RISK BASED CONSIDERATIONS FOR ADJUVANT THERAPY IN HR+ EBC

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Disclosure of interest

Consulting/Advisor: Roche , Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp&Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics.

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Stock: MedSIR, Nektar Pharmaceuticals, Leuko (relative)
Travel, accommodation, expenses: Roche, Novartis, Eisai, pfizer, Daiichi Sankyo, Astrazeneca, Gilead.

Patents: Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A.

Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/ 0338368 A1.

How to select patients that will need or not chemotherapy? Adjuvant

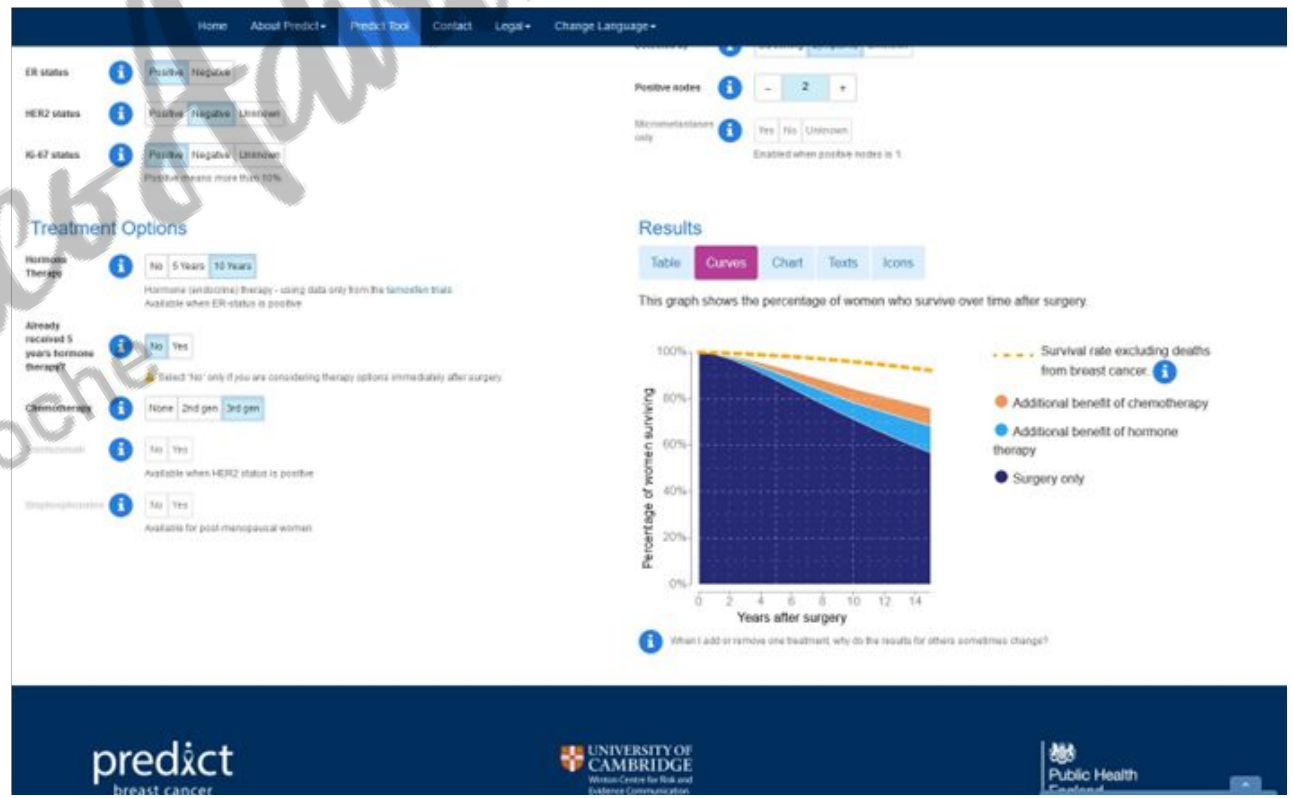
High risk factors (at least one):

- Tumor grade III
- pT3
- pN1 in premenopausal
- pN2 in postmenopausal

Low risk factors (all present):

- Tumor grade I
- pT1
- pN0/i+/mi
- Low baseline Ki67
- No LVI

Online tools that may help in estimating the benefit of chemotherapy (https://breast.predict.nhs.uk/tool)



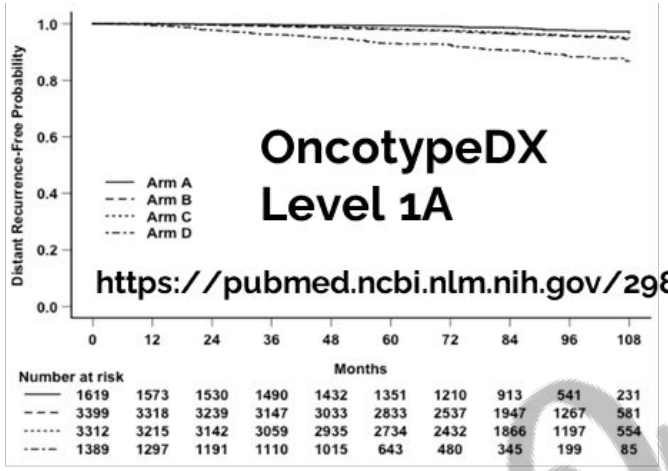
Current Guidelines for determining High Risk in HER-+/HER2- eBC

FDA,[1] NCCN[2]	ASCO[3]
▪ ≥ 4 positive ALNs, or ▪ 1 to 3 positive ALNs and ≥ 1 of the following: ▪ Tumor grade 3 ▪ Tumor size ≥ 5 cm	▪ ≥ 4 positive ALNs or ▪ 1 to 3 positive ALNs and ≥ 1 of the following: ▪ Grade 3 ▪ Tumor size ≥ 5 cm ▪ Ki-67 ≥ 20%

ALN, axillary lymph node; ASCO, American Society of Clinical Oncology; BC, breast cancer; EBC, early breast cancer; ET, endocrine therapy; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; NCCN, National Comprehensive Cancer Network.

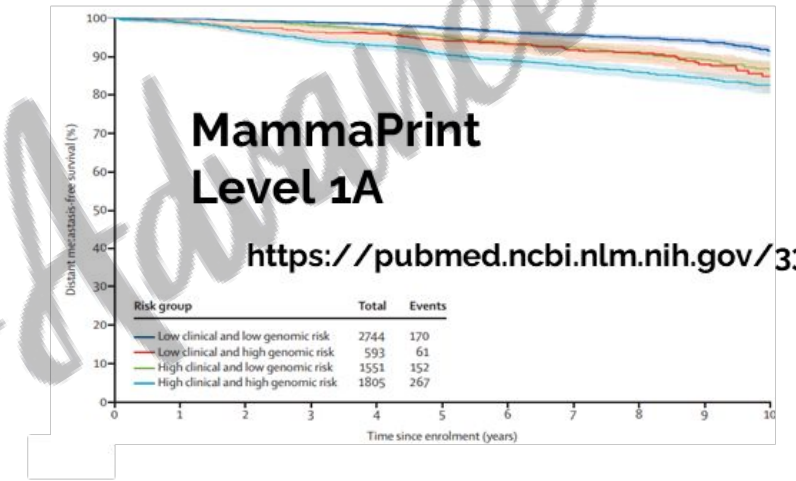
1. Abemaciclib [PI]. Approved 2017. Revised March 2023; 2. NCCN. 2023. Accessed September 9, 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 3. Giordano SH, et al. J Clin Oncol. 2022;40:307-309.

Prognostic gene expression-based tests for early-stage HR+/HER2-



OncotypeDX
Level 1A

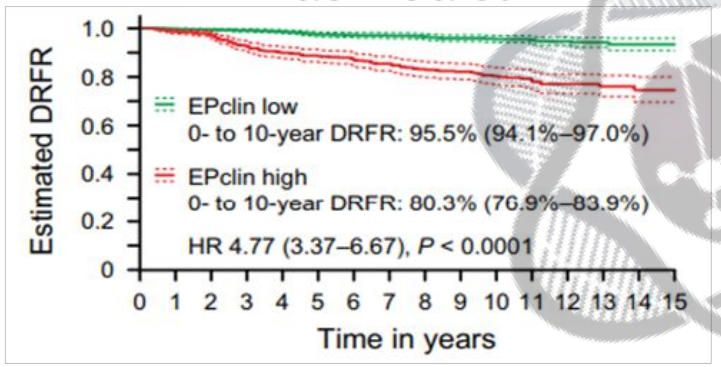
https://pubmed.ncbi.nlm.nih.gov/29860917/



MammaPrint
Level 1A

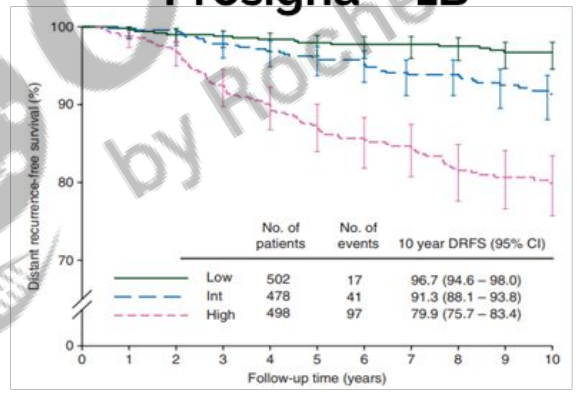
https://pubmed.ncbi.nlm.nih.gov/33721561/

EndoPredict – 1B



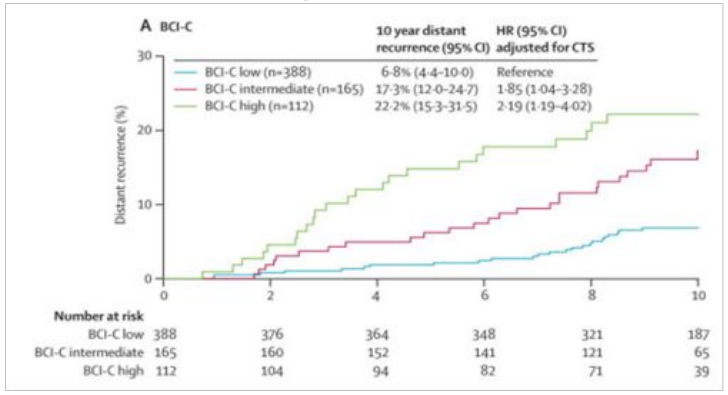
https://pubmed.ncbi.nlm.nih.gov/31064782/

Prosigna – 1B



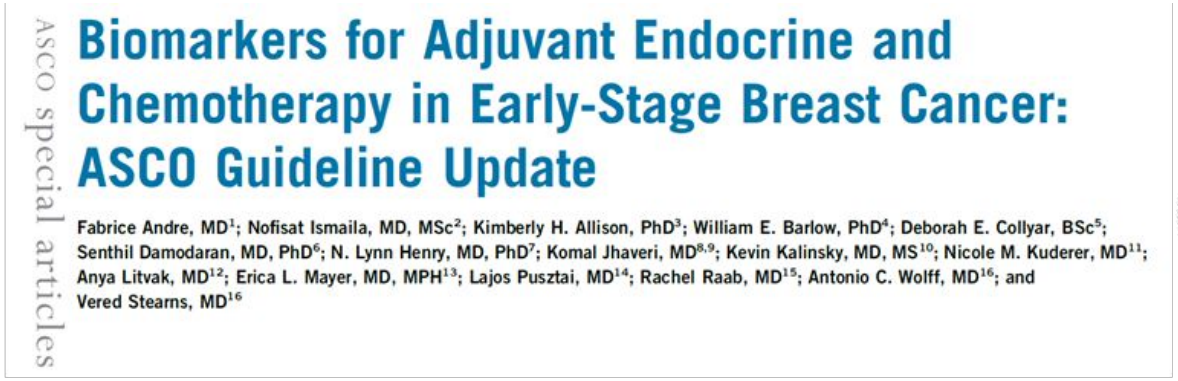
https://pubmed.ncbi.nlm.nih.gov/24347518/

BCI – 1B



https://pubmed.ncbi.nlm.nih.gov/24035531/

Prognostic gene expression-based tests for early-stage HR+/HER2-



2022 ASCO Guidelines in HR+/HER2-

In front of a patient with early-stage HR+/HER2-, if you have doubts about indicating chemotherapy, a genomic test can help you make that decision:

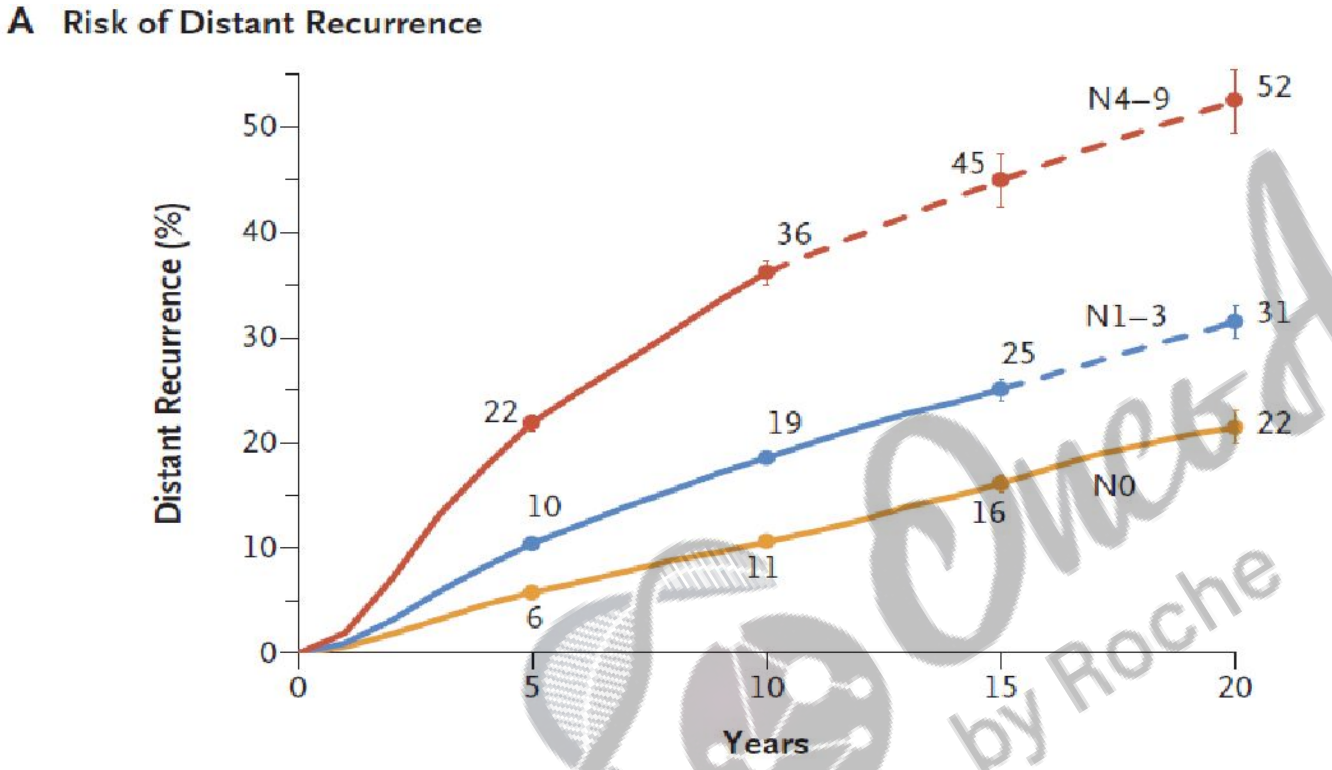
In **post-menopausal** patients with N0 or pN1:

- Genomic low or intermediate risk: no chemo
- Genomic high risk: chemo

In **pre-menopausal** patients with pN0:

- Genomic low risk: no chemo
- Genomic intermediate or high risk: chemo or LHRH or both?

