UC San Diego Health

Updates in the Management of early HR+ Breast Cancer: What's New and What's on the Horizon

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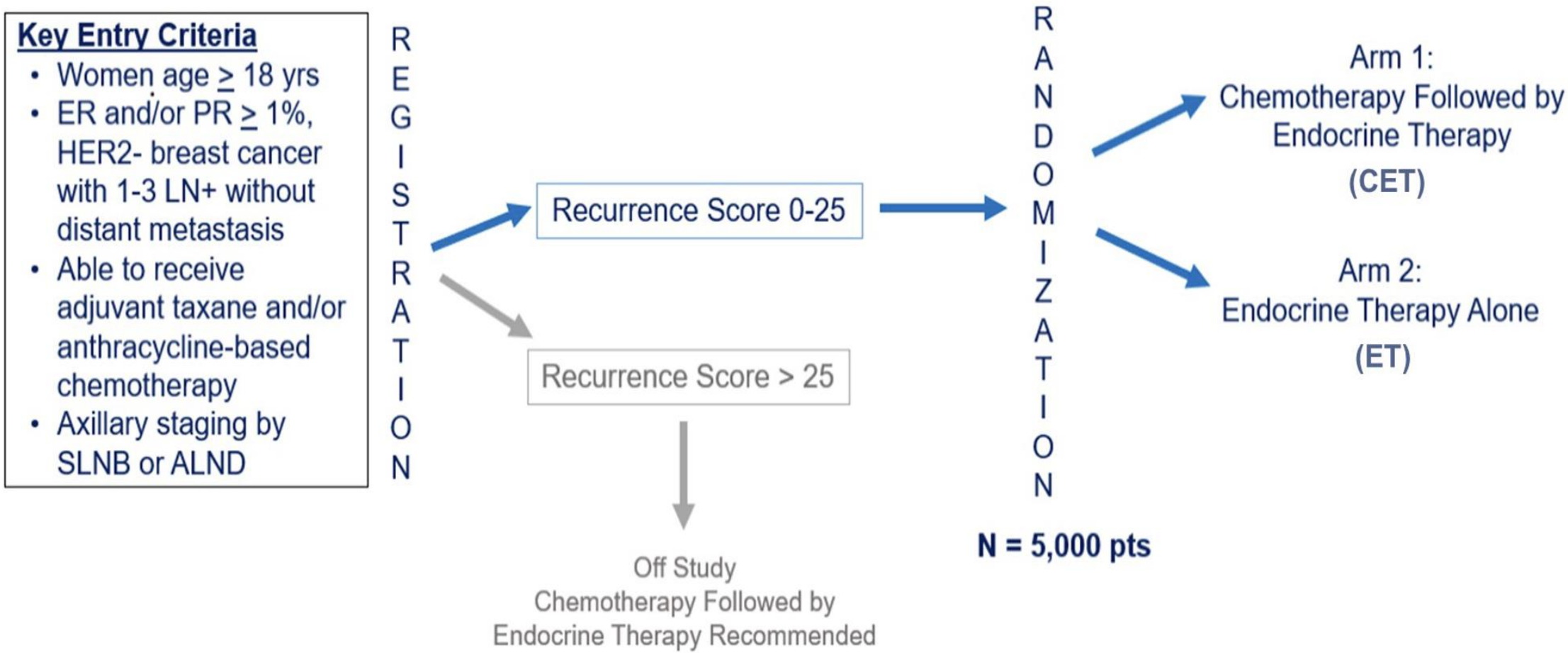
Which patients with HR+/HER2- EBC need chemotherapy?

- **Node negative:**
  - For tumors >0.5cm, use genomic assay (e.g., Oncotype or Mammaprint) to help decide about need for chemotherapy (typically adjuvant TC x 4)
    - Relevant trials: **TailorRx** (Oncotype), **MINDACT** (Mammaprint)

- **1-3+ LN:**
  - For postmenopausal women only - use genomic assay (e.g., Oncotype or Mammaprint) to help decide about need for chemotherapy (typically adjuvant TC x 4)
    - Relevant trial: **RxPONDER** (Oncotype), **MINDACT** (Mammaprint)

- **4+ SLN:**
  - Chemotherapy is recommended (typically ddAC-T)
  - Can be given neoadjuvantly (preferred to assess response, downstage) or adjuvantly

RxPONDER Trial



Kalinsky, et al. NEJM 2021

RxPonder Trial Results

- **Results:** Chemo benefit in terms of iDFS and DRFS differed by menopausal status:
  - Premenopausal: **All** pts benefit from chemo?
  - Postmenopausal: No benefit from chemo

- **Issue with the premenopausal group:**
  - For endocrine therapy, **75% received tamoxifen alone, only 17% had OFS**
  - Similarly, unclear if benefit in premenopausal women due to ovarian function suppression from chemotherapy or actually from the chemotherapy

Kalinsky K et al *EEJM*. 2021;
Cardoso et al, ASCO 2020;
Piccart et al, *Lancet Oncol* 2021;
Kalinsky SABCS 2021

Important RxPonder Update From ASCO 2024!

2024 ASCO ANNUAL MEETING

SWOG Leading cancer research. Together.

Serum anti-Mullerian hormone levels refine identification of premenopausal patients with HR+, HER2-, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in SWOG S1007 (RxPONDER)

Kevin Kalinsky, William E Barlow, Harsh Pathak, Julie Gralow, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen KL Chia, Priya Rastogi, Anne F Schott, Steven Shak, Debasish Tripathy, Gabriel N Hortobagyi, Funda Meric-Bernstam, Priyanka Sharma, Lajos Pusztai, Alastair Thompson, Andrew K Godwin

