III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

Redefiniendo los inhibidores de ciclinas en neo/adyuvancia

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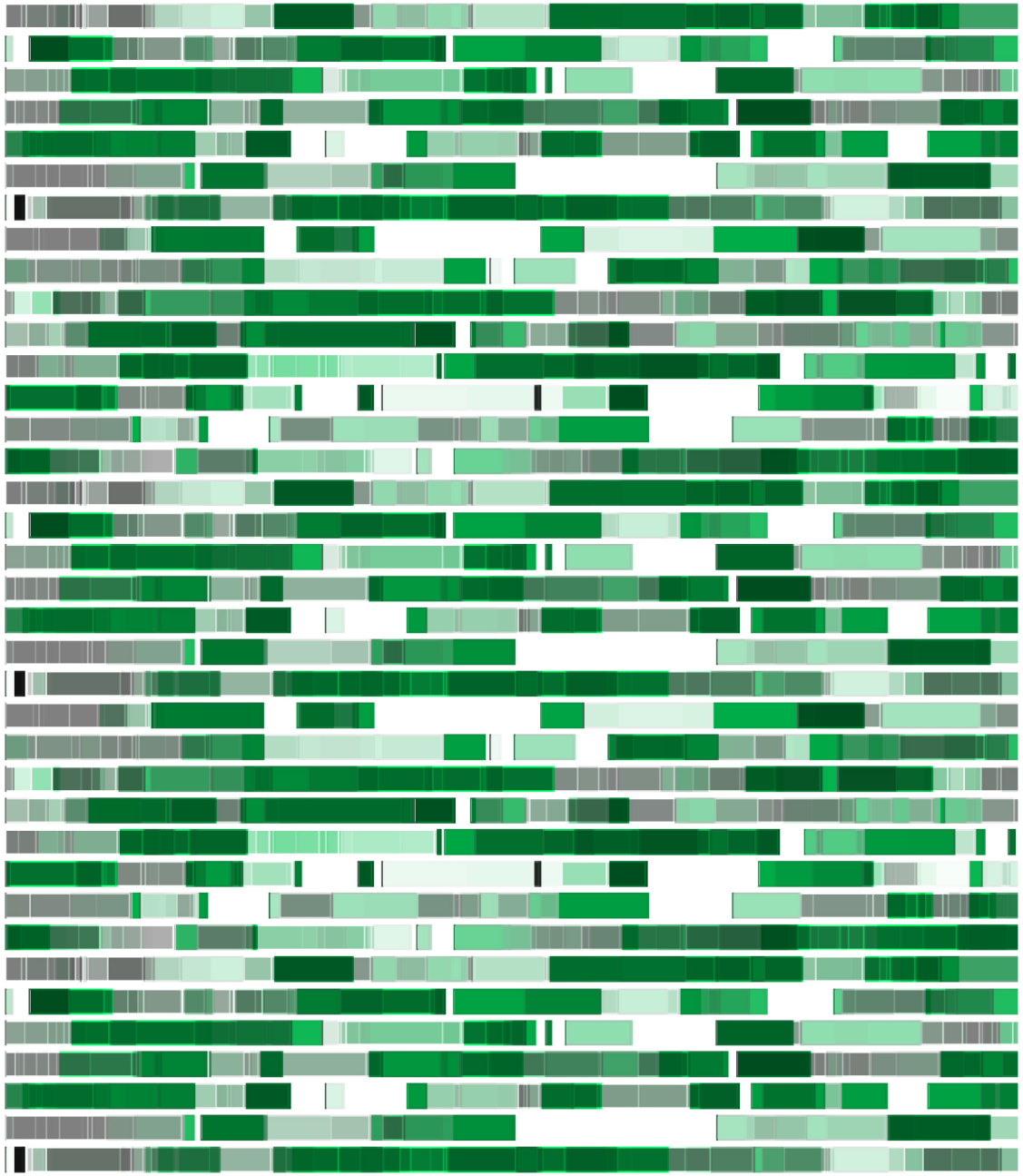
Organizador por:
HENDERE HEALTHCARE



Conflictos de interés

Trabajo en Osakidetza / Servicio Vasco de salud

Hospital Quiron-Bizkaia

Honorarios por ponencias/ asesorías:

Novartis, Pfizer, lilly, Astrazeneca, Daiichi-Sankyo, Roche, Gilead, MSD

Ayudas para asistir a congresos:

Novartis, Pfizer, Daiichi-Sankyo, AstraZeneca, Lilly

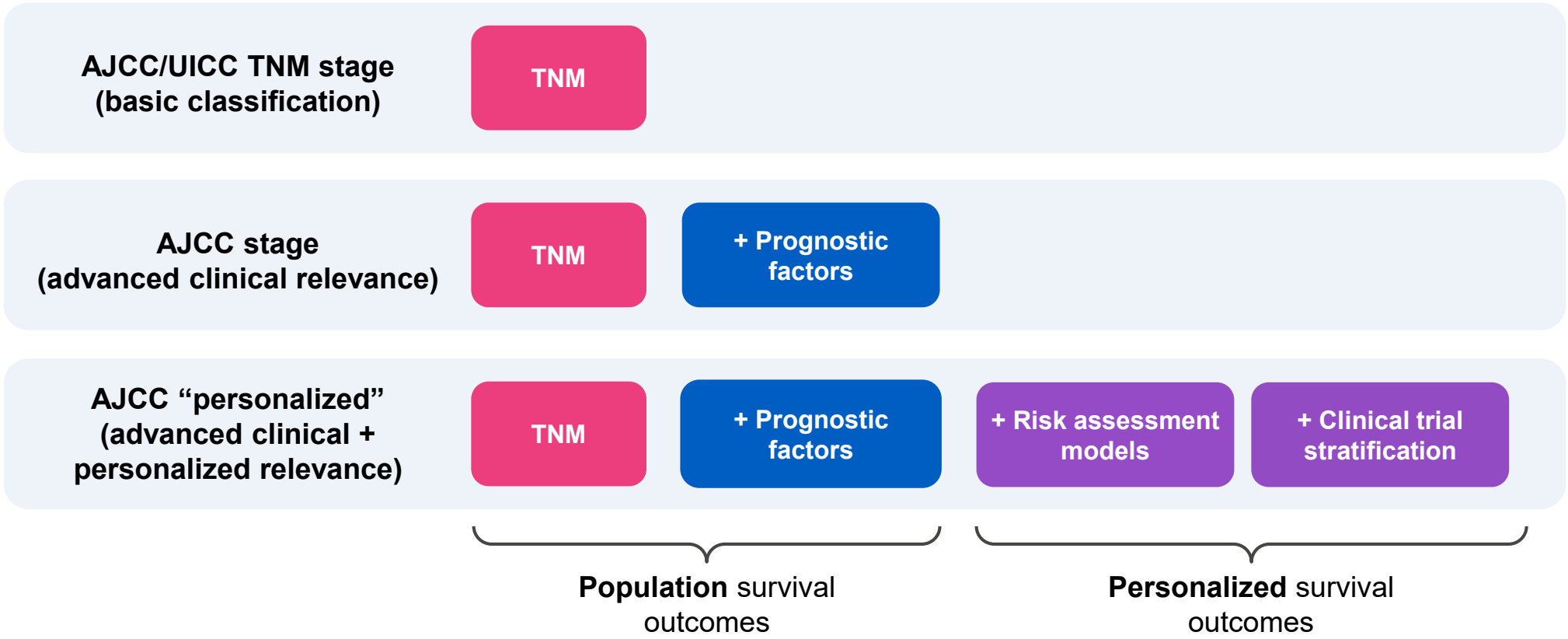
¿Por qué Redefinir los iCDK 4/6 en CMP?

- Dónde estamos hoy en adyuvancia con iCDK4/6 (abemaciclib, ribociclib).
  - Gran heterogeneidad (luminal A vs luminal B) y riesgo de recaída.
  - La adyuvancia con iCDK4/6 ya es una realidad en “alto riesgo”
  - El reto es precisión (quién, cuándo, cuánto).
  - El reto es adherencia.

- Qué nos aporta la neo/“ventana biológica”
- Cómo “redefinir” la práctica: selección de pacientes, secuencias y manejo de toxicidad

Loibl S et al. Ann Oncol 2024

Early breast cancer classification has evolved from a “population” approach to a more “personalized” approach[1]

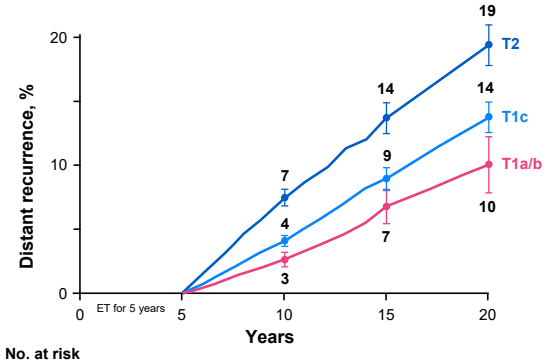


AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastasis; UICC, Union for International Cancer Control.