Long term outcomes



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

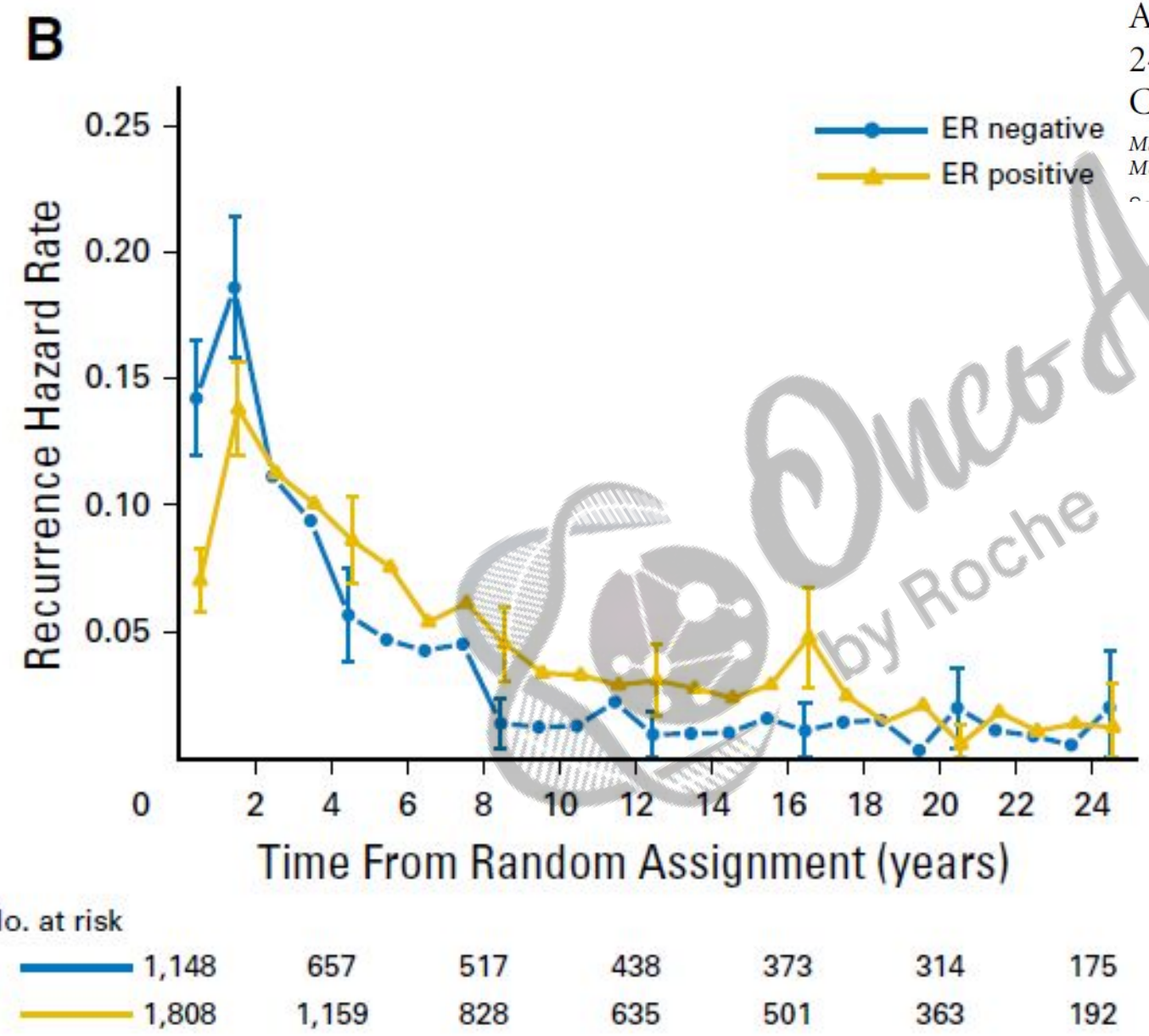
No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D.,

Which patients need additional modern therapies on top of 5 years of standard endocrine therapy ?

Annual Recurrence HR



Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V

Marco Colleoni, Zhuoxin Sun, Karen N. Price, Per Karlsson, John F. Forbes, Beat Thürlimann, Lorenzo Gianni, Monica Castiglione, Richard D. Gelber, Alan S. Coates, and Aron Goldhirsch

What should be the optimal duration of additional therapy with a CDK 4/6 inhibitor ?

1 year ?

2 years?

5 years ?

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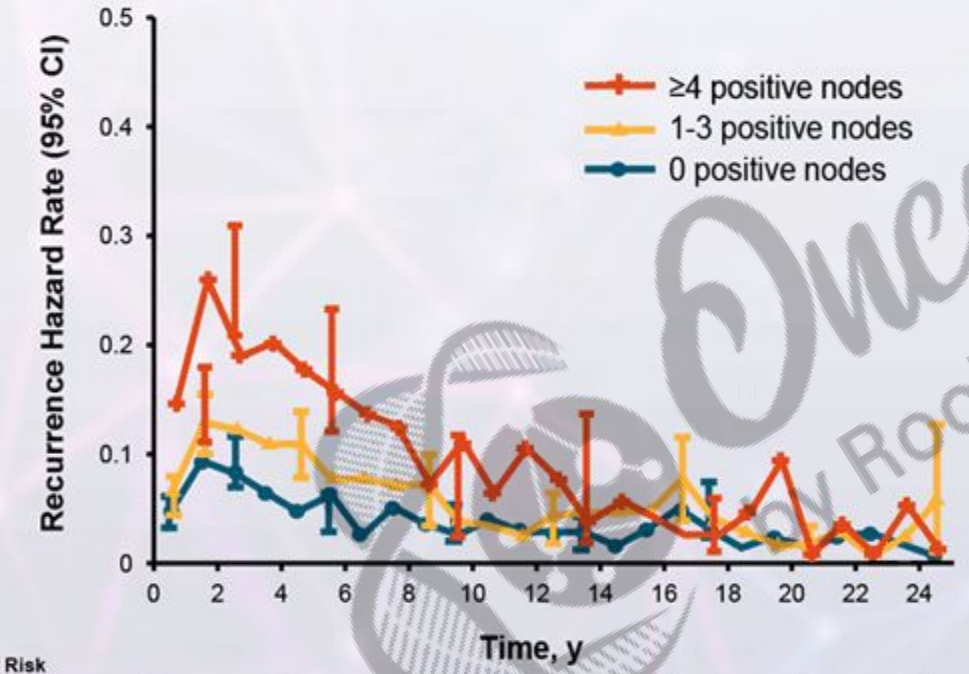
JOURNAL OF CLINICAL ONCOLOGY

Risk of Recurrence with eBC: IBCSG Trials I to V

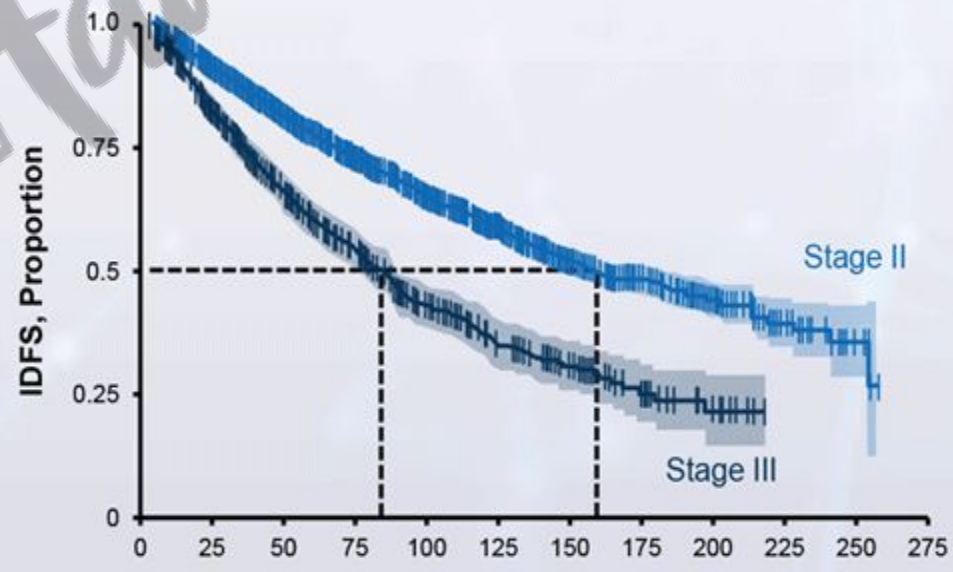
Annual Hazard of BC Recurrence for ER+ BC



No. at Risk							
0 positive LNs	640	488	402	316	256	199	124
1-3 positive LNs	671	445	306	242	185	121	48
≥4 positive LNs	497	226	120	77	60	43	20

Invasive Disease-Free Survival of Stage II/III Breast Cancer Patients: RWE US Database 1995-2021

IDFS in Patients With Stage II and Stage III Disease



No. at Risk (No. Censored)												
Stage II	2,535 (0)	2,098 (199)	1,405 (693)	1,006 (967)	702 (1,179)	474 (1,347)	291 (1,484)	174 (1,582)	89 (1,655)	31 (1,707)	7 (1,729)	0 (1,735)
Stage III	598 (0)	433 (56)	284 (127)	193 (172)	128 (201)	72 (239)	46 (257)	23 (275)	9 (266)	0 (295)	0 (295)	0 (295)

1. Collioni M et al. *J Clin Oncol*. 2016;34:927-935. 2. O'Shaughnessy J et al. SABCS 2022. Oral presentation.

PeerView.com

Improving Overall Survival in HR+ Early Breast Cancer

A. Tamoxifen vs No Treatment[1]

30% reduction in risk of death

Breast cancer mortality Δ at 15 years: 9.2%

B. Aromatase inhibitor (AI) vs Tamoxifen[2]

15% reduction in risk of death

Breast cancer mortality Δ at 10 years: 2.1%

C. 5 years ET vs extended AI[3]

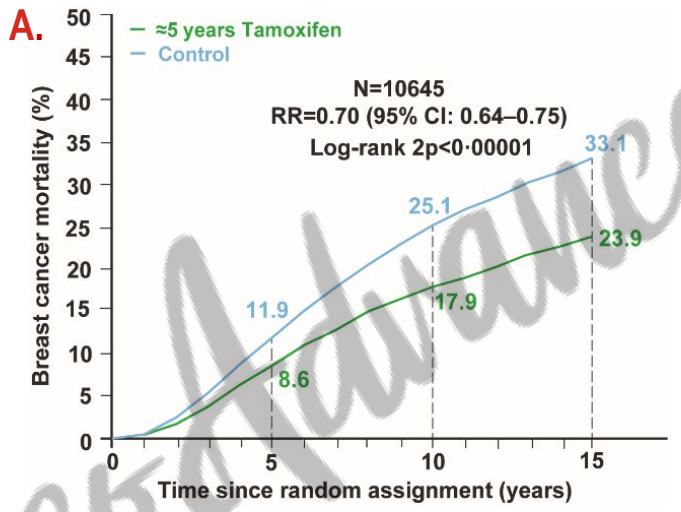
10% reduction is risk of death

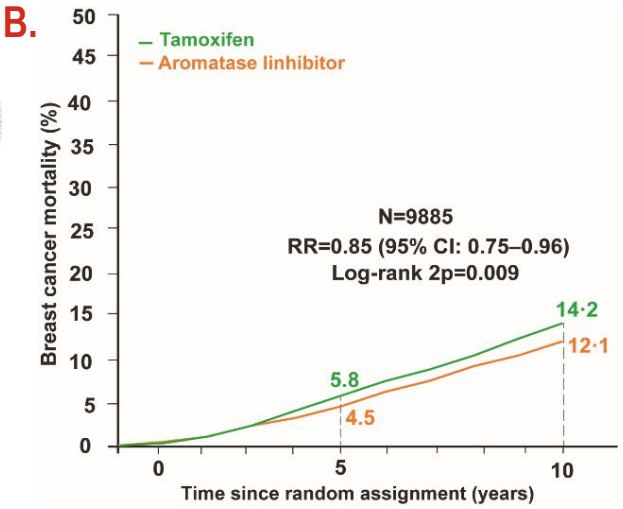
Breast cancer mortality Δ at 15 years: 0.6%

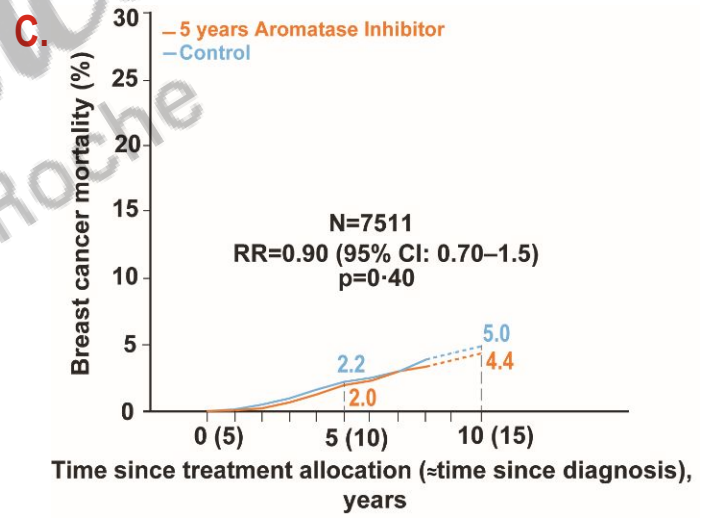
D. Exemestane + Ovarian Function Suppression (OFS) vs Tamoxifen[4]

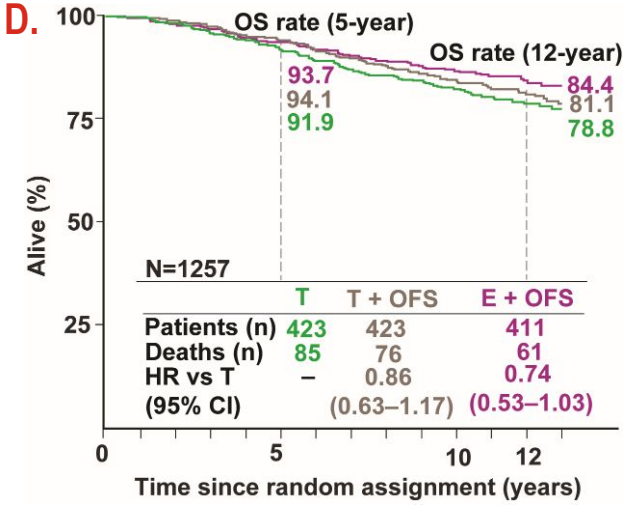
26% reduction in risk of death

Breast cancer mortality Δ at 12 years: 5.6%









E, exemestane; OFS, ovarian function suppression; RR, rate ratio; T, tamoxifen

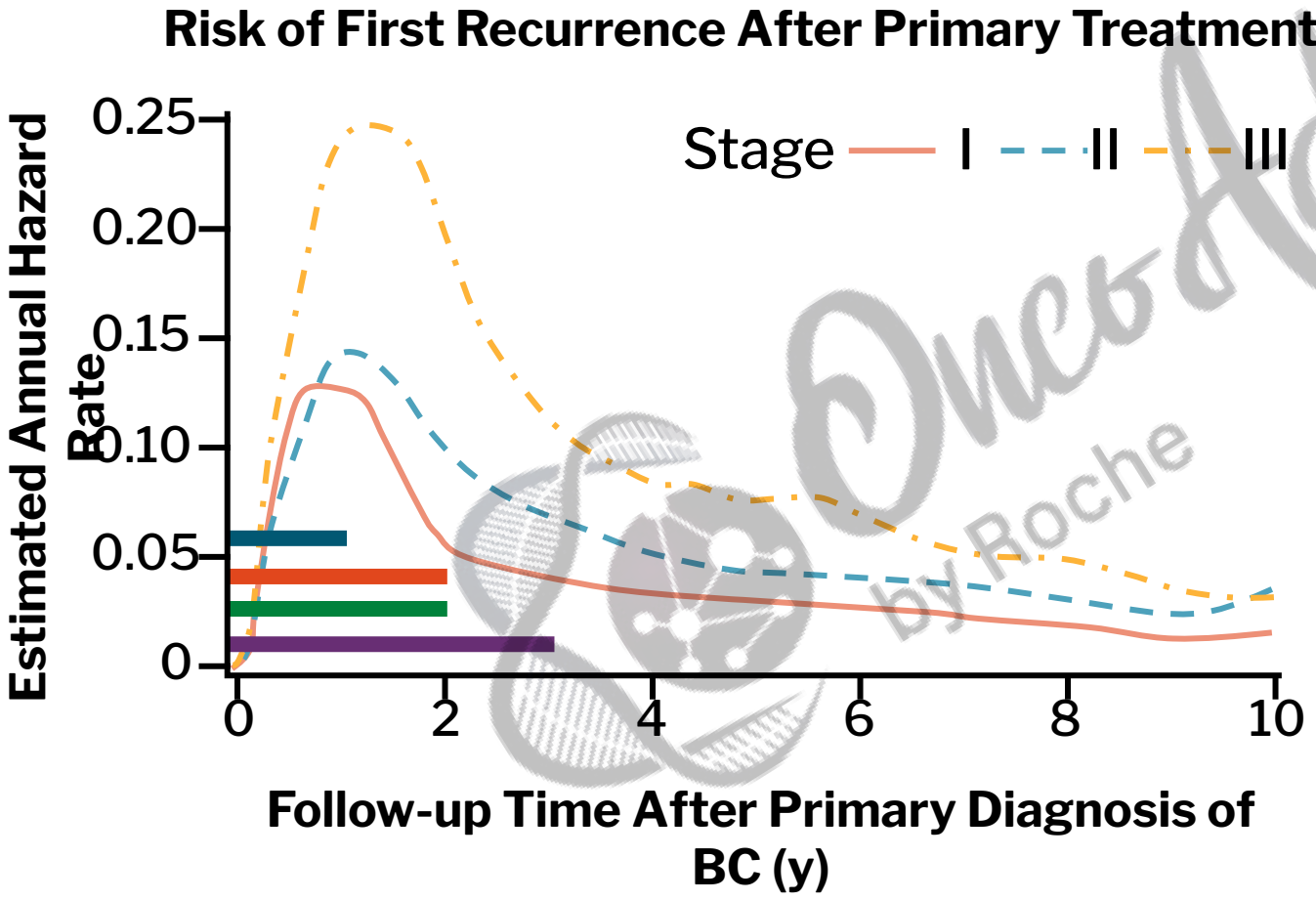
Data form:

1. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2011;378(9793):771–784.
2. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2015;386(10001):1341–1352.
3. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2025;406(10503):603–614.
4. Francis PA. *J Clin Oncol*. 2023;41(7):1370–1375.

