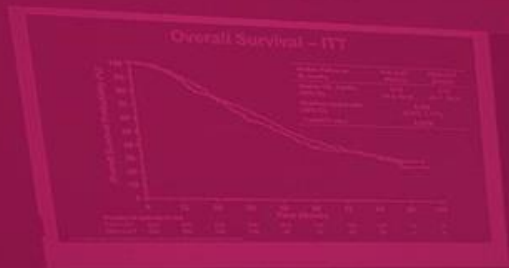
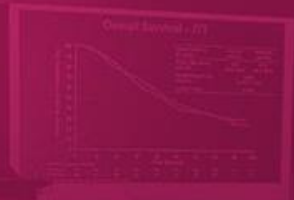


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REALIZAÇÃO



Avaliação de risco e tratamento de paciente na pré-menopausa com tumores luminiais e envolvimento nodal

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São Paulo, 15 de março de 2024.

Conflitos de interesse

Daniela Dornelles Rosa

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

Apresentações como palestrante convidado: Roche, Novartis, AstraZeneca, Lilly, GSK, Sanofi, Libbs, Eisai, Pfizer, DrReddy's, Amgen, Teva, Zodiac, United Medical, MSD, Daiichi Sankyo

Apoio em atividades de consultoria: Roche, Novartis, Pfizer, AstraZeneca, Lilly, Zodiac, Teva

Apoio para pesquisa clínica: NA

Não possuo ações de quaisquer destas companhias farmacêuticas.

Os meus pré requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão que estas empresas respeitam.

CA mama luminal

Avaliação de risco na paciente pré-menopáusia com axila (+)

IMUNOHISTOQUIMICA

Luminal A

RE e RP altos

Ki67 < 20%

Luminal B

RE+, RP < 20%

Ki67 ≥ 20%

CALCULADORAS

Predict Breast

CancerMath

PAINEIS GENOMICOS SOMATICOS

Oncotype DX

MammaPrint

Prosigna (PAM50)

EndoPredict

Goldhirsch A, Winer EP, Coates AS, et al; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol.* 2013;24:2206-2223.

Decisão de quando fazer QT adjuvante

- Magnitude do benefício da QT depende do risco de recorrência;
- Avaliação de risco de recidiva por parâmetros de AP e IHQ (biologia é mais importante do que tamanho);
- Dados que sugerem benefício da QT vem da metanálise do EBCTCG em 2012 que mostrou benefício das antraciclinas:
 - redução no risco de recorrência (RR=0,73; 0,68-0,79)
 - redução na mortalidade por CA mama (RR=0,79;0,72-0,85)
 - redução na mortalidade global (RR=0,84; 0,78-0,91)

Peto et al. Lancet 2012;379:432

Decisão de quando fazer QT adjuvante

- Quais recursos temos para definir benefício da QT?
 - Calculadoras online
 - Testes genômicos somáticos

Calculadoras de risco: Predict



Home

About Predict ▾

Predict Tool

Contact

Legal ▾

Change Language ▾

What is Predict?

Predict is an online tool that helps patients and clinicians see how different treatments for early invasive breast cancer might improve survival rates after surgery.

It is endorsed by the American Joint Committee on Cancer (AJCC).

[> Start Predict](#)

Did you mean to visit [Predict Prostate?](#)



<https://breast.predict.nhs.uk/>

Calculadoras de risco: Predict

Reset

Predict is not designed to be used in all cases. [Click here for more details.](#)

If you are unsure of any inputs or outputs, click on the **i** buttons for more information.

DCIS or LCIS only?

i Yes No

Age at diagnosis

i - 45 +

Age must be between 25 and 85

Post Menopausal?

i Yes No Unknown

ER status

i Positive Negative

HER2 status

i Positive Negative Unknown

Ki-67 status

i Positive Negative Unknown

Positive means more than 10%

Invasive tumour size (mm)

i - 25 +

If there was more than one tumour, enter the size of the largest tumour. If neo-adjuvant therapy was undertaken, enter the size before neo-adjuvant therapy.

Tumour grade

i 1 2 3

Detected by

i Screening Symptoms Unknown

Detected as part of a preventive [screening programme](#)

Positive nodes

i - 0 +

Micrometastases only

i Yes No Unknown

Enabled when positive nodes is 1. [Why can't I enter micrometastases?](#)

Calculadoras de risco: Predict

Results


Table Curves Chart Texts Icons

Select number of years since surgery you wish to consider:






5 10 15

This table shows the percentage of women who survive at least 5 years after surgery.

Treatment	Additional Benefit	Overall Survival %
Surgery only	-	95%
+ Hormone therapy	1.2% (0.7% – 1.5%)	96%
+ Chemotherapy	1% (0.7% – 1.2%)	97%

If death from breast cancer were excluded, 99% would survive at least 5 years, and 1% would die of other causes. 



-  1 death due to other causes
-  2 deaths related to breast cancer
-  1 extrasurvivor due to chemotherapy
-  1 extra survivor due to hormone therapy
-  95 survivor with surgery alone

Results


Table Curves Chart Texts Icons

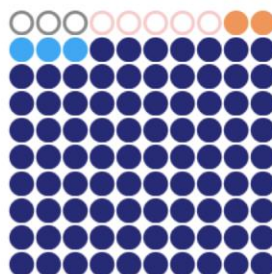
Select number of years since surgery you wish to consider:






5 10 15

This table shows the percentage of women who survive at least 10 years after surgery.

Treatment	Additional Benefit	Overall Survival %
Surgery only	-	87%
+ Hormone therapy	3.1% (1.8% – 3.8%)	90%
+ Chemotherapy	2.4% (1.8% – 3.0%)	93%

If death from breast cancer were excluded, 97% would survive at least 10 years, and 3% would die of other causes. 



-  3 deaths due to other causes
-  5 deaths related to breast cancer
-  2 extra survivors due to chemotherapy
-  3 extra survivors due to hormone therapy
-  87 survivors with surgery alone

Results


Table Curves Chart Texts Icons

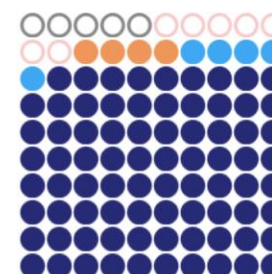
Select number of years since surgery you wish to consider:






5 10 15

This table shows the percentage of women who survive at least 15 years after surgery.

Treatment	Additional Benefit	Overall Survival %
Surgery only	-	79%
+ Hormone therapy	4.6% (2.7% – 5.7%)	84%
+ Chemotherapy	3.7% (2.7% – 4.5%)	87%

If death from breast cancer were excluded, 94% would survive at least 15 years, and 6% would die of other causes. 



-  5 deaths due to other causes
-  7 deaths related to breast cancer
-  4 extra survivors due to chemotherapy
-  5 extra survivors due to hormone therapy
-  79 survivors with surgery alone

Calculadoras de risco: CancerMath

CancerMath.net
Cancer web-calculators for medical professionals.

Breast Cancer

Melanoma

Renal Cell Carcinoma

About

Outcomes Calculator

Conditional Survival Calculator

Therapy Calculator

Nodal Status Calculator

Nipple Involvement Calculator

This calculator gives the breast cancer survival and other information, projected over time, with and without various adjuvant chemo- and hormonal therapies, presuming the same reduction in death values that were adopted by AdjuvantOnline.

