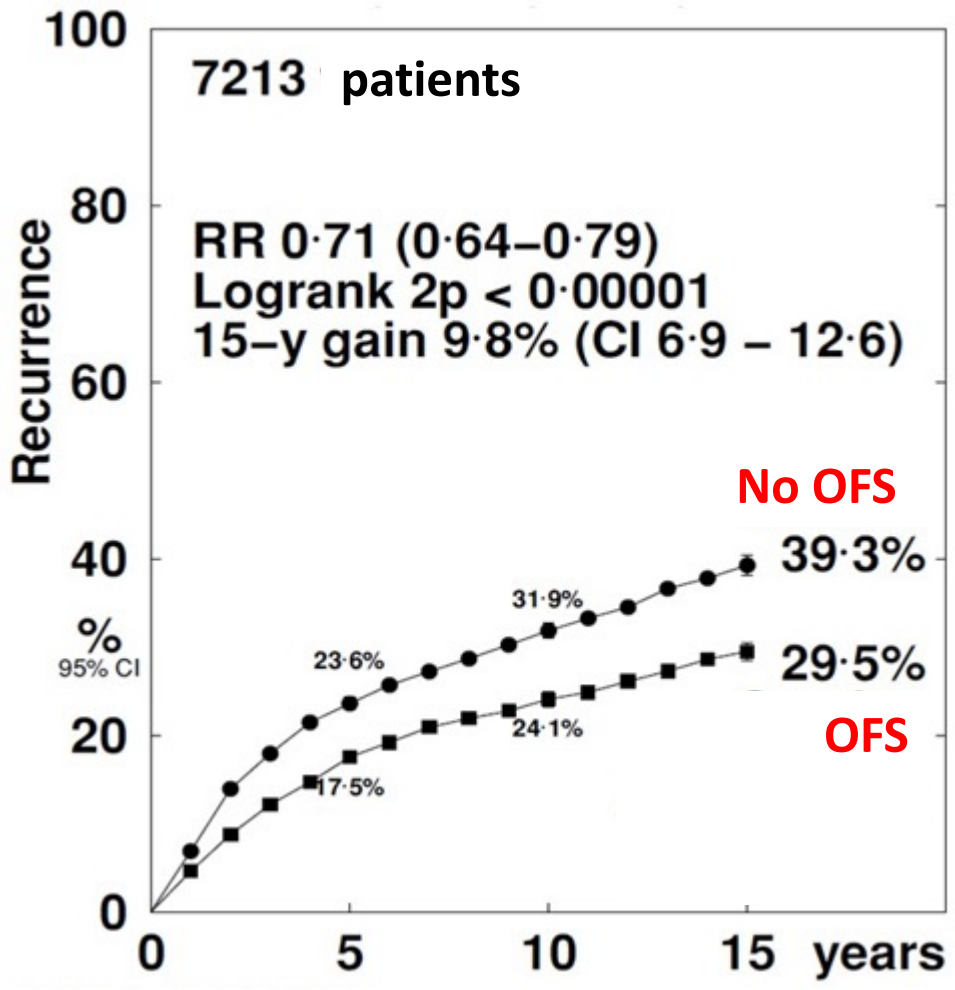
** Randomization is 1:1.

OFS
vs
No OFS

EBCTCG meta-analysis of 14,999 patients from 25 randomized trials: effects of ovarian ablation/suppression on breast cancer recurrence and survival

Recurrence Risk

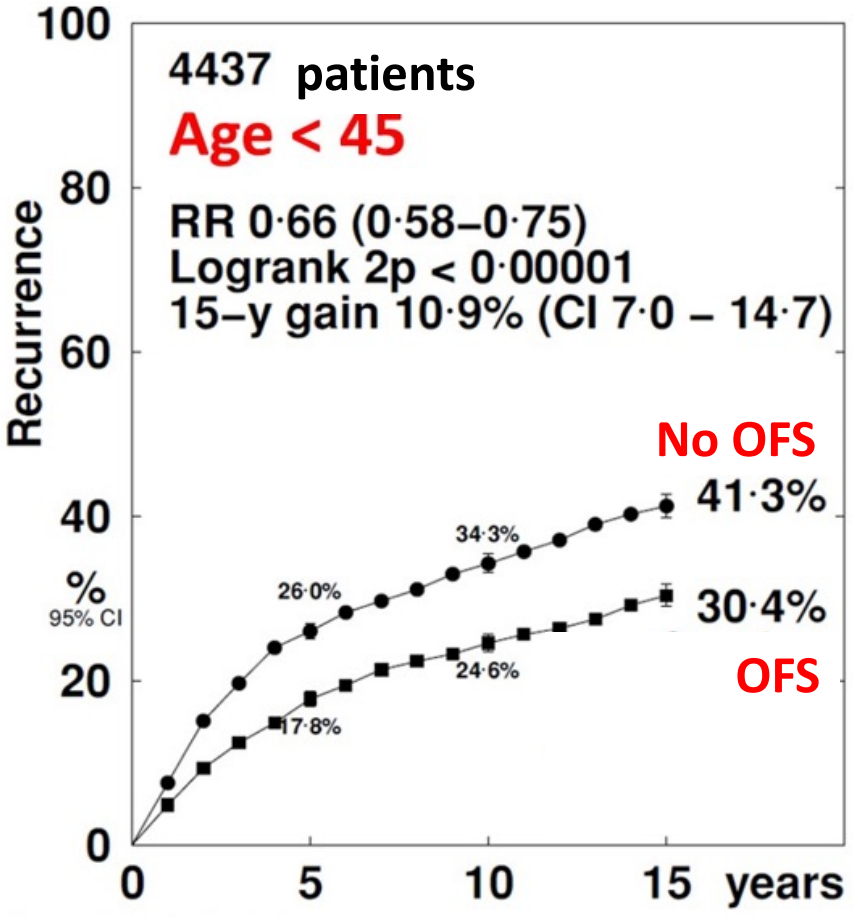
No chemotherapy or
Remained premenopausal
after chemotherapy



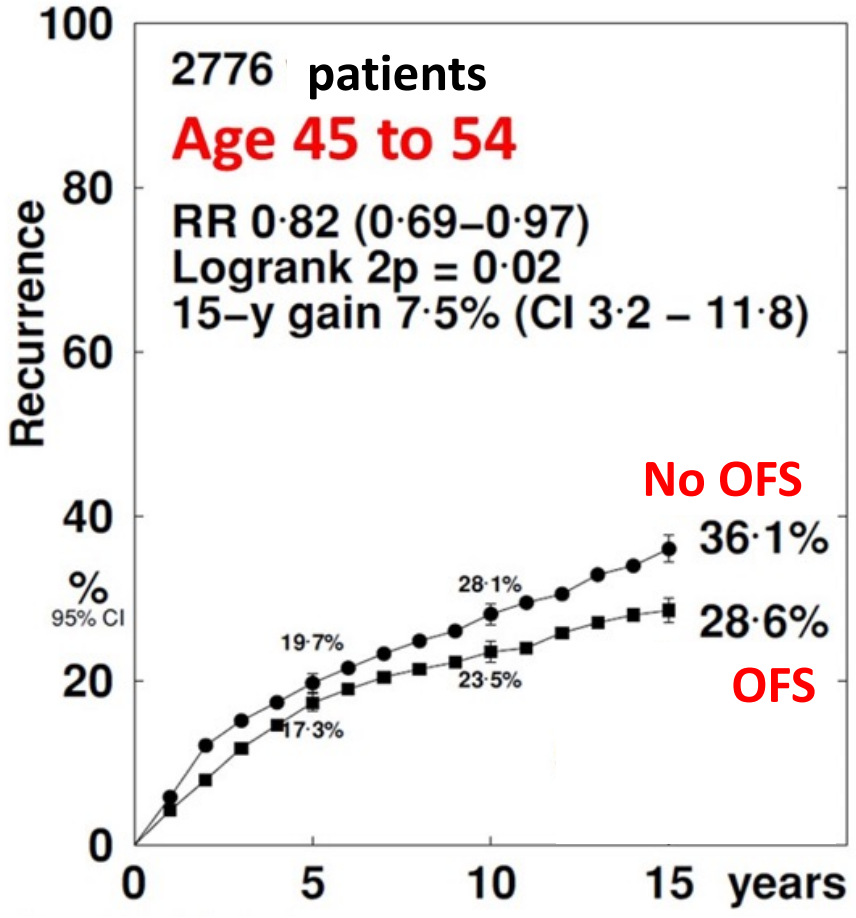
Abs Diff: ~10%

Richard Gray. ASCO 2023

Recurrence Risk per age
No chemotherapy or premenopausal <u>after</u> chemotherapy



