2024 Breast Cancer Congress

with Updates from the 2023 SABCS

Friday, February 2, 2024
10:40 AM – 11:05 AM CST

Adjuvant Treatment of ER-Positive Breast Cancer with SABCS Updates

Mei Wei, MD

Huntsman Cancer Institute at the University of Utah

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal

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- **Adjuvant chemotherapy**
- **Adjuvant ovarian function suppression**
- **Adjuvant CDK4/6 inhibitors**

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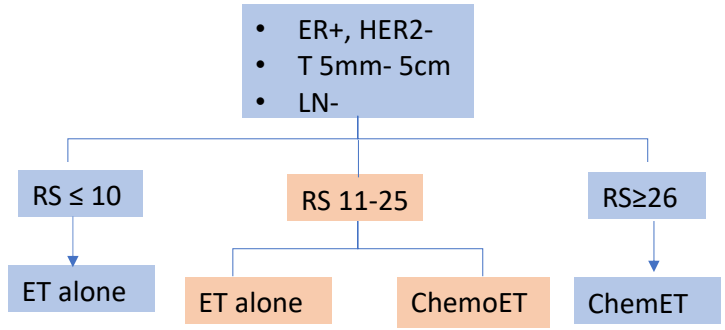
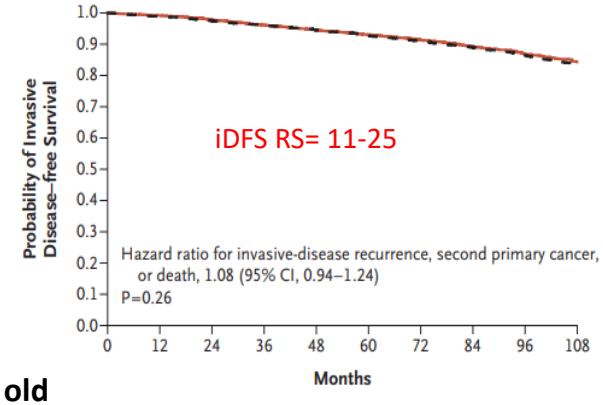
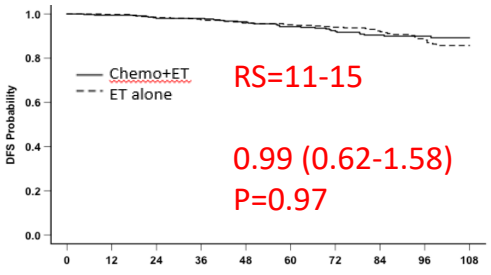
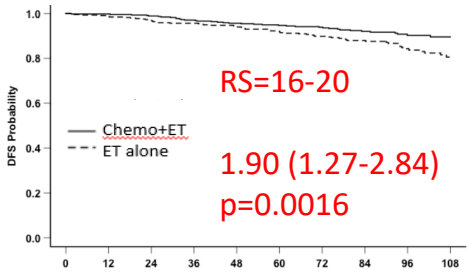
TAILORx Study – Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in BC

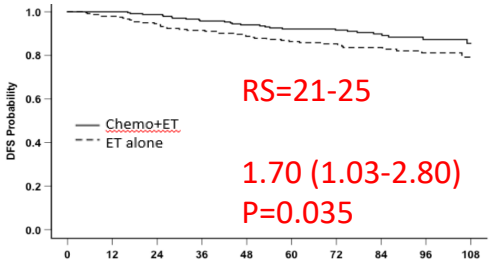




iDFS for women ≤ 50 years old







Chemotherapy seems to be beneficial among women **≤ 50 yo with RS ≥ 16**

Sparano JA, et al. NEJM 2018

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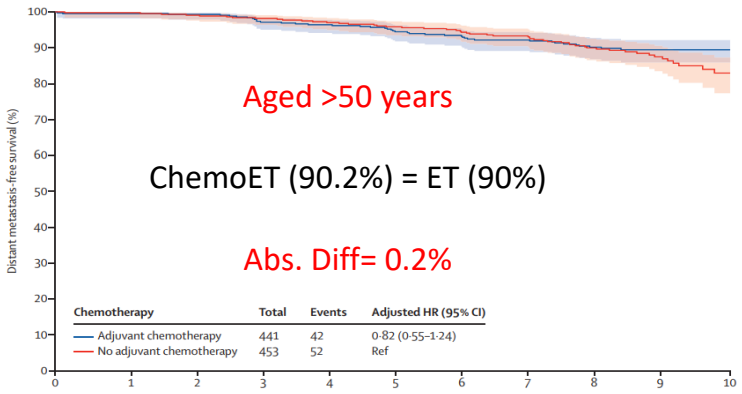
MINDACT Study – 70 Gene Signature as an Aid to Treatment Decisions in Early-Stage BC

- ER+, HER2- (9% HER2+)
- T1-T3
- N0-N1

→ High clinical risk
Low genomic risk
N=1550

→ ET alone
→ ChemoET

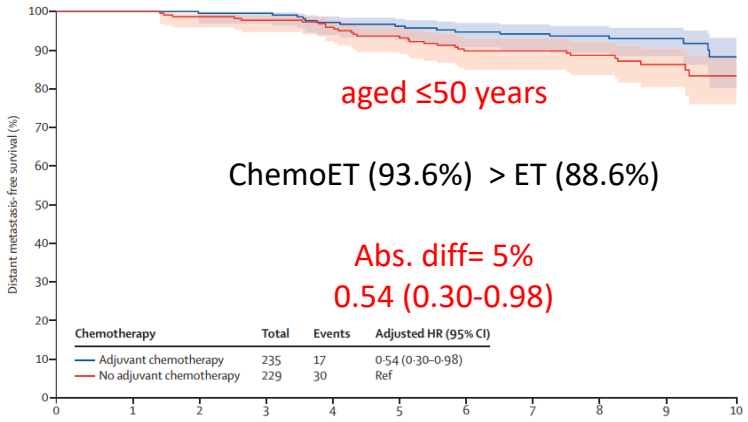
Distant metastasis free survival by age, 8.7 years follow up