1. Amin MB, et al. *CA Cancer J Clin*. 2017;67(2):93–99.

CMP RRHH +/ Her2 - riesgo de recaída

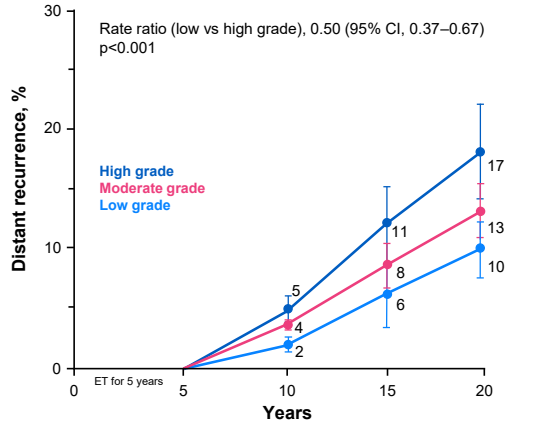
Tumor size[a]



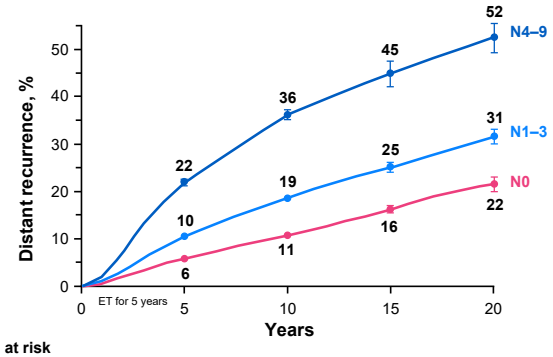
No. at risk

T2	9,445	3,901	1,129	218
T1c	13,875	5,967	1,641	309
T1a/b	5,527	2,053	704	131

Tumor grade[1]



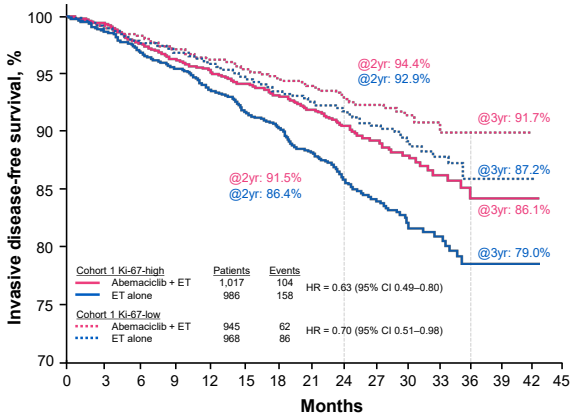
Nodal status



No. at risk

N4–9	12,333	8,116	2,165	259	52
N1–3	31,936	23,576	7,250	949	183
N0	29,925	24,081	8,571	1,982	414

Ki-67[2,a]



[a]MonarchE Kaplan–Meier curve in Cohort 1 Ki-67 high versus Ki-67 low at additional follow-up 1.
CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; yr, year rate

1. Pan H, et al. *N Engl J Med.* 2017;377:1835–1846. 2. Harbeck N, et al. *Ann Oncol.* 2021;32(12):1571–1581.

Invasive-Disease-Free Survival, Distant Disease-Free Survival and Overall Survival

At 5 and 10 years, iDFS were 87.9% and 74.3%, DDFS were 89.5% and 77.7%, and OS were 94.0% and 84.2%, respectively

Fig. 3. Kaplan-Meier Plot for iDFS by Cohorts

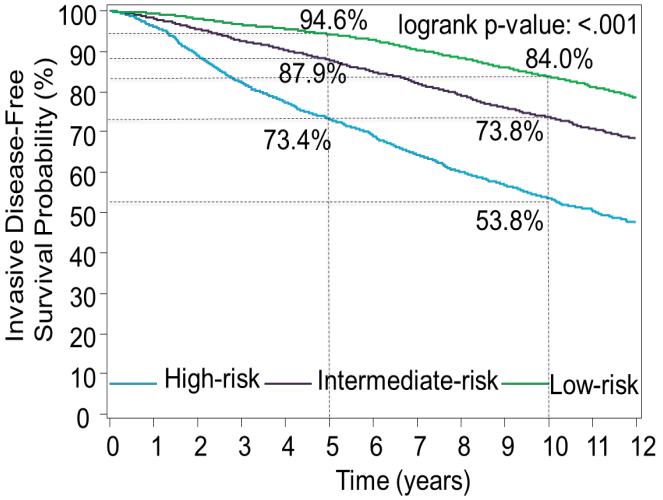


Fig. 4. Kaplan-Meier Plot for DDFS by Cohorts

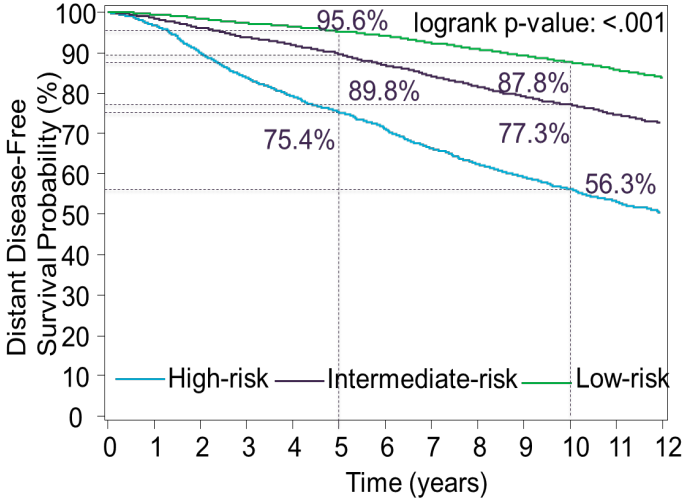
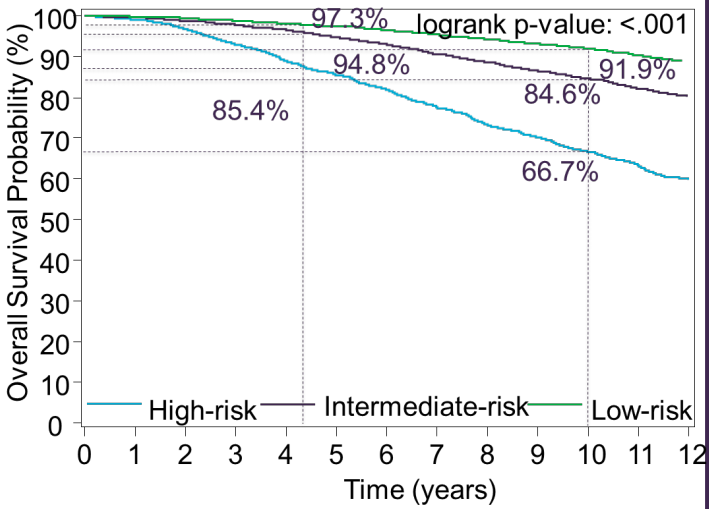