Calculadoras de risco: CancerMath

Age:

Factors affecting cancer lethality

Tumor Diameter: (cm)

of Positive Nodes:

Nodal detail [input here](#) (optional)

ER Status:

PR Status:

HER2 Status:

Histological Type:

Grade:

Therapy options

Hormonal therapy:

Chemo-therapy:

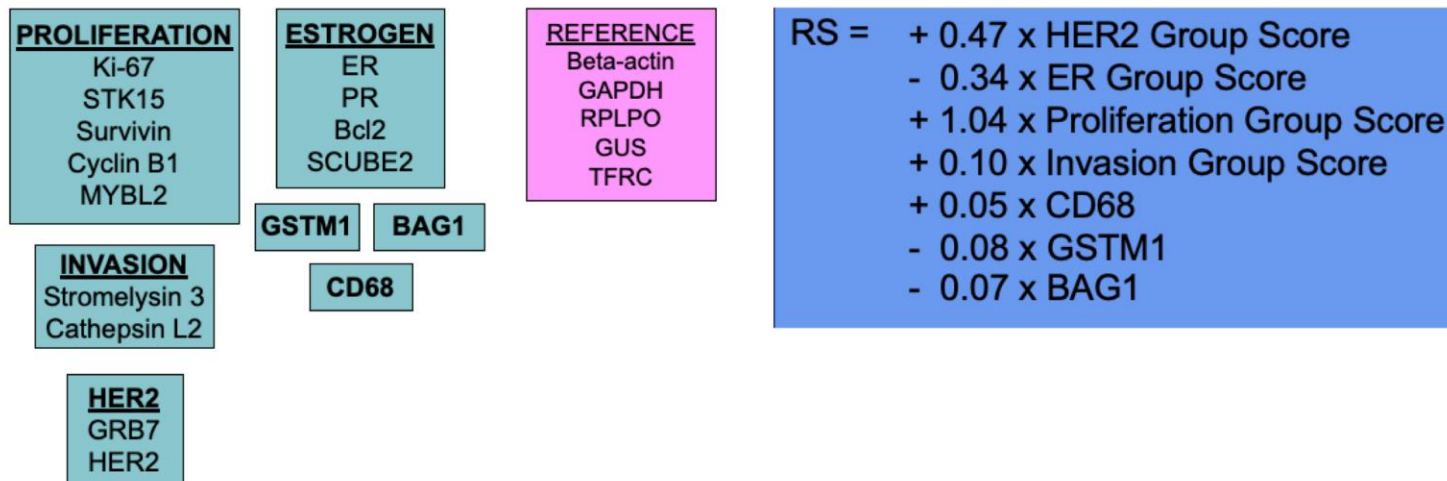
Classification:	TxNxMx	AJCC Stage:	unknown
Cancer Mortality:	8.1% expected 15-year Cancer Death Rate. 8.3% 15-year Kaplan-Meier cancer death rate		
Life Expectancy:	Without therapy, this cancer shortens the life expectancy of a 45-year-old woman by 6.6 years . (from 37.3 years to 30.7 years)		
Therapy benefit:	The therapy selected would improve average life expectancy by 4.1 years , or 1496 days over expectancy without therapy. 61.9% fewer cancer deaths after 15 years		

Testes genômicos somáticos

- Oncotype DX 21-gene Recurrence Score (RS)
 - EndoPredict (EP)
 - Predictor Analysis of Microarray 50 (PAM50)
 - Breast Cancer Index
 - Amsterdam 70-gene profile (MammaPrint)
-
- Todos são prognósticos - apenas Oncotype DX é preditivo do benefício de QT adjuvante

Oncotype DX

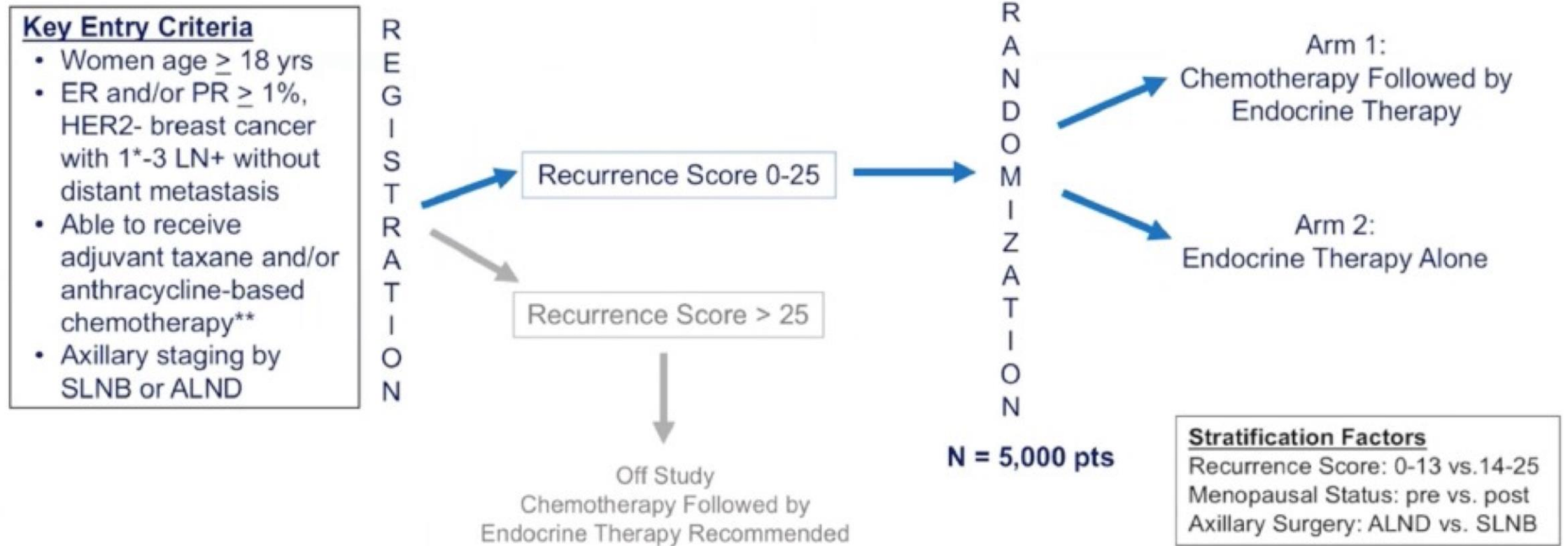
- Validado em CA mama luminal/HER2- com N- e N+;
- Desenvolvido a partir da identificação de 250 genes candidatos na literatura e testado em 447 pacientes de 3 bancos de dados;
- Identificou 16 genes que predizem recidiva à distância a despeito do uso de tamoxifeno (+ 5 genes de referência).



Oncotype DX: RxPonder (axila +)

- Resultados do TailorX poderiam ser extrapolados?
- SWOG S8814 retrospectivo sugeriu papel do RS em axila+

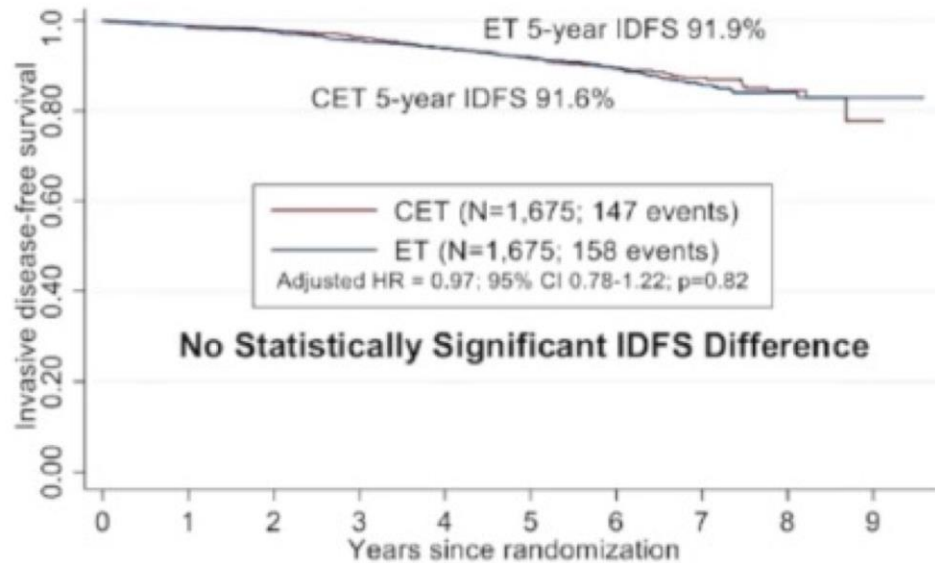
RxPONDER Schema



Oncotype DX: RxPonder (axila +)