Stephen Johnston, MD, PhD

Optimizing outcomes in patients with HR+/HER2- EBC

Is There a Role for CDK4/6 Inhibition for Early-Stage HR+ Disease?



PENELOPE-B
palbociclib
After neoadjuvant, high risk

monarchE
abemaciclib
High-risk anatomic factors, Ki67

PALLAS
palbociclib
Stage II, III

NATAL
EE
ribociclib
Stage II, III

- Cheng L, et al. Cancer Epidemiol Biomarkers Prev. 2012;21:800-809.

NATALEE

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

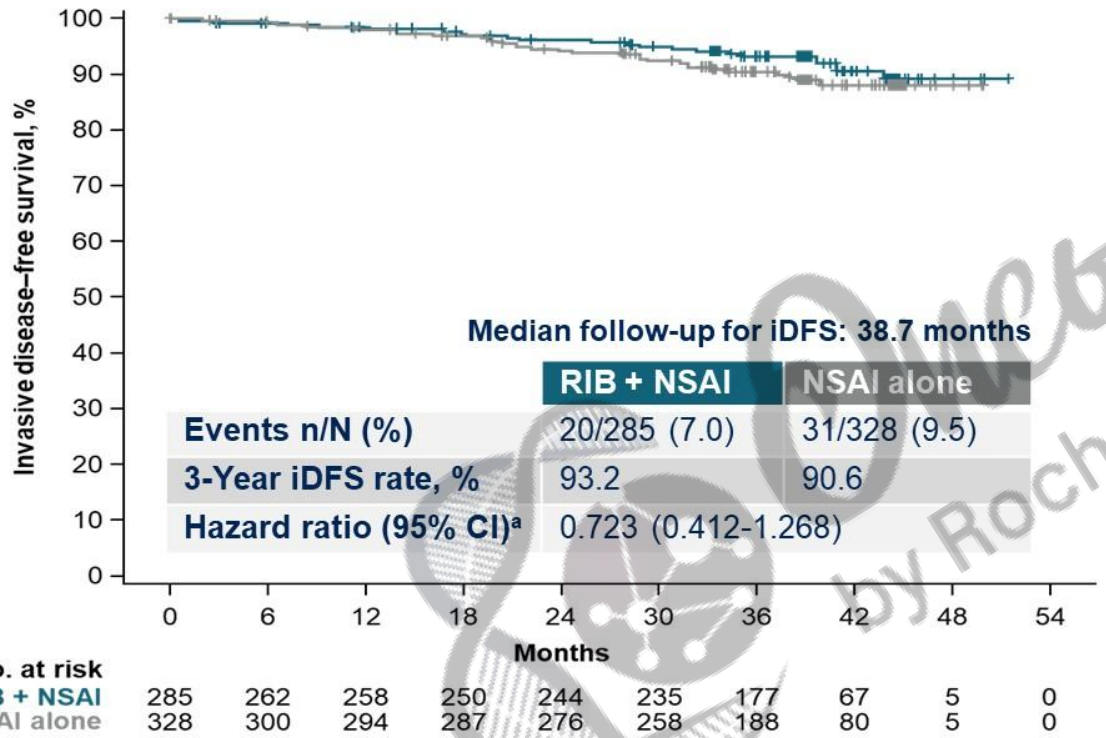
Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Slamon D, et al. ASCO 2023

Ribociclib improved iDFS, DDFS, and DRFS in the NATALEE node-negative subgroup

iDFS in Node-Negative Subgroup



Median follow-up for iDFS: 38.7 months

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

DDFS and DRFS in Node-Negative Subgroup

Efficacy outcome	RIB + NSAI n = 285	NSAI alone n = 328
DDFS		
Events, n	17	27
3-y rate (95% CI), %	94.3 (90.6-96.6)	91.5 (87.6-94.2)
Hazard ratio (95% CI)	0.703 (0.383-1.290)	
DRFS		
Events, n	12	23
3-y rate (95% CI), %	96.3 (93.0-98.1)	92.5 (88.8-95.1)
Hazard ratio (95% CI)	0.580 (0.289-1.170)	

[a] This was not a preplanned analysis and no formal *P* value was spent or tested.
DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; iDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

PRESENTED BY: Denise A Yardley, MD

MonarchE

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- 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**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

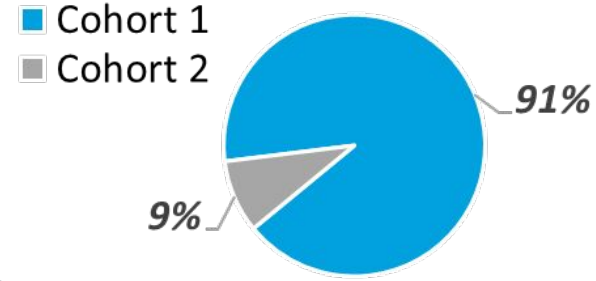
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

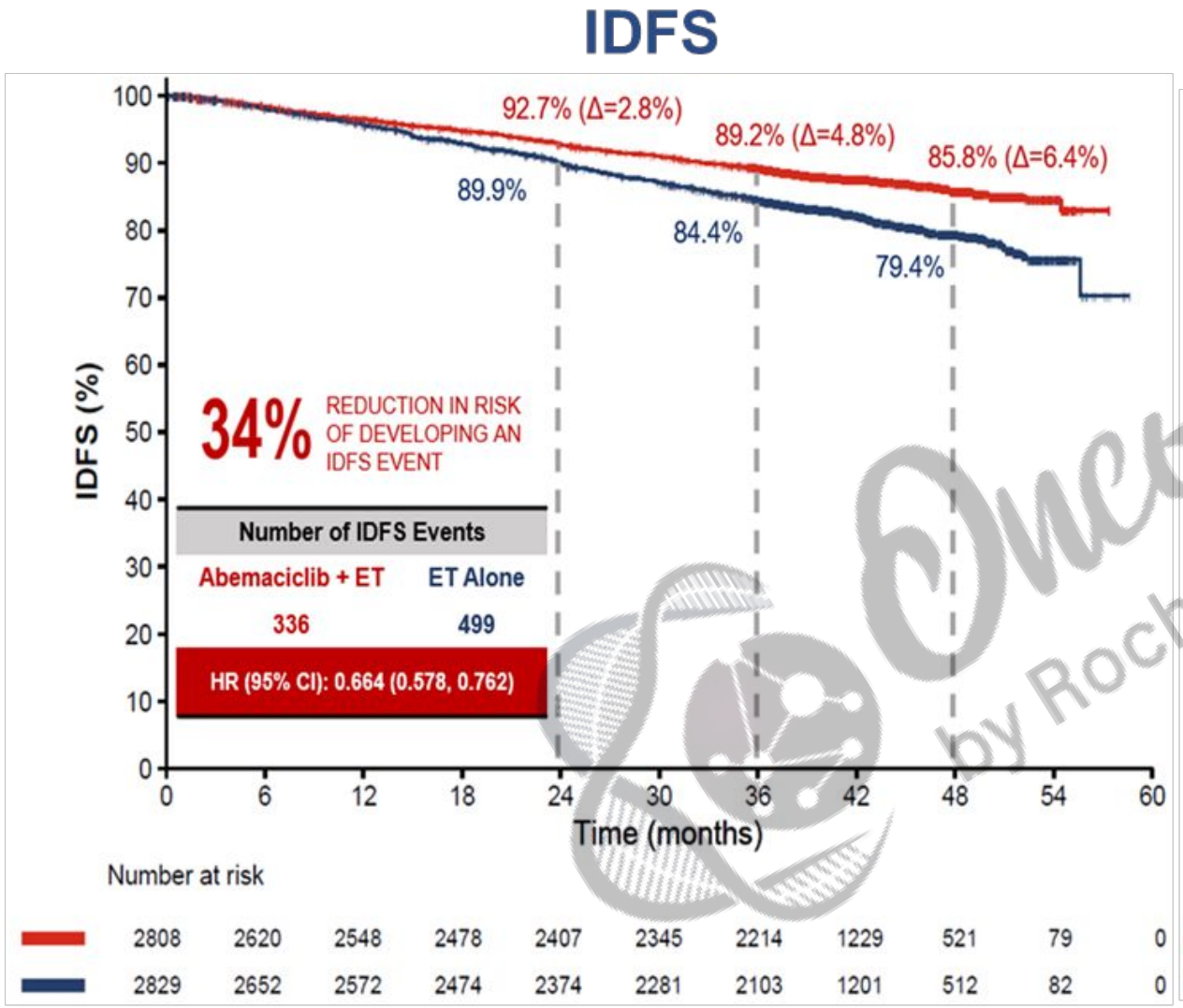
Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