Fig. 5. Kaplan-Meier Plot for OS by Cohorts



Invasive Relapse Rate, Distant Relapse Rate and Death Rate

High-risk Intermediate-risk Low-risk

Fig. 6. IRR at 1-10 years

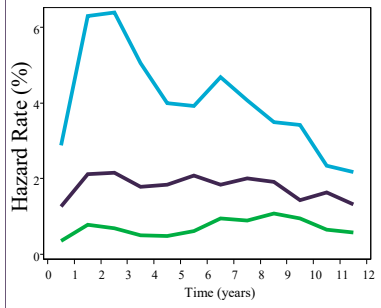


Fig. 7. DRR at 1-10 years

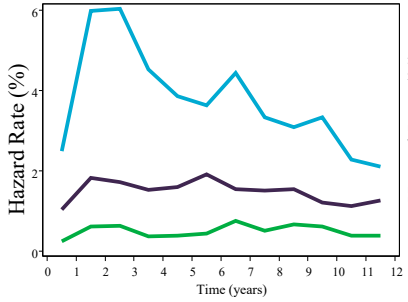
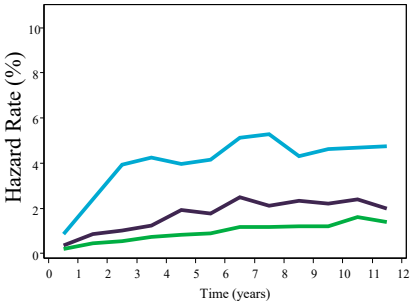
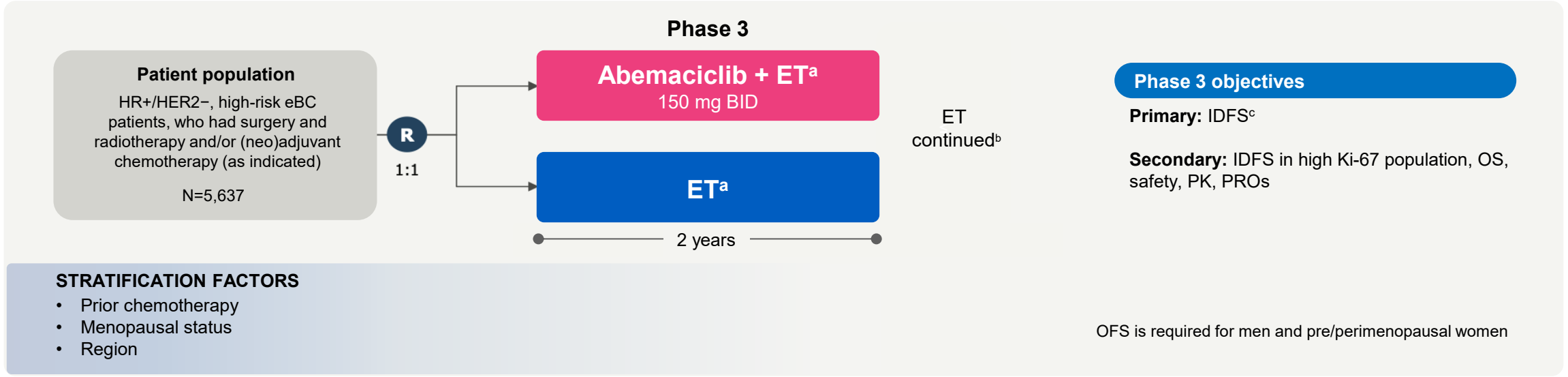
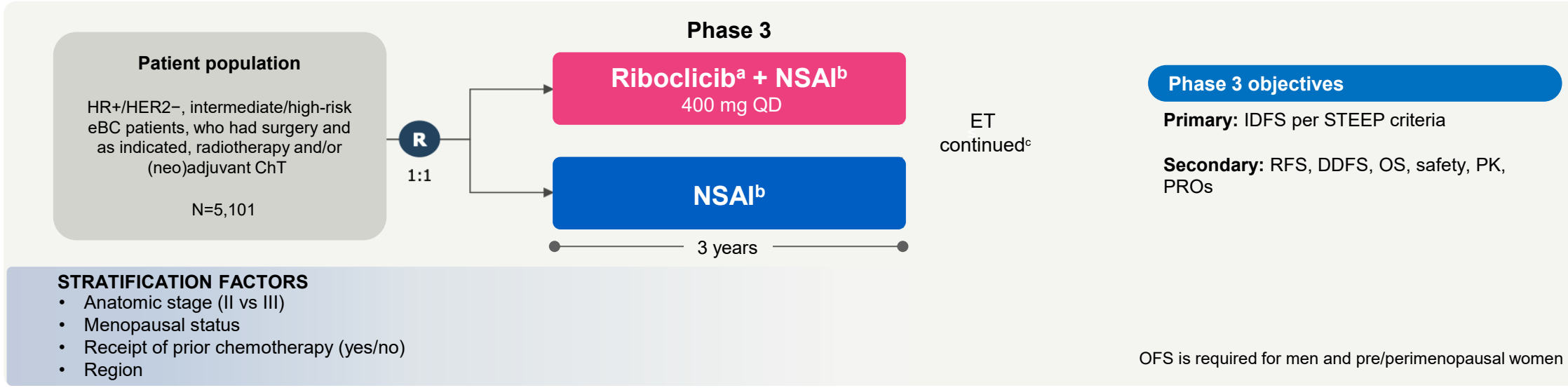


Fig. 8. DR at 1-10 years



Icdk 4/6(ribociclib/abemaciclib) +HT estándar adyuvante en CMP RRHH +/ Her2 –





Slamon DJ et al. *N Engl J Med* 2024, Johnston SRD et al. *J Clin Oncol* 2020

Icdk 4/6(ribociclib/abemaciclib) +HT estándar adyuvante en CMP RRHH +/ Her2 – **en alto riesgo**

AJCC anatomical staging	TN (M0)	NATALEE	monarchE
Stage IIA	T0 N1	Y	Grade 3 or Ki-67 ≥ 20%
	T1 N1	Y	Grade 3 or Ki-67 ≥ 20%
	T2 N0	G3 or G2 with Ki-67 ≥20% or high genomic risk[b]	N
Stage IIB	T2 N1	Y	Grade 3 or Ki-67 ≥ 20%
	T3 N0	Y	N
Stage IIIA	T0 N2	Y	Y
	T1 N2	Y	Y
	T2 N2	Y	Y
	T3 N1	Y	Y
	T3 N2	Y	Y
Stage IIIB	T4 N0	Y	N
	T4 N1	Y	Tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4 N2	Y	Y
Stage IIIC	Any TN3	Y	Y

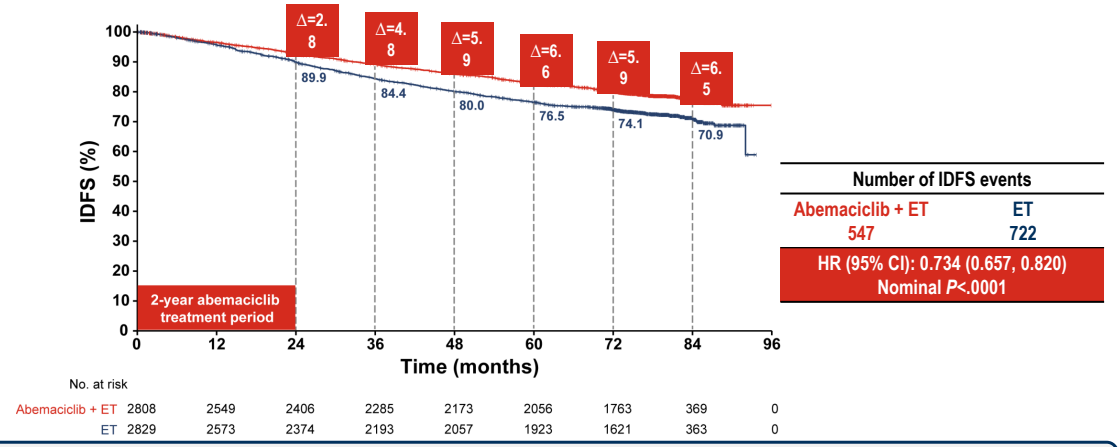
[a]Choice of therapy will depend on approval, access, risk, long-term efficacy, safety profile, and patient preference. [b]High risk as determined by Oncotype DX, Prosigna PAM50, MammaPrint, or EndoPredict EPclin Risk Score.
AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N, node status; T, tumor size.