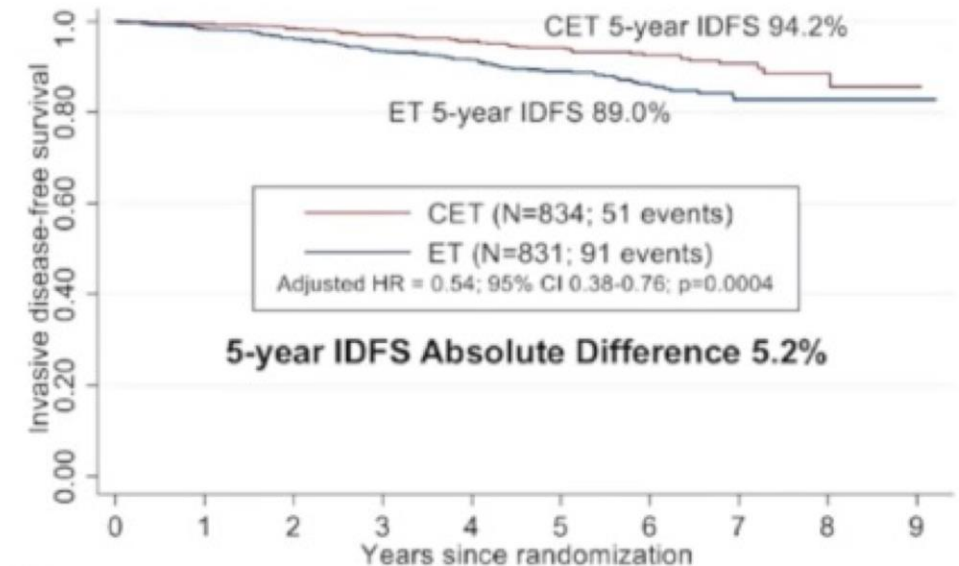
IDFS Stratified by Menopausal Status

Postmenopausal



Number at risk	0	1	2	3	4	5	6	7	8	9
CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

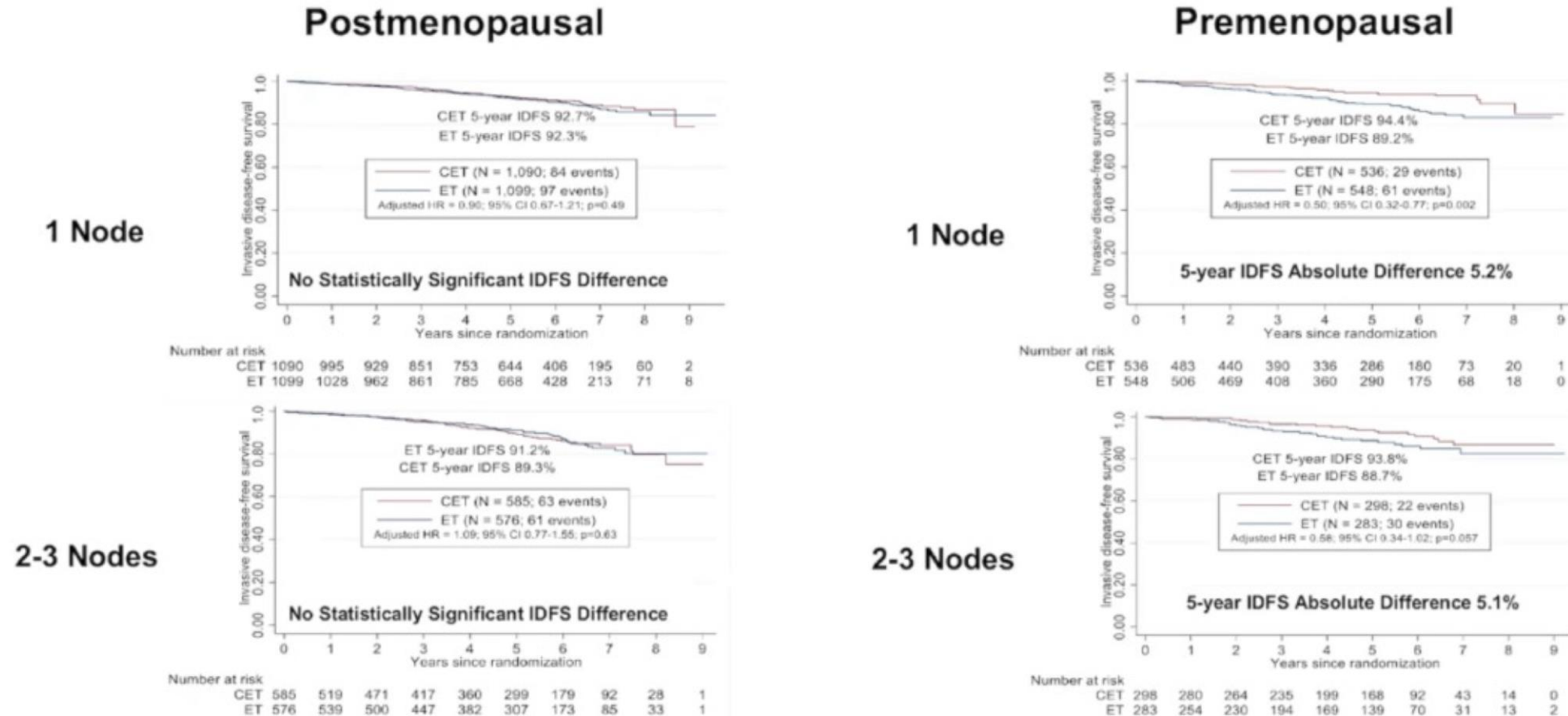
Premenopausal



Number at risk	0	1	2	3	4	5	6	7	8	9
CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

Oncotype DX: RxPonder (axila +)

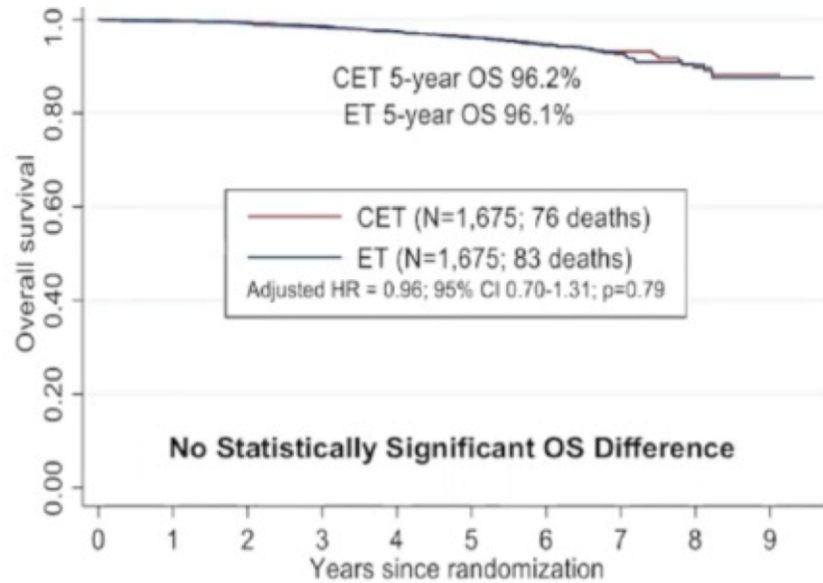
IDFS Stratified by Number of Nodes and Menopausal Status



Oncotype DX: RxPonder (axila +)