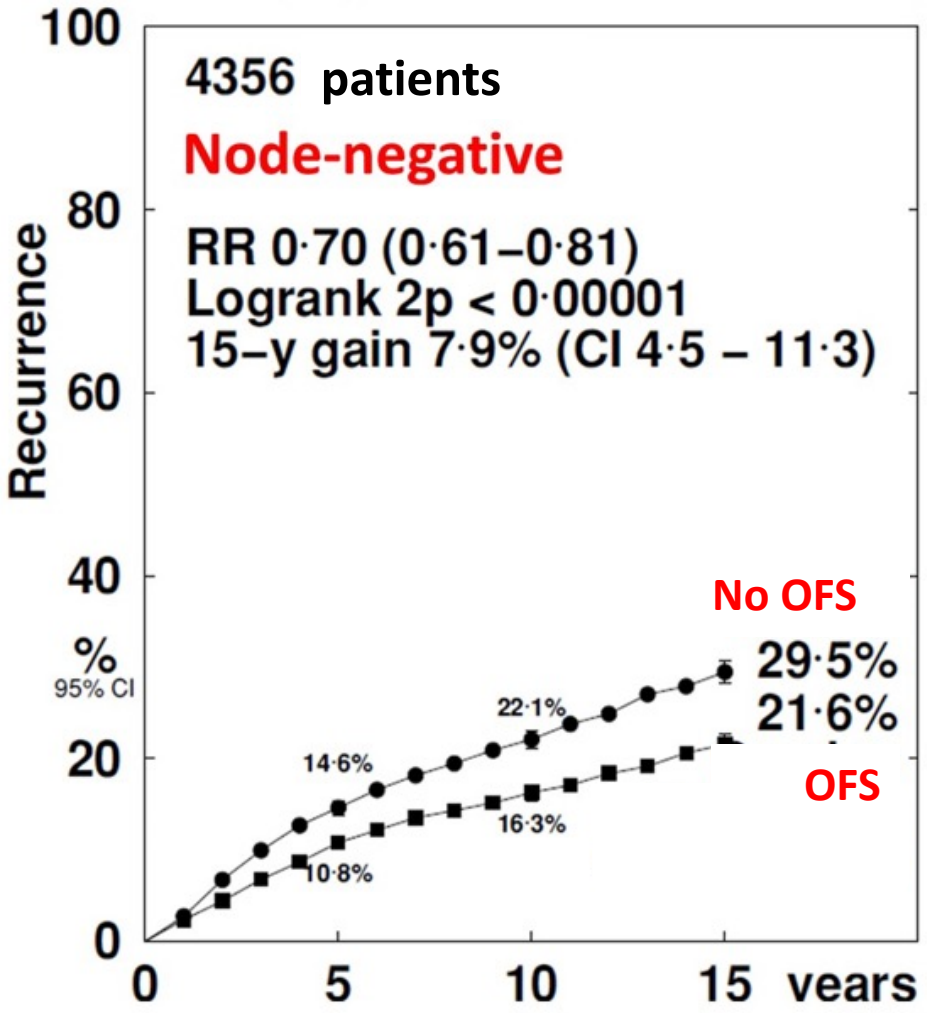
Abs Diff: ~11%



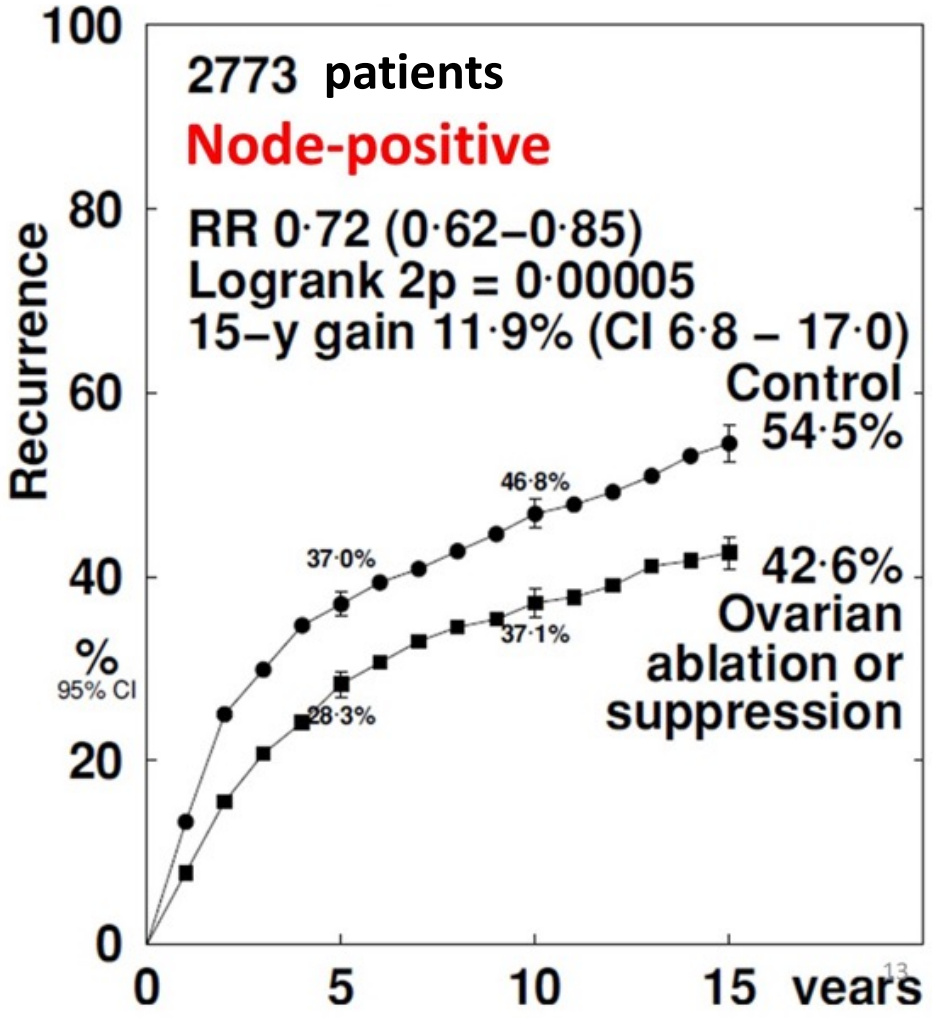
Abs Diff: 7.5%

Richard Gray. ASCO 2023

Recurrence Risk per Node Status
No chemotherapy or premenopausal <u>after</u> chemotherapy