1. Slamon DJ, et al. *Ther Adv Med Oncol.* 2023;15:17588359231178125.

Slamon DJ et al. *N Engl J Med* 2024, Johnston SRD et al. *J Clin Oncol* 2020

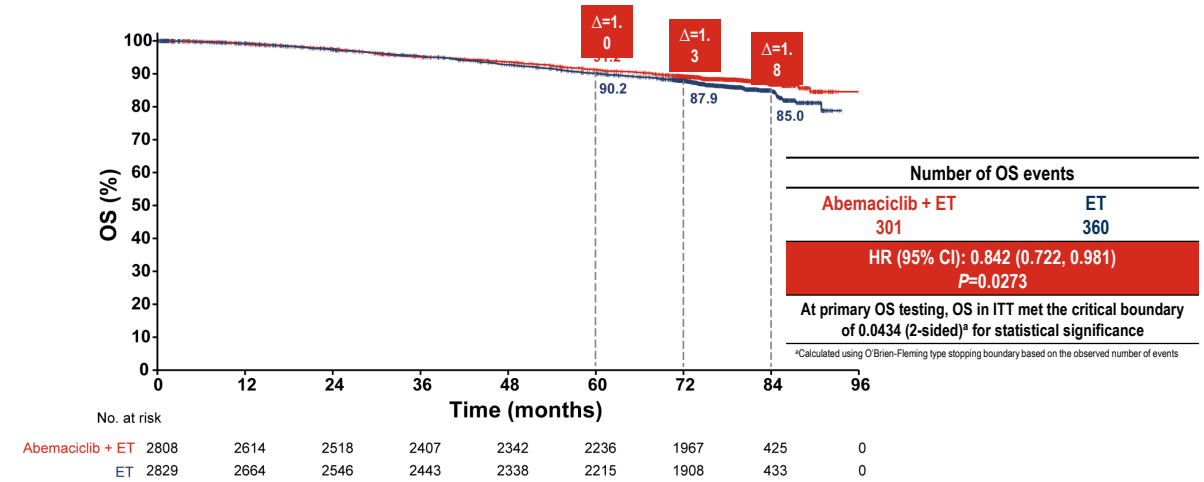
Monarch-e actualización 2025

Sustained IDFS Benefit in ITT: Evolution of Yearly Rates



Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone

Key Secondary Endpoint: Overall Survival in ITT



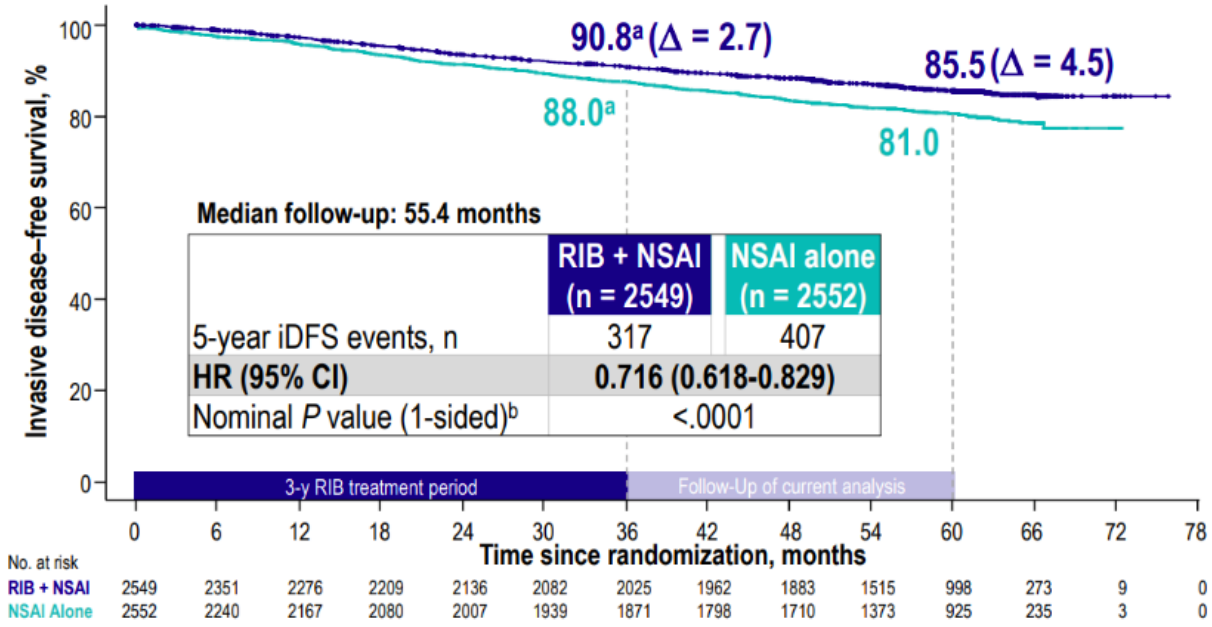
At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

Johnston, S. et al. Annals of Oncology, Volume 37, Issue 2, 155 - 165

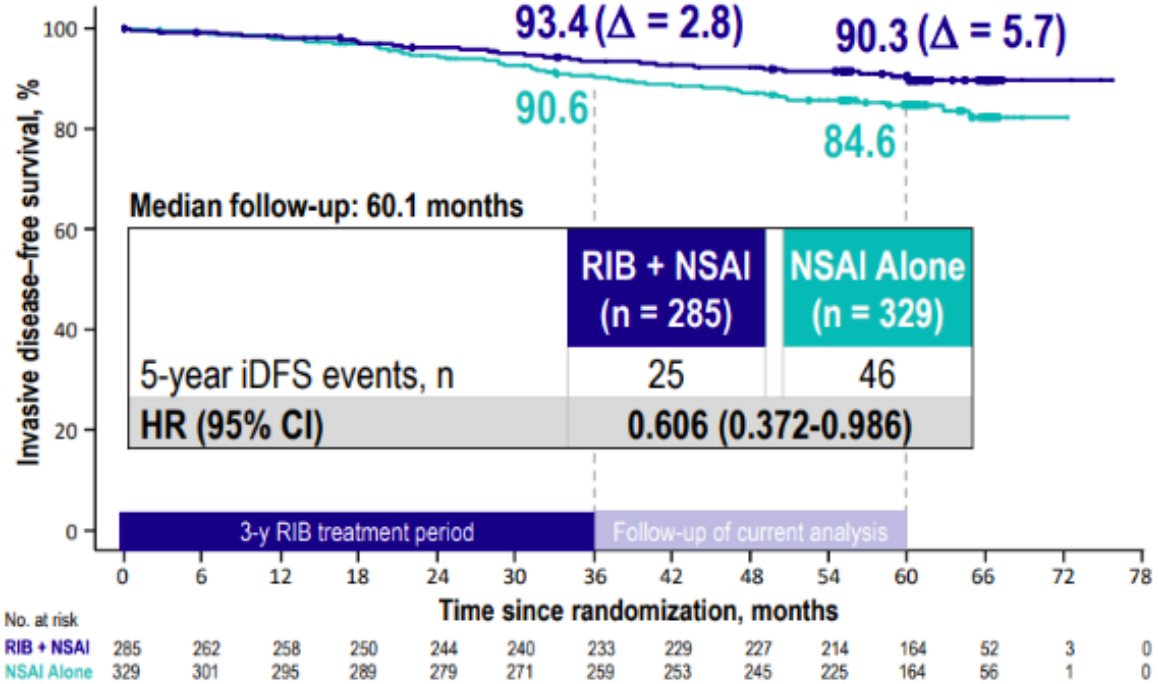
Natalee actualización 2025

iDFS in the ITT Population

With 55.4 months of follow-up, RIB continues to demonstrate a durable iDFS benefit



N0



Crown J . ESMO congress 25

Summary of ongoing studies investigating oral SERDs as adjuvant therapy for HR+/HER2− eBC

Patient population			ELEGANT[1]	EMBER-4[2,3]	CAMBRIA-1[3,4]	lidERA[3,5,6]	CAMBRIA-2[3,7]
N			4,220	8,000	4,300	4,200	5,500
Intervention			Elacestrant	Imlunestrant	Camizestrant	Giredestrant	Camizestrant (± abema 2 y)
Trial design			TREATMENT SWITCH AFTER 2-5 YEARS OF ADJUVANT ET			UPFRONT ADJUVANT TREATMENT	
Risk of recurrence			+++	++	+	+	+
Patient population			Pure high-risk	High-risk	Intermediate/high-risk	Intermediate/high-risk	Intermediate/high-risk
Prior CDK4/6i exposure allowed			YES	YES	YES	NO	NO
ECOG PS			0–1			0–2	0–1
Disease stage	IIA	T0 N1	If grade 3	If grade 3	NO	YES	NO
		T1 N1	If grade 3	If grade 3	If ≥2 LN+, or grade 3, or genomic high-risk, or Ki-67 ≥20% (incl N0 mic)	YES	If ≥2 ILN+, or grade 3, or genomic high-risk, or Ki-67 ≥20% (including N0 mic)
		T2 N0	NO	If tumor size 5 cm or grade 3	If grade 3 or genomic high-risk or Ki-67 ≥20%	If grade 3 or genomic high-risk[c] or Ki-67 ≥20%	If grade 3, or genomic high-risk, or Ki-67 ≥20%
	IIB	T2 N1	If tumor size 5 cm or grade 3	If tumor size 5 cm or grade 2/3	YES[a]	YES	YES[a]
		T2 N0	NO	If tumor size 5 cm or grade 3	If grade 3, or genomic high-risk, or Ki-67 ≥20%	If grade 3 or genomic high-risk[c] or Ki-67 ≥20%	If grade 3, or genomic high-risk, or Ki-67 ≥20%
	IIIA		YES	YES	YES	YES	YES
	IIIB	T4 N0	NO	If tumor size ≥5 cm, or grade 3 and 2–5 cm	YES[b]	YES	YES
		T4 N1	If tumor size ≥5 cm or grade 3	If tumor size ≥5 cm, or grade 3 or grade 2 and 2–5 cm	YES[b]	YES	YES
		T4 N2	YES	YES	YES[b]	YES	YES
	IIIC		YES	YES	YES	YES	YES

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a]For 1 LN+ only if grade 3, or genomic high risk, or Ki-67 >20%.[b]T4d excluded. Abema, abemaciclib. [c]Oncotype DX or MammaPrint high. CDK4/6i cyclin-dependent kinase 4/6 inhibitor; eBC, early breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILN, ipsilateral lymph node; incl, including; LN, lymph node; mic, microinvasion; N, node status; SERD, selective estrogen receptor degrader; T, tumor size; y, year.