Aged >50 years

ChemoET (90.2%) = ET (90%)

Abs. Diff= 0.2%



aged ≤50 years

ChemoET (93.6%) > ET (88.6%)

Abs. diff= 5%
0.54 (0.30-0.98)

Chemotherapy seems to be beneficial among women **≤ 50 with H-clinical; L-genomic risk BC**

F Cardoso, et al. NEJM 2016; Lancet Oncology 2021

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NCCN Guidelines – LN negative

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NCCN Guidelines Version 1.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
21-gene (Oncotype Dx) (for postmenopausal patients with pN0 and pN1 [1–3 positive nodes])[c]	<26	Patients with T1b/c–2, pN0, HR-positive, HER2-negative tumors, with risk scores (RS) between 0–10 have a risk of distant recurrence of <4% and those with RS 11–25 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1] Postmenopausal patients with pT1–3, pN1, HR-positive, HER2-negative, with RS <26 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective RxPONDER study.[2]
	≥26	In postmenopausal patients with pT1–3, HR-positive, HER2-negative, and pN0 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1,2]
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with T1b/c –2, pN0, HR-positive, HER2-negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1]
	16–25	In premenopausal patients with RS between 16–25, a small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients.[1,2] For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1]
21-gene (Oncotype Dx) (for premenopausal patients with 1–3 positive nodes)[c]	<26	In premenopausal patients with pT1–3 and pN1 (1–3 positive nodes) tumors and an RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy[c] but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.[2]
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[2]

Menopause	ODX RS	Recommendations
Pos - M	<26	ET
	≥26	ChemoET
Pre - M	<16	ET
	16-25	***Consider*** ChemoET or OFS+ ET
	≥26	ChemoET

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 1.2024).
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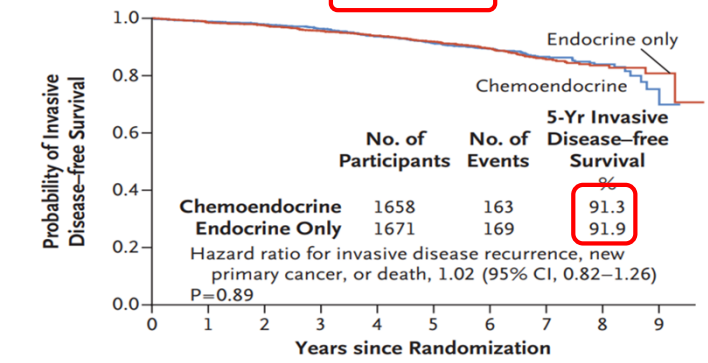
RxPonder – 21 Gene Assay to Inform Chemotherapy Benefit in Node-Positive BC

- HR+, HER2-
- 1-3 LN+
- T1-T3
- ODX RS ≤ 25

→ **ET alone**

→ **ChemoET**

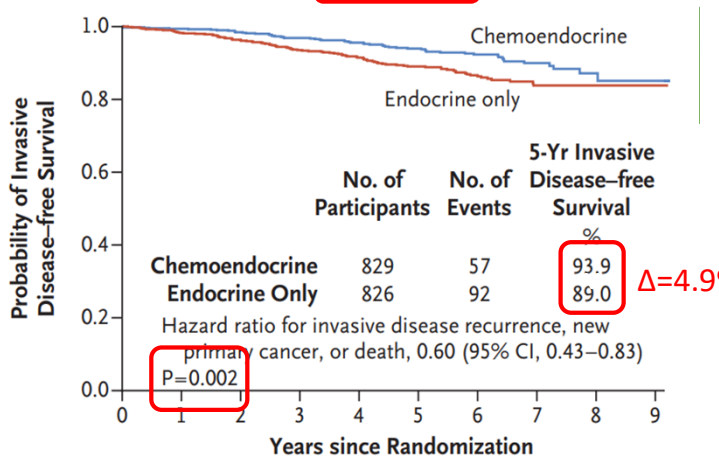
B Invasive Disease–free Survival, Postmenopausal Participants



No. at Risk

Chemoendocrine group	1658	1515	1413	1298	1145	993	659	358	129	14
Endocrine-only group	1671	1568	1474	1343	1196	1030	679	364	137	21

C Invasive Disease–free Survival, Premenopausal Participants



Δ=4.9%

No. at Risk

Chemoendocrine group	829	764	710	642	546	484	312	153	46	5
Endocrine-only group	826	760	703	622	542	463	290	138	44	2

Among women with N1 BC, no chemo benefit among post-m women, but there is chemo benefit among pre-m women

K Kalinsky, et al. NEJM. 2021

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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