Overall Survival by Menopausal Status

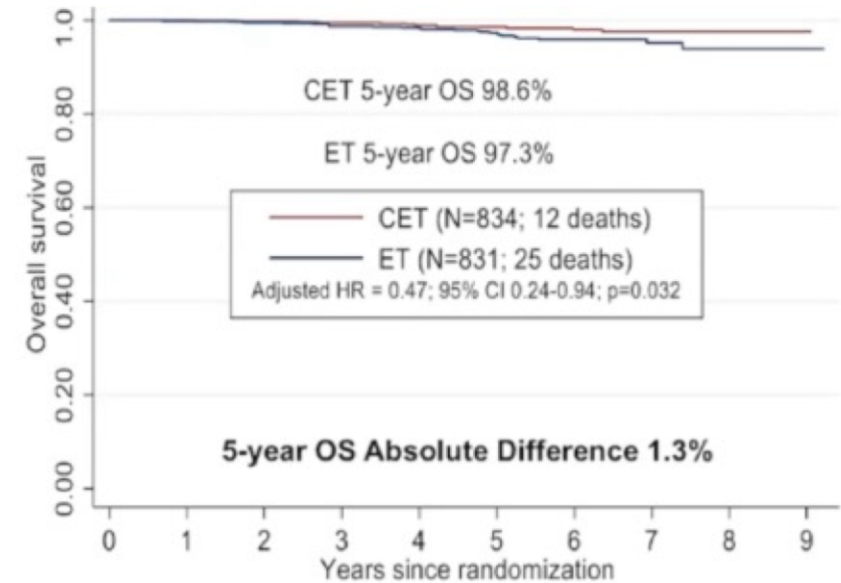
Postmenopausal



Number at risk

CET	1675	1524	1418	1296	1156	988	618	313	98	4
ET	1675	1584	1484	1346	1213	1021	639	325	110	9

Premenopausal



Number at risk

CET	834	768	714	642	552	473	290	126	39	1
ET	831	772	722	635	565	467	275	117	34	2

Oncotype DX: RxPonder (axila +)

- Pós-menopausa com RS 0-25 e 1-3LFN+: não houve benefício com QT adjuvante
- Pré-menopausa:
 - redução de 46% no risco de doença invasora
 - redução de 53% no risco de morte (ganho absoluto de 1,3% na SG em 5 anos)

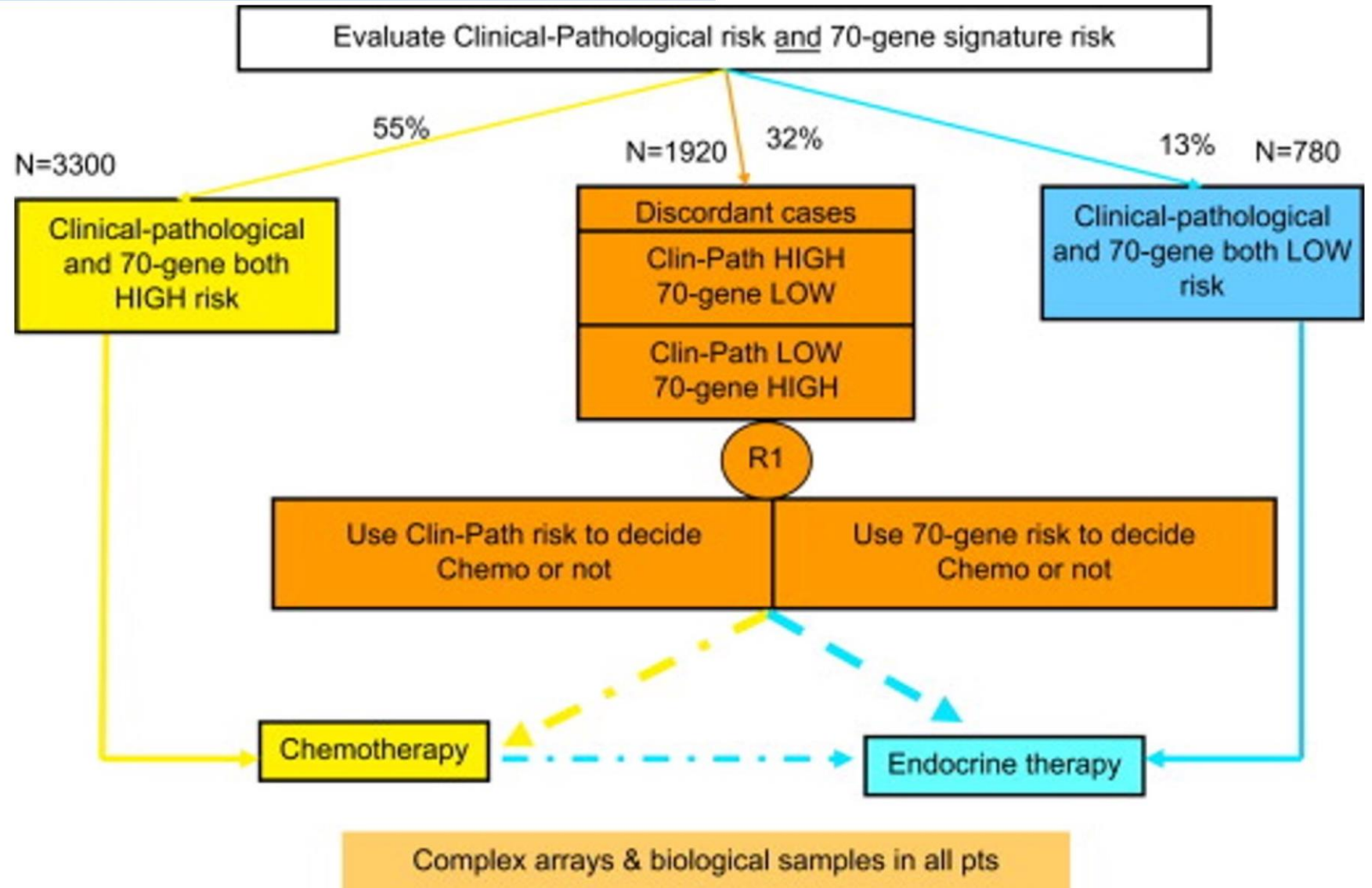
MINDACT

T1, T2

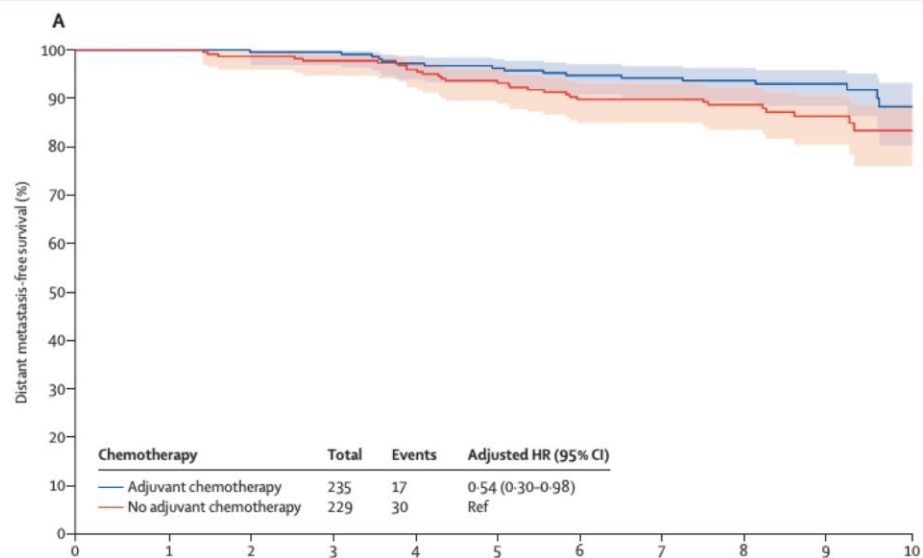
T3 operável

N0

N+ (1-3)