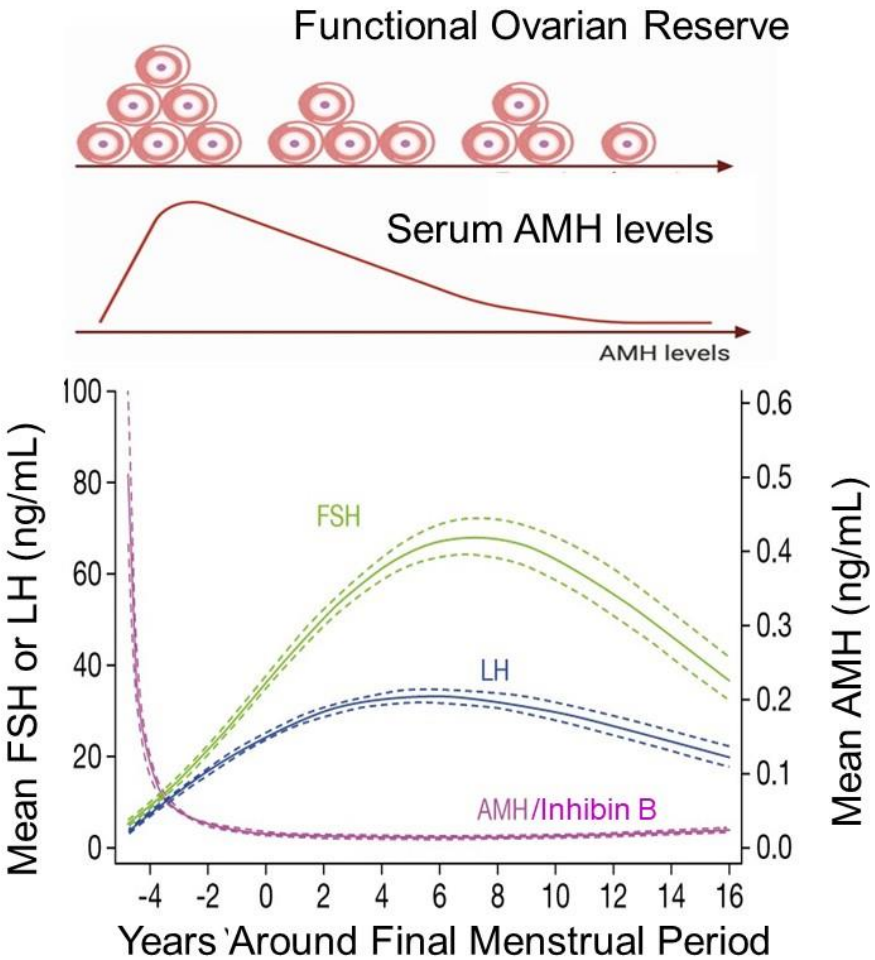
Ovarian Function Reserve Substudy of RxPonder

- In RxPonder 1/3 of patients were classified as “premenopausal”
- Premenopausal vs. postmenopausal definitions are imprecise
- AMH is a blood test that measures ovarian reserve
- Objective of this substudy was to determine benefit of chemo if <55 using serum markers of ovarian function reserve and not just age and absence or presence of period

Serum Hormone Levels in Postmenopausal Women	
Low	**High**
Estradiol	Follicular Stimulating Hormone (FSH)
Progesterone	Luteinizing Hormone (LH)
Anti-Mullerian hormone (AMH)	
Inhibin B	

Low serum AMH and Inhibin B are markers of diminished ovarian reserve

- Lower Anti-Mullerian hormone (AMH) reflects fewer growing follicles
  - AMH is more stable and reliable during menstrual cycle than estradiol and FSH
  - AMH decreases prior to final menstrual period (*i.e.,* menopause) before FSH elevation
- Inhibin B declines before menopause due to lower follicular number and function

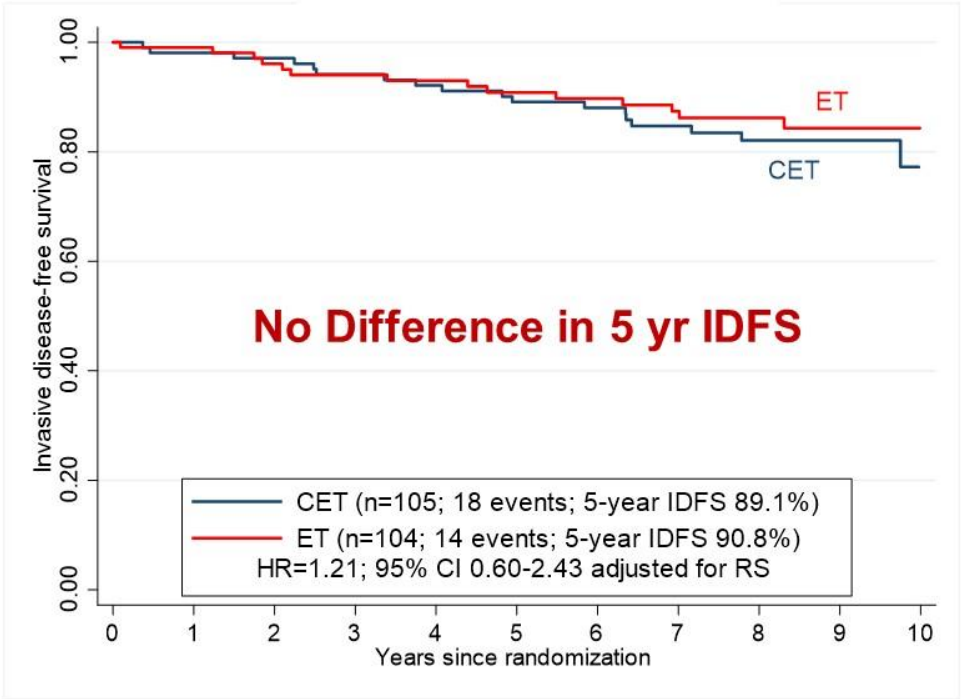


FSH = Follicular Stimulating Hormone

Bozza C et al Endo-Related Cancer 2014, Moolhuijsen L et al, J Clin Endo Metablism 2020, Wen J et al Front Endo 2021, Nelson P et al Human Reproduction Update 2023

"Premenopausal" < 55 years with low AMH have no IDFS benefit with chemotherapy

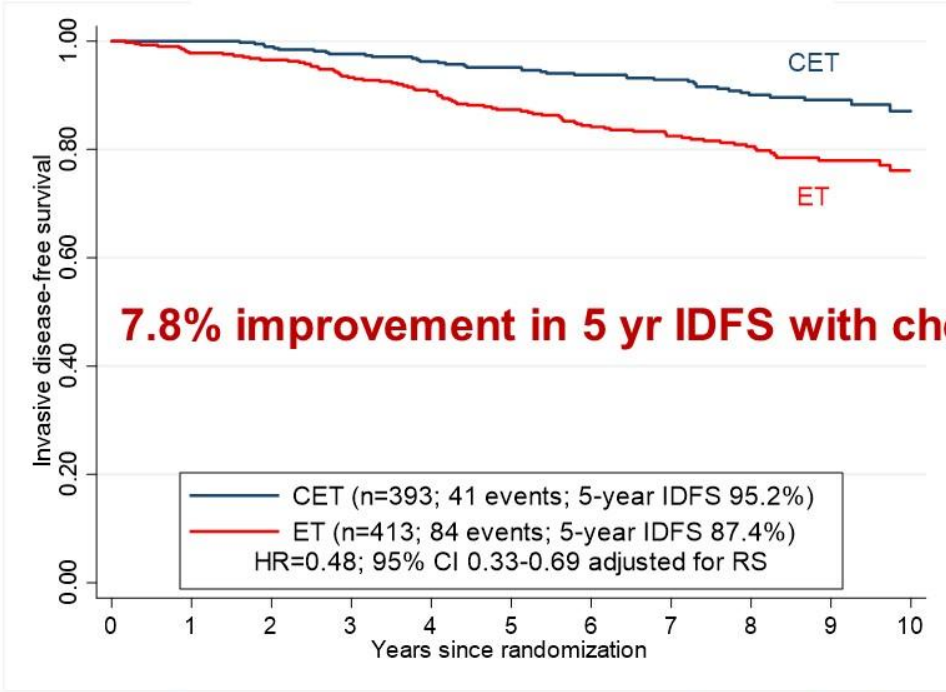
Low AMH (n=209)