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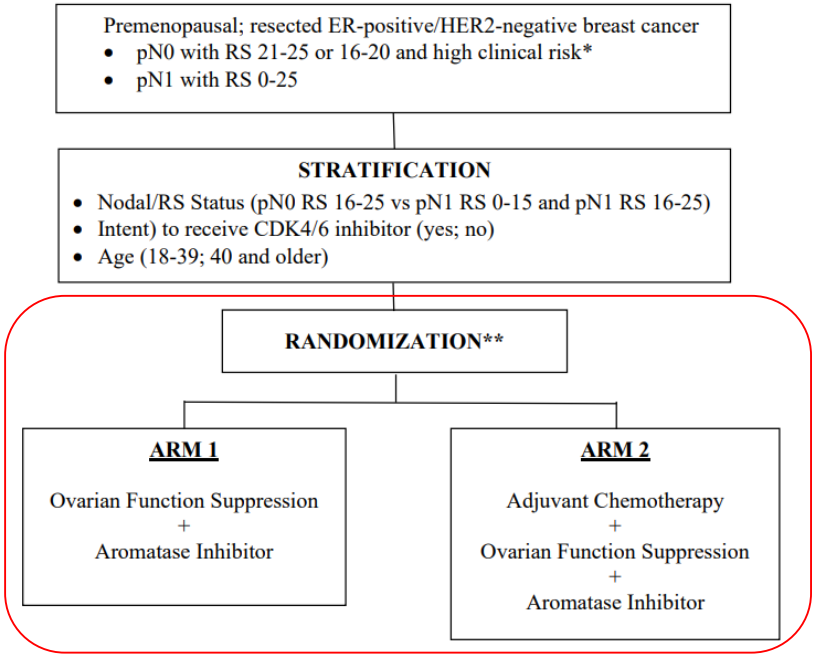
NRG-BR009 (aka OFSET Study)

- 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.

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- Adjuvant chemotherapy

- **Adjuvant ovarian function suppression**
  - **OFS vs No OFS**
  - **AI +OFS vs TAM + OFS**

- Adjuvant CDK4/6 inhibitors

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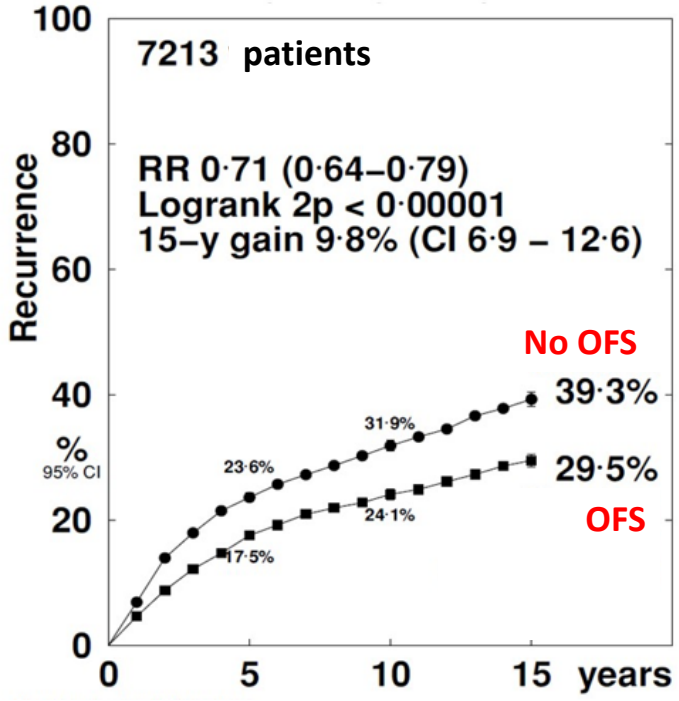
OFS
vs
No OFS

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%

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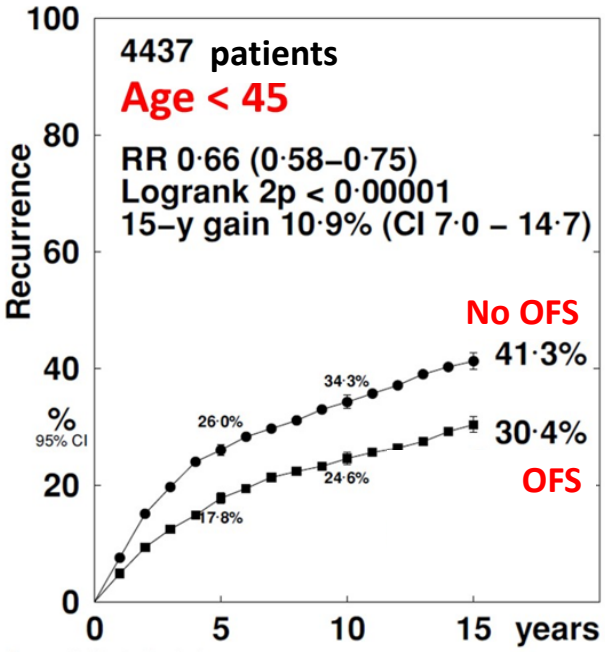
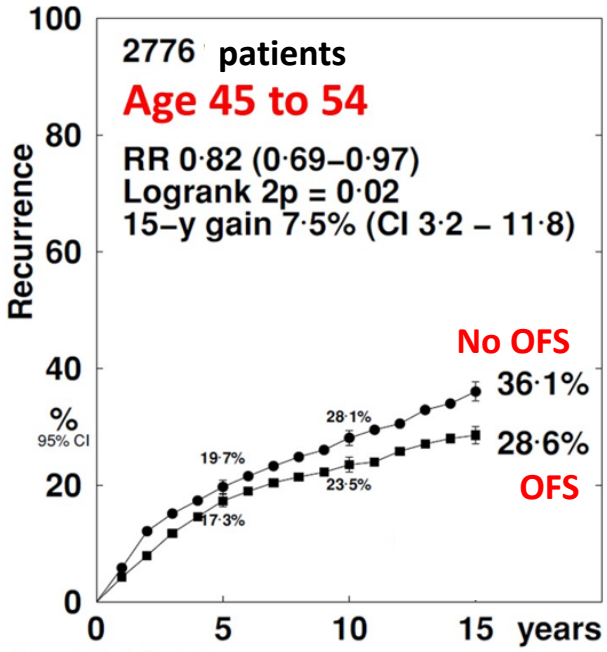
Recurrence Risk per age
No chemotherapy or premenopausal after chemotherapy