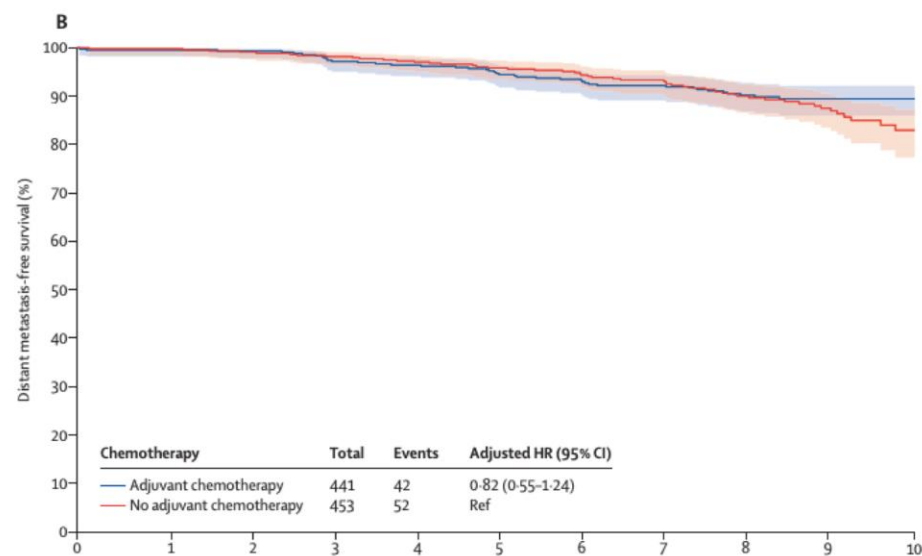


Pré-menopausa



Chemotherapy	Total	Events	Adjusted HR (95% CI)
— Adjuvant chemotherapy	235	17	0.54 (0.30-0.98)
— No adjuvant chemotherapy	229	30	Ref

Pós-menopausa



Chemotherapy	Total	Events	Adjusted HR (95% CI)
— Adjuvant chemotherapy	441	42	0.82 (0.55-1.24)
— No adjuvant chemotherapy	453	52	Ref

Assinaturas genômicas na pré-menopausa

- Não devem ser realizadas para pacientes com axila positiva!
- Quimioterapia adjuvante pode ser omitida em pré-menopausa com axila negativa e RS 0-15 (discutir em RS 16-20)

Assinaturas genômicas na vida real

- Custo é o principal limitante
- Axila positiva na pré-menopausa: quimio adjuvante

TABLE 1. Risk Stratification by Multigene Assay for Adjuvant Treatment Decisions for Women Age 50 or Younger With Early-Stage, Hormone Receptor-Positive, HER2-Negative Breast Cancer

	Setting	Multiparameter Gene Expression Assays
Low Risk: No benefit from the addition of chemotherapy to ET	T ≤ 2.0 cm, node-negative, grade 1	NA
	T ≤ 1.0 cm, node-negative, grade 2	
	T ≤ 0.5 cm, node-negative, grade 3	
	Other node-negative	Oncotype Recurrence Score ≤ 15
High Risk: Addition of chemotherapy to ET is recommended	T = 2.1–3.0 cm, node-negative, grade 1	MammaPrint Low Score
	T = 1.1–2.0 cm, node-negative, grade 2	
	T = 0.6–1.0 cm, node-negative, grade 3	
	Node-negative	Oncotype Recurrence Score > 15*
	1–3 positive nodes	Any Oncotype Recurrence Score or MammaPrint Score**
	≥ 4 positive nodes	Assay is not recommended

Assinaturas genômicas na vida real

Table 2. Surrogate definitions of intrinsic subtypes of breast cancer according to the 2015 St Gallen Consensus Conference [23] and also recommended by the ESMO Clinical Practice Guidelines

Intrinsic subtype	Clinicopathologic surrogate definition	Notes
Luminal A	'Luminal A-like' ER-positive HER2-negative Ki67 low* PgR high** low-risk molecular signature (if available)	*Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low, **Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.
Luminal B	'Luminal B-like (HER2-negative)' ER-positive HER2-negative and either Ki67 high or PgR low high-risk molecular signature (if available)	

Hormonioterapia adjuvante em pacientes de alto risco de recidiva

NATALEE study design^{1,2}

- Adult patients with HR+/HER2- EBC
 - Prior ET allowed up to 12 mo
 - **Anatomical stage IIA^a**
 - **N0** with:
 - Grade 2 and evidence of high risk:
 - Ki-67 ≥ 20%
 - Oncotype DX Breast Recurrence Score ≥ 26 or
 - High risk via genomic risk profiling
 - Grade 3
 - **N1**
 - **Anatomical stage IIB^a**
 - N0 or N1
 - **Anatomical stage III**
 - N0, N1, N2, or N3
- N = 5101^b**

R 1:1^c

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

Randomization stratification

Anatomical stage: II vs III

Menopausal status: men and premenopausal women vs postmenopausal women

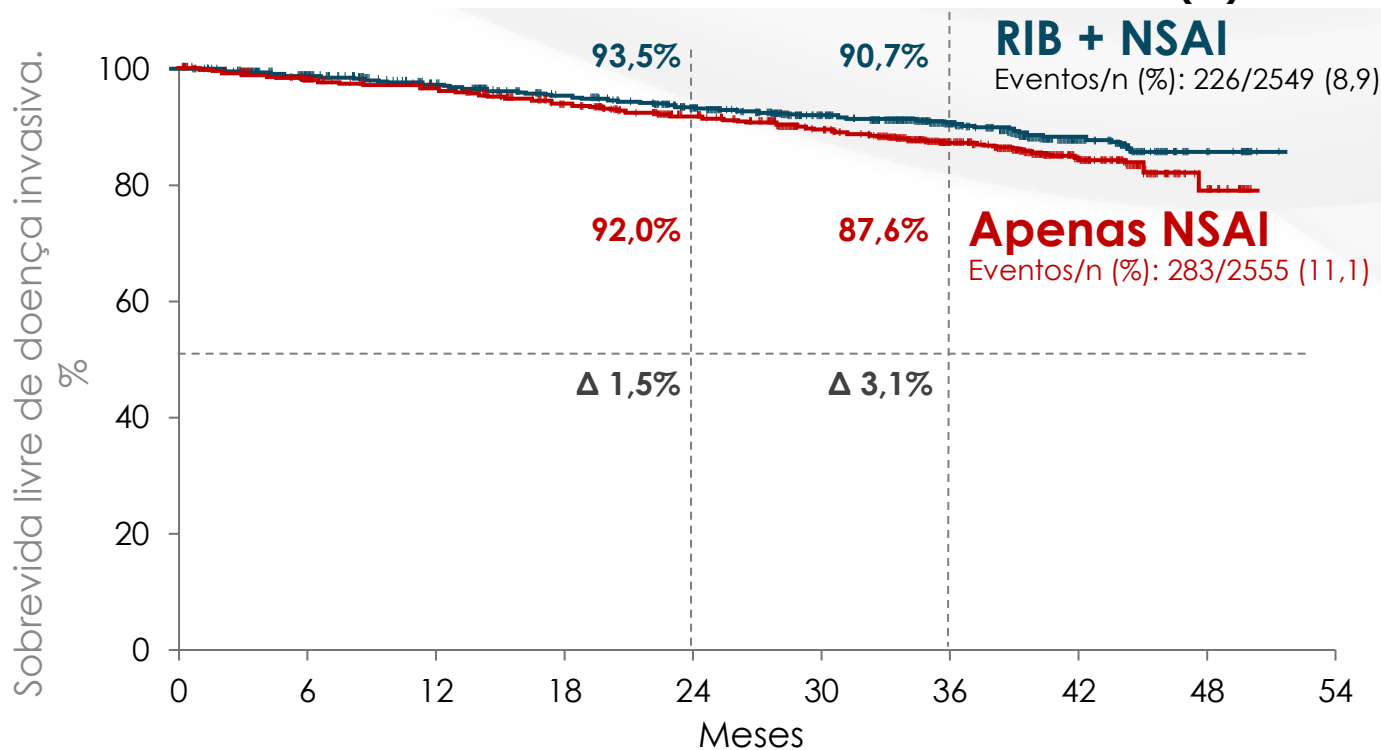
Receipt of prior (neo)adjuvant chemotherapy: yes vs no

Geographic location: North America/Western Europe/Oceania vs rest of world

^a Enrollment of patients with stage II disease was capped at 40%. ^b 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. ^c Open-label design. ^d Per investigator choice. CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials. 1. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03701334>. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597].