1. ClinicalTrials.gov. NCT06492616. 2. ClinicalTrials.gov. NCT05514054. 3. Ascione L, et al. *Curr Opin Oncol.* 2024;36(6):465–473. 4. ClinicalTrials.gov. NCT05774951. 5. ClinicalTrials.gov. NCT04961996. 6. ClinicalTrials Register EU. Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=LidERA (accessed March 2025). 7. ClinicalTrials.gov. NCT05952557.

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

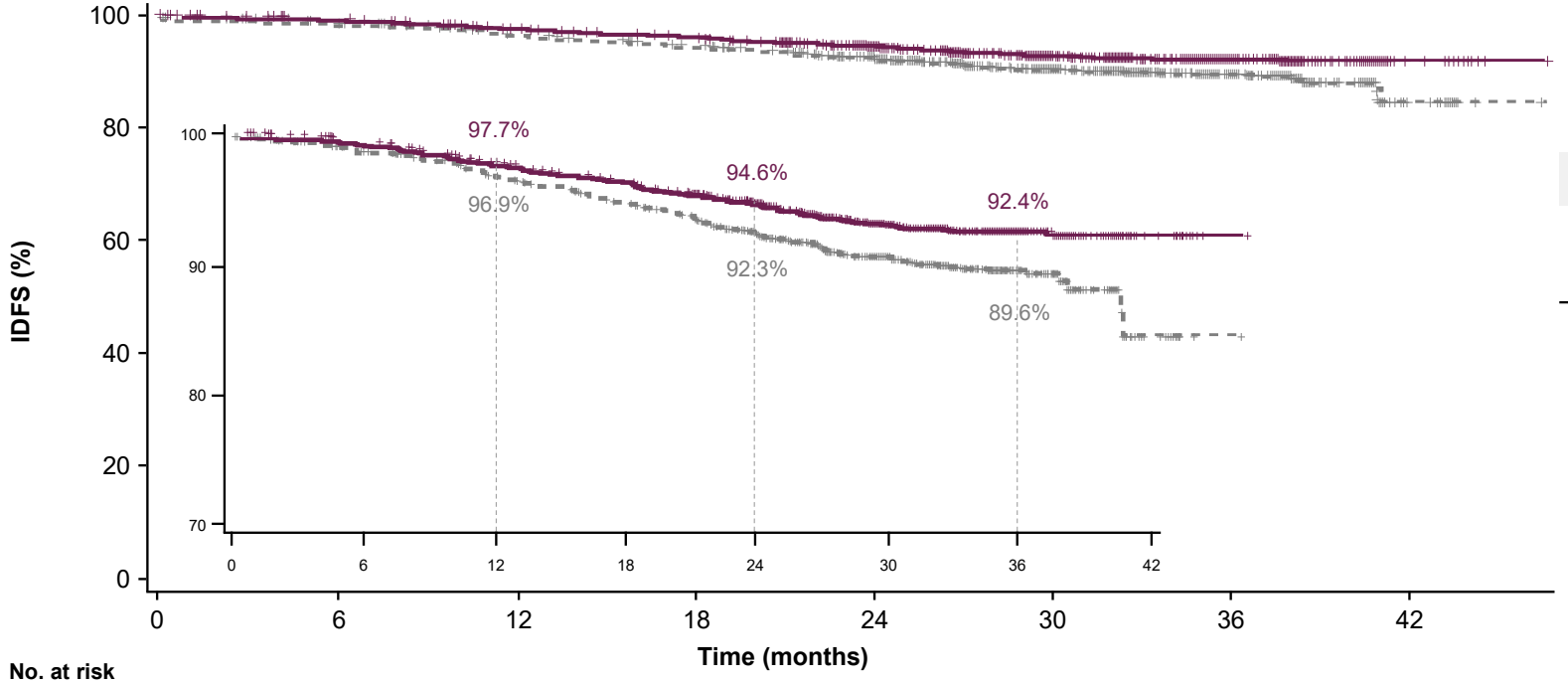
- DFS, DRFI, IDFS (including second primary non-breast invasive cancer with exception of non-melanoma skin cancers and *in situ* carcinomas of any site), LRRFI, OS, safety

Bardia A et al. *SABCS 2025*

lidERA Breast Cancer

SAN ANTONIO BREAST CANCER SYMPOSIUM®

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***	

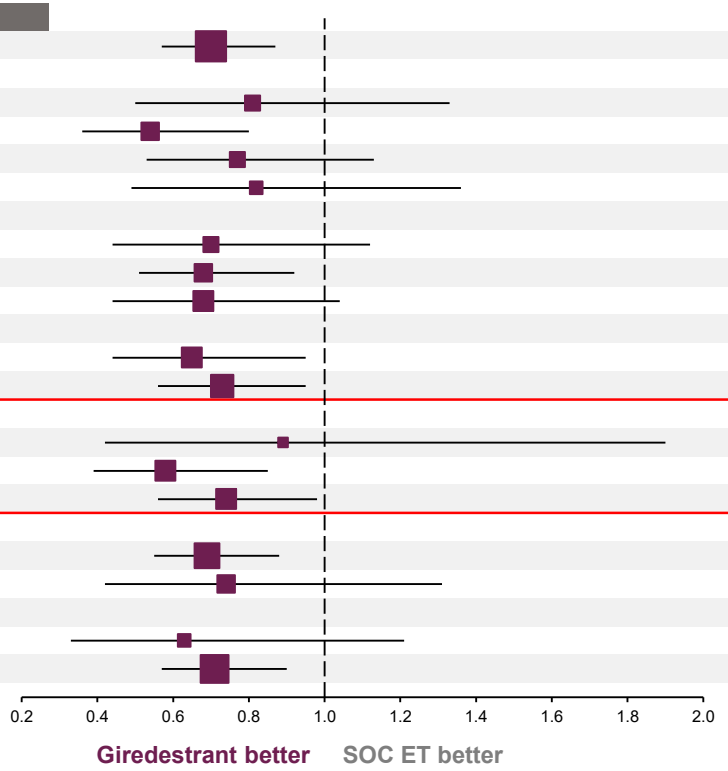
Median follow-up: 32.3 months

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

	Total, n	Patients, n: Giredestrant	Patients, n: 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)