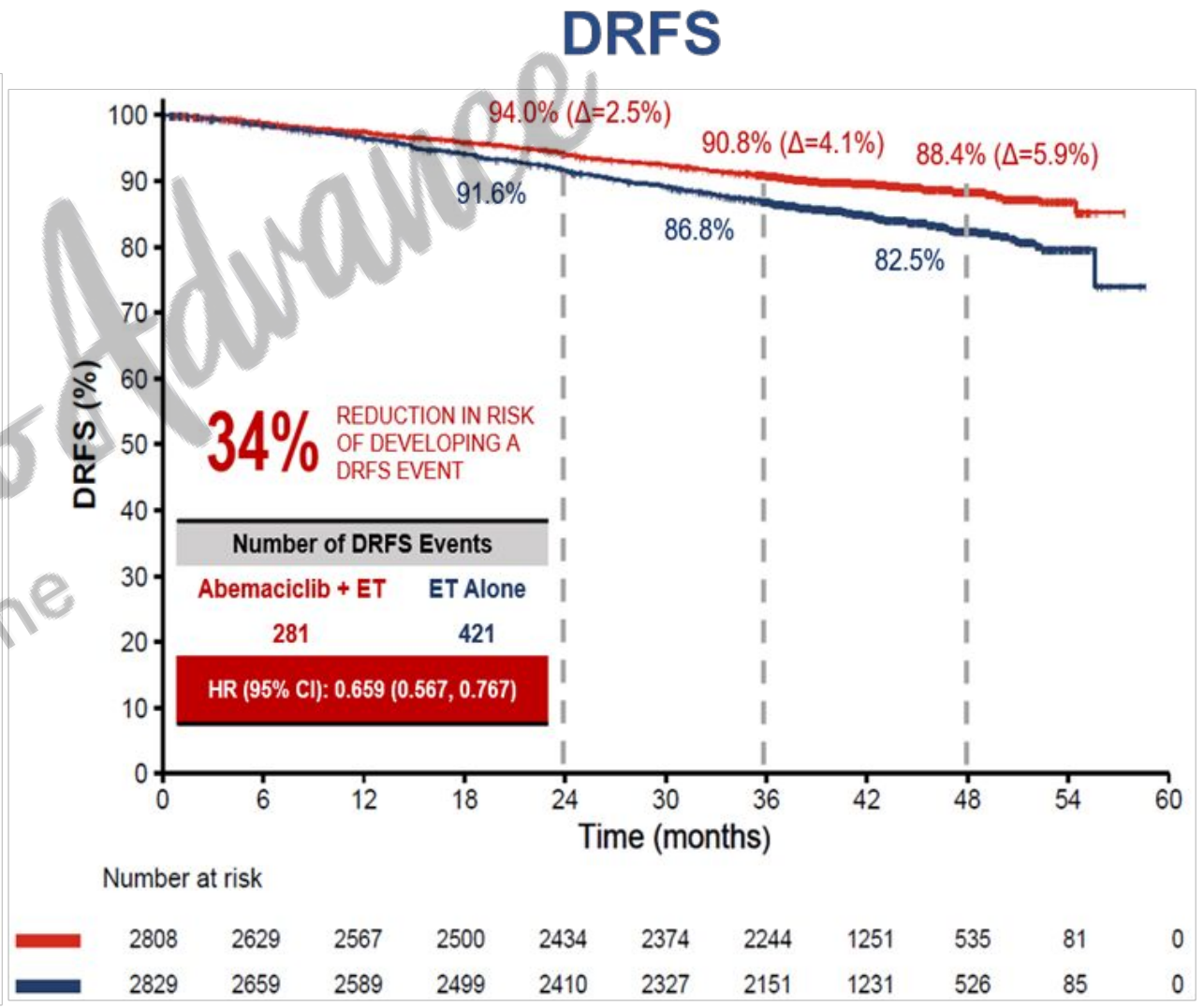
ITT Population



Johnston S, et al. SABCS 2022

MonarchE: iDFS & DRFS



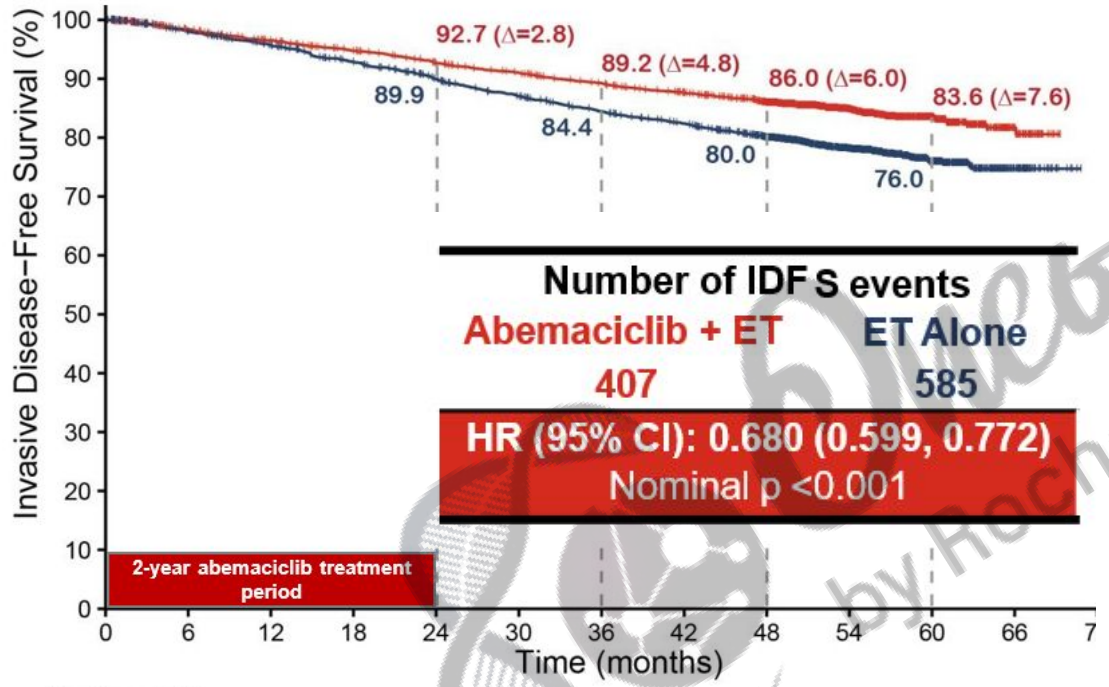


*From ITT analysis

Johnston S, et al. SRD 2023; Johnston S, et al. Lancet Oncol 2023

monarchE 5-Year Update: iDFS and DRFS

iDFS: Difference Between Arms 7.6% at 5 Years

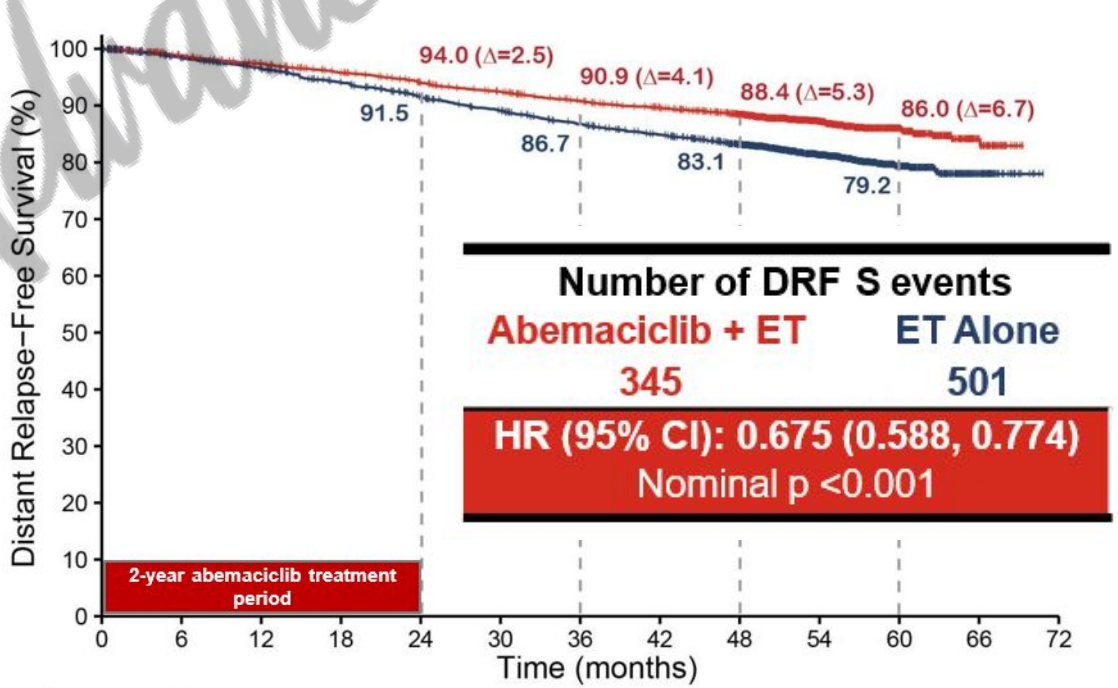


Number at risk

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

32% reduction in the risk of developing an iDFS event

DRFS: Difference Between Arms 6.7% at 5 Years



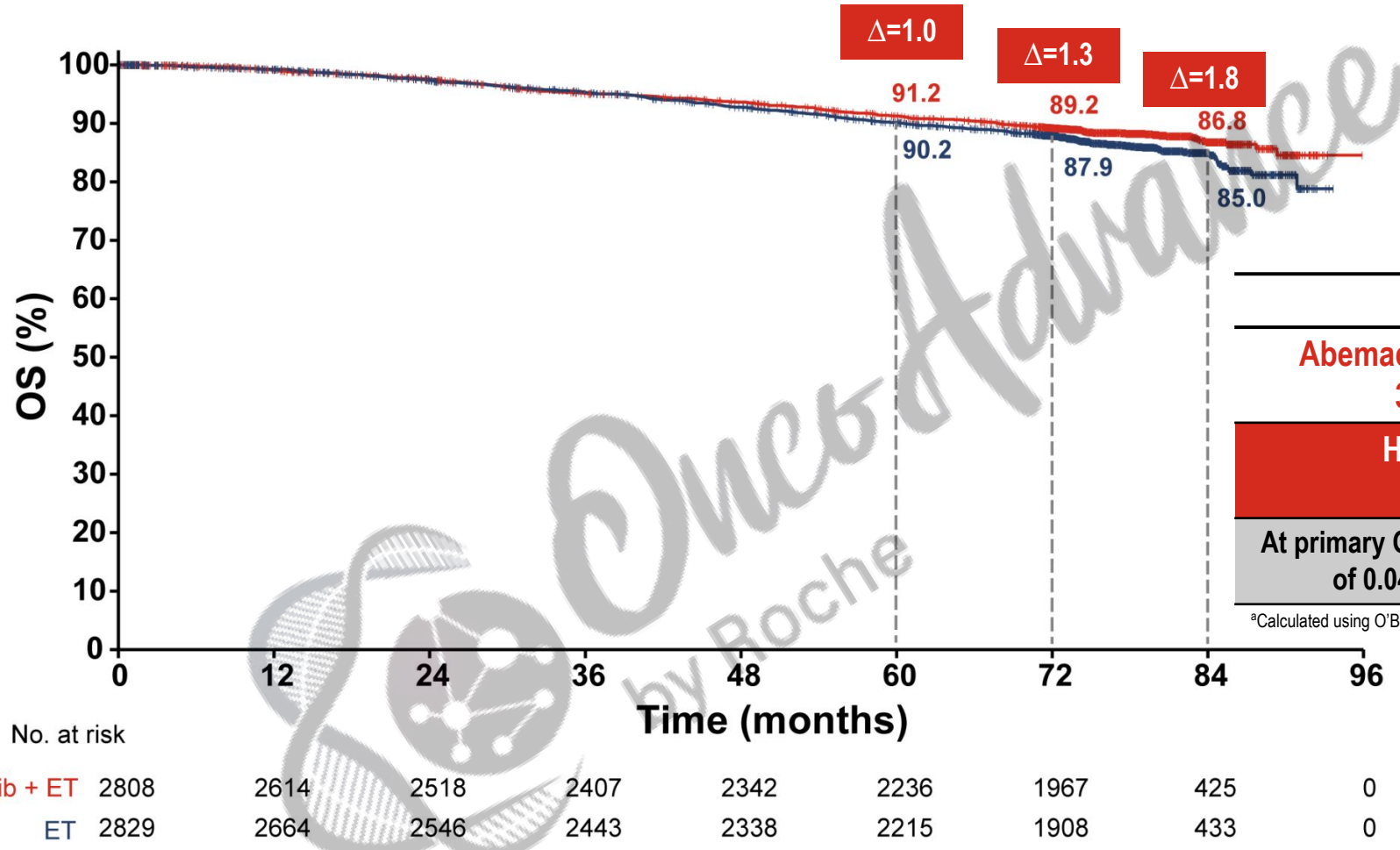
Number at risk

Abemaciclib + ET	2808	2630	2567	2500	2434	2375	2313	2258	2141	1202	500	75	0
ET alone	2829	2660	2590	2499	2410	2327	2243	2176	2032	1161	488	72	0

32.5% reduction in the risk of developing a DRFS event

Harbeck N et al, ESMO 2023

Key Secondary Endpoint: Overall Survival in ITT



Number of OS events	
Abemaciclib + ET	ET
301	360

HR (95% CI): 0.842 (0.722, 0.981)
***P*=0.0273**

At primary OS testing, OS in ITT met the critical boundary of 0.0434 (2-sided)[a] for statistical significance

[a]Calculated using O'Brien-Fleming type stopping boundary based on the observed number of events

At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

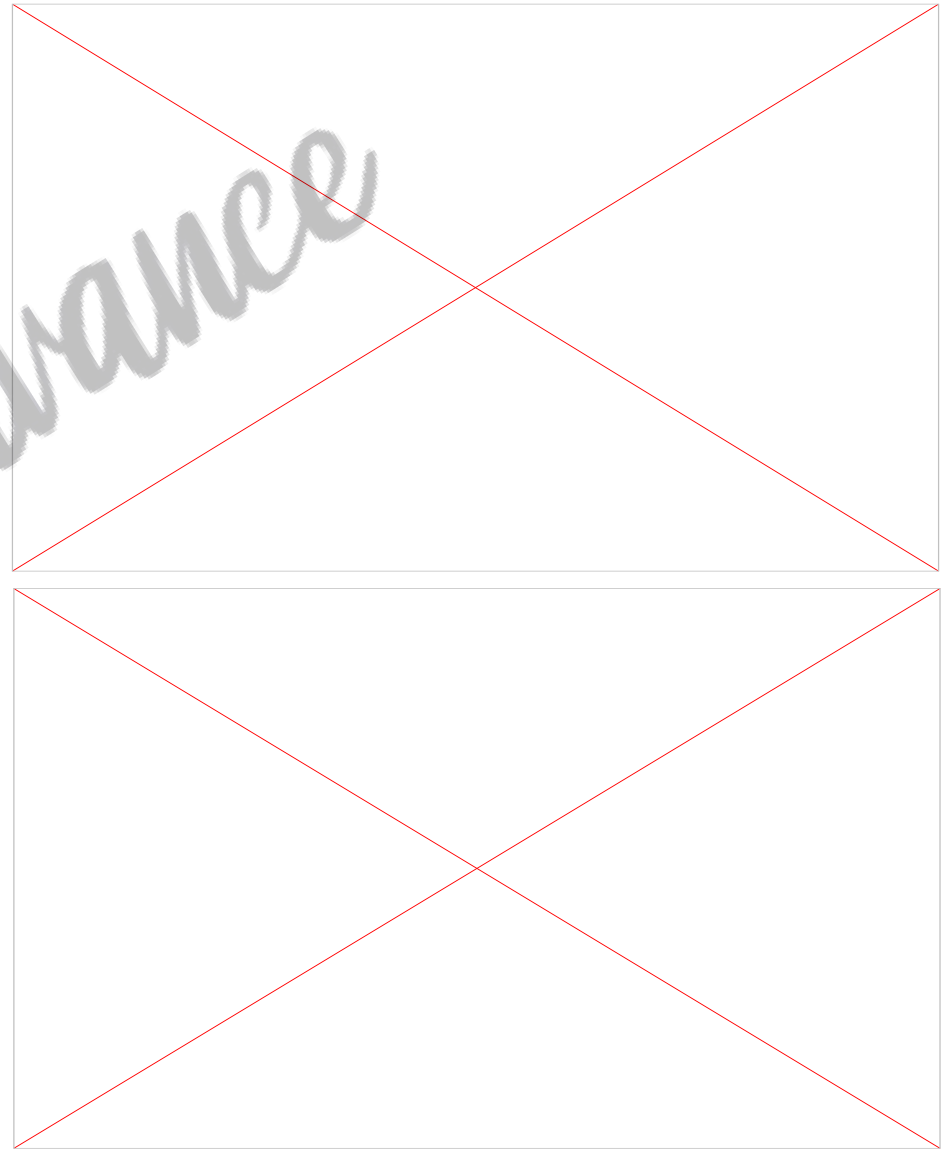
Stephen Johnston, MD, PhD

Consistent Treatment Effect Across ITT and ctDNA Cohort

	OS IA3 July 2023
ITT population (N=5637)	
IDFS event	**18%**
ctDNA cohort (N=910)	
IDFS event	**27%**

OSIA3, overall survival interim analysis 3

*The ctDNA cohort was enriched for early IDFS events (<24 months) leading to further increases in IDFS events over time. As a result, this sub cohort does not accurately reflect the broader ITT.



Loi S, et al. ASCO 2024

ctDNA Detection

ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative (–), undetected	840 (92)
Persistently –	749/831* (90)
Became +	82/831* (10)
Baseline Positive (+), detected	70 (8)
Persistently +	34/58** (59)
Became – (undetected)	24/58** (41)

*Longitudinal analysis in patients who were Baseline ctDNA– limited to 831/840 patients with at least 1 post-baseline sample assessed
**Longitudinal analysis in patients who were Baseline ctDNA+ limited to 58/70 patients with at least 1 post-baseline sample assessed

- **ctDNA detection at baseline was 8% (n=70)**
- **Among patients who were Baseline ctDNA–, 82 (10%) Became + on treatment**
- **Among patients who were Baseline ctDNA+, 59% remained Persistently + on treatment**

Loi S, et al. ASCO 2024

ctDNA Detection

ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative (–), undetected	840 (92)
Persistently –	749/831* (90)
Became +	82/831* (10)
Baseline Positive (+), detected	70 (8)
Persistently +	34/58** (59)
Became – (undetected)	24/58** (41)

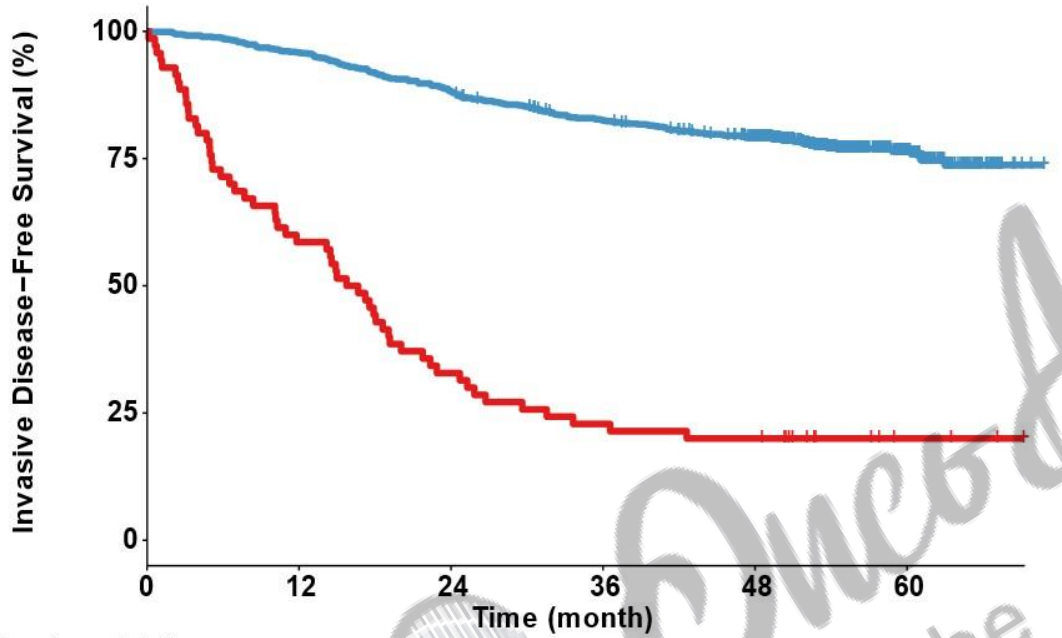
Any time Positive (+)	152 (17%)

*Longitudinal analysis in patients who were Baseline ctDNA– limited to 831/840 patients with at least 1 post-baseline sample assessed
**Longitudinal analysis in patients who were Baseline ctDNA+ limited to 58/70 patients with at least 1 post-baseline sample assessed

- **ctDNA detection at baseline was 8% (n=70)**
- **Among patients who were Baseline ctDNA–, 82 (10%) Became + on treatment**
- **Among patients who were Baseline ctDNA+, 59% remained Persistently + on treatment**