Sobrevida livre de doença invasiva^{1,2}

Taxa de iDFS em 3 anos (%)



HR (IC 95%): 0,749 (0,628-0,892)

p 0,0006

No. em risco	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	2549	2350	2273	2204	2100	1694	1111	368	21	0
Apenas NSAI	2552	2241	2169	2080	1975	1597	1067	354	26	0

A mediana do acompanhamento para iDFS foi de 33,3 meses (máximo, 51 meses) - um acréscimo de 5,6 meses em relação à segunda análise de eficácia interina¹

O benefício absoluto de iDFS com ribociclibe + NSAI foi de 3,1% em 3 anos

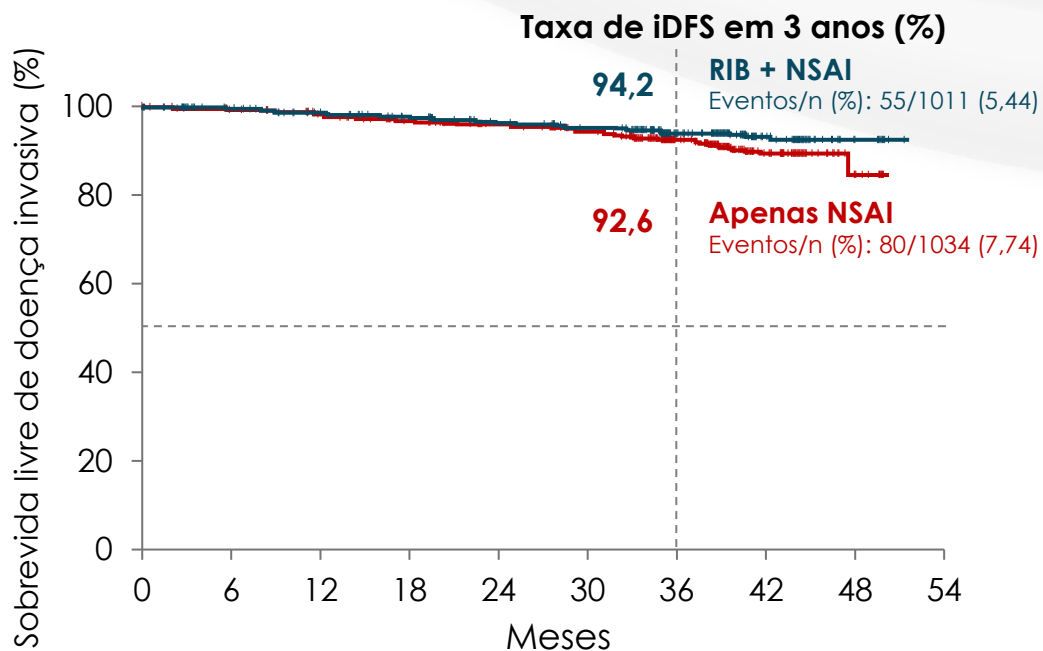
O risco de doença invasiva foi reduzido em 25,1% com ribociclibe + NSAI, em comparação com apenas NSAI

HR: hazard ratio; IC: intervalo de confiança; iDFS: intervalo de sobrevida livre de doença; NSAI: inibidor de aromatase não esteroide; RIB: ribociclibe. 1. Slamon D, Stroyakovskiy D, Yardley DA et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial. J Clin Oncol. 2023;41(17):LBA500-LBA500; 2. Adaptado de: Hortobagyi G. N, et al. Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer: Final Invasive Disease-Free Survival Analysis From the NATALEE Trial. San Antonio Breast Cancer Symposium, San Antonio, abstr GS03-03, 2023, disponível em: <https://sabcs2023.eventscribe.net/login.asp>.

iDFS por estágio anatômico¹

O risco de doença invasiva foi reduzido em 30,0% para o estágio II e em 24,5% para o estágio III com ribociclibe + NSAI em comparação com apenas NSAI

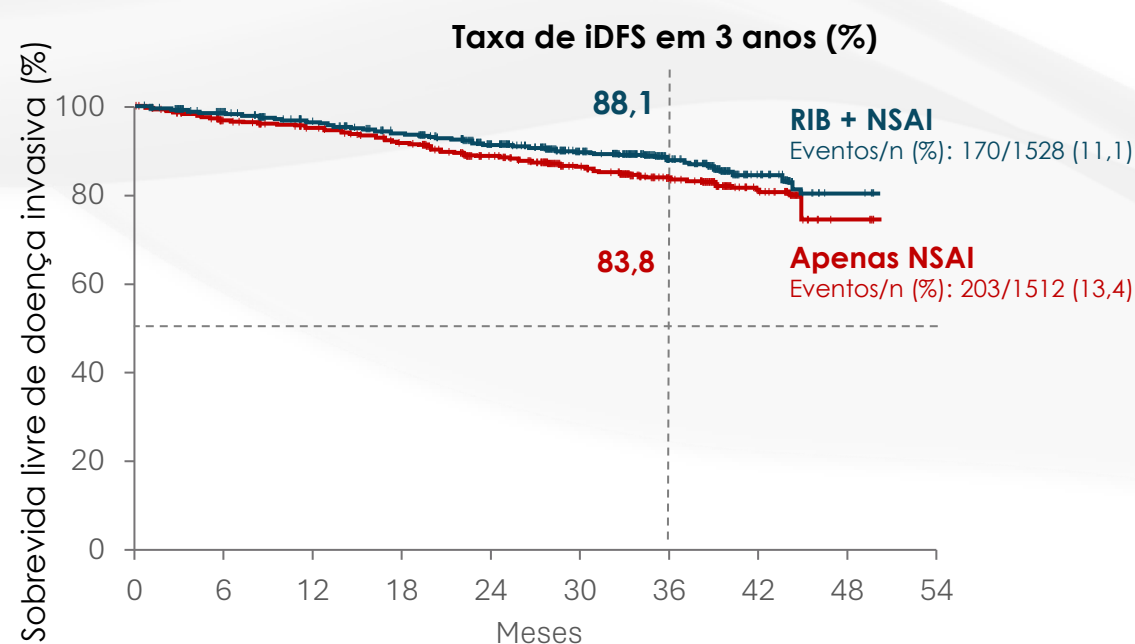
Estágio II



Acompanhamento mediano: 38,6 meses

HR (IC 95%): 0,700 (0,496-0,986)

Estágio III



Acompanhamento mediano: 33,1 meses

HR (IC 95%): 0,755 (0,616-0,926)

No. em risco

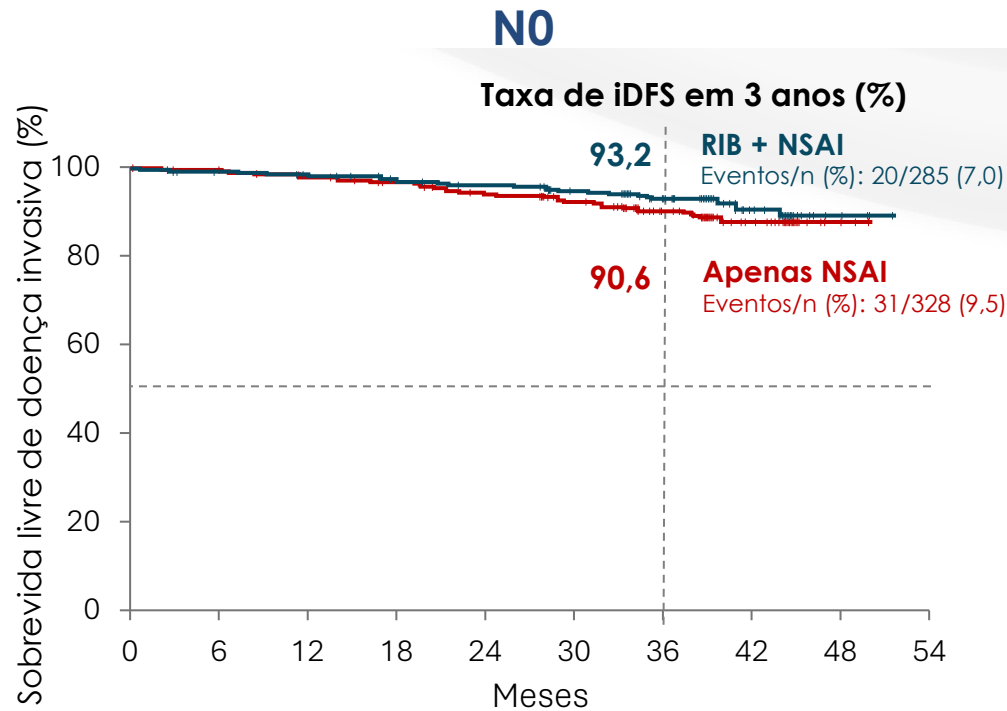
RIB + NSAI	1011	929	902	883	859	841	611	194	15	0
Apenas NSAI	1034	948	924	893	872	840	609	203	18	0