Abs Diff: ~11%



Abs Diff: 7.5%

Richard Gray. ASCO 2023

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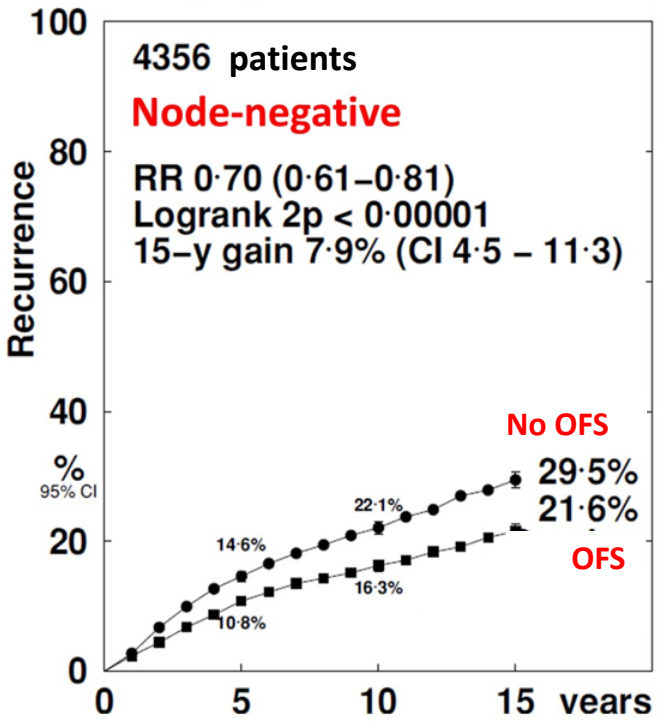
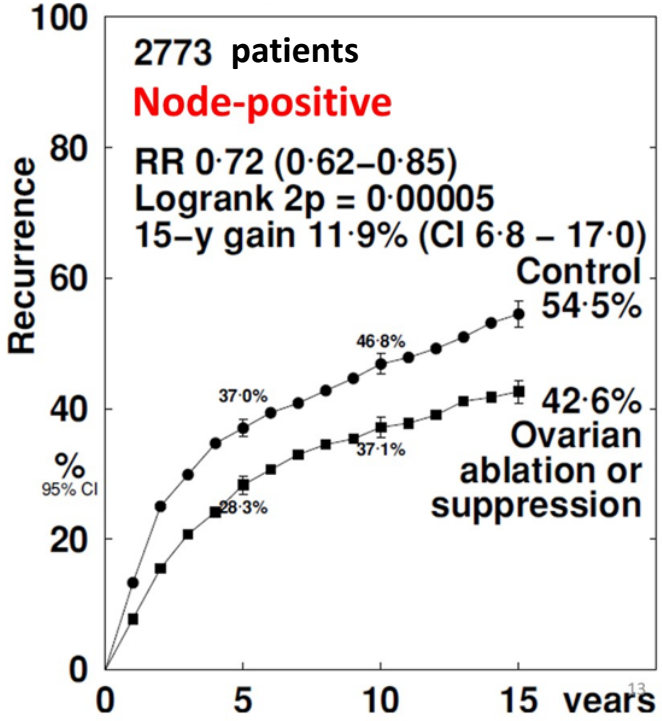
Recurrence Risk per Node Status
No chemotherapy or premenopausal after chemotherapy



Abs Diff: ~8%



Abs Diff: 12%

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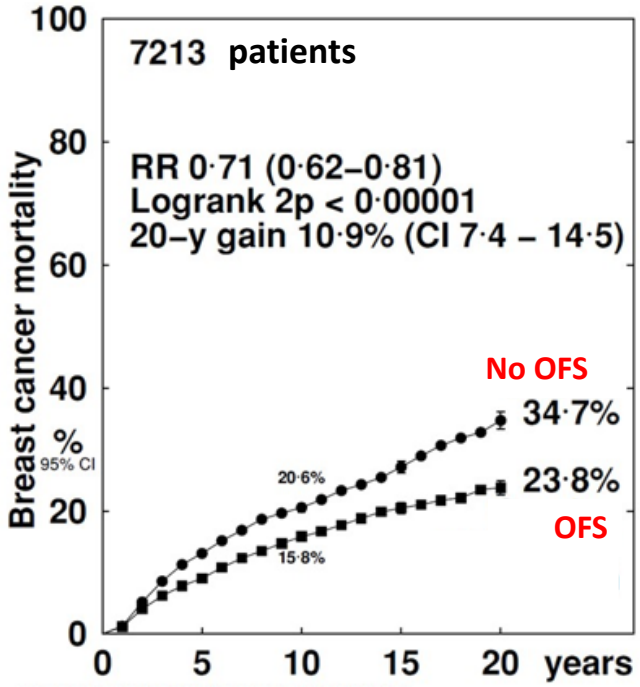
Breast cancer mortality



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

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AI +OFS

vs

TAM + OFS

Four Clinical Trials:

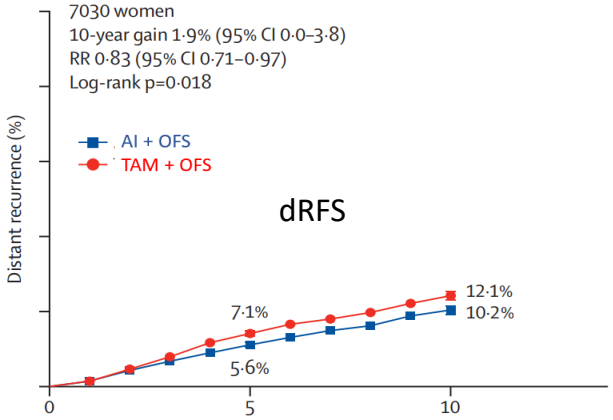
ABCSG:
NEJM 2009
Ann Oncol 2015

TEXT:
NEJM 2014
NEJM 2018

SOFT:
NEJM. 2014
NEJM 2018

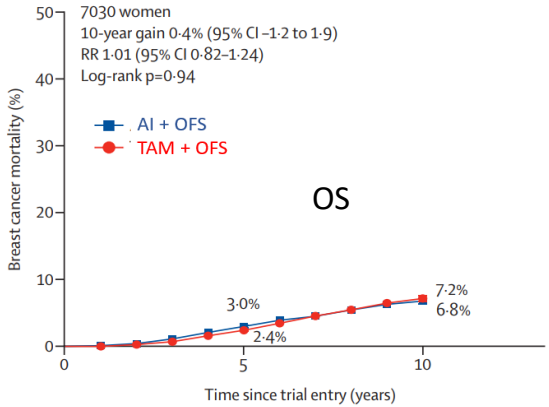
HOBOE
Eur J Cancer. 2019

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.

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- Adjuvant chemotherapy
- Adjuvant ovarian function suppression
- **Adjuvant CDK4/6 inhibitors**
  - **Abemaciclib vs Ribociclib**

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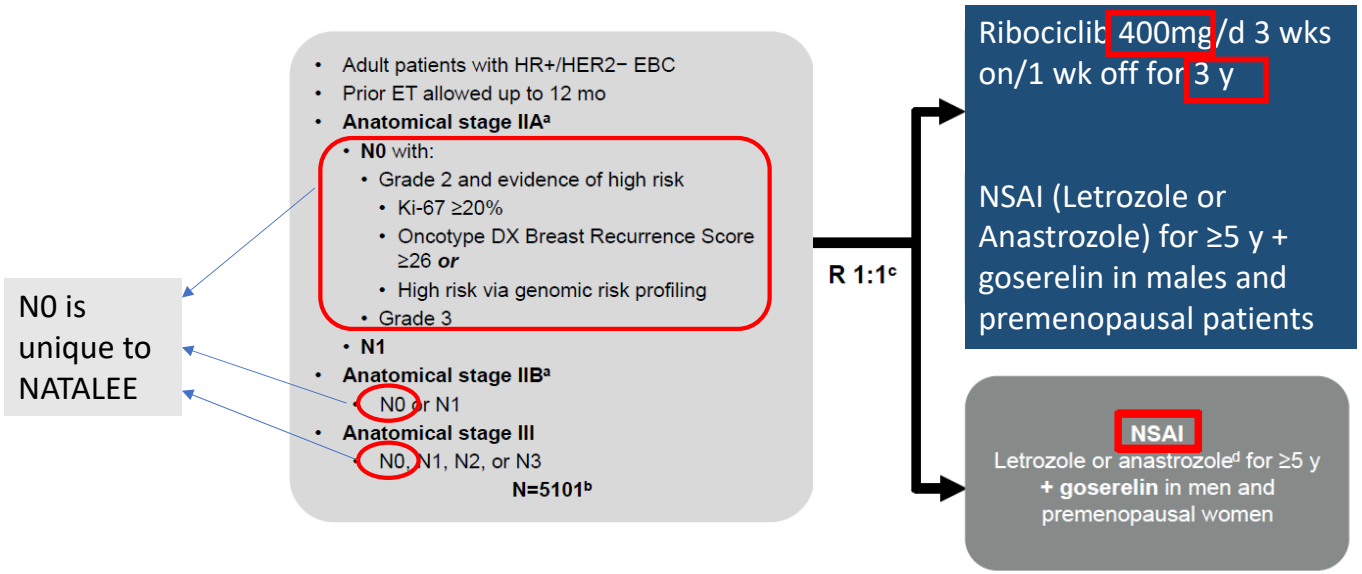
NATALEE Trial: Ribociclib + Nosteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients with HR+/HER2- Early Breast Cancer