Loi S, et al. ASCO 2024

Baseline ctDNA Detection is Associated with Worse Outcomes



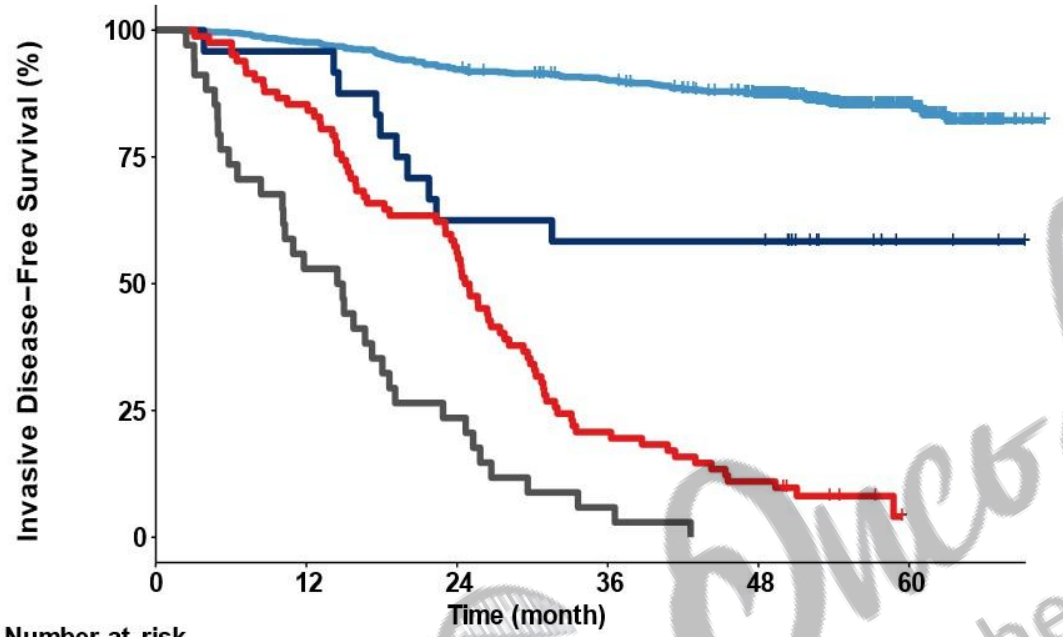
	Baseline Analysis* N=910	
	Baseline (–), undetected N=840	Baseline (+), detected N=70
IDFS event, n (%)	191 (23)	56 (80)
4-year IDFS rate, % (95% CI)	79.1 (76.4-82.0)	20.0 (12.5-32.0)
Log-rank test	Nominal p-value < 0.0001	

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population

Patients who were ctDNA+ at baseline were more likely to experience an IDFS event compared to those who were ctDNA– at baseline (80% vs 23%, respectively)

Loi S, et al. ASCO 2024

Dynamics of ctDNA Detection on Treatment is Associated with Outcomes



Longitudinal Analysis (N=889)*				
	Baseline (–), undetected N=831		Baseline (+), detected N=58	
	Persistently –	Became +	Persistently +	Became – (undetected)
N	749 (90)	82 (10)	34 (60)	24 (40)
IDFS event, n (%)	107 (14)	76 (93)	34 (100)	10 (42)
4-year IDFS rate, % (95% CI)	87.5 (85.1-89.9)	11.0 (5.9-20.3)	NA	58.3 (41.6-81.8)

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population. Robust assessment was limited in 194 patients with <3 post-baseline timepoints and there may be differences in IDFS; total events 227.

Patients who remained Persistently + or Became + on treatment were more likely to experience an IDFS event compared to those who Became – (undetected) or remained Persistently – on treatment

PRESENTED BY: Sherene Loi, MD; PhD

Loi S, et al. ASCO 2024

Median Lead Times from ctDNA Detection to IDFS Event

ctDNA subgroup	N	IDFS event (%)	Median time to IDFS event, months (range)
Baseline +	70*	56 (80)	12 (0-43)†
Persistently +	34/58**	34 (100)	15 (2-43)†
Became – (undetected)	24/58**	10 (42)	19 (4-32)†
Became + (Baseline –)	82	76 (93)	7 (0-48)‡

*Includes 12 patients with only baseline sample assessed who had a lead time of 2 (0-8) months
**Longitudinal analysis limited to 58/70 patients with at least 1 post-baseline sample assessed and robust assessment limited in 14 patients with only 1 post-baseline timepoint
†Represents time from baseline ctDNA detection in patients with an IDFS event
‡Represents time from earliest post-baseline ctDNA detection in patients with an IDFS event

Overall, patients who were ctDNA+ had a relatively short lead time from ctDNA detection to IDFS event, with shortest lead time observed in patients who Became + on treatment

Loi S, et al. ASCO 2024

TRADE: 6-month abemaciclib tolerability after initial dose escalation in HR+, HER2- EBC

Objective

- To evaluate the impact of dose escalation on the tolerability of adjuvant abemaciclib + ET in patients with HR+, HER2- EBC at 6-month follow-up

Key inclusion criteria
- HR+, HER2- EBC
- Adjuvant abemaciclib indicated based on patient risk/stage

Screening

N=90

Adjuvant ET

Abemaciclib **50 mg BID**	Abemaciclib **100 mg BID**	Abemaciclib **150 mg BID**
Days 1–14	**Days 15–28**	**>28 Days**

→ **Abemaciclib + ET (up to 2 years)**

Intra-patient dose escalation requirements: Absence of ongoing Grade 3/4 or persistent Grade 2 toxicity

Supportive care, including anti-diarrhea medication, provided as needed

Primary endpoint

- Composite AE rate: Discontinuation of adjuvant abemaciclib for any reason and/or inability to reach or maintain target dose of 150 mg BID by 12 weeks of therapy

Secondary endpoints

- TEAEs, discontinuation/hold rates, incidence of Grade ≥2 diarrhea, QoL, adherence, dose intensity, correlative science

Schlam I, et al. SABCS 2025

TRADE: 6-month abemaciclib tolerability after initial dose escalation in HR+, HER2- EBC

Dose escalation outcomes
(n=89 evaluable, n=1 excluded progression within 24 weeks)

82% remained on abemaciclib at 24 weeks

64.4% were on target dose (150 mg BID) by 24 weeks. Most patients maintained the same dose from Week 12 onwards

13.5% did not reach the target dose

32.6% required dose reductions within 24 weeks

Treatment discontinuation, n (%)	(n=89)
Discontinued by 24 weeks	16 (18.0)
Within first 12 weeks	6 (6.7)
Between Weeks 12–24	10 (11.2)

Reasons for treatment discontinuation, n (%)	(n=16)
Unacceptable adverse event	7 (7.9)
Pneumonitis	2 (2.2)
Diarrhea	2 (2.2)
Elevated ALT	1 (1.1)
Allergic reaction to abemaciclib	1 (1.1)
Other	1 (1.1)
Subject withdrew consent/patient preference	5 (5.6)
Subject noncompliance	2 (2.2)
Physician decision	1 (1.1)
Other	1 (1.1)

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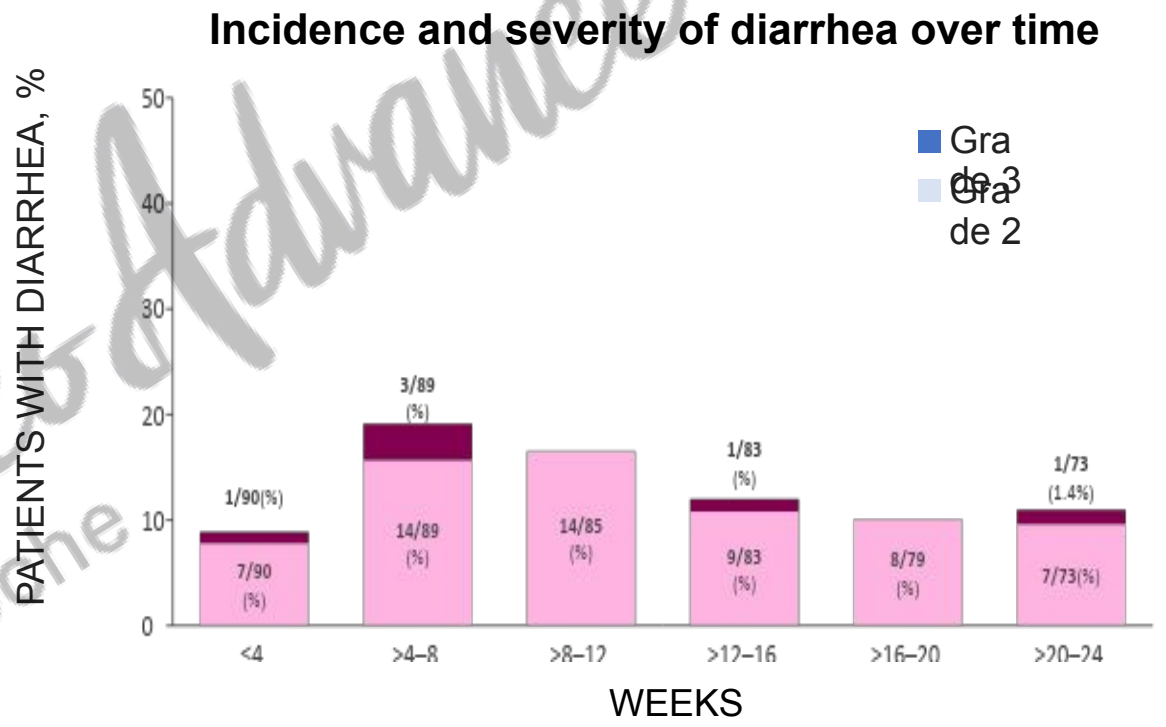
TRADE: 6-month abemaciclib tolerability after initial dose escalation in HR+, HER2- EBC

TEAEs occurring in ≥10% of patients, n (%)	Grade 2	Grade 3–4	Total
Any grade	51 (56.7)	26 (28.9)	77 (85.6)
Diarrhea	25 (27.8)	5 (5.6)	30 (33.3)
Neutrophil count decreased[a]	24 (26.7)	4 (4.4)	28 (31.1)
Fatigue	24 (26.7)	0	24 (26.7)
Hypertension	10 (11.1)	5 (5.6)	15 (16.7)
White blood cell decreased	14 (15.6)	1 (1.1)	15 (16.7)
Lymphocyte count decreased	8 (8.9)	3 (3.3)	11 (12.2)
Abdominal pain	9 (10.0)	1 (1.1)	10 (11.1)
Nausea	9 (10.0)	0	9 (10.0)



[a]One patient had a Grade 4 AE.

Conclusions

- Abemaciclib, administered with a dose-escalation strategy, was generally well tolerated, with most patients continuing treatment as adverse events were manageable and decreased over time

Schlam I, et al. SABCS 2025

NATALEE & MonarchE

Clinical Trial Design

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Ribociclib
400 mg/day
3 weeks on/1 week off for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y **+ goserelin** in men and premenopausal women

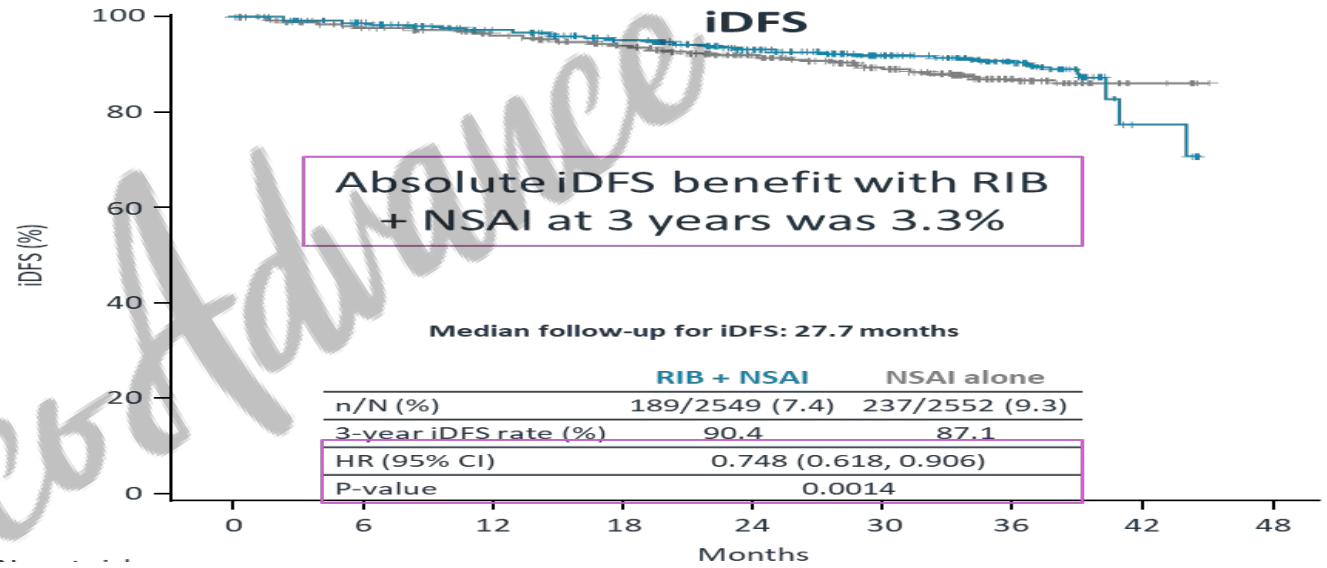
NSAI
Letrozole or anastrozole[d] for ≥ 5 y **+ goserelin** in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Primary endpoint (IDFS)



Clinical Trial Design

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- 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**
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

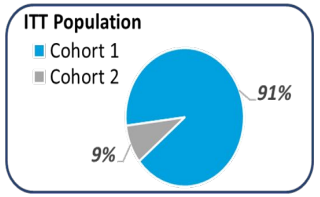
On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

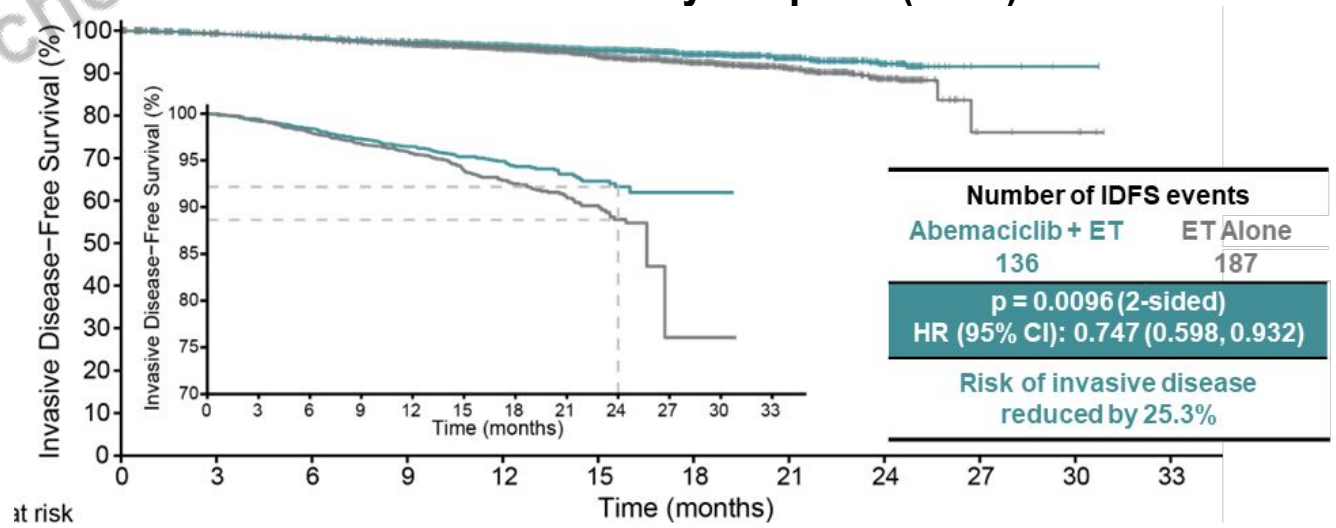
Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