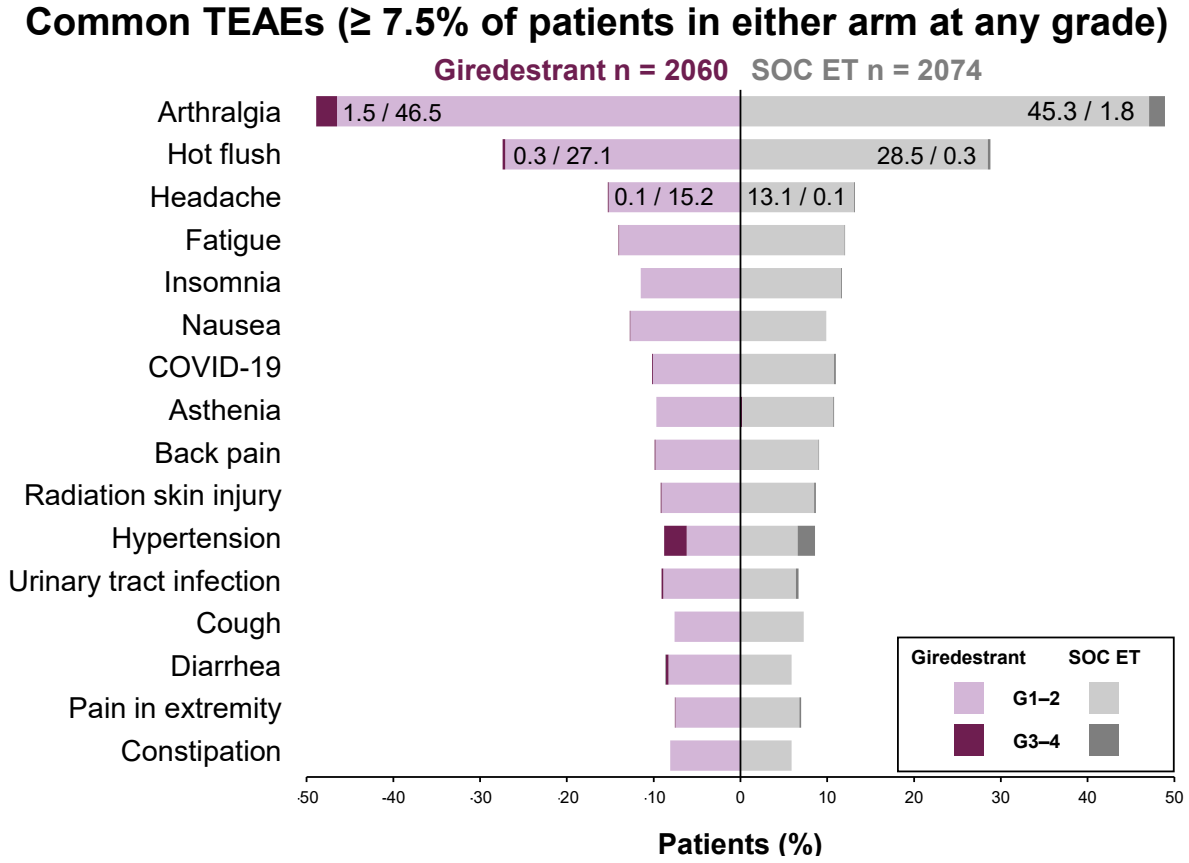


IDFS benefit was consistent across key prespecified subgroups

RETO :adherencia

lidERA Breast Cancer

AE overview *(safety-evaluable popu*

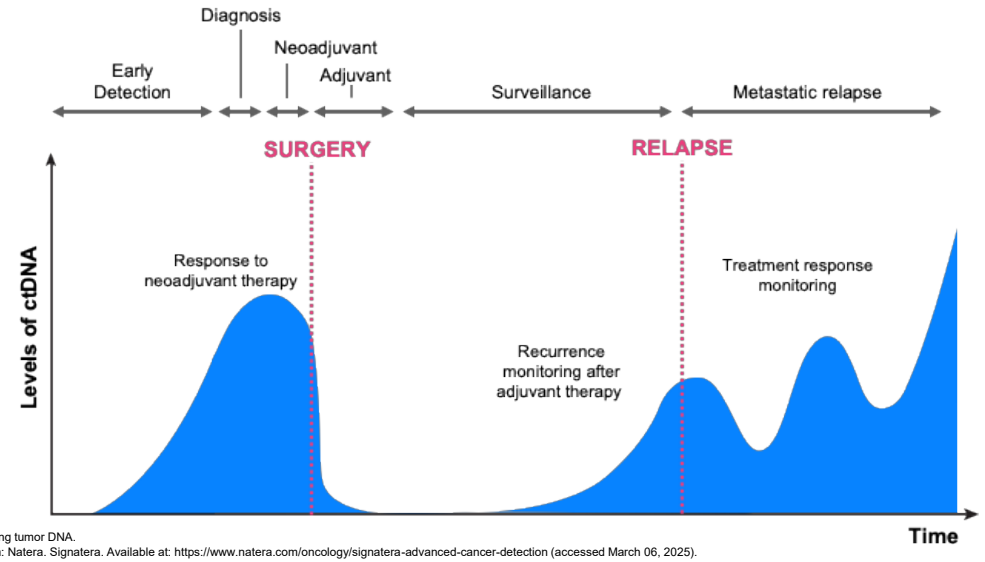


Ensayo	Fármaco	Tasa de discontinuación
NATALEE	Ribociclib 400 mg (3 años) + NSAI vs NSAI	20.0% [1]
monarchE	Abemaciclib (2 años) + ET vs ET	25.8%/ 18.5%[2](Aes)
lidERA	Giredestrant vs ET estándar	5.3% vs 8.2%[3]

1. Fasching PA. *JAMA Oncol* 2025
2. Rugo HS, et al. *Ann Oncol* 2022
3. Bardia A et al. *SABCS 2025*

Reto : selección de pacientes para escalada/desescalada

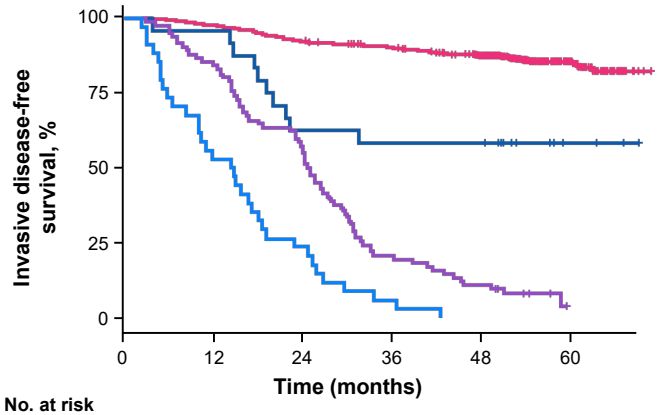
Monitoring of minimal residual disease through ctDNA is likely to prove beneficial for anticipating recurrence[1]



ctDNA, circulating tumor DNA.
1. Adapted from: Natera. Signatera. Available at: https://www.natera.com/oncology/signatera-advanced-cancer-detection (accessed March 06, 2025).

In monarchE, patients with persistent ctDNA positivity exhibited a higher risk of IDFS events compared to those who achieved ctDNA clearance[1]

Patients who remained or became ctDNA+ on treatment were more likely to experience recurrence compared to those who became or remained undetected



No. at risk						
Persistently −	749	731	691	664	611	162
Became −	24	23	15	14	14	3
Became +	82	70	46	17	9	0
Persistently +	34	18	8	2	0	0

Longitudinal analysis (N=889)[a]	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)	n/a	58.3 (41.6-81.8)

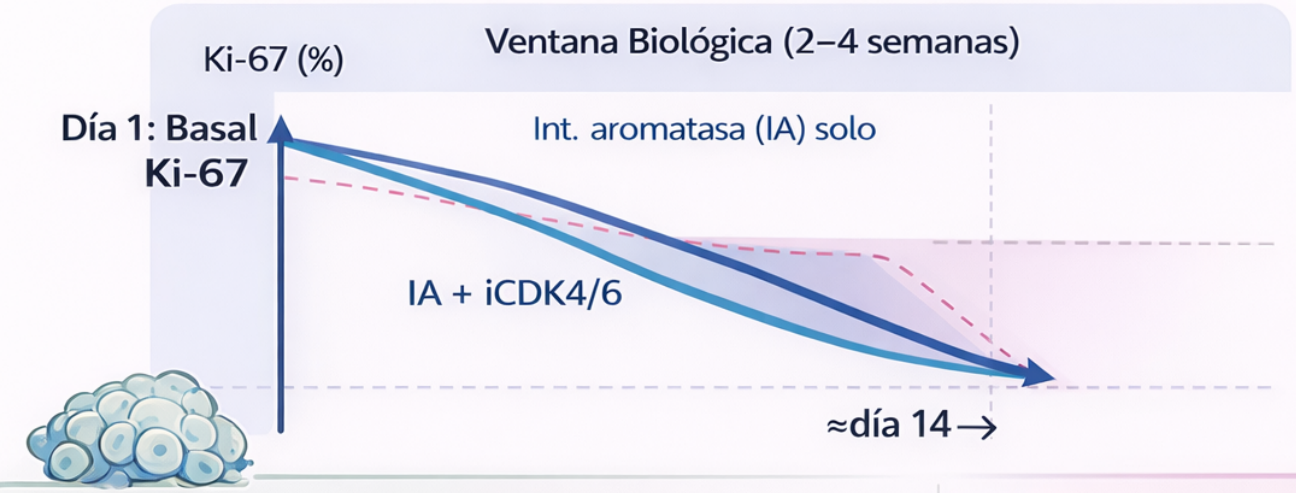
[a]The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population. Robust assessment was limited in 194 patients with <3 post-baseline timepoints and there may be differences in IDFS;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

CI, confidence interval; ctDNA, circulating tumor deoxyribonucleic acid; IDFS, invasive free survival; n/a, not available
1.Loi et al. ASCO 2024. Abstract LBA507

Reto : selección de pacientes para escalada/desescalada

Ventana biológica: qué medimos y para qué

En HR+/HER2−, medimos supresión del Ki-67 en ventana biológica (≈ día 14) para lectura temprana de sensibilidad endocrina y arresto del ciclo.