No Difference in 5 yr IDFS

Postmenopausal: < 10 pg/mL

Medium/High AMH (n=806)



7.8% improvement in 5 yr IDFS with chemo

Premenopausal: ≥ 10 pg/mL

Significant interaction p=0.019, adjusting for RS

Ovarian Reserve Substudy Take Aways

1. Checking an AMH level in patients under 55 with HR+/Her2- BC and 1-3 positive lymph nodes may be helpful to decide whether a genomic assay (Oncotype or Mammaprint) can guide chemotherapy decisions

2. Study suggests it's highly likely that the benefit of chemotherapy is due to chemotherapy induced ovarian suppression

3. We need a phase III randomized trial to answer this question!...

BR009: Schema

- **Premenopausal; HR+/HER2- BC**
- **pN0 with RS 16-20 (high clinical risk) or RS 21-25**
- **pN1 with RS 0-25**

Stratification

- **Nodal Status (pN0 vs. pN1)**
- **RS (0-15 vs. 16-25)**

Randomization

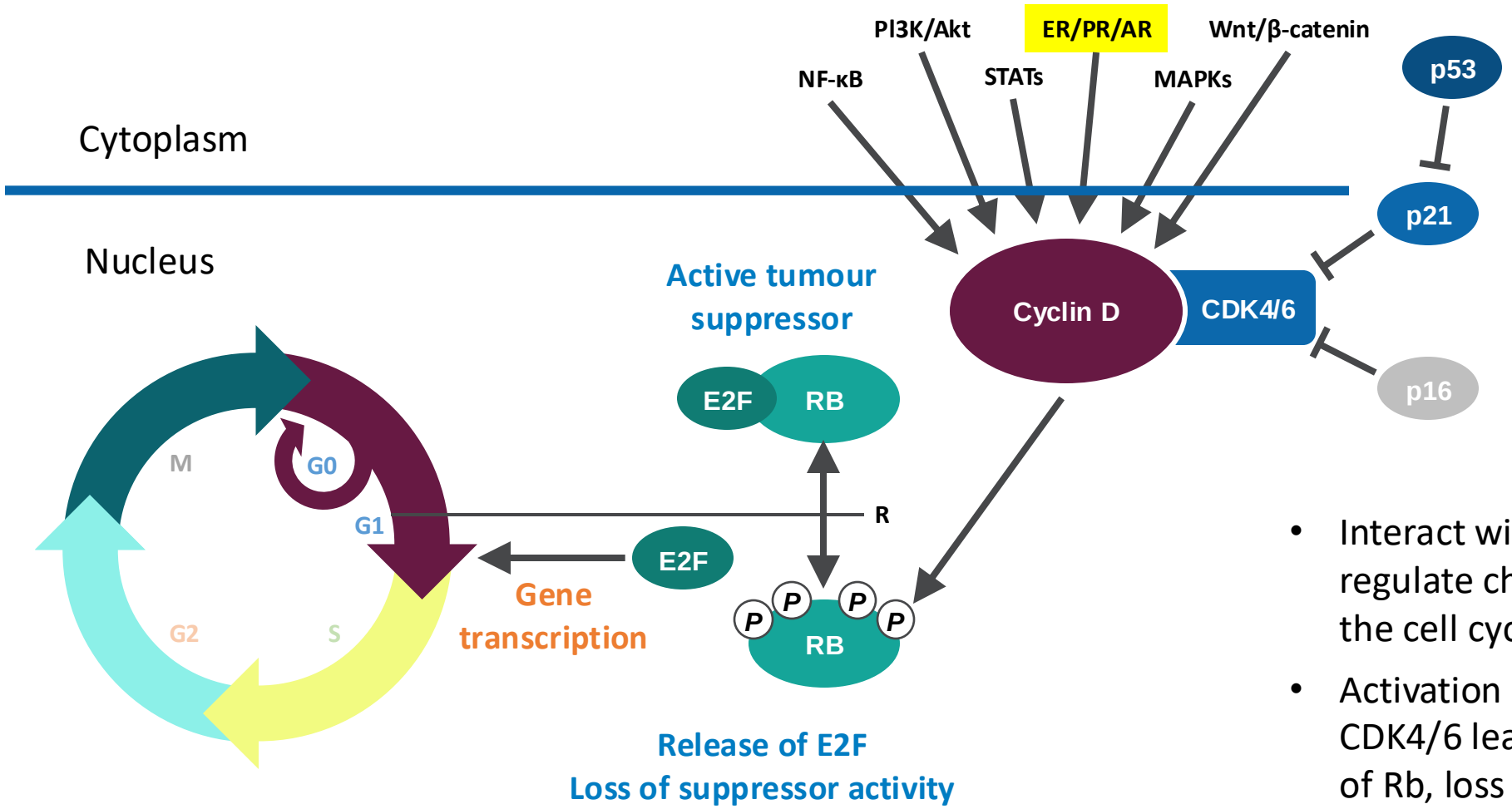
N=3,960

Chemotherapy + Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years

Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years

* Tamoxifen can be used if AI is not tolerated

Regulation of the G1/S Checkpoint in Breast Cancer



CDKs:

- Interact with partner cyclins to regulate checkpoints involved in the cell cycle
- Activation of Cyclin D with CDK4/6 leads to phosphorylation of Rb, loss of Rb's tumor suppressor activity, and entry into cell cycle

Lange, et al. *Endocr Rel Cancer.* 2011;18:C19-C24; 1. Caldon CE, et al. *J Cell Biochem.* 2006;97:261-274; 2. Buckley MF, et al. *Oncogene*. 1993;8:2127-2133; 3. Dickson C, et al. *Cancer Lett.* 1995;90:43-50; 4. Finn RS, et al. *Breast Cancer Res.* 2009;11:R77.

monarchE: Study Design[1,2]

Eligibility

- HR+/HER2– high-risk EBC
- Women (regardless of menopausal status) or men
- Underwent definitive surgery of the primary breast tumor
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on clinical pathological features (91% of pts)

- ≥4 ALNs, or
- 1-3 ALNs and ≥1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on Ki-67 (9% of pts)