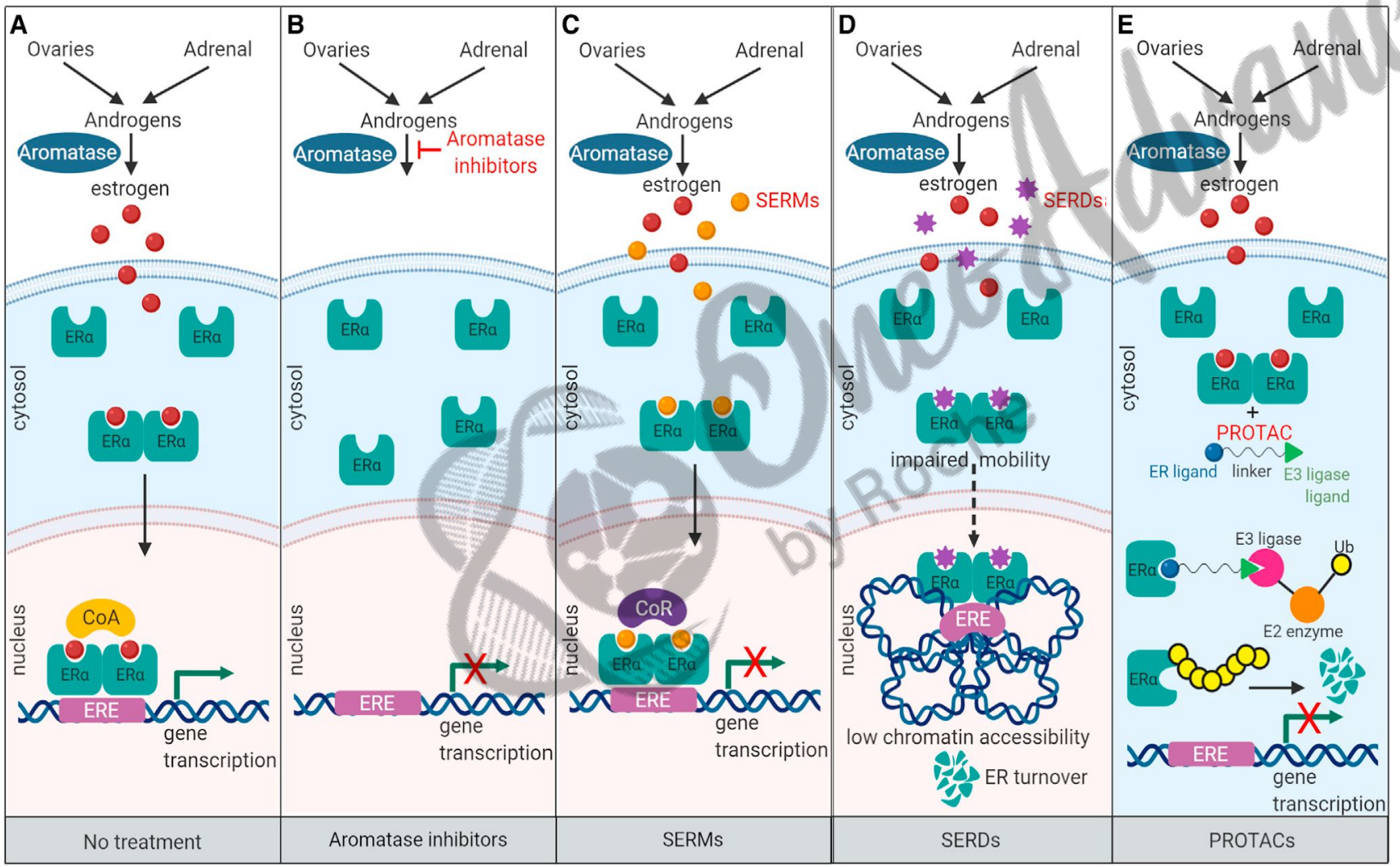
Primary endpoint (IDFS)

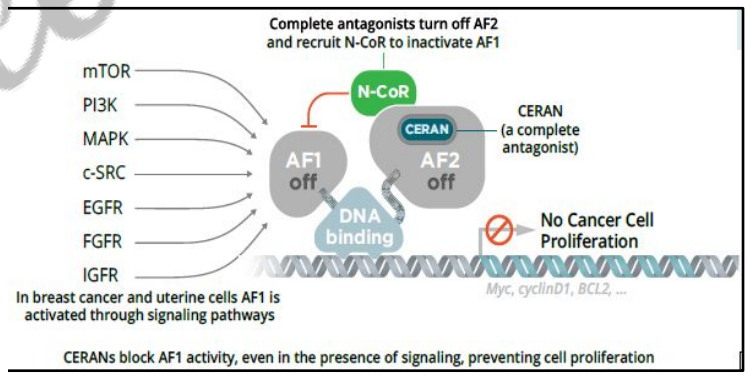


Slamon D, et al. ASCO 2023; Johnston S, et al. ESMO 2020

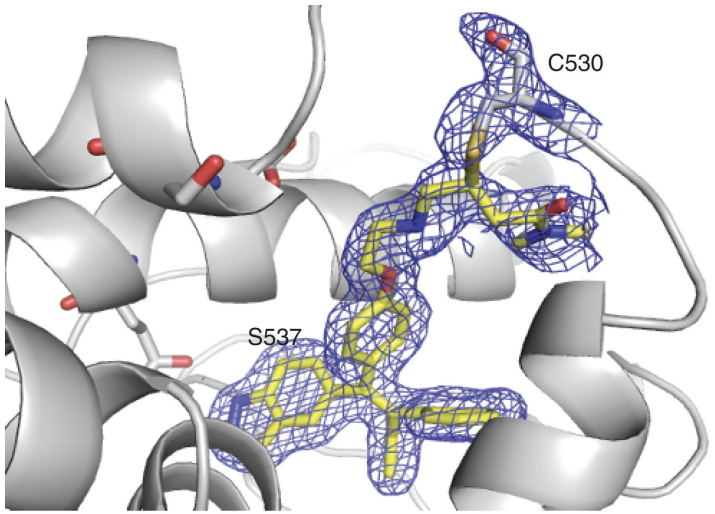
Mechanism of Action of New Endocrine Agents Targeting the ER Domain

SERM | SERD | PROTAC | CERAN





SERCAs



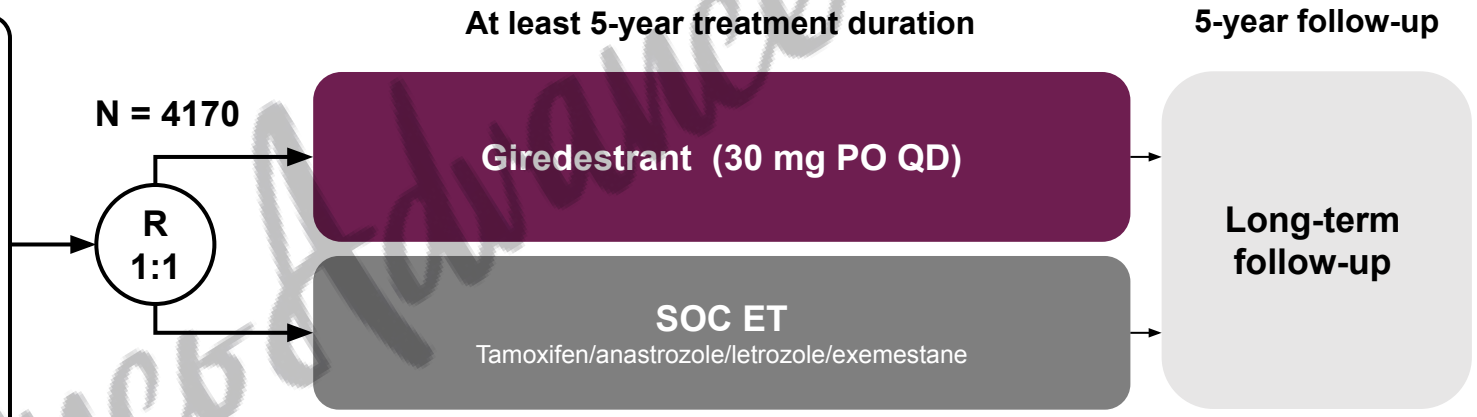
Hanker AB et al. *Cancer Cell*. 2020;37:496-513; Jhaveri SABCS 2021

lidERA Breast Cancer study design

A global, randomized, open-label, multicenter Phase III trial

Key eligibility criteria

- Participants with ER+, HER2-negative early breast cancer
- Stage I–III disease (anatomical)
  - pN0 and pT > 1 cm with Grade 3, or Ki67 ≥ 20%, or high score on genomic assay,* or pT4N0
  - Node-positive
- Pre- or post-menopausal†
- Breast cancer surgery within 12 months
- (Neo)adjuvant chemotherapy if indicated



Stratification factors

- Risk: Medium-‡ vs high-risk§ Stage I–III breast cancer
- Region: USA/Canada/Western Europe vs Asia–Pacific vs RoW
- Previous chemotherapy: No vs yes
- Menopausal status: Pre-menopausal vs post-menopausal

Primary endpoint

- IDFS (excluding second primary non-breast cancer)

Key secondary endpoints

- DFS, DRFI, IDFS (including second primary non-breast invasive cancer with exception of non-melanoma skin cancers and *in situ* carcinomas of any site), LRRFI, OS, safety

Giredestrant is currently also being investigated in combination with abemaciclib in the adjuvant setting (lidERA Breast Cancer substudy 1)

Enrollment: August 2021 to September 2023. Up to 12 weeks of ET ± CDK4/6i were allowed. ER+ was defined as ≥ 1% positive cells by immunohistochemistry. * OncotypeDx ≥ 26 or high-risk Mammaprint.
† Pre-menopausal patients on aromatase inhibitors or giredestrant had to receive ovarian function suppression with an approved luteinizing hormone-releasing hormone agonist. ‡ Medium risk: pN0 and primary tumor > 1 cm with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or high score on genomic assay [if available]) and pN1 with low-risk biologic features (Grade 1/2 and Ki67 < 20% and tumor ≤ 5 cm and low score on genomic assay [if available]). § High risk: pT4, or pN2, or pN3 and pN1 with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or tumor > 5 cm, or high score on genomic assay [if available]).
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DFS, disease-free survival; DRFI, distant recurrence-free interval; ER+, estrogen receptor-positive; ET, endocrine therapy; IDFS, invasive disease-free survival; LRRFI, locoregional recurrence-free interval; OS, overall survival; PO, orally; QD, once daily; R, randomization; RoW, rest of the world; SOC, standard-of-care.
ClinicalTrials.gov number, NCT04961996. Adapted from Geyer CE, *et al*. ASCO 2023 (TPS616), with permission.

Presented by: Aditya L. Bardia, MD.

Eligibility overview: lidERA, NATALEE & MonarchE

Anatomic Stage (AJCC 8)	TNM Stage	lidERA	NATALEE	monarchE
IA	*T1 N0 M0*	Tumour >1 cm and ≥1 high risk feature: Grade 3, or Ki67 ≥20%, or Oncotype DX ≥ 26 or High-Risk MammaPrint	X	X
IB	*T0 N1mi M0*	✓	X	N1 with one high risk feature
	T1 N1mi M0	✓	X	N1 with one high risk feature
IIA	*T0 N1 M0*	✓	✓	N1 with one high risk feature
	T1 N1 M0	✓	✓	N1 with one high risk feature
	T2 N0 M0	One high risk feature: Grade 3, or Ki67 ≥20%, or Oncotype DX ≥ 26 or High-Risk MammaPrint	Grade 3 or high risk Grade 2	X
IIB	*T2 N1 M0*	✓	✓	✓
	T3 N0 M0	One high risk feature: Grade 3, or Ki67 ≥20%, or Oncotype DX ≥ 26 or High-Risk MammaPrint	✓	X
IIIA	*T0 N2 M0*	✓	✓	✓
	T1 N2 M0	✓	✓	✓
	T2 N2 M0	✓	✓	✓
	T3 N1 M0	✓	✓	✓
	T3 N2 M0	✓	✓	✓
IIIB	*T4 N0 M0*	✓	✓	X
	T4 N1 M0	✓	✓	✓
	T4 N2 M0	✓	✓	✓
IIIC	*Any T N3 M0*	✓	✓	✓

Baseline demographics and characteristics

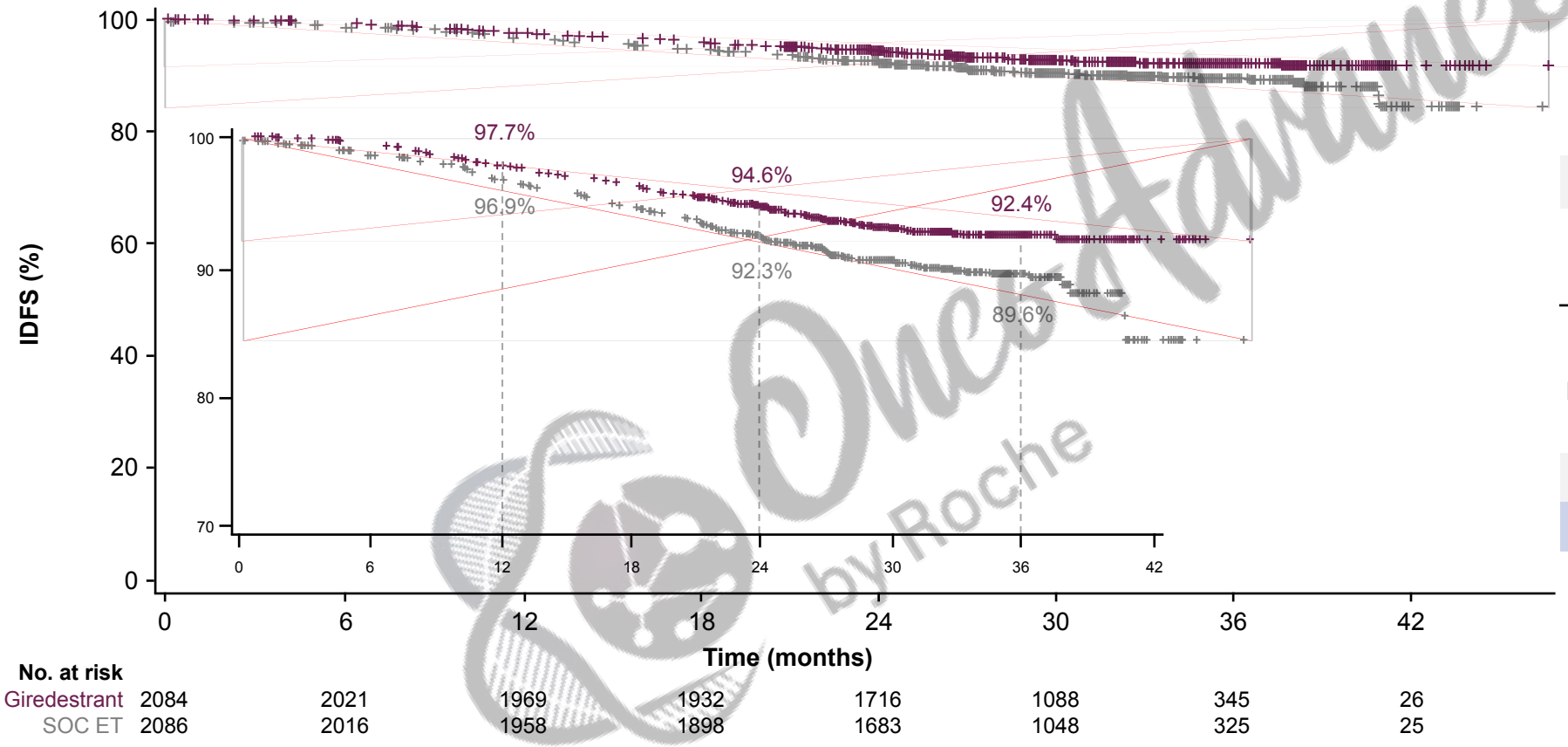
	Giredestrant n = 2084	SOC ET n = 2086
Median age, years (range)	54.0 (22–91)	54.0 (25–89)
Female sex, n (%)	2073 (99.5)	2075 (99.5)
Race, n (%)		
American Indian or Alaska Native	77 (3.7)	62 (3.0)
Asian	461 (22.1)	467 (22.4)
Black or African American	50 (2.4)	50 (2.4)
Other*	263 (12.6)	232 (11.1)
White	1233 (59.2)	1275 (61.1)
Region, n (%)		
Asia–Pacific	544 (26.1)	544 (26.1)
USA/Canada/Western Europe	860 (41.3)	905 (43.4)
Latin America/Africa/Eastern Europe	680 (32.6)	637 (30.5)
Menopausal status, n (%)†		
Pre-menopausal	849 (41.0)	838 (40.4)
Post-menopausal	1220 (59.0)	1236 (59.6)

	Giredestrant n = 2084	SOC ET n = 2086
ER status, n (%)‡		
Low-positive (1–10% of cells positive)	45 (2.2)	52 (2.5)
Positive (> 10% of cells positive)	2030 (97.8)	2031 (97.5)
AJCC stage at surgery, n (%)§		
I	254 (12.3)	283 (13.6)
II	1013 (49.0)	950 (45.7)
III	799 (38.7)	844 (40.6)
Nodal status, n (%) on surgical specimen‖		
pN0	449 (21.6)	441 (21.2)
pN1	968 (46.6)	953 (45.7)
pN2–3	662 (31.8)	691 (33.1)
Risk, n (%)		
High	1448 (69.5)	1447 (69.4)
Medium	636 (30.5)	639 (30.6)
Previous chemotherapy, n (%)		
No	396 (19.0)	450 (21.6)
Yes	1688 (81.0)	1636 (78.4)

Baseline demographics and characteristics were balanced

Data cutoff: August 8, 2025. * "Other" refers to "multiple", "Native Hawaiian or Other Pacific Islander", "not reported", or "unknown". † Twenty-seven patients had unknown menopausal status (15 in the giredestrant arm and 12 in the SOC ET arm). ‡ Twelve patients had unknown ER status (nine in the giredestrant arm and three in the SOC ET arm). § One patient had Stage 0 disease (SOC ET arm); 26 had unknown Stage (18 in the giredestrant arm and eight in the SOC ET arm). ‖ Six patients had unknown nodal status (five in the giredestrant arm and one in the SOC ET arm). AJCC, American Joint Committee on Cancer; ER, estrogen receptor; ET, endocrine therapy; SOC, standard-of-care.