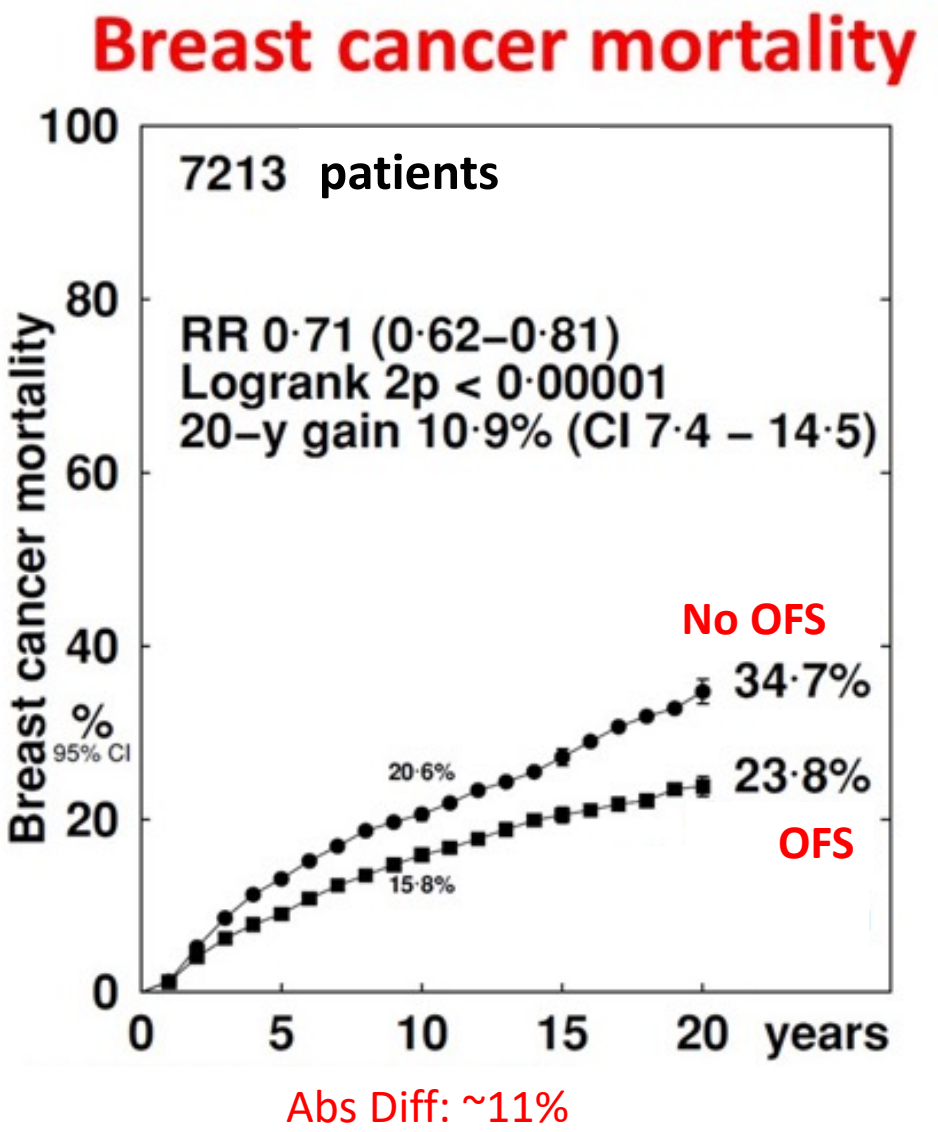


Abs Diff: ~8%



Abs Diff: 12%

Richard Gray. ASCO 2023



Abs Diff: ~11%

OFS

- Decrease recurrence risk
- Improves OS
- Benefit regardless LN status,
- More significant benefit if LN+, age < 45 years old

- *5 yrs OFS is not easy.*
- *Adherence can be challenge*

Richard Gray. ASCO 2023

AI +OFS

VS

TAM + OFS

Four Clinical Trials:

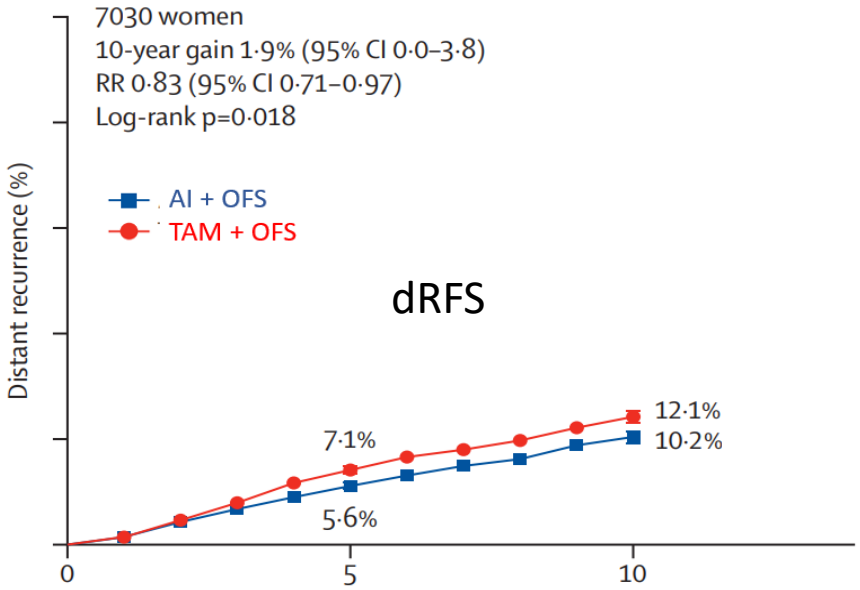
ABCSG:
NEJM 2009
Ann Oncol 2015

TEXT:
NEJM 2014
NEJM 2018

SOFT:
NEJM. 2014
NEJM 2018

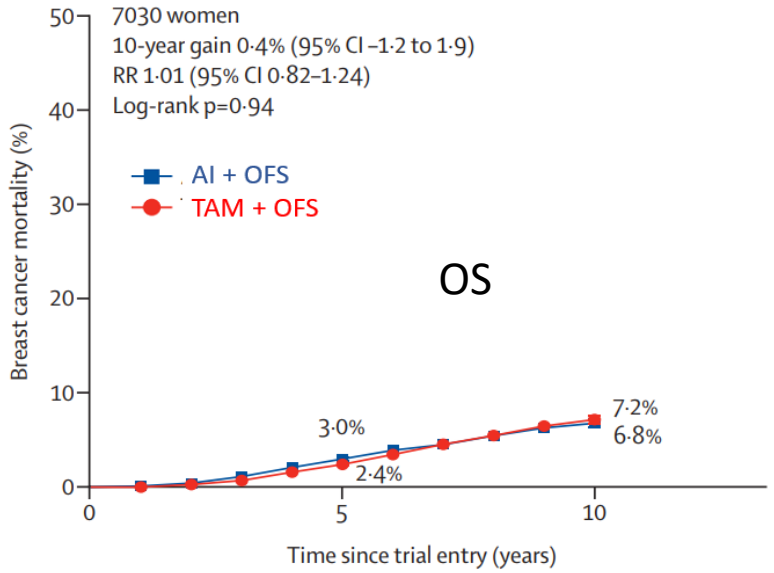
HOBOE
Eur J Cancer. 2019

EBCTCG meta-analysis of 7030 patients from four randomized trials: AI + OFS versus TAM + OFS in premenopausal patients with ER+ early-stage breast cancer



Distant recurrence rates per year (% [events/women-years]) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
1·16 (190/16 386)	1·01 (93/9222)	0·60 (3/502)
1·44 (233/16 169)	1·08 (97/9016)	0·00 (0/490)
0·78 (0·65–0·95)	0·91 (0·68–1·22)	7·86 (0·72–85·91)
–24·8/101·8	–4·3/45·8	1·4/0·7



Death rates from breast cancer per year (% [95% CI]) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
0·60 (0·48–0·72)	0·85 (0·66–1·03)	0·76 (0·02–1·51)
0·47 (0·37–0·57)	1·03 (0·82–1·23)	0·57 (0·08–1·22)
1·25 (0·93–1·68)	0·80 (0·60–1·08)	1·45 (0·33–6·44)
9·7/43·4	–9·6/43·5	0·6/1·7

AI+OFS vs TAM+ OFS: improves dRFS (mainly during the year 0-4) but not OS

Early Breast Cancer Trialists' Collaborative Group; Lancet Oncol. 2022

PRINCIPLES OF ADJUVANT ENDOCRINE THERAPY
(for pT1-3pN+M0)