Primary End Point: iDFS

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

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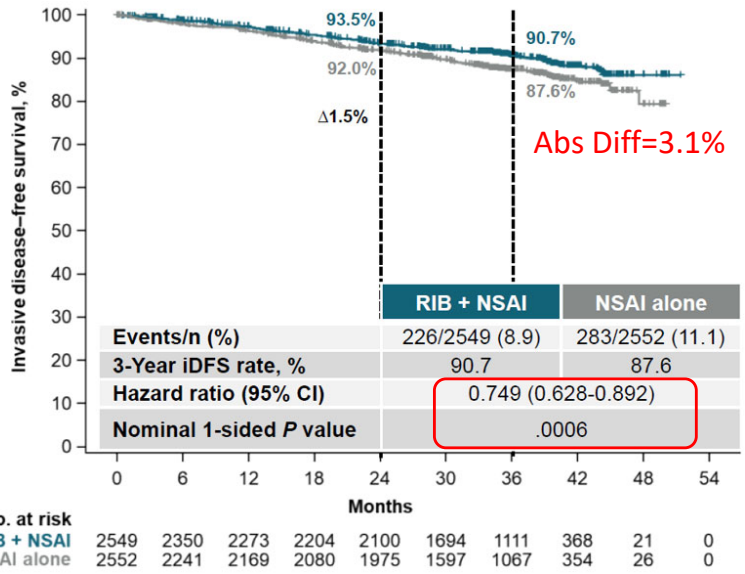
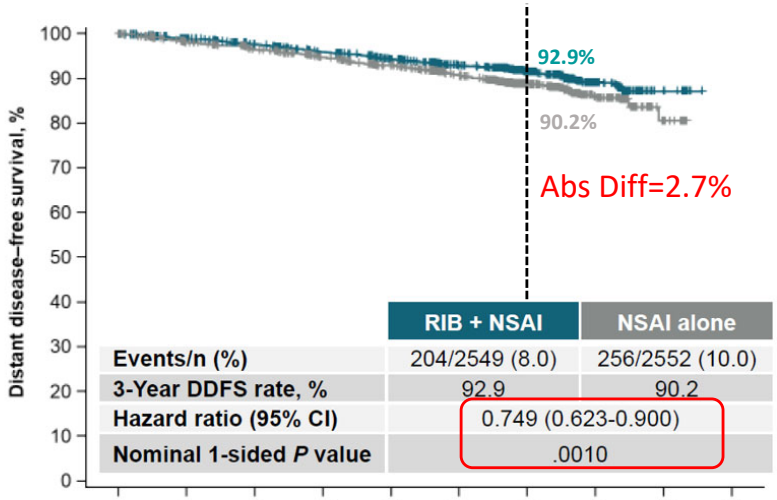
3 years invasive disease-free survival



	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided *P* value	.0006	

No. at risk										
RIB + NSAI	2549	2350	2273	2204	2100	1694	1111	368	21	0
NSAI alone	2552	2241	2169	2080	1975	1597	1067	354	26	0

3 years distant disease- free survival



	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

No. at risk										
RIB + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI alone	2552	2245	2171	2091	1990	1609	1080	356	26	0

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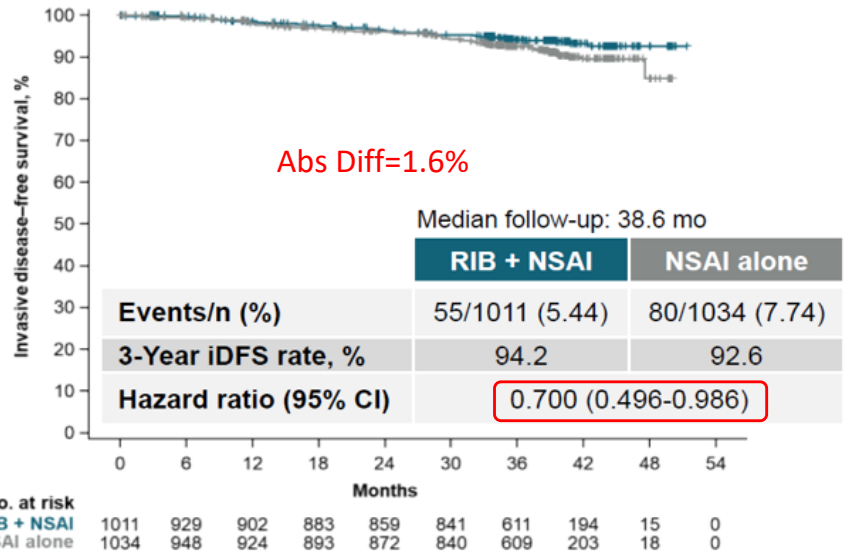
iDFS by anatomic stage

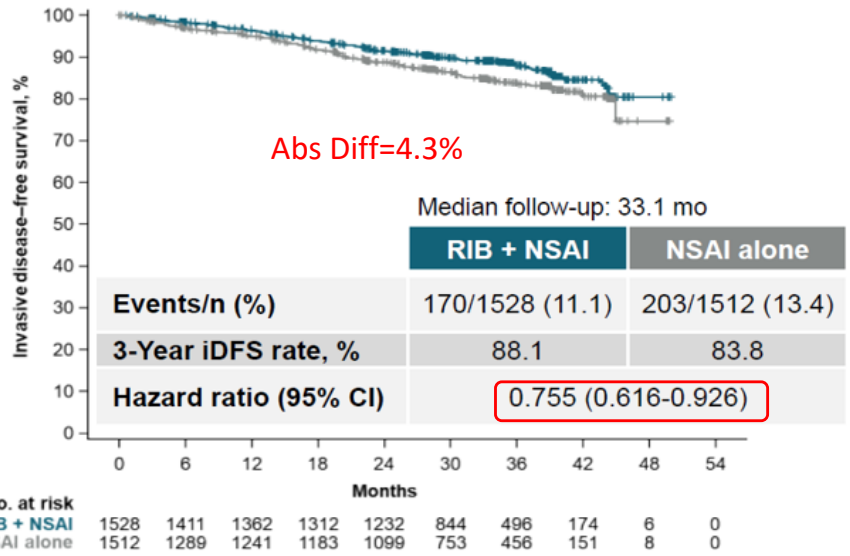
Stage II 40% of patients



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



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)	