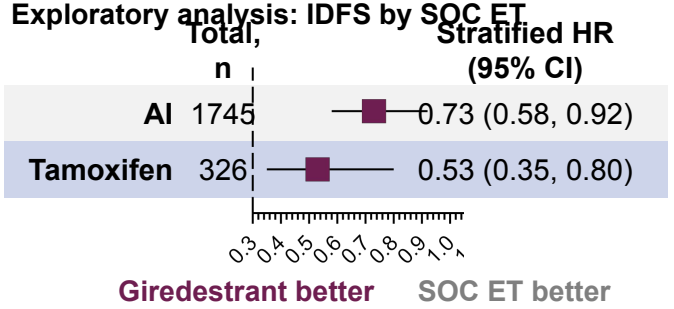
Primary endpoint: IDFS



No. at risk								
Giredestrant	2084	2021	1969	1932	1716	1088	345	26
SOC ET	2086	2016	1958	1898	1683	1048	325	25

	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	140 (6.7)	196 (9.4)
Stratified HR (95% CI)	**0.70** (0.57, 0.87); **p = 0.0014***	

Exploratory analysis: IDFS by SOC ET



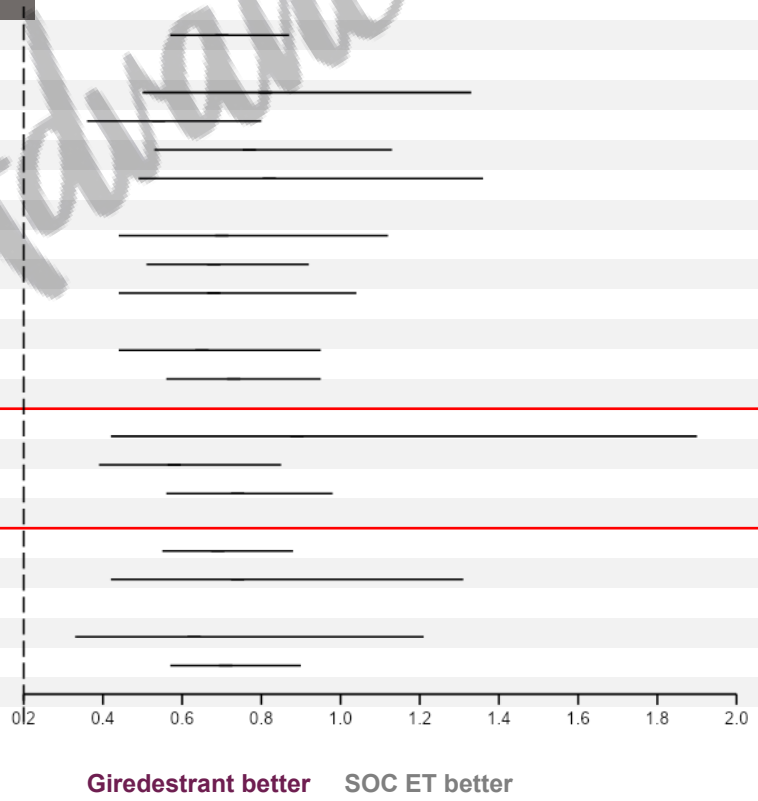
Median follow-up: 32.3 months

Statistically significant and clinically meaningful improvement in IDFS:
Giredestrant reduced the risk of invasive disease recurrence or death by 30% compared with SOC ET

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. * Log-rank (2-sided). p-value boundary for IDFS interim analysis was 0.0217 (2-sided). AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

IDFS in key subgroups

	Patients, n			
	Total, n	Giredestrant	SOC ET	HR (95% CI)
All patients	4170	2084	2086	0.70 (0.57, 0.87)
Age group, years				
≤ 45	906	472	434	0.81 (0.50, 1.33)
> 45 to ≤ 55	1355	660	695	0.54 (0.36, 0.80)
> 55 to ≤ 65	1118	567	551	0.77 (0.53, 1.13)
> 65	791	385	406	0.82 (0.49, 1.36)
Region				
Asia–Pacific	1088	544	544	0.70 (0.44, 1.12)
Latin America/Africa/Eastern Europe	1317	680	637	0.68 (0.51, 0.92)
USA/Canada/Western Europe	1765	860	905	0.68 (0.44, 1.04)
Menopausal status				
Pre-menopausal	1680	841	839	0.65 (0.44, 0.95)
Post-menopausal	2490	1243	1247	0.73 (0.56, 0.95)
AJCC stage at surgery*				
I	537	254	283	0.89 (0.42, 1.90)
II	1963	1013	950	0.58 (0.39, 0.85)
III	1643	799	844	0.74 (0.56, 0.98)
Risk				
High	2895	1448	1447	0.69 (0.55, 0.88)
Medium	1275	636	639	0.74 (0.42, 1.31)
Previous chemotherapy				
No	787	392	395	0.63 (0.33, 1.21)
Yes	3383	1692	1691	0.71 (0.57, 0.90)



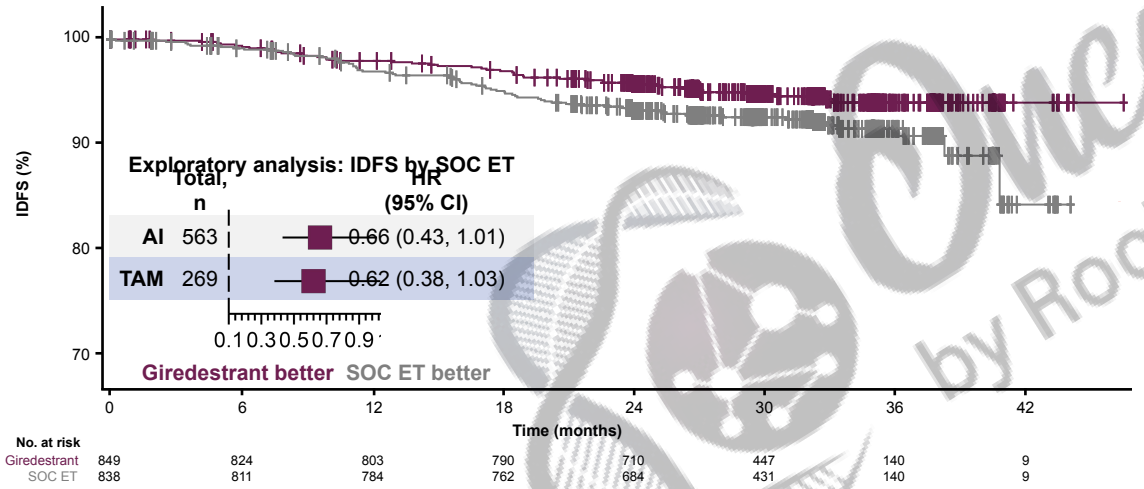
IDFS benefit was consistent across key prespecified subgroups

Data cutoff: August 8, 2025. HR estimates are unstratified. Median follow-up of 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively.
* One patient had Stage 0 disease (SOC ET arm); 26 had unknown Stage (18 in the giredestrant arm and eight in the SOC ET arm).
AJCC, American Joint Committee on Cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

IDFS by menopausal status

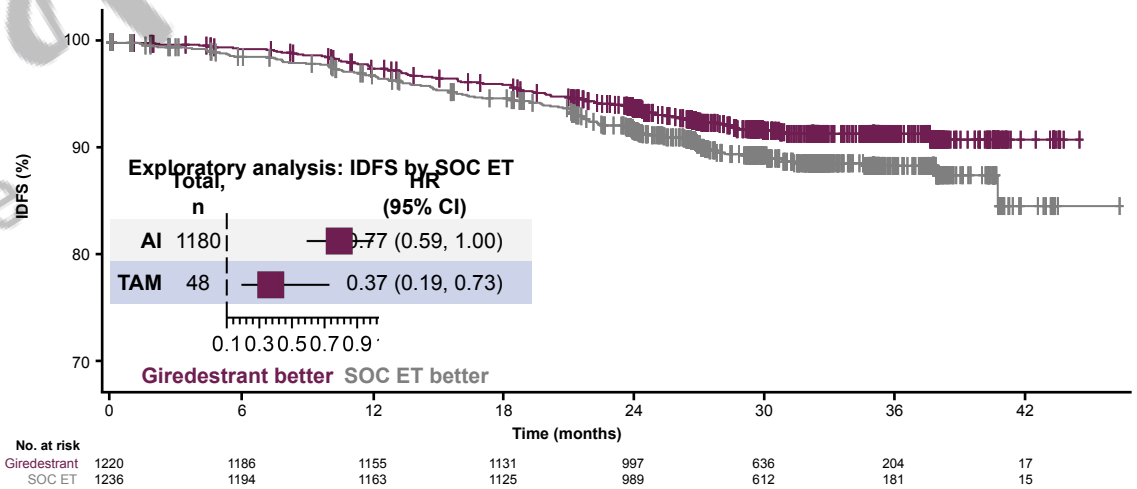
Pre-menopausal

	Giredestrant n = 849	
Events, n (%)	44 (5.2)	66 (7.9)
3-year rate, %	94.0	91.5
HR (95% CI)	**0.65** (0.44, 0.95)	



Post-menopausal

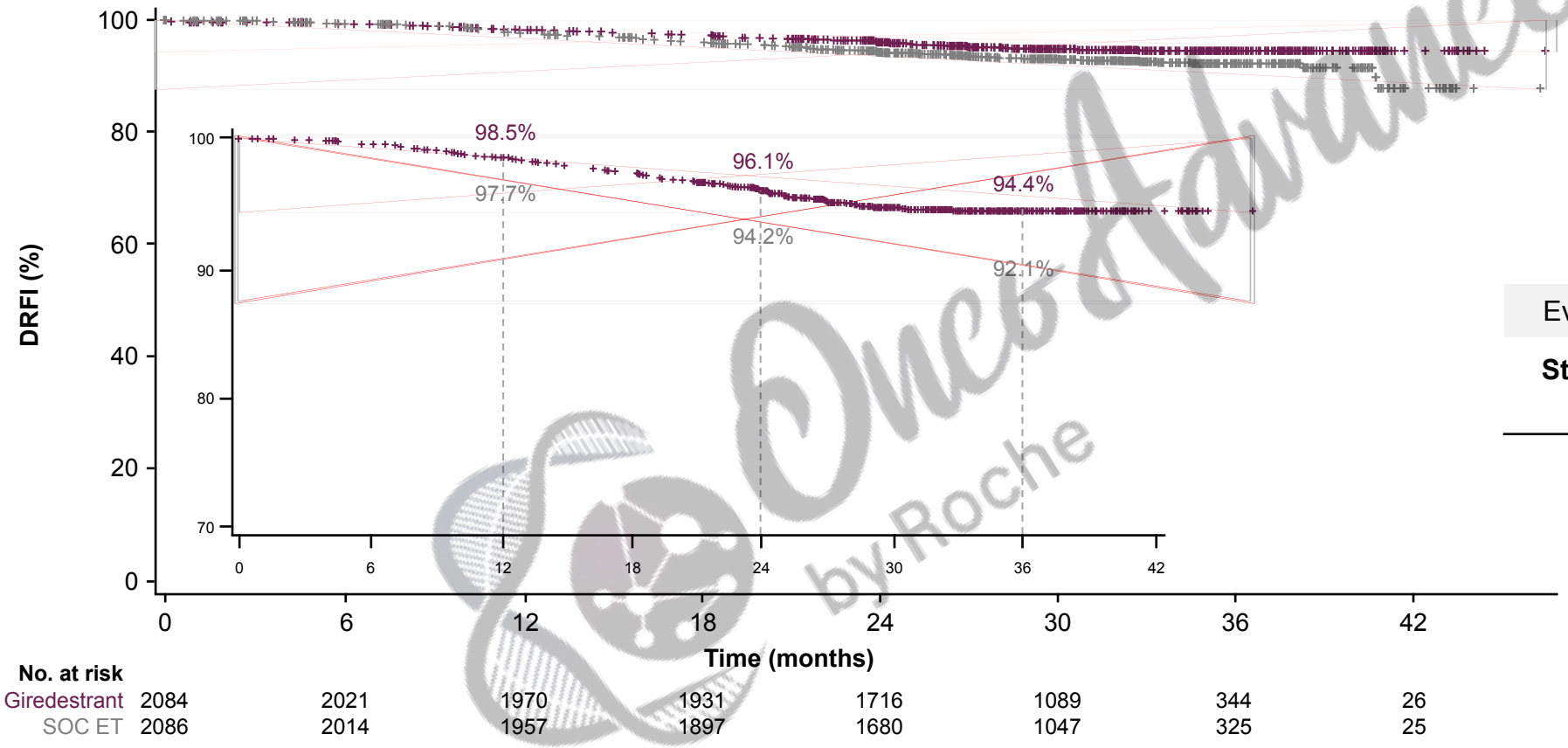
	Giredestrant n = 1220	
Events, n (%)	96 (7.9)	129 (10.4)
3-year rate, %	91.3	88.3
HR (95% CI)	**0.74** (0.57, 0.96)	



Giredestrant showed IDFS benefit and higher 3-year rates in both pre-menopausal and post-menopausal subgroups

Data cutoff: August 8, 2025. HR estimates are unstratified vs SOC ET.
AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care; TAM, tamoxifen.