En **CORALLEEN**, un "downstaging molecular" mide cambios en el ROR de PAM50

De Luminal B/alto riesgo

A Luminal A/bajo riesgo

Endocrino-sensible: caída profunda del Ki-67

Piensa en estrategias endocrinas o desescalada

Biológicamente resistente:

Ki-67 persiste alto

Piensa en escalado sistèmico o ensayos clínicos

Ventana biológica, lectura temprana: Ki-67 bajo ≈ sensibilidad endocrina.

POETIC — *Lancet Oncol* 2020
PALLET — *J Clin Oncol* 2019
neoMONARCH — *Clin Cancer Res* 2020
CORALLEEN — *Lancet Oncol* 2020
ADAPT (WSG) — *J Clin Oncol* 2022
ADAPTcycle (WSG) — *ESMO Open* 2025

SOLTI-1911 Neoadjuvant and adjuvant ribociclib and endocrine therapy for clinically high-risk estrogen receptor-positive and HER2-negative breast cancer (RIBOLARIS)

Study Design NCT05296746

N = 1100

- Pre/post-menopausal/male
- HR+/HER2-negative
- ER+ cells > 10%
- Clinical Stage II
- Grade 2 or 3
- Ki67 ≥20% or high-genomic risk platform

24 weeks

Ribociclib 600 mg 3w ON/ 1w OFF + Letrozole +/- LHRH

SURGERY

N ~ 400

ROR Low COHORT
ROR-low after 24 weeks of Letrozole + Ribociclib

(defined by: If N0: ROR ≤ 30 points; If N1mi: ROR ≤ 20 points; If N1: ROR ≤ 10 points; N2-3: NA)

2.5 years	≥2.5 years
Ribociclib 400 mg + Letrozole +/- LHRH	ET +/- LHRH

N ~ 600

ROR Med/High COHORT
ROR-med/high after 24 weeks of Letrozole + Ribociclib

Chemo-therapy

2.5 years	≥2.5 years
Ribociclib 400 mg + Letrozole +/- LHRH	ET +/- LHRH

Primary objective

DMFS in ROR-Low COHORT
A 5-year DMFS of >90.6% will be considered clinically relevant. This estimate is based on a historical cohort from the MINDACT trial, where patients with high-risk HR+/HER2- disease (by both clinical and genomic criteria) received adjuvant multi-agent chemotherapy[5]

LHRH: *Luteinizing hormone-releasing hormone*
HR: *Hormone receptor*
ET: *Endocrine Therapy*
ROR: *Risk of Recurrence*
DMFS: *Distant metastasis-free survival*

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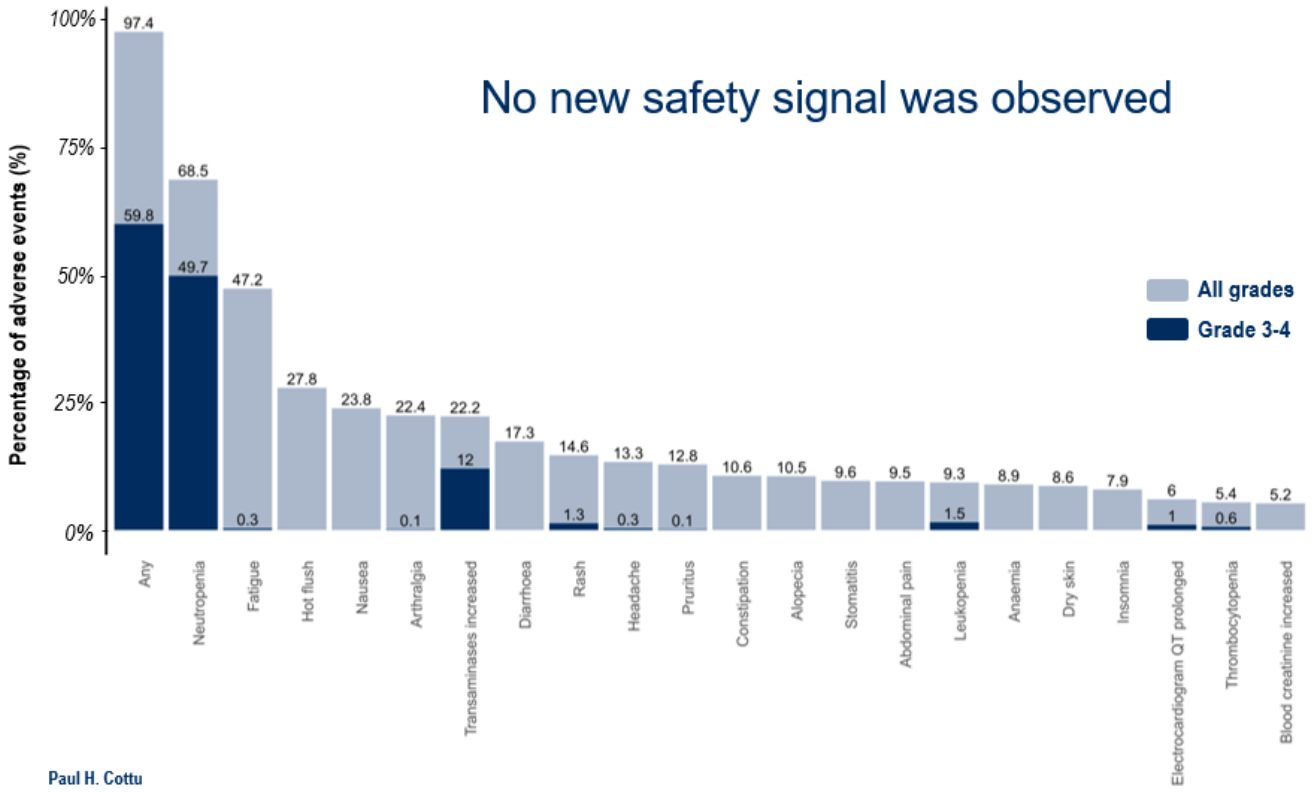
SOLTI-1911 Neoadjuvant and adjuvant ribociclib and endocrine therapy for clinically high-risk estrogen receptor-positive and HER2-negative breast cancer (RIBOLARIS)

	ROR-low	ROR-med/high
Expected	*40%*	*60%*
Current results *(IC95 %)*	**52.6%** *(48.8% ; 56.4%)*	**47.4%** *(43.6% ; 51.2%)*

Surgery results	ROR-low	ROR-med/high
Age (years)		
Median (IQR 25-75)	*55 (47; 64)*	*59 (50; 67)*
Menopausal status		
Postmenopausal	*203 (56.4%)*	*218 (67.9%)*
Pre/perimenopausal	**157 (43.6%)**	**103 (32.1%)**
ROR Score		
Mean [IC 95%]	**11.3** *[10.5 ; 12.2]*	**36.9** *[34.2 ; 39.5]*
Pathological T status		
ypT0	*12 (3.3%)*	*0 (0.0%)*
ypTis	*5 (1.4%)*	*2 (0.6%)*
ypT1	**238 (65.9%)**	*159 (48.9%)*
ypT2	*98 (27.1%)*	*141 (43.4%)*
ypT3	*8 (2.2%)*	*23 (7.1%)*
Pathological N *status*		
ypNx	*1 (0.3%)*	*1 (0.3%)*
ypN0	**251 (69.5%)**	*80 (24.6%)*
ypN1mi	*39 (10.8%)*	*18 (5.5%)*
ypN1	*70 (19.5%)*	*144 (44.3%)*
ypN2	*0 (0.0%)*	*68 (20.9%)*
ypN3	*0 (0.0%)*	*14 (4.3%)*
Type of surgery		
Breast-conserving surgery	**278 (77.0%)**	**228 (70.2%)**
Unilateral mastectomy	*77 (21.3%)*	*90 (27.7%)*
Bilateral mastectomy	*6 (1.7%)*	*7 (2.2%)*