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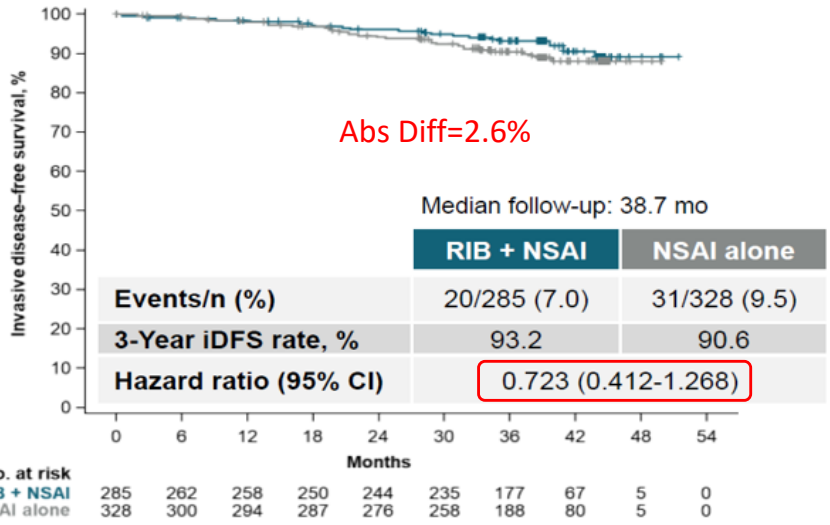
iDFS by Nodal Status

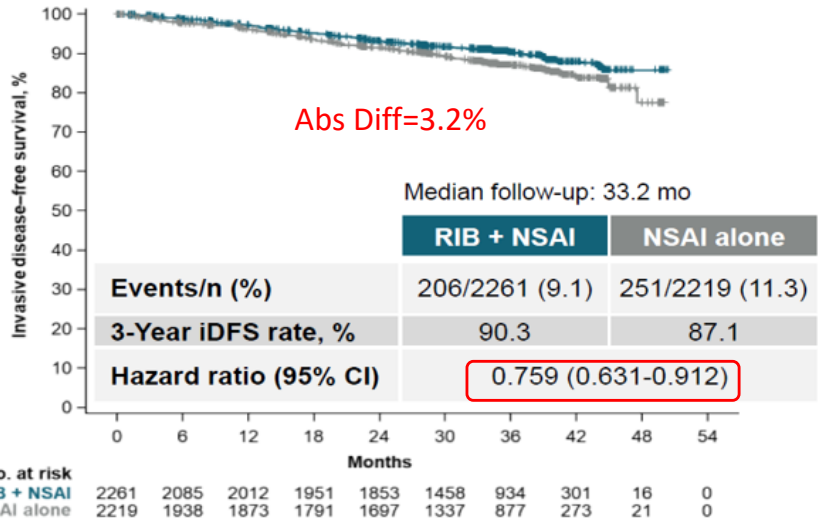
N0 28% of the patients



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)	

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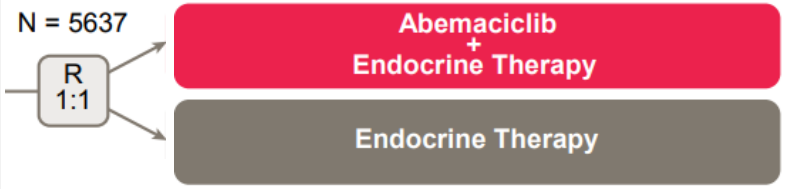
MonarchE Study: Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer

- 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*

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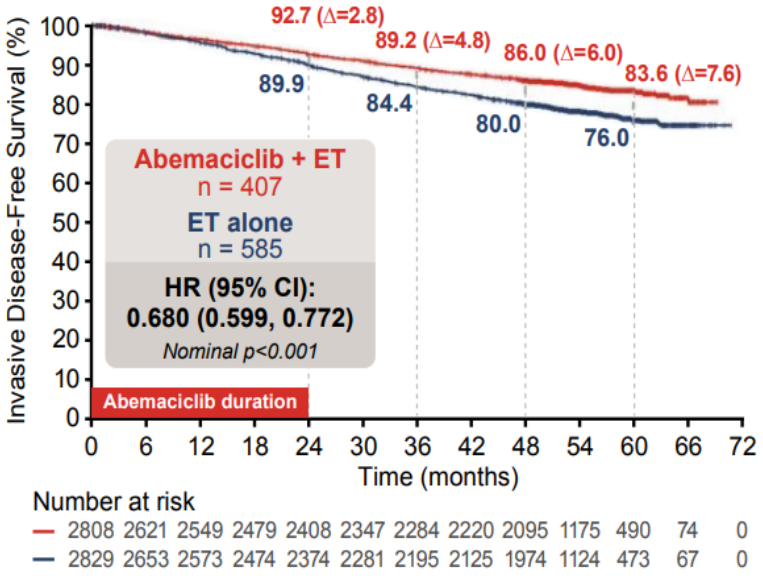
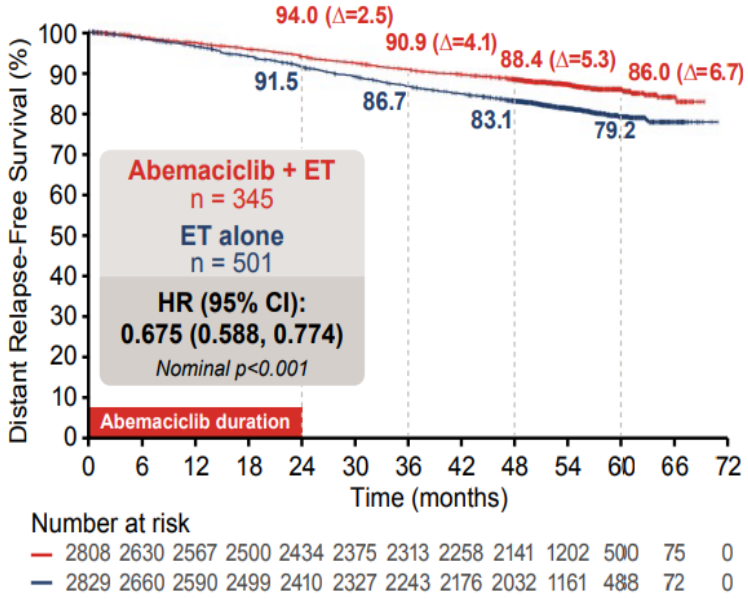
5 years IDFS Benefit in ITT