General Principles

- Hormone receptor-positive (HR+) tumors: Breast tumors may be positive for estrogen receptors (ER+), progesterone receptors (PR+) or both (ER+/PR+). See Principles of Biomarker Testing (BINV-A).
  - ER+ tumors: ER testing should be used to determine if a patient is a candidate for endocrine therapies.[a] Patients with cancers with 1%–100% ER IHC staining are considered ER+ and eligible for endocrine therapies, there are limited efficacy data on the subgroup of cancers with ER-low-positive (1%–10%) results. The ER-low-positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making.
  - PR+ tumors: Patients with ER-negative, PR+ cancers may be considered for endocrine therapies, but the data on this group are noted to be limited. The same overall interpretation principles apply but PR should be interpreted as either positive (if 1%–100% of cells have nuclear staining) or negative (if <1% or 0% of cells have nuclear staining).
- Considering that majority of all HR+ breast cancers are ER+ or ER+/PR+ and ER-negative/PR+ tumors are relatively uncommon, ER and/or PR+ tumors are referred to as HR+ throughout the guidelines.
- The magnitude of risk reduction from adjuvant endocrine therapy is dependent on:
  - Level of ER expression: Low ER+ expression is less likely to benefit from endocrine therapy.
  - Recurrence score (RS) on gene expression assay test results: Patients with high RS will gain relatively less benefit from adjuvant endocrine alone compared to those with low RS.

Candidates for ovarian suppression + endocrine therapy

- Premenopausal
- Endocrine sensitive tumors with high enough recurrence risk where the additional absolute decrease in recurrence compared with tamoxifen alone is worth the additional toxicity (young age, high-grade tumor, lymph node involvement).[b]

Ovarian function assessment

- Menopausal status cannot be determined while receiving OFS.[a]
- Monitor estradiol and follicle-stimulating hormone (FSH)/LH levels:
  - If under 60 y and amenorrheic for ≤12 months prior to treatment with adjuvant endocrine therapy
  - Amenorrheic after chemotherapy or after tamoxifen +/- ovarian function suppression (OFS).
  - After switching from tamoxifen to an AI, or if taken off OFS
  - Prior to next dose of GNRH agonist, particularly in women under the age of 45. Frequency of testing of estradiol and FSH/LH levels should be individualized.
- AI can stimulate ovarian function. If vaginal bleeding occurs while on AI, contact physician immediately.

Methods for OFS

- GNRH agonists
  - Goserelin 3.6 mg SC every 4w or 10.8 mg SC every 12w
  - Leuprolide 3.75–7.5 mg IM every 4w or 11.25–22.5 mg IM every 12w
- Radiation therapy
- Bilateral oophorectomy

Initiation of OFS

- With start of chemotherapy (neoadjuvant or adjuvant)
- If no chemotherapy planned, then OFS should be started alone for at least 1-2 cycles or concurrently with tamoxifen until estradiol level in postmenopausal range at which time an aromatase inhibitor could considered.
  - Concurrently with RT or upon completion

Duration of OFS

- 5 years optimal according to SOFT and TEXT trial. No efficacy or safety date to support prolonged OFS. It is encouraged to complete a minimum 2 years of OFS (The 8-year DFS was 85.4% with OFS + tamoxifen versus 80.2% with tamoxifen alone.[c]
- Premenopausal patients wishing to continue adjuvant endocrine therapy after OFS stopped should use tamoxifen.

[a] Definition of Menopause (BINV-O).

[b] A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical, including the potential side effects of premature menopause. Aromatase inhibitor or tamoxifen for 5 years plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal patients at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement).

[c] Baek SY, Noh WC, Ahn SH, et al. Adding ovarian suppression to tamoxifen for premenopausal women with hormone receptor-positive breast cancer after chemotherapy: An 8-year follow-up of the ASTRRA Trial. J Clin Oncol 2023;41:4864-4871.

Adjuvant CDK4/6 inhibitors

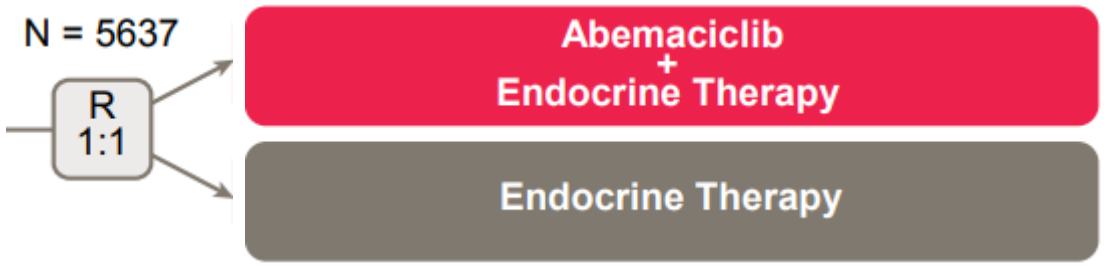
Abemaciclib vs Ribociclib

MonarchE Study: Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer

- HR+, HER2-,
- Node-positive,
- High risk early breast cancer

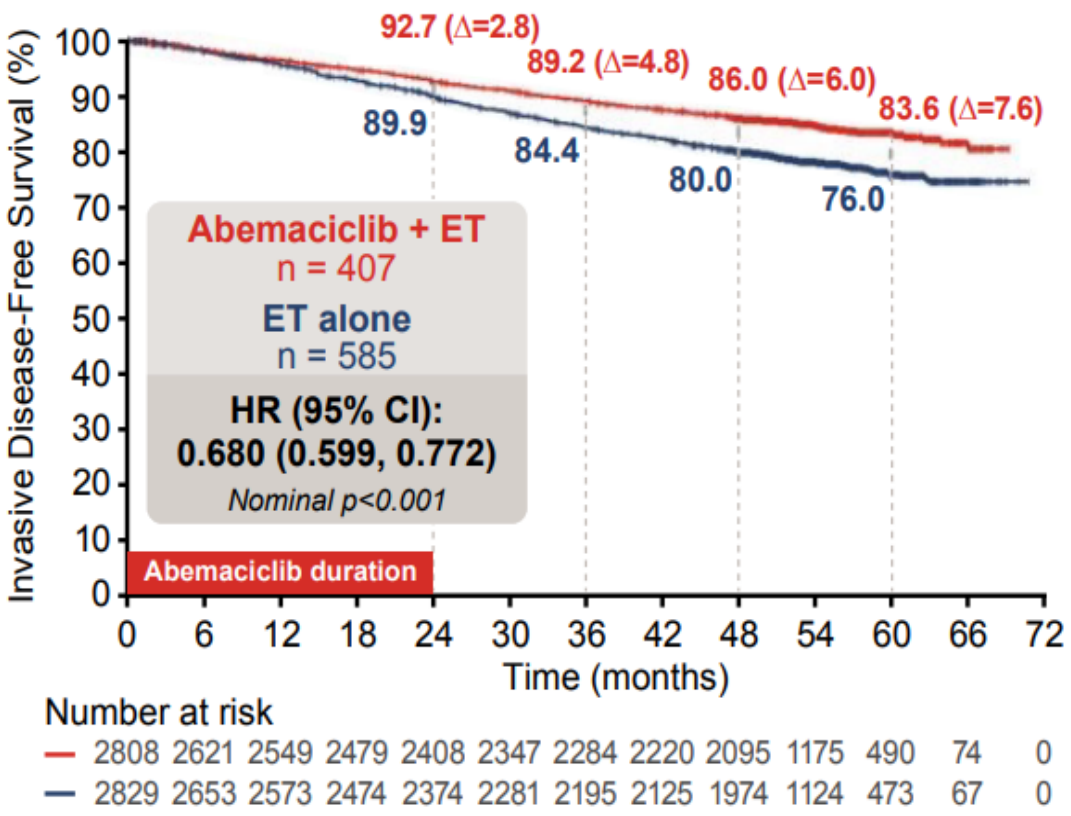
Cohort 1 (91% of patients)
≥4 positive ALN or 1-3 positive ALNs plus G3 and/or tumor ≥5cm