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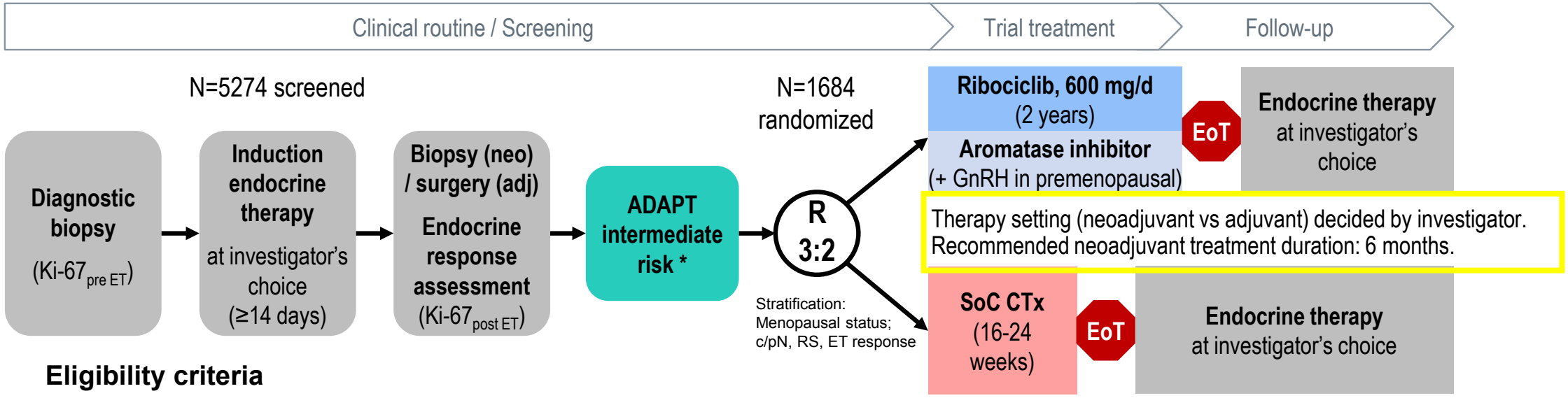
ADAPT^{CYCLE}: TRIAL DESIGN (NCT04055493)



Eligibility criteria

- Luminal-B-like early breast cancer
- c/pN0-1 with additional risk factors
- High clinical risk: (i) Grade 3 and/or (ii) Ki-67$_{pre\ ET}$ ≥20% and/or (iii) c/pN2-3 and/or (iv) c/pT2-4c
- Recurrence Score® assessed with Oncotype DX® test

ADAPT intermediate risk

- RS ≤25 and Ki67$_{postET}$ >10%
- RS >25 and Ki67$_{postET}$ ≤10% in c/pN0-1
- RS ≤25 and Ki67$_{postET}$ ≤10% in c/pN2-3

* Participation of premenopausal N1 and N0 with RS 16-25, irrespective of ET-responder status, allowed by the investigator's decision, postmenopausal only if several risk factors.

Primary outcomes

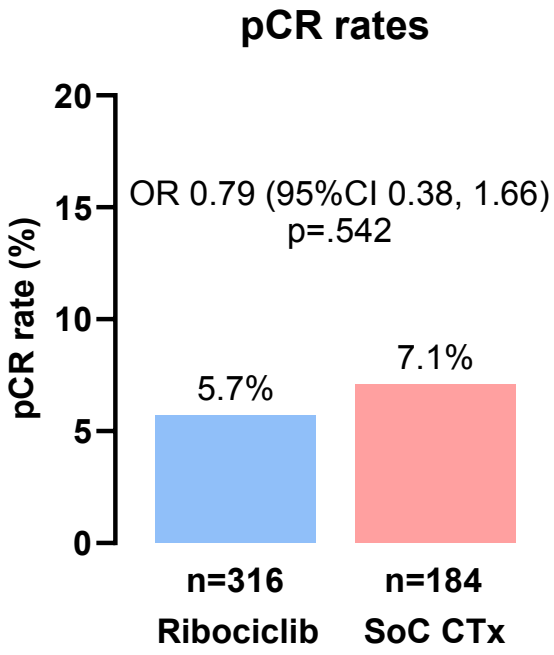
• iDFS • dDFS

Secondary outcomes

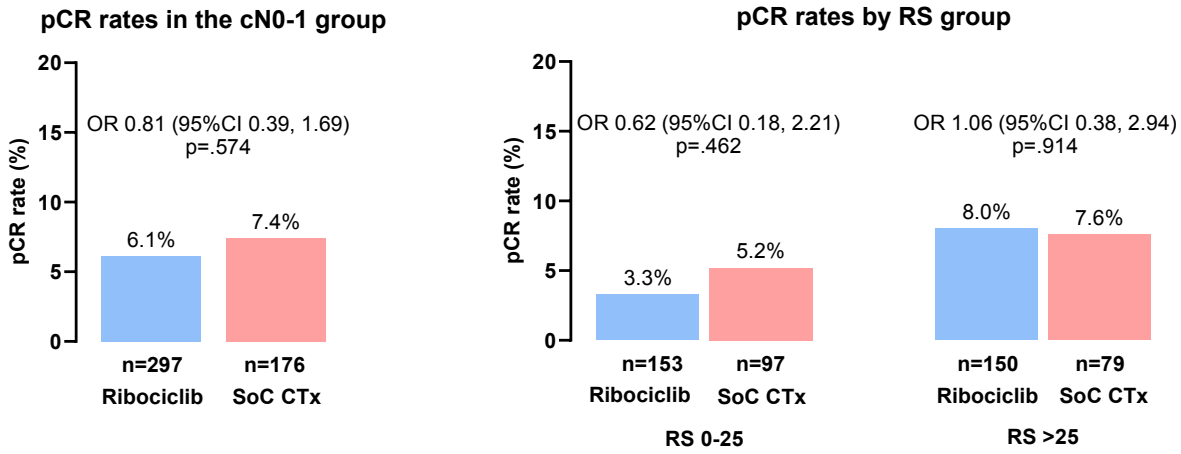
• OS • QoL • treatment adherence
• pCR • clinical response rate
• breast-conservation therapy rate

Nadia Harbeck, MD

ADAPT^{CYCLE}: NEOADJUVANT COHORT

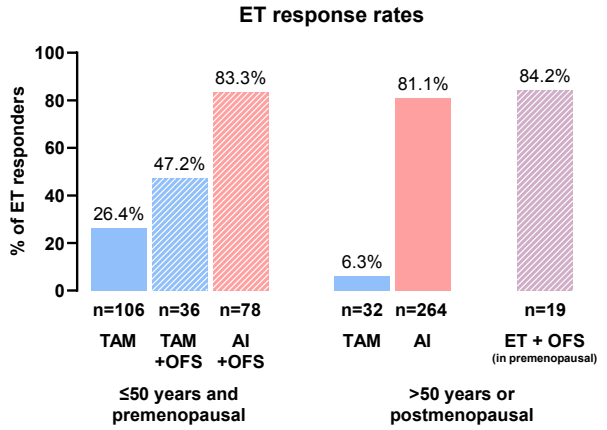


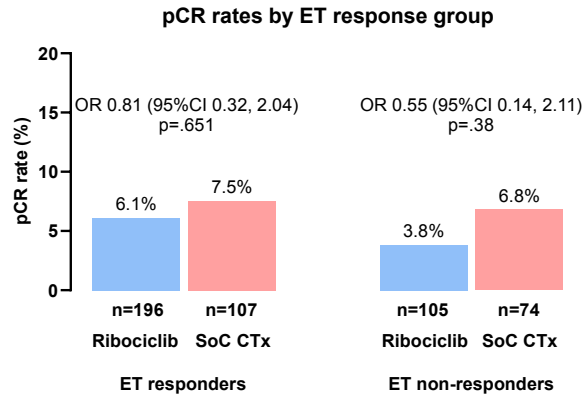
pCR rates in subgroups



- In cN2-3 patients, neither pCR nor near-pCR was observed

pCR rates in ET responders





- ET response defined as $Ki67_{post\ ET}$ ≤10%

Harbeck N.ESMO breast 25

Redefiniendo los inhibidores de ciclinas en neo/adyuvancia conclusiones

- ✓ Los iCDK4/6 (abemaciclib y ribociclib) + HT ya son estándar en adyuvancia en HR+/HER2− temprano de alto riesgo
  - Reducción del riesgo de recaida invasiva a distancia aprox 1/3
  - Abemaciclib reducción de 15% riesgo de mortalidad
- ✓ Necesitamos identificar las pacientes para estrategias de intensificación/ desescalada
  - Estudios neoadyuvancia→ selección molecular/sensibilidad hormonal
  - Monitorización molecular dinámica
- ✓ Mejorar la adherencia al tratamiento hormonal
- ✓ Todo en el marco de las nuevas hormonas en el entorno precoz

GRacias!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025