5 years DRFS Benefit in ITT



Rastogi P, et al. JCO. 2024

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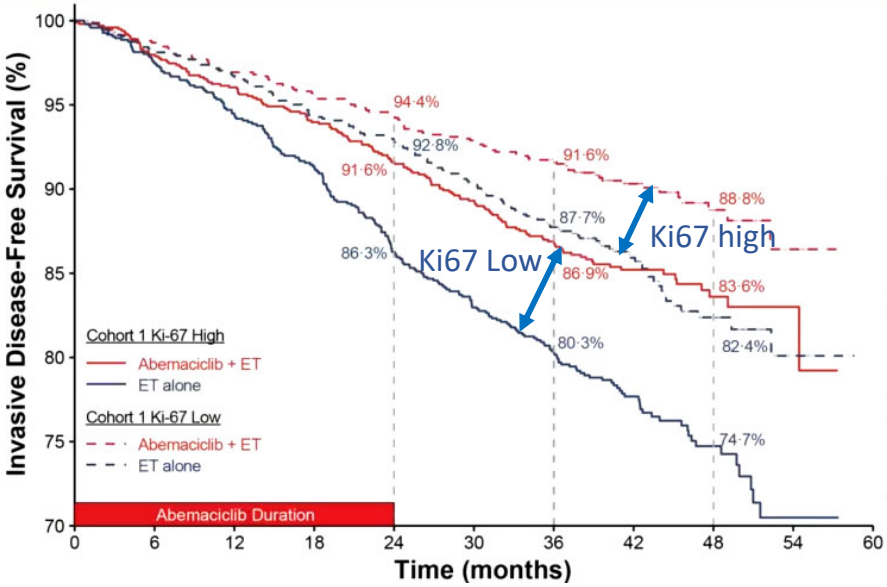
Does Ki67 Matter?

– 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

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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

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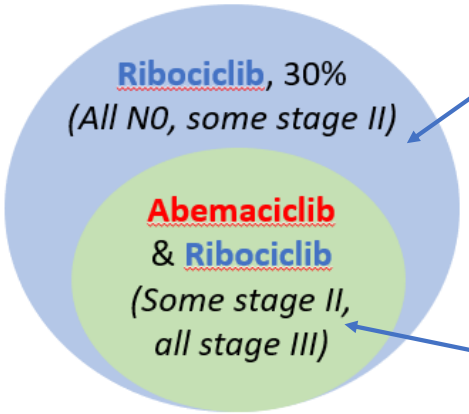
Factors to consider when making decisions

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

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Summary

Adjuvant chemotherapy

- **Postmenopausal:** per NCCN Guidelines
- **Premenopausal:**

  RS<26: encourage to consider OFSET study

  RS≥26: chemoET

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. But revisit when longer follow up data is available

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NCCN Member Institutions

Who We Are

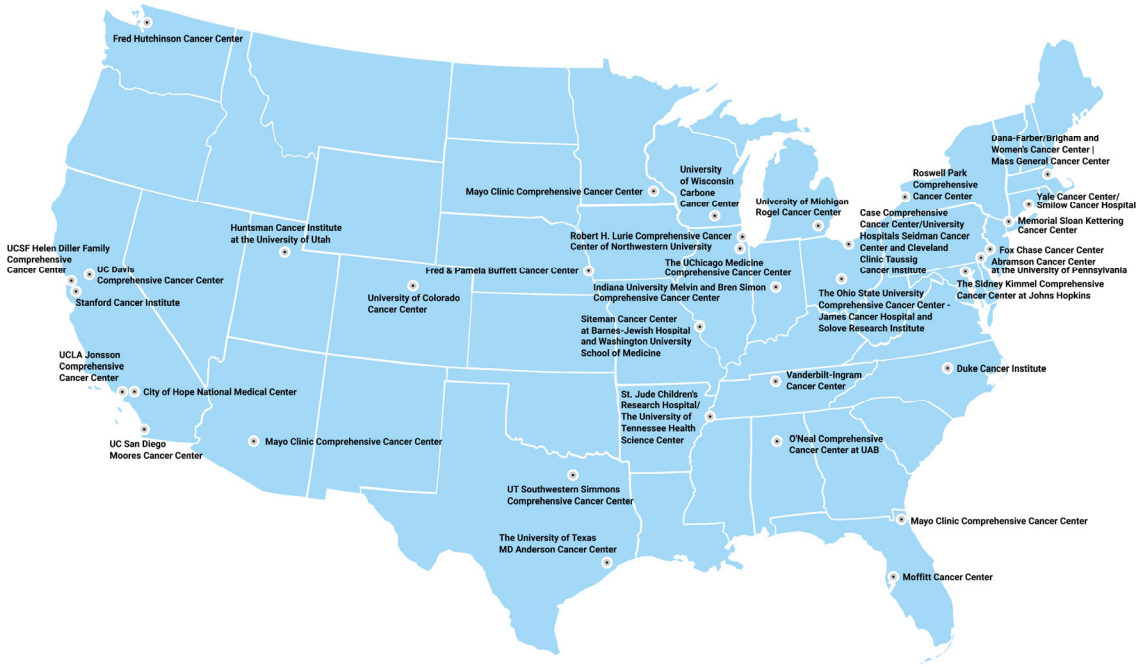
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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