Distant recurrence-free interval



No. at risk								
Giredestrant	2084	2021	1970	1931	1716	1089	344	26
SOC ET	2086	2014	1957	1897	1680	1047	325	25

	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	102 (4.9)	145 (7.0)
Stratified HR (95% CI)	**0.69** (0.54, 0.89)	

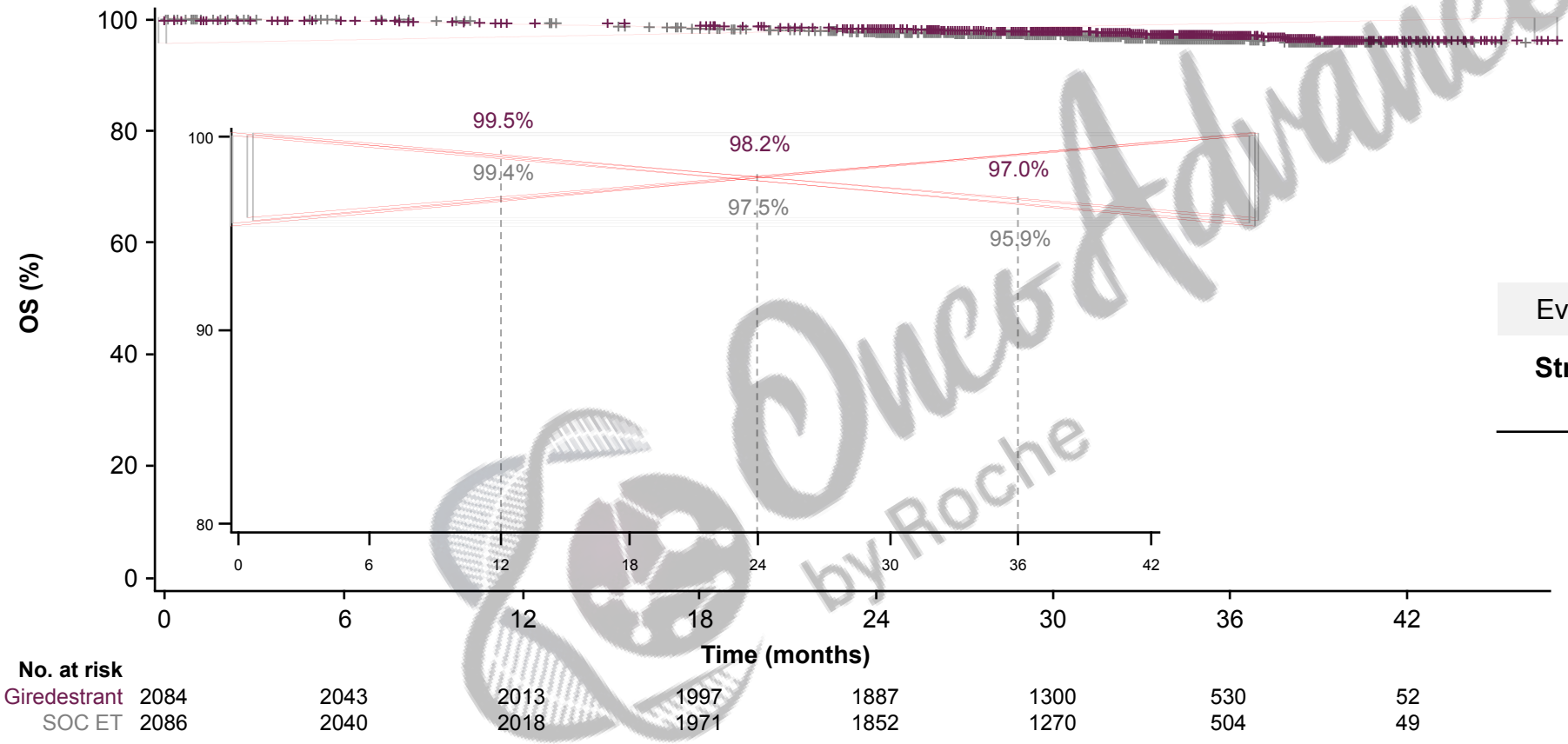
Median follow-up: 32.3 months

DRFI was improved vs SOC ET, with a 31% reduction in risk of developing metastatic disease

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively.
CI, confidence interval; DRFI, distant recurrence-free interval; ET, endocrine therapy; HR, hazard ratio; SOC, standard-of-care.

Presented by: Aditya L. Bardia, MD.

Interim overall survival



	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	57 (2.7)	71 (3.4)
Stratified HR (95% CI)	**0.79** (0.56, 1.12); p = 0.1863*	

Median follow-up: 32.3 months

While OS data were immature, a clear positive trend was observed. OS testing will continue at future analyses

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. At the data cutoff, the 1st OS IA was conducted (maturity 31.2% with respect to the final OS analysis). * Log-rank (2-sided). p-value boundary for the 1st OS IA was 0.0001 (2-sided). Includes one death from a patient who was randomized but never dosed. Excludes one death from a patient with missing date of death. CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IA, interim analysis; OS, overall survival; SOC, standard-of-care.

Safety overview *(safety-evaluable population)*

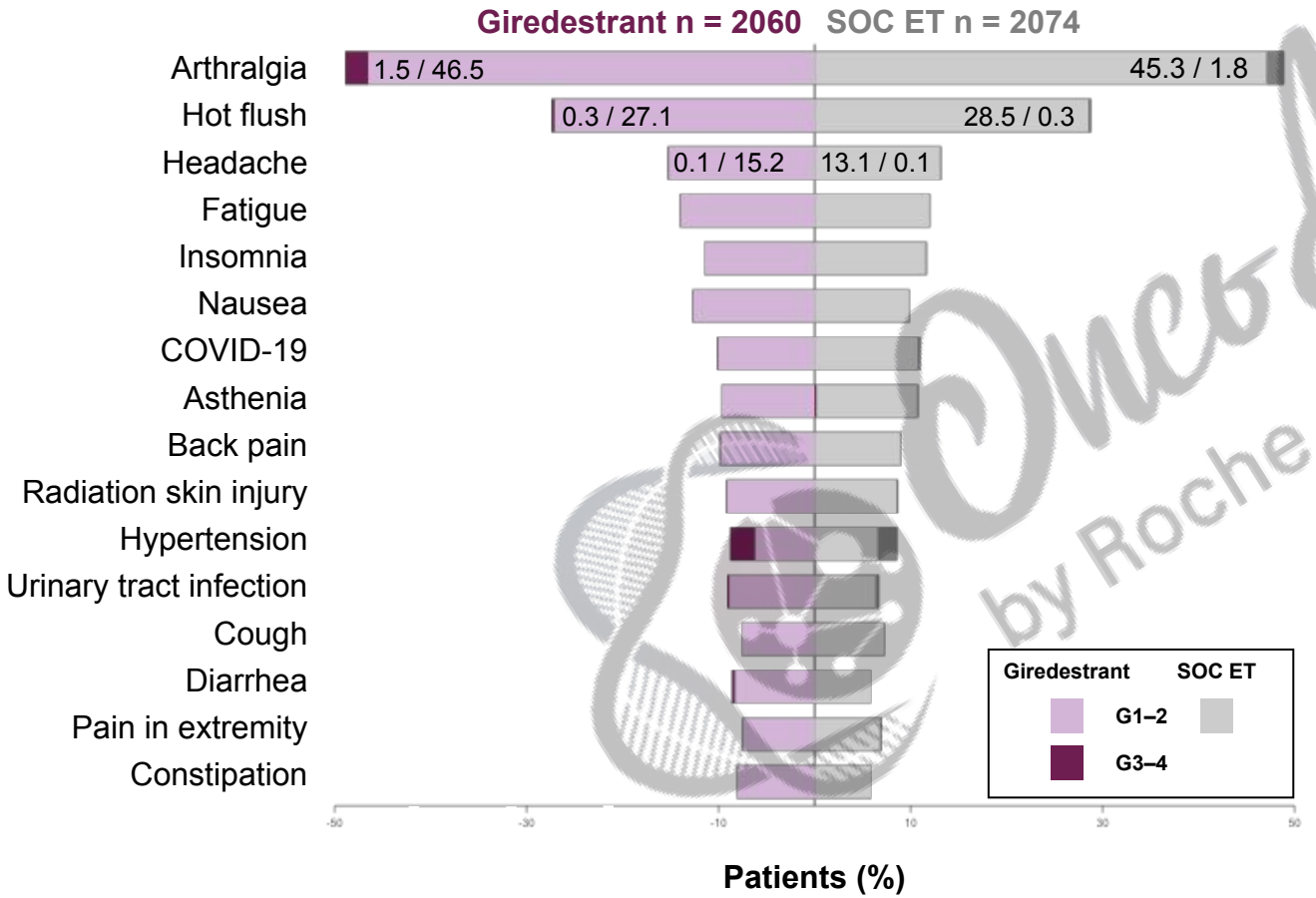
	Giredestrant n = 2060	SOC ET n = 2074
Median treatment duration, months (range)	31.64 (0.03–46.36)	30.88 (0.03–46.26)
Mean dose intensity, % (SD)	98.77 (3.07)	98.68 (3.73)
Patients with ≥ 1 AE, n (%)		
AEs (all grades)	1955 (94.9)	1957 (94.4)
TRAEs	1510 (73.3)	1498 (72.2)
AEs with fatal outcome*	6 (0.3)	16 (0.8)
TRAEs with fatal outcome	0	1 (< 0.1)
Grade 3–4 AEs†	407 (19.8)	372 (17.9)
Serious AEs	223 (10.8)	209 (10.1)
AEs leading to dose interruption	261 (12.7)	136 (6.6)
AEs leading to discontinuation from treatment	110 (5.3)	171 (8.2)

AEs, TRAEs, Grade 3–4 AEs, and serious AEs were comparable between treatment arms

Data cutoff: August 8, 2025. * Giredestrant arm: Secondary cancers (colon and gastric); sepsis; gastrointestinal hemorrhage (n = 2); intestinal obstruction. SOC ET arm: Secondary cancers (pancreatic [n = 2], acute lymphocytic leukemia, bile duct, colon, gastric); sepsis (n = 1); cellulitis; endocarditis; gastrointestinal hemorrhage (n = 2); intestinal obstruction; death (n = 2); respiratory failure (n = 2); embolism; hypovolemic shock; acute myocardial infarction; hemophagocytic lymphohistiocytosis; acute kidney injury. † Most common Grade 3–4 AEs were hypertension (2.6% in the giredestrant arm vs 2.0% in the SOC ET arm) and arthralgia (1.5% vs 1.8%, respectively). AE, adverse event; ET, endocrine therapy; SD, standard deviation; SOC, standard-of-care; TRAE, treatment-related adverse event.

AE overview *(safety-evaluable population)*

Common TEAEs (≥ 7.5% of patients in either arm at any grade)



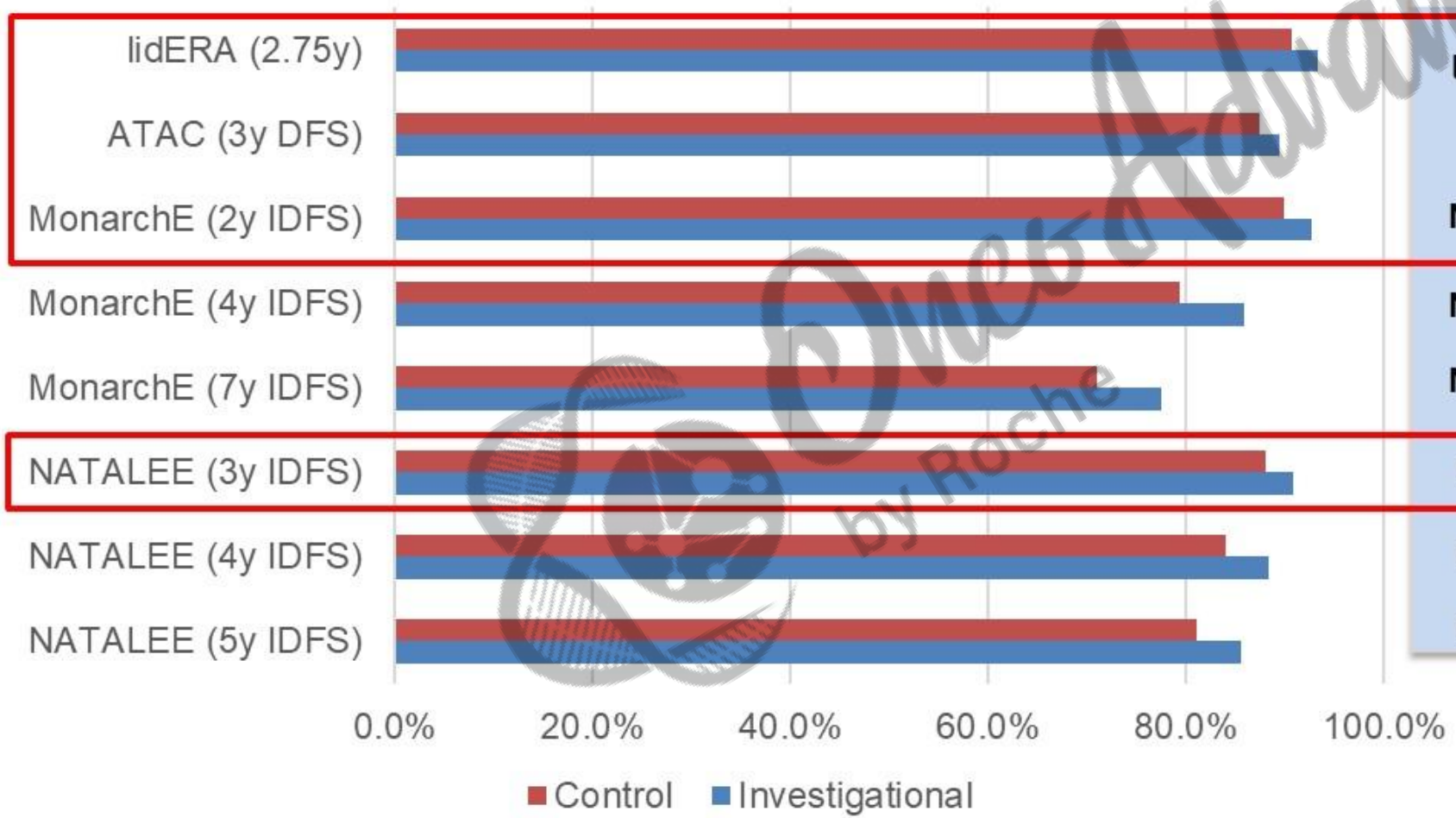
Selected AEs

	Giredestrant n = 2060	SOC ET n = 2074
Patients, n (%) with treatment discontinuations due to AEs		
Musculoskeletal disorders	38 (1.8)	92 (4.4)
• Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (< 0.1)	18 (0.9)
• Hot flush (PT)	1 (< 0.1)	16 (0.8)

	Giredestrant n = 2060			SOC ET n = 2074		
Patients, n (%) with selected AEs by medical concept*						
	G1	**G2**	**G3–4**	**G1**	**G2**	**G3–4**
Bradycardia†	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (< 0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (< 0.1)‡	3 (0.1)	7 (0.3)	7 (0.3)

Data cutoff: August 8, 2025. * Assessed as medical concepts using grouped terms; all other AEs by medical concept were comparable between arms, including four patients per arm (0.2%) who experienced photopsia. † G2 events occurred in 17 patients; 13 resolved, four patients discontinued treatment and the events resolved. ‡ G3 only. AE, adverse event; ET, endocrine therapy; G, grade; PT, preferred term; SOC, standard-of-care; TEAE, treatment-emergent adverse event.

lidERA in Context of Other Adjuvant Advances



	absolute Δ	HR
lidERA (2.75y)	2.8%	0.70
ATAC (3y)	2.0%	0.83
MonarchE (2y)	2.8%	0.75
MonarchE (4y)	6.4%	0.66
MonarchE (7y)	6.5%	0.73
NATALEE (3y)	2.7%	0.75
NATALEE (4y)	4.4%	0.72
NATALEE (5y)	4.5%	0.72

Bardia A, SABCS2025; ATAC Trialists, Lancet 2005; Johnston S, JCO2020; Lancet Oncol 2023; ESMO2025; Hortobagyi G, Ann Oncol2025; Fasching PA, JAMA Oncol 2025; Crown J, ESMO2025

My take home messages

- For high risk N0 patients - Giredestrant could be considered as a new SoC
- For N+ patients - Abemaciclib/Ribociclib continues to be SoC, longer follow up/ lidERA sub-study is needed for Giredestrant to become the endocrine treatment
- Patients with N1 disease and no biologically aggressive features may be candidates for treatment with giredestrant rather than CDK4/6 inhibitor–based therapy