No. em risco

RIB + NSAI	1528	1411	1362	1312	1232	844	496	174	6	0
Apenas NSAI	1512	1289	1241	1183	1099	753	456	151	8	0

HR: hazard ratio; IC: intervalo de confiança; iDFS: sobrevida livre de doença invasiva; NSAI: inibidor de aromatase não esteroide; RIB: ribociclib. 1. Adaptado de: Hortobagyi G. N, et al. Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer: Final Invasive Disease-Free Survival Analysis From the NATALEE Trial. San Antonio Breast Cancer Symposium, San Antonio, abstr GS03-03, 2023, disponível em: <https://sabcs2023.eventscribe.net/login.asp>.

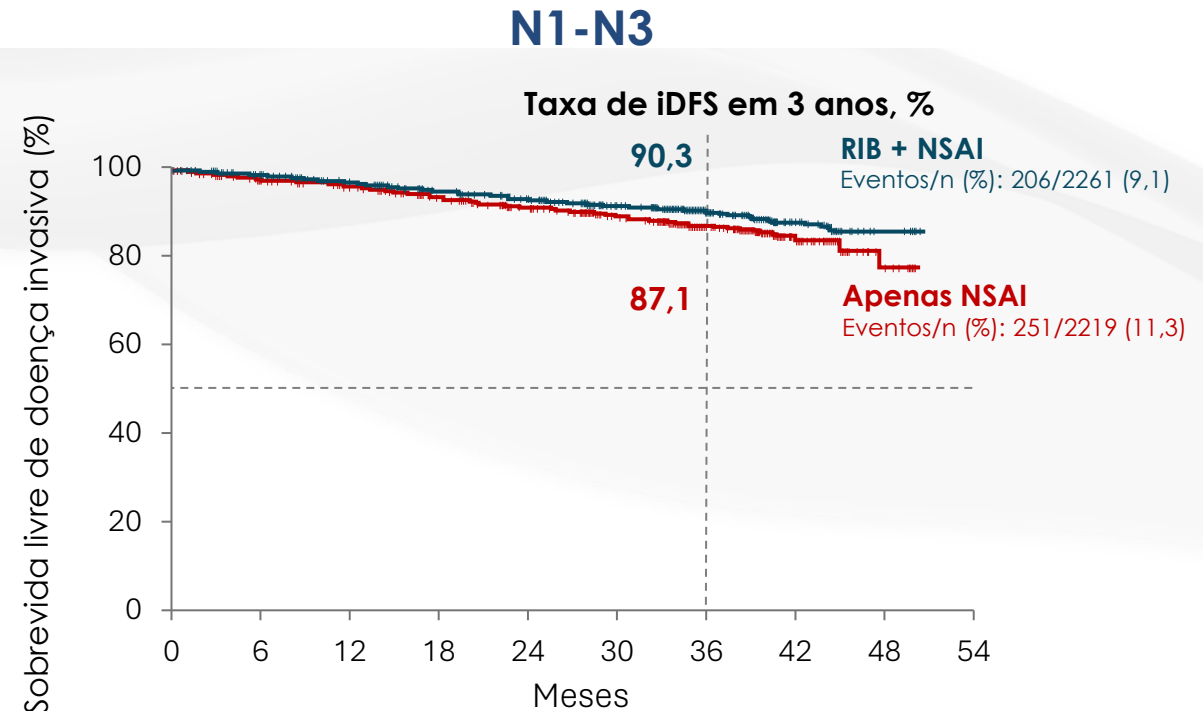
iDFS pelo status nodal¹



Acompanhamento mediano: 38,7 meses

HR (IC 95%): 0,723 (0,412-1,268)

No. em risco	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	285	262	258	250	244	235	177	67	5	0
Apenas NSAI	328	300	294	287	276	258	188	80	5	0



Acompanhamento mediano: 33,2 meses

HR (IC 95%): 0,759 (0,631-0,912)

No. em risco	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	2261	2085	2012	1951	1853	1458	934	301	16	0
Apenas NSAI	2219	1938	1873	1791	1697	1337	877	273	21	0

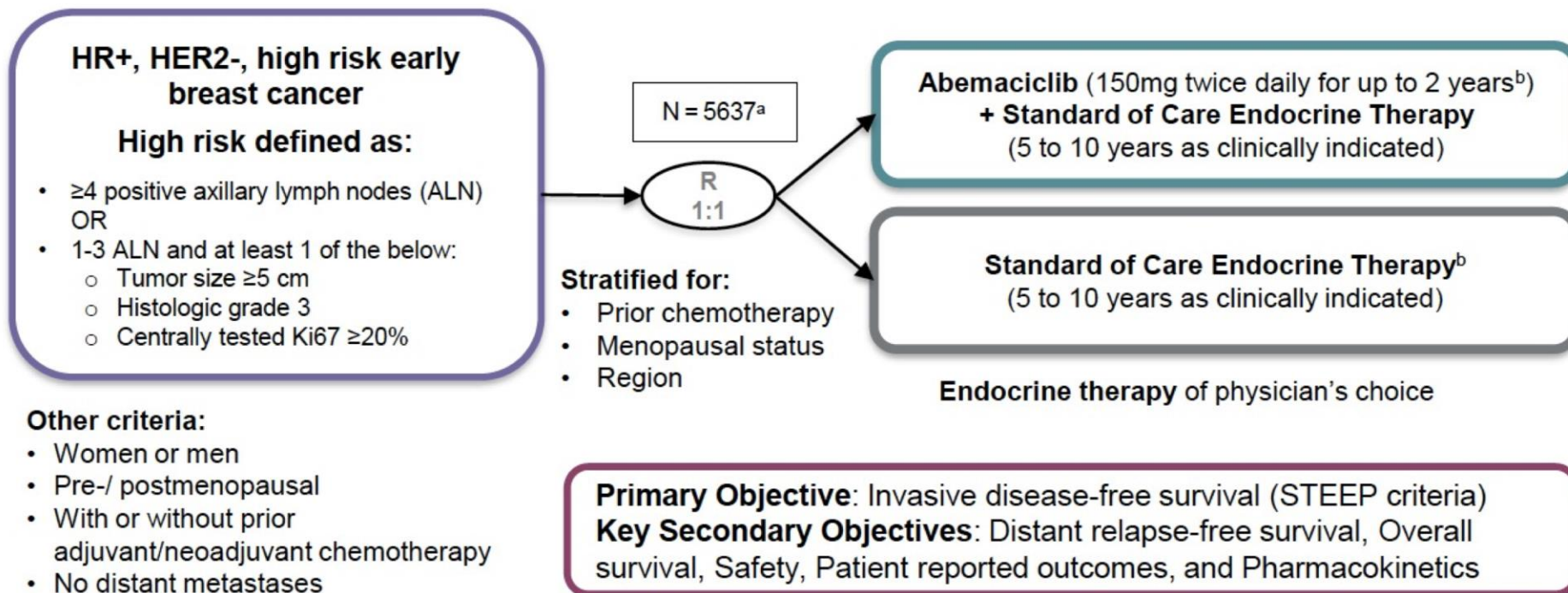
O risco de doença invasiva foi reduzido em 27,7% para doença sem comprometimento dos linfonodos e em 24,1% para doença com comprometimento dos linfonodos, com ribociclibe + NSAI em comparação com apenas NSAI

HR: hazard ratio; IC: intervalo de confiança; iDFS: sobrevida livre de doença invasiva; NSAI: inibidor de aromatase não esteroide; RIB: ribociclibe. 1. Adaptado de: Hortobagyi G. N, et al. Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer: Final Invasive Disease-Free Survival Analysis From the NATALEE Trial. San Antonio Breast Cancer Symposium, San Antonio, abstr GS03-03, 2023, disponível em: <https://sabcs2023.eventscribe.net/login.asp>.