- 1-3 ALN
- Tumor size < 5 cm and grade < 3
- Ki-67 ≥ 20%[3,a]

Randomized 1:1

N=5637

- Abemaciclib 150 mg bid + ET[b]
- ET[b]

On-study treatment period: 2 years
Follow-up period: ET 3-8 years as clinically indicated

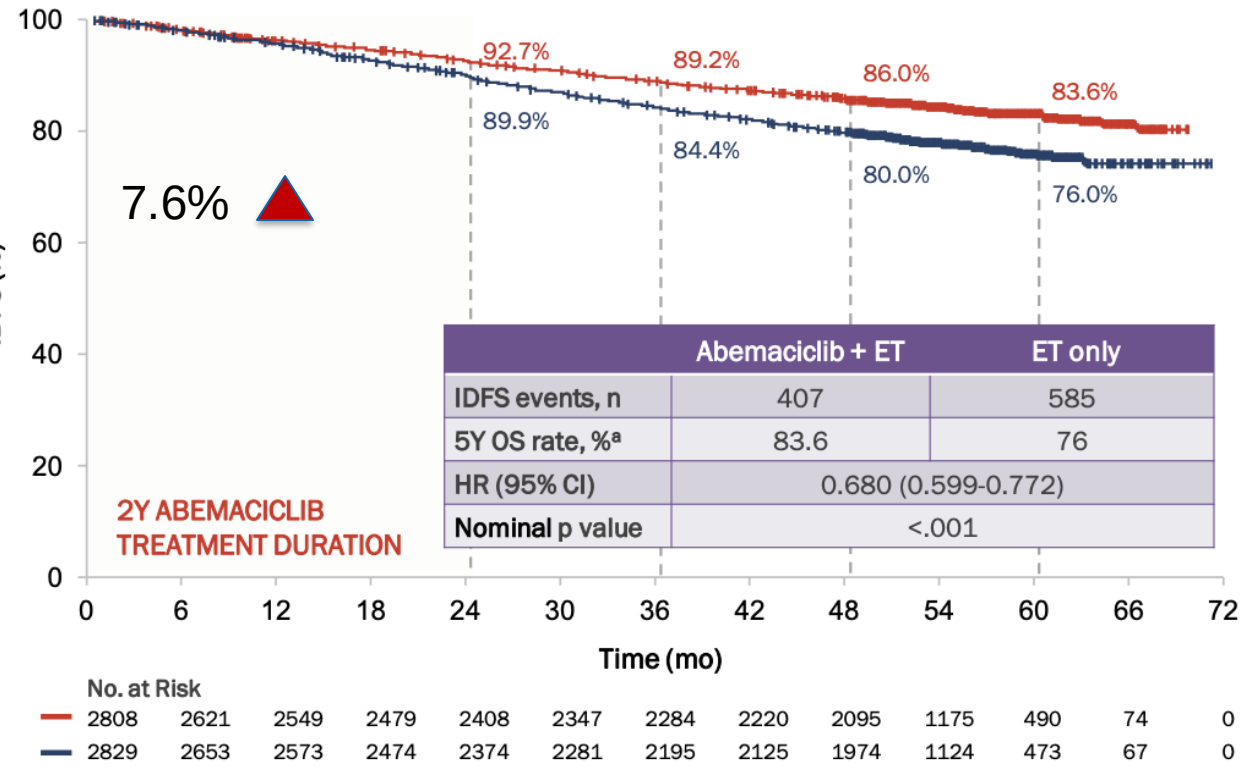
[a] Ki-67 expression was centrally assessed in all patients with suitable untreated breast tissue via IHC during the study screening period. Cohort 1 was not required to submit a tissue sample prior to randomization, but a sample was requested, where available, to support Ki-67 analyses. Cohort 2 had to submit an untreated tissue sample for Ki-67 analysis to determine eligibility.[3]

[b] ET includes antiestrogen agents (eg, tamoxifen) or aromatase inhibitors ± a gonadotropin-releasing hormone agonist.

1. Harbeck N, et al. *Ann Oncol.* 2021;32(12):1571-1581. 2. ClinicalTrals.gov. Accessed October 28, 2021. https://clinicaltrials.gov/ct2/show/NCT03155997 3. Johnston SRD, et al. *J Clin Oncol.* 2020;38(34):3987-3998.

monarchE Data at 60 Months' Median Follow-Up: IDFS

IDFS of ITT



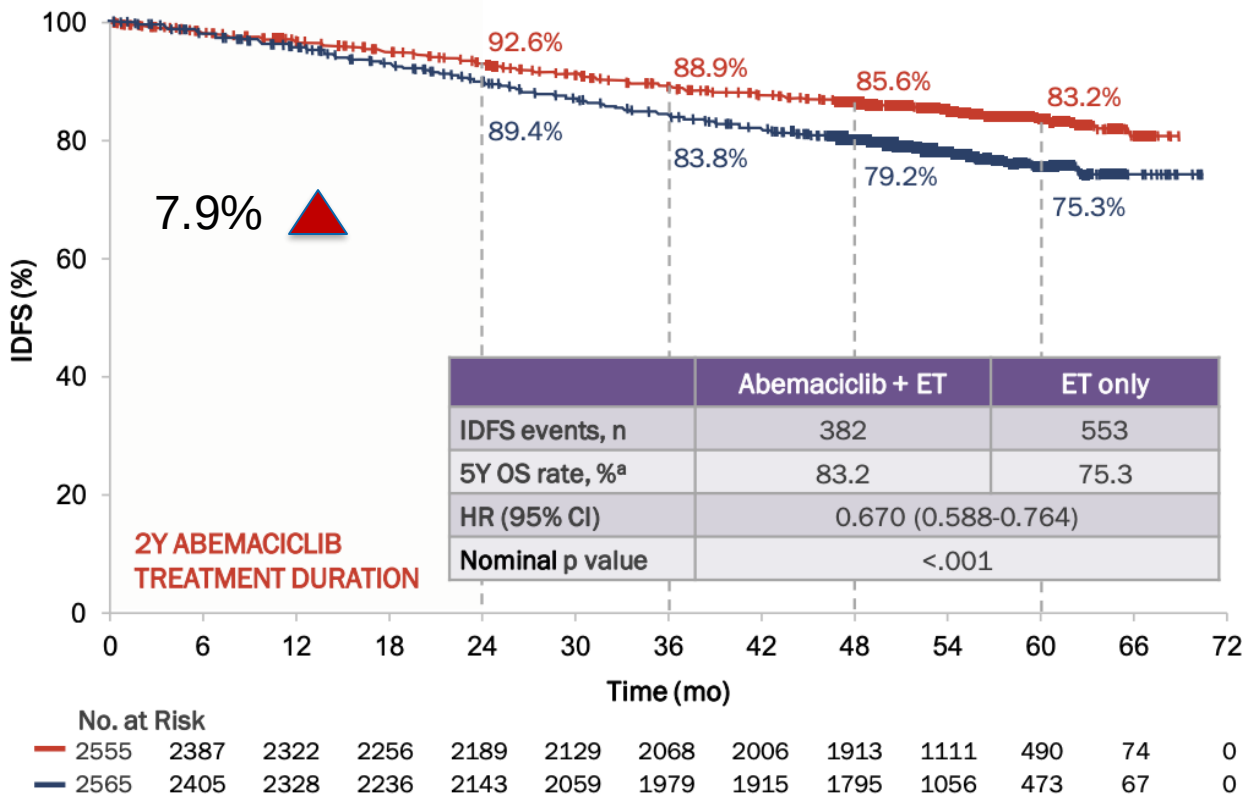
	Abemaciclib + ET	ET only
IDFS events, n	407	585
5Y OS rate, %[a]	83.6	76
HR (95% CI)	0.680 (0.599-0.772)	
Nominal p value	<.001	