Cohort 2 (9% of patients)
1-3 positive ALNs, ki-67 ≥20%, G1-2, tumor size <5cm

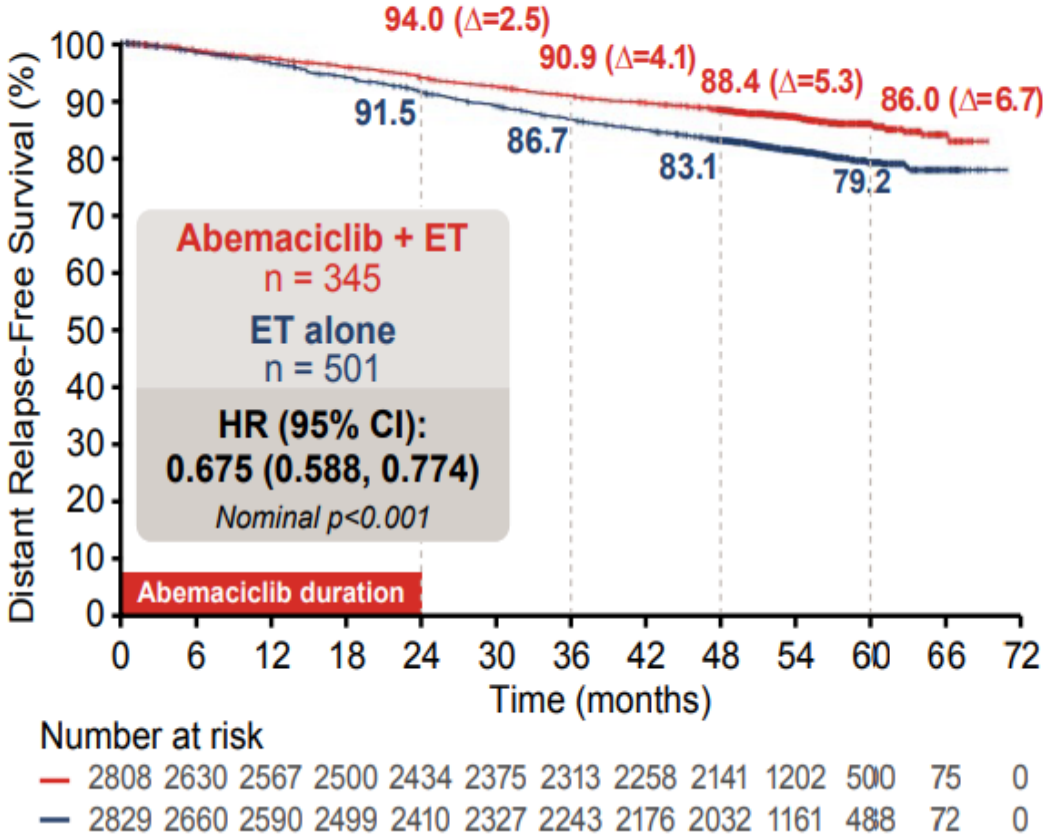


- *Abemaciclib x 2 years*
- *ET for 3-8 years as clinically indicated in both arms*

5 years IDFS Benefit in ITT



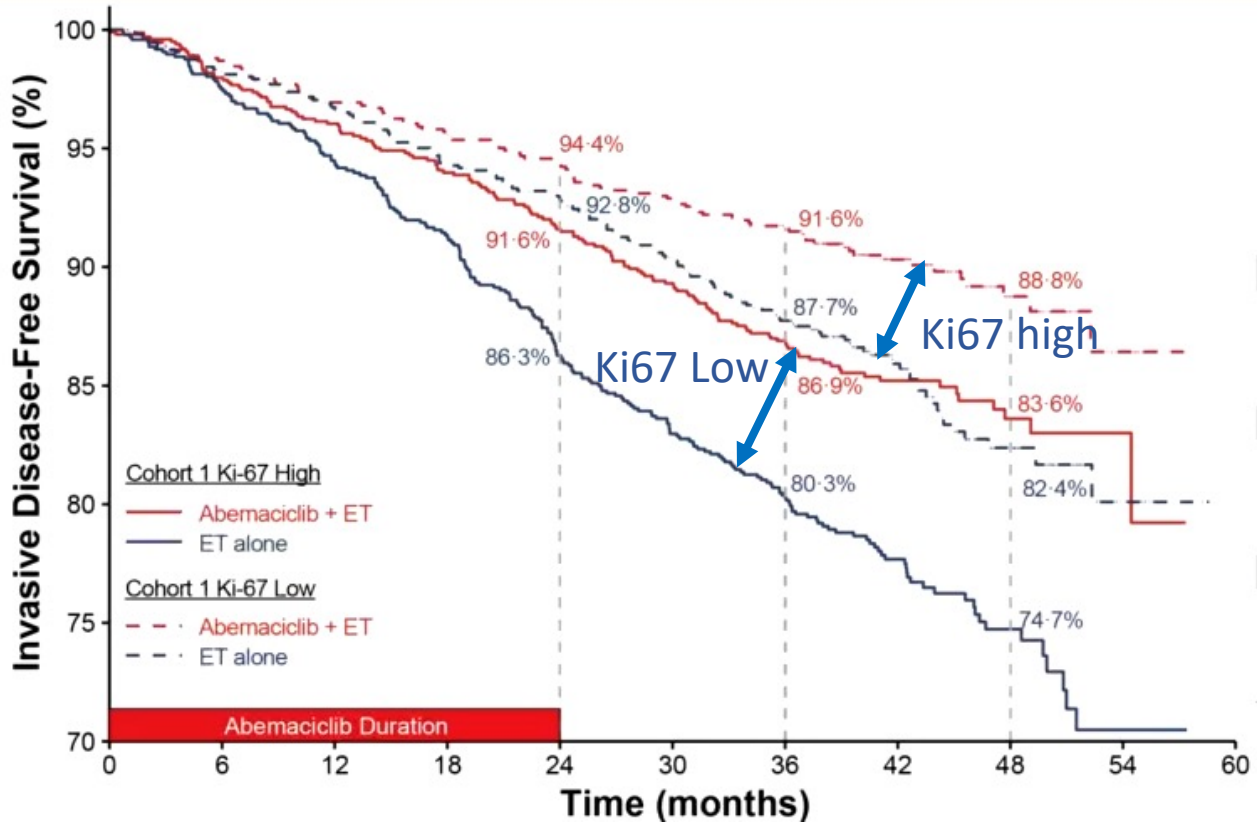
5 years DRFS Benefit in ITT



Rastogi P, et al. JCO. 2024

Does Ki67 Matter?

– Why FDA removed Ki67 testing requirement for adjuvant abemaciclib use?