CA mama luminal: monarchE



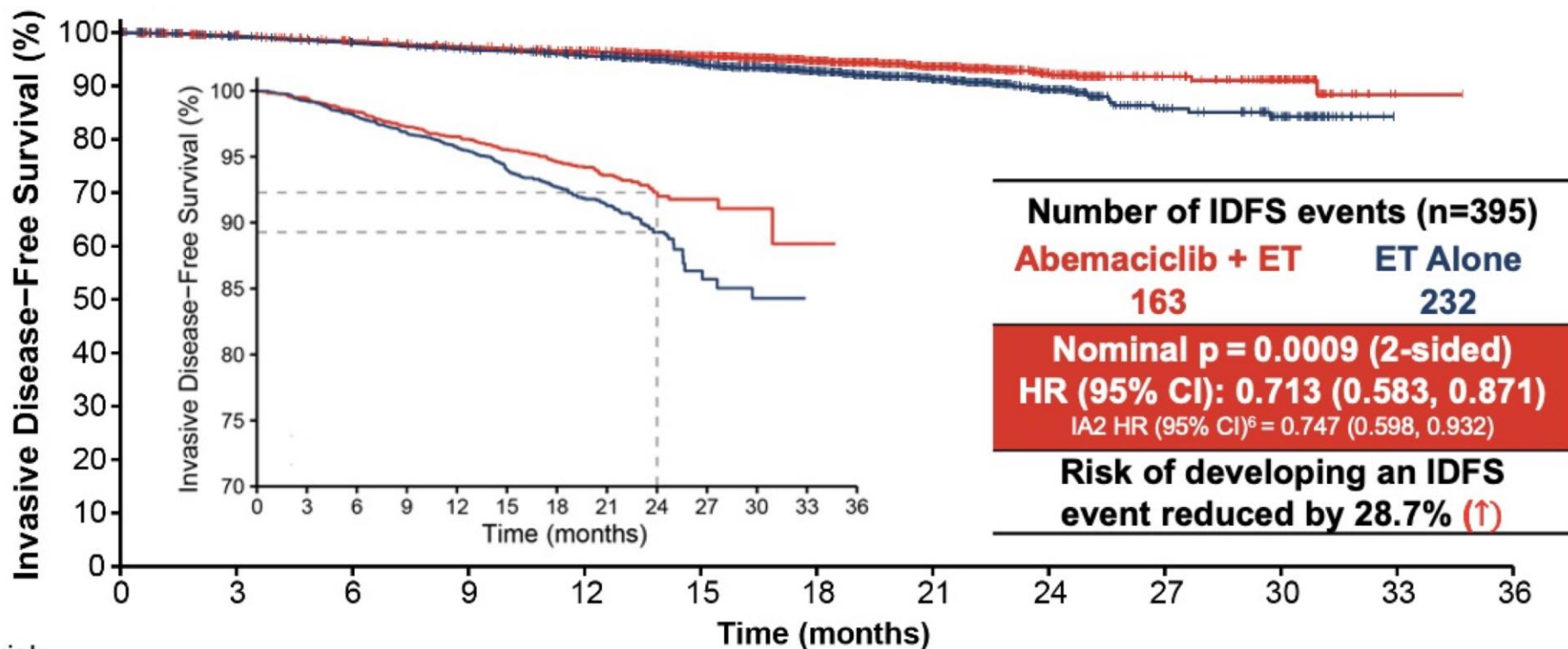
monarchE Study Design



^aRecruitment from July 2017 to August 2019; ^bTreatment period = first 2 years on study treatment after randomization

CA mama luminal: monarchE

Median FU 19.1 mo at the Primary Analysis



Number at risk

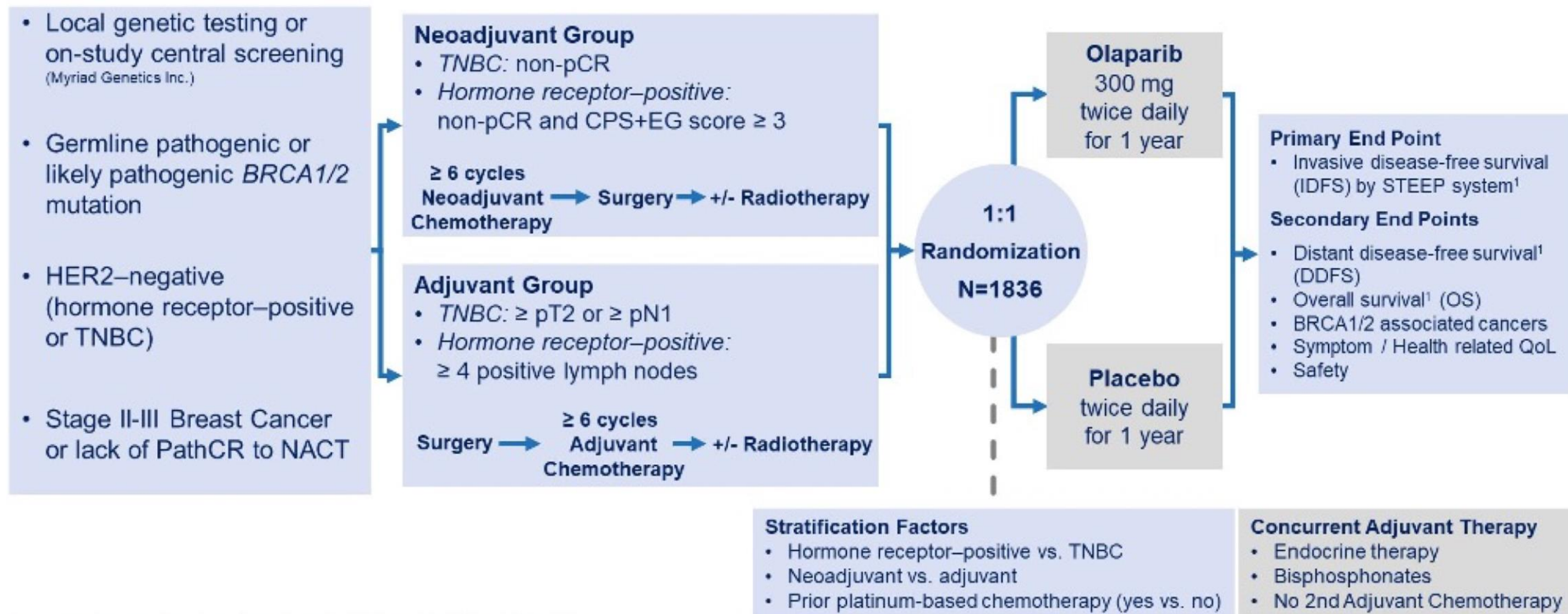
Abemaciclib + ET	2808	2680	2619	2573	2519	2076	1487	1029	619	133	94	1	0
ET Alone	2829	2700	2653	2609	2548	2093	1499	1033	627	131	102	0	0

Statistically significant and clinically meaningful improvement in IDFS with greater treatment benefit at PO analysis

Two-year IDFS rates were 92.3% in the abemaciclib + ET arm and 89.3% in the ET arm - 