No. at Risk

2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0

The IDFS benefit was maintained in the ITT population, with an absolute improvement of 7.6% at 5 years compared with 2- and 3-year DRFS rates of 2.8% and 4.8% respectively

IDFS of Cohort 1[b]



	Abemaciclib + ET	ET only
IDFS events, n	382	553
5Y OS rate, %[a]	83.2	75.3
HR (95% CI)	0.670 (0.588-0.764)	
Nominal p value	<.001	

No. at Risk

2555	2387	2322	2256	2189	2129	2068	2006	1913	1111	490	74	0
2565	2405	2328	2236	2143	2059	1979	1915	1795	1056	473	67	0

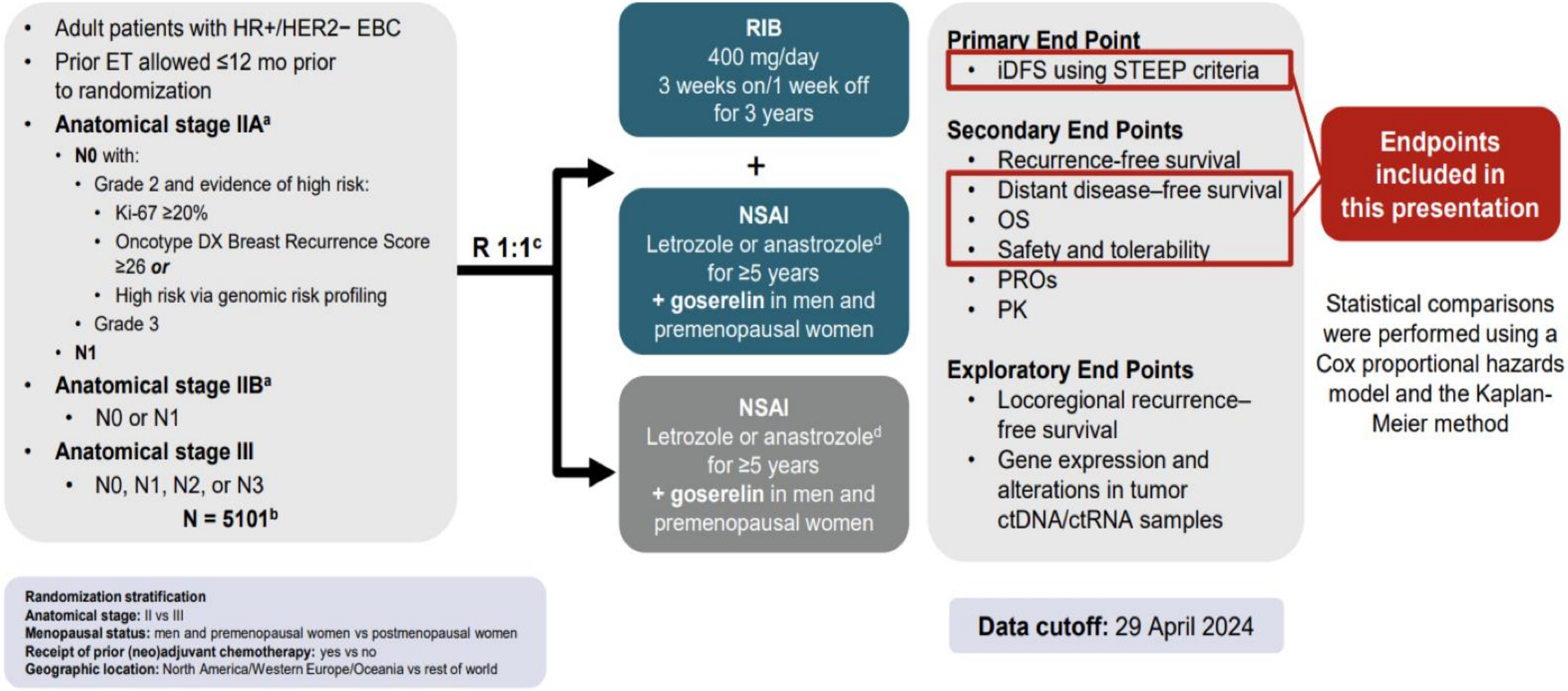
The IDFS benefit was maintained in the Cohort 1 subpopulation, with an absolute improvement of 7.9% at 5 years compared with 2- and 3-year IDFS rates of 3.2% and 5.1% respectively

[a]mFU of 54mo. [b]Statistical significance was achieved in the Cohort 1 High Ki-67 population at the primary outcome analysis. This population was the basis of approval by the FDA.

Rastogi P et al. *J Clin Oncol.* 2024;42(9):987-993.