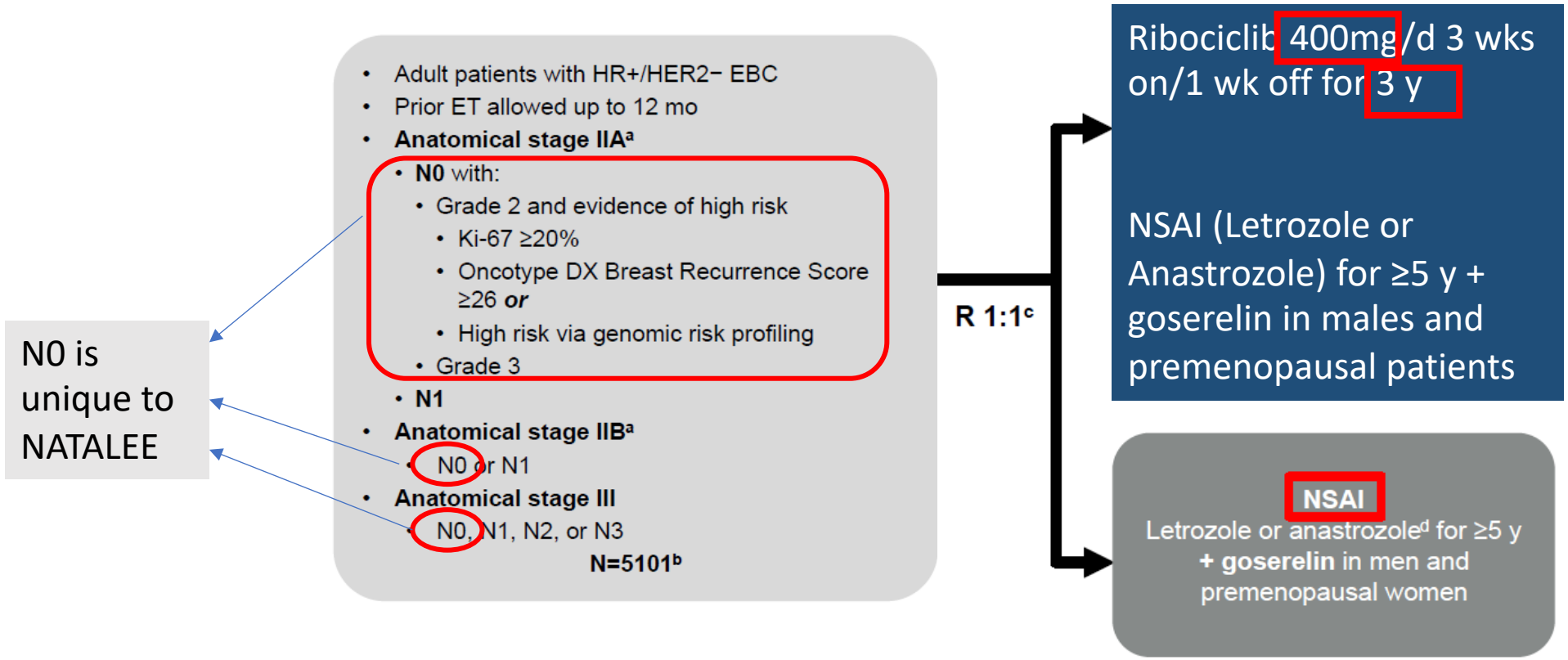
	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Benefit of adjuvant abemaciclib exists regardless of Ki67 status

Johnston et al. JCO 2022

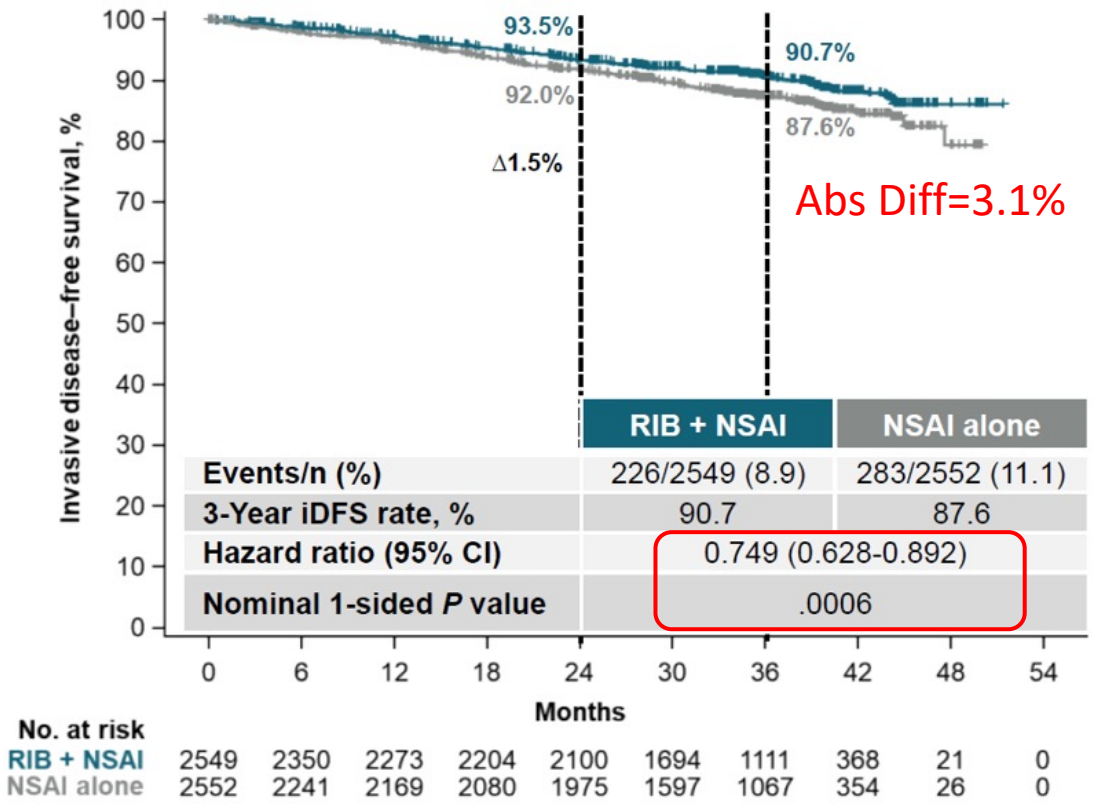
NATALEE Trial: Ribociclib + Nosteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients with HR+/HER2- Early Breast Cancer