Consistent benefit across ER & PR expression levels, Ki-67, high/low RS, gBRCAm, and molecular subtypes

NATALEE Study Design



Fasching P et al ESMO 2024

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NATALEE and monarchE Population Criteria

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IB	T0N1mi/T1N1mi		Only if grade 3 or Ki-67 ≥20%
Stage IIA	T0N1		Only if grade 3 or Ki-67 ≥20%
	T1N1		Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if grade 3 or grade 2 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		

N0 not allowed in monarchE

NATALEE allowed[3]:
- Any **N1, N2,** or **N3**
- **N0: T2** (*G2 + high genomic risk or Ki-67 ≥20% or G3*), **T3,** or **T4**

monarchE allowed[4]:
- Any **N2** or **N3**
- **N1** only if G3 or tumor size ≥5 cm or Ki-67 ≥20%

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; mi, micrometastasis; N, node; T, tumor; TN, tumor, node.
[a] High risk as determined by Oncotype DX/Prosigna/MammaPrint/EndoPredict.[2]

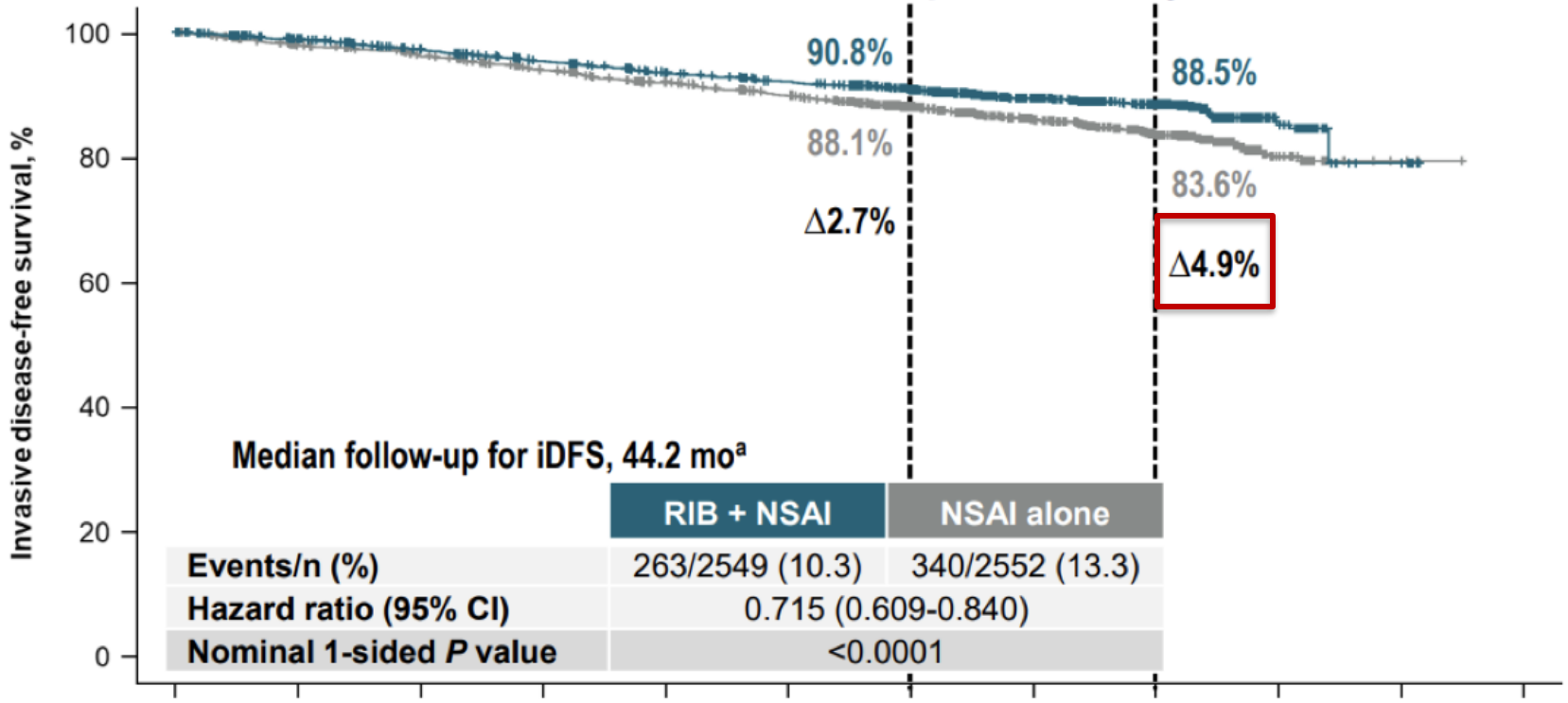
References: 1. Amin MB et al. AJCC Cancer Staging Manual. 8th ed. Springer; 2017:587-636. **2**. Slamon D et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.
3. Slamon D et al. *N Engl J Med*. 2024;390(12):1080-1091. **4**. Harbeck N et al. *Ann Oncol*. 2021;32(12):1571-1581.
Table adapted from Slamon D et al. with permission.

NATALEE Trial 2nd Interim Analysis

iDFS in ITT Population

BARCELONA 2024 ESMO congress

Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment



	RIB + NSAI	NSAI alone
Events/n (%)	263/2549 (10.3)	340/2552 (13.3)
Hazard ratio (95% CI)	0.715 (0.609-0.840)	
Nominal 1-sided *P* value	<0.0001	

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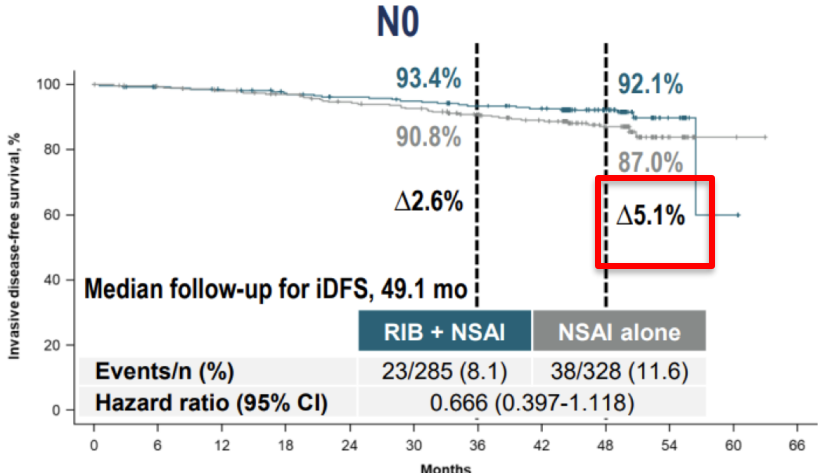
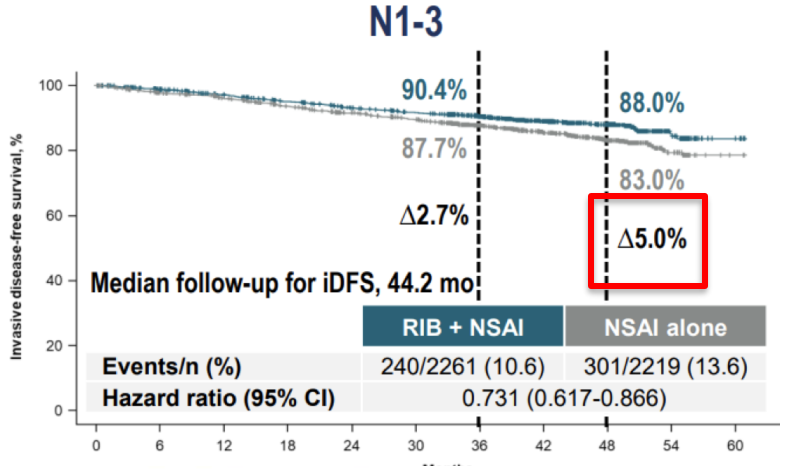
iDFS by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease



	RIB + NSAI	NSAI alone
Events/n (%)	23/285 (8.1)	38/328 (11.6)
Hazard ratio (95% CI)	0.666 (0.397-1.118)	

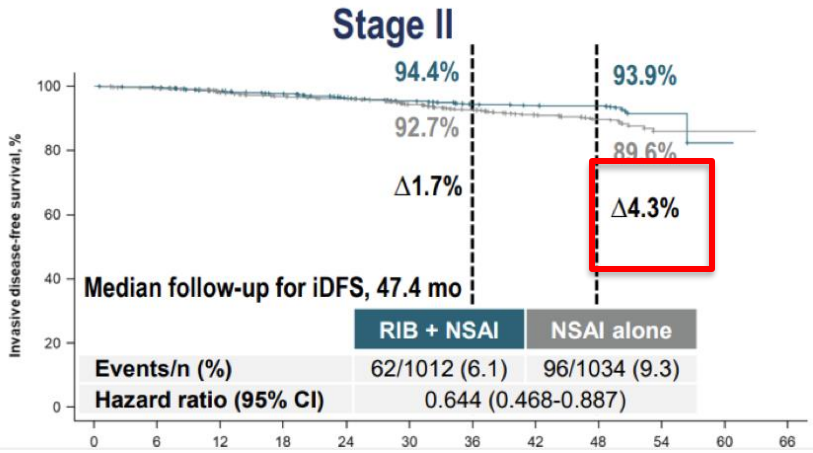


	RIB + NSAI	NSAI alone
Events/n (%)	240/2261 (10.6)	301/2219 (13.6)
Hazard ratio (95% CI)	0.731 (0.617-0.866)	

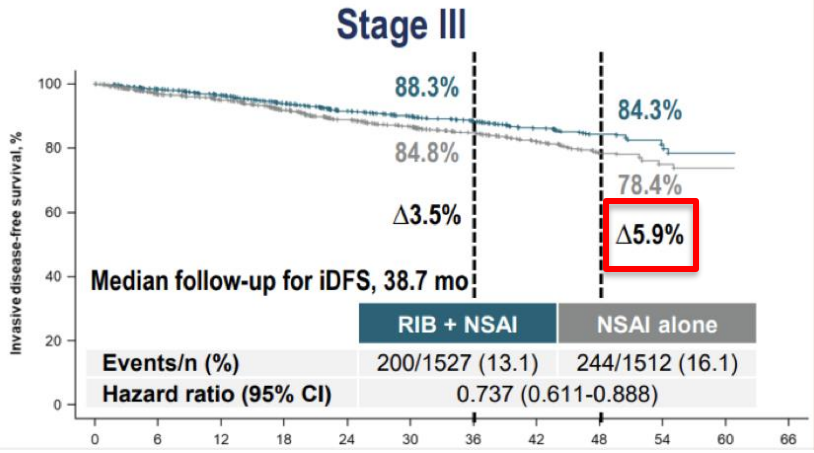
Overall survival data immature

iDFS by Stage

RIB + NSAI demonstrated an increasing magnitude of iDFS benefit over time for stage II/III disease



	RIB + NSAI	NSAI alone
Events/n (%)	62/1012 (6.1)	96/1034 (9.3)
Hazard ratio (95% CI)	0.644 (0.468-0.887)	



	RIB + NSAI	NSAI alone
Events/n (%)	200/1527 (13.1)	244/1512 (16.1)
Hazard ratio (95% CI)	0.737 (0.611-0.888)	

Fasching P et al ESMO 2024

CDK4/6 inhibitors in Early HR+ Breast Cancer

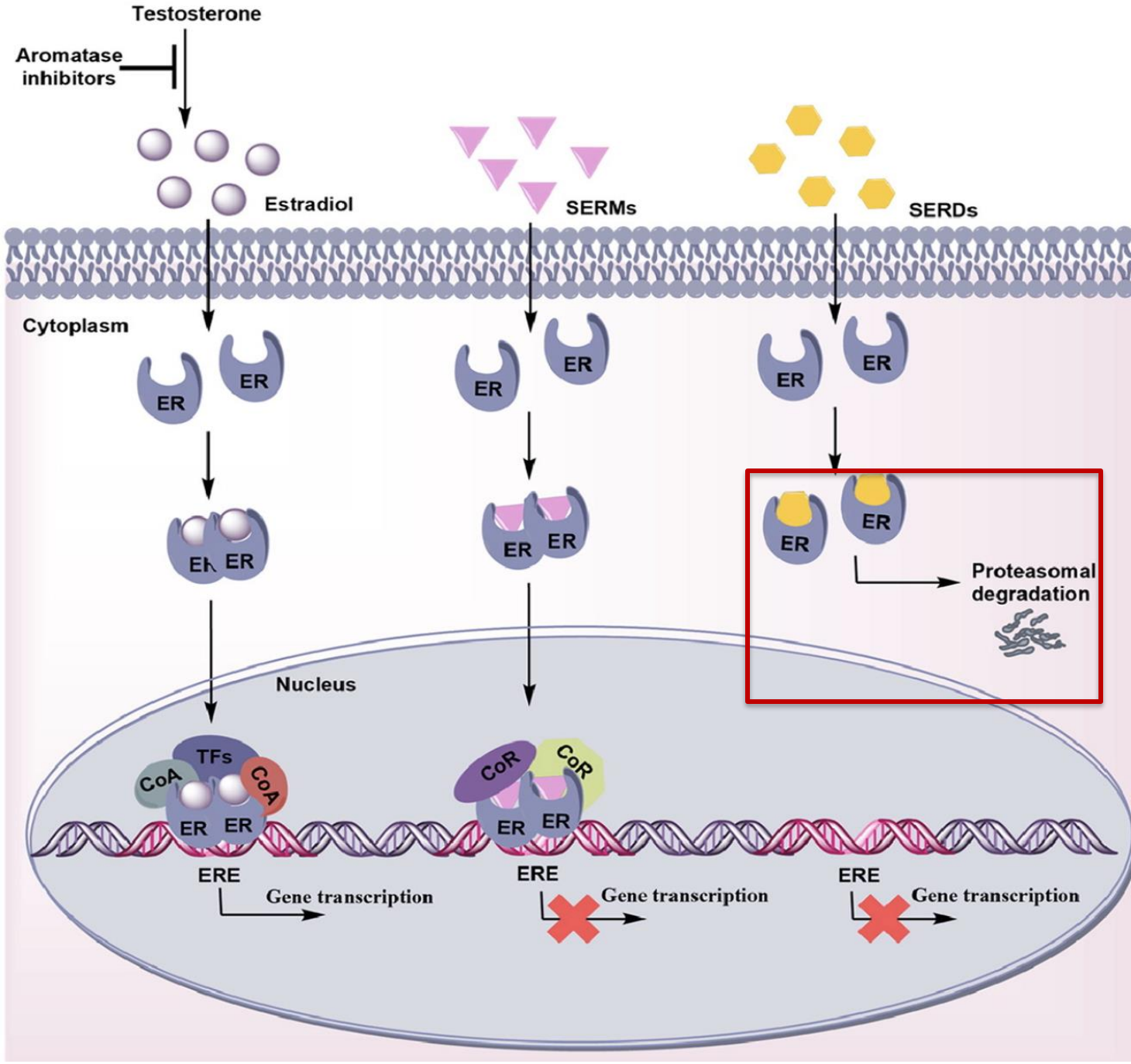
- 2 years of adjuvant abemaciclib significantly improves 5-year iDFS and DDFS in N+ high risk HR+ HER2- EBC patients