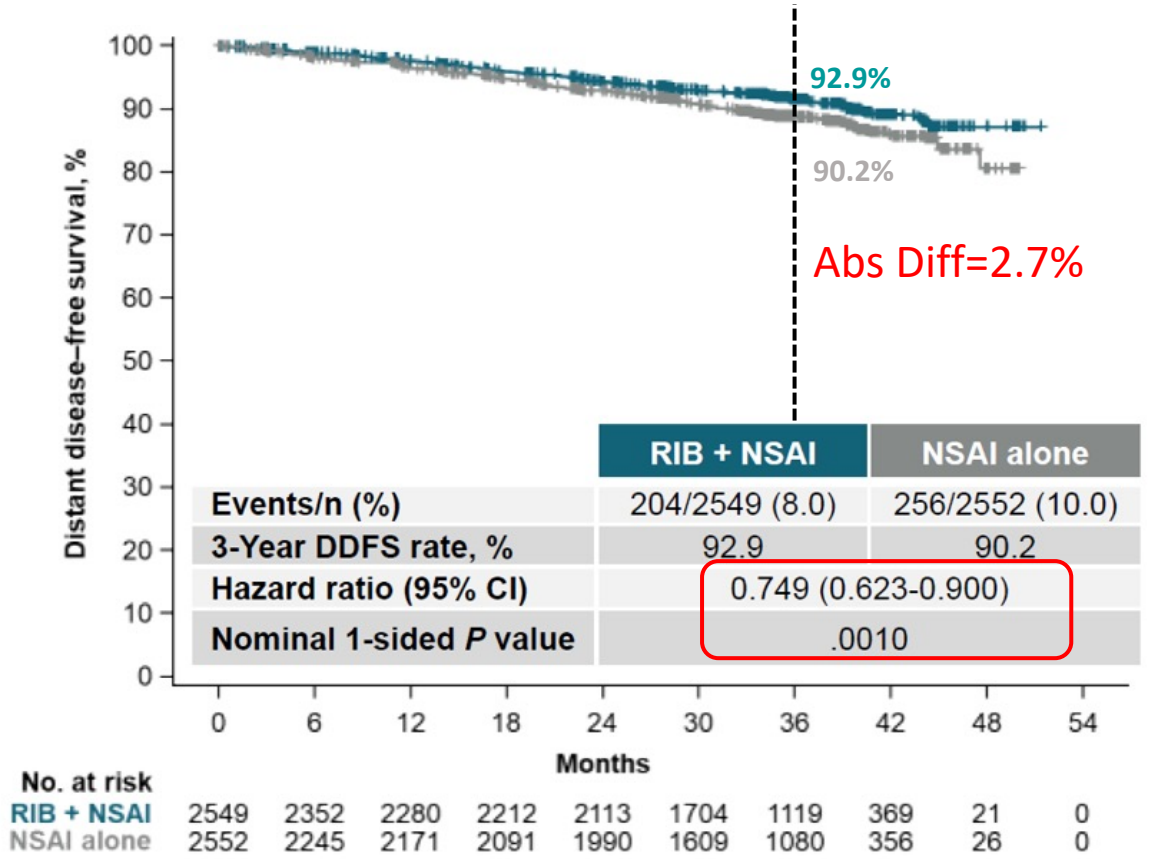
Primary End Point: iDFS

Slamon D, et al. ASCO 2023. Gabriel N. Hortobagyi, MD. SABCS 2023

3 years invasive disease-free survival

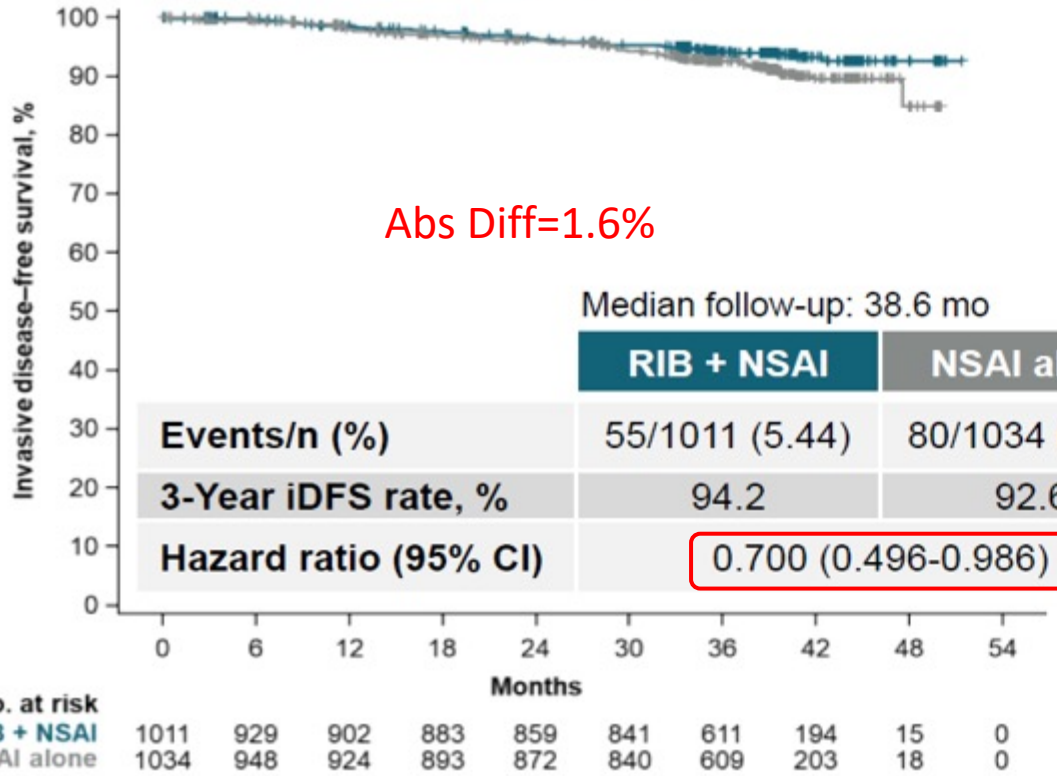


3 years distant disease- free survival



iDFS by anatomic stage

Stage II 40% of patients

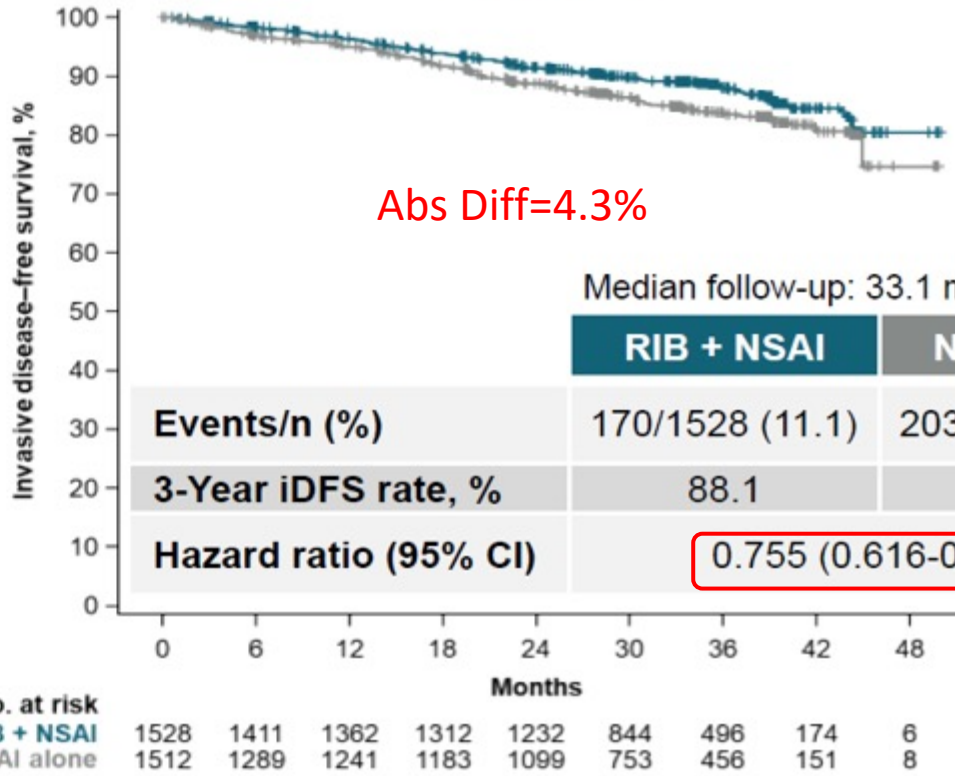


Abs Diff=1.6%

Median follow-up: 38.6 mo

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

Stage III 60% of patients



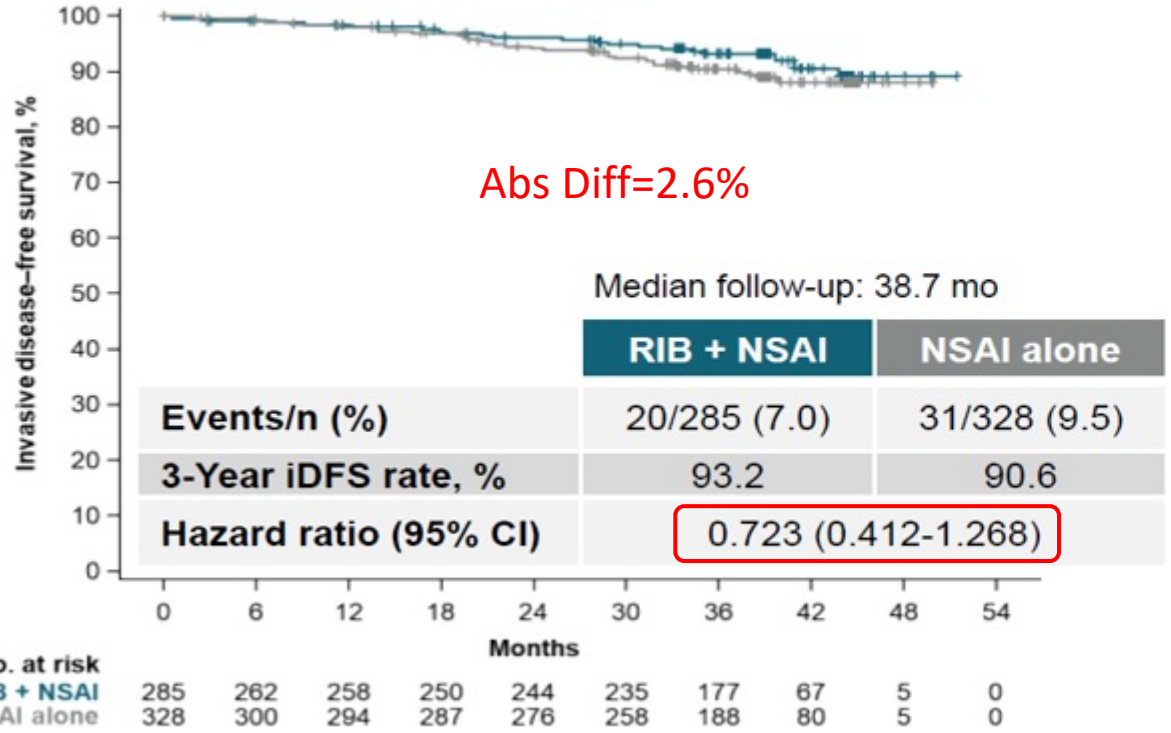
Abs Diff=4.3%

Median follow-up: 33.1 mo

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

iDFS by Nodal Status

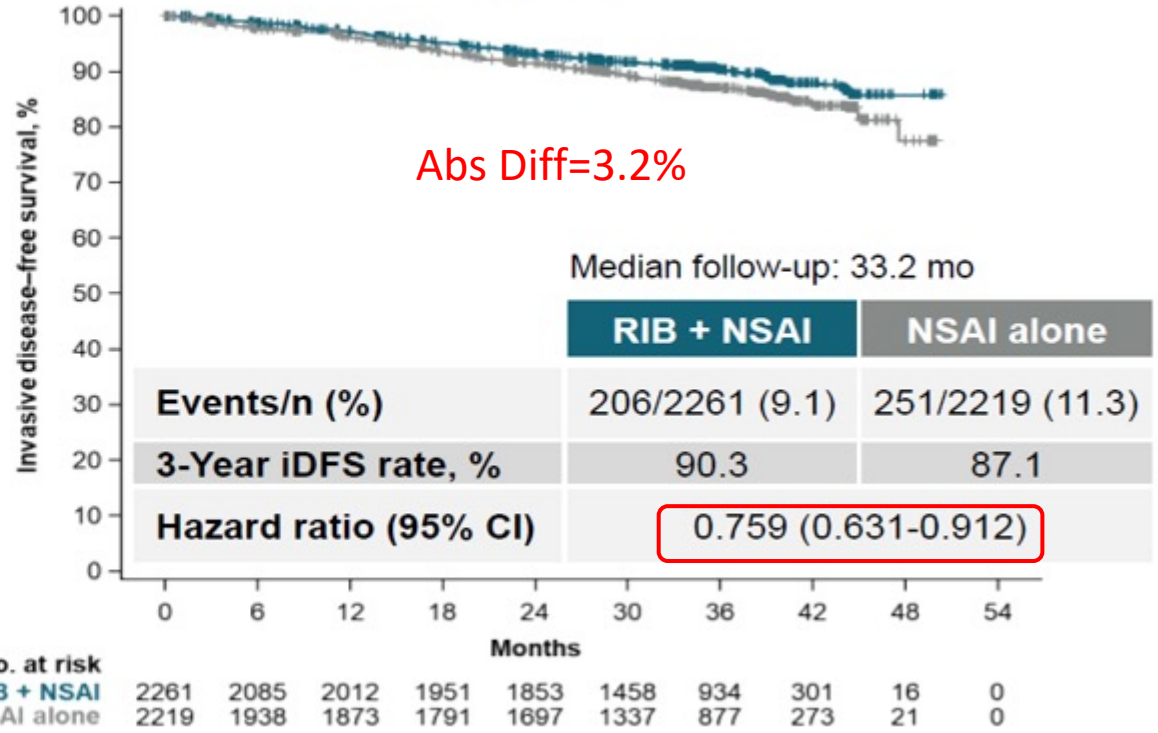
N0 28% of the patients



Median follow-up: 38.7 mo

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

N1-N3 60% of the patients



Median follow-up: 33.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

Ribociclib (NATALEE) vs Abemaciclib (MonarchE)

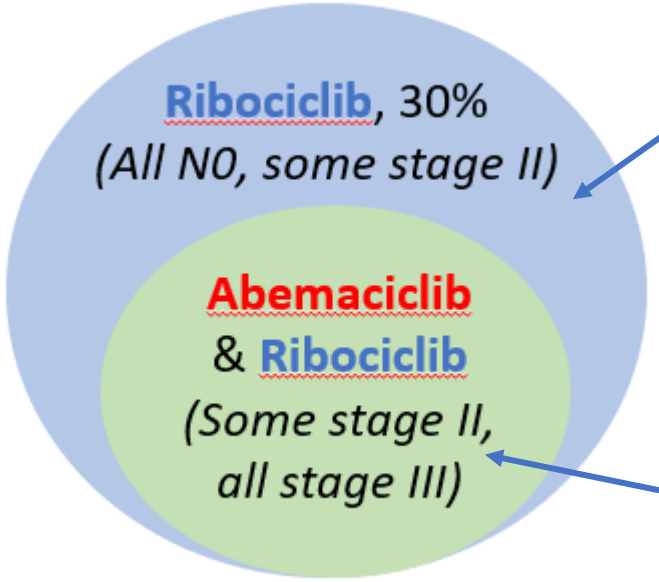
	NATALEE	MonarchE
N	5101	5637
Stage	II/III: 40%/60%	II/III: 26%/74%
LN	N0/N1-N3: 28%/60%	N0/N1-N3: 0.2%/99.8%
Treatment duration	Ribociclib 3 y	Abemaciclib 2 y
Treatment completion	3 yr completion: 42.8% Ribociclib on going: 20.7%	Abemaciclib on going: none
iDFS diff (vs ET alone)	3 yr: 3.1% 5 yr: N/A	3 yr: 5.4%; 5 yr: 7.6%

Safety Profile (≥ Grad3 AEs)

	Ribociclib	Abemaciclib
Discon % due to AE	19%	18.5%
Neutropenia	43.8% 1st common	19.0% 1st common
LFTs elevation	8.3% 2nd common	1.8-2.6%
Diarrhea	0.6%	7.8% 2nd common
PE/DVT	0.6%	1.1%
QT prolongation	1.0%	N/A

Factors to consider when making decisions (assuming both available)

Efficacy	not fair to compare due to different pts population
Tolerance	similar disco rate
Rx Duration	3 yrs vs 2 yrs
$ toxicity	3 yrs vs 2 yrs $ cost
Data maturity	Re-visit when longer follow up data is available



- Stage II: Appropriate to offer Ribociclib
- N0: current data shows no benefit. Carefully assess the benefit and toxicity.

- Re-visit when longer follow up data is available
- More accurate biomarker need for patient selection to avoid overtreating or undertreating

- Toxicity profile
- Abemaciclib likely wins

Summary

Adjuvant ovarian function suppression

- OFS decrease recurrence risk, Improves OS
- OFS provides benefit regardless of LN status. More significant benefit if LN+, age < 45 years old
- AI + OFS vs TAM + OFS: improves dRFS but not OS

Adjuvant CDK4/6 inhibitors (if Ribociclib is approved)

- If eligible for both Ribociclib and Abemaciclib: shared decision. Likely Abemaciclib wins for now (short treatment, confirmed efficacy)
- If eligible for Ribociclib only: offer Ribociclib based on current data? Revisit when longer follow up data is available!