- 3 years of ribociclib significantly improves 4-year iDFS and DDFS in N+ and high risk N0 HR+ HER2- EBC patients
  - recent FDA approval establishes new therapeutic option

Oral SERDs

(selective estrogen receptor degraders)

- Already approved in Stage IV ER+/Her2- breast cancer
- Effective in ESR1 mutant cancers
- Now being investigated in the curative setting!



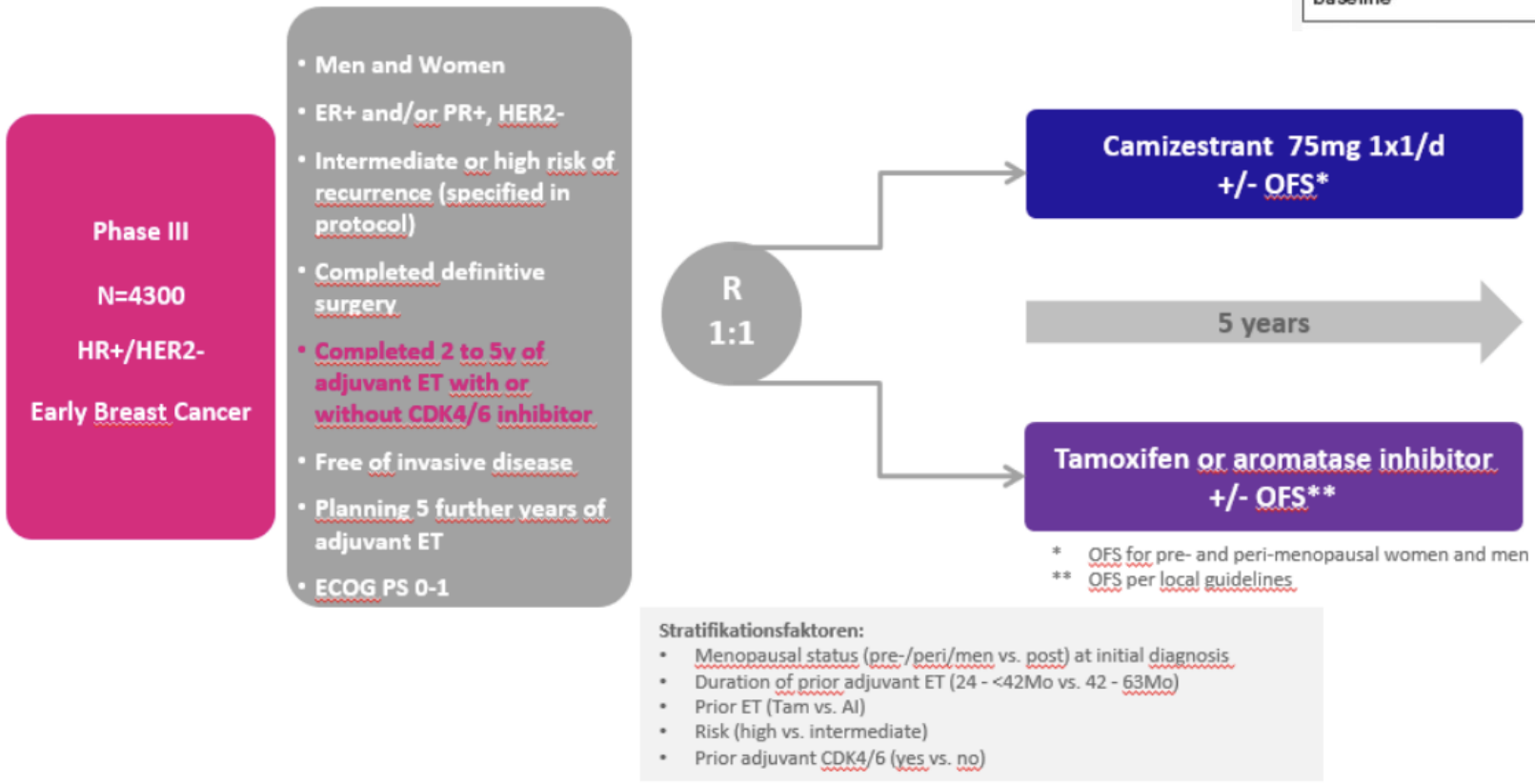
Patel et.al. Pharmcology and Therapeutics, 2018

CAMBRIA-1 – now enrolling at UCSD

- Oral SERD
- Camizestrant was superior to fulvestrant in the SERENA-2 trial among pts with HR+ MBC who had progressed on 1 line of ET

TABLE 1: Median Progression-Free Survival in Subsets From SERENA-2

Outcome	Camizestrant (75 mg/d)	Camizestrant (150 mg/d)	Fulvestrant (500 mg/d)
PFS, overall	7.2 months	7.7 months	
Adjusted HR vs fulvestrant	HR = 0.58 (*P* = .0124)	HR = 0.67 (*P* = .0161)	3.7 months
PFS, prior CDK4/6 inhibitor	5.5 months HR = 0.49	3.8 months HR = 0.68	2.1 months
PFS, visceral metastases	7.2 months HR = 0.43	5.6 months HR = 0.55	2.0 months
PFS, *ESR1*-mutant at baseline	6.3 months HR = 0.33	9.2 months HR = 0.55	–



Eligibility Criteria:

- T4Nany
- T3Nany
- Any T + ≥2+LN
- T1c-T2 + 1+LN and:
  - Grade 3, high risk NGS, or Ki67 ≥20%
- T1c-T2 + N0 and:
  - Grade 3, high risk NGS, or Ki67 ≥20% or prior cytotoxic chemo

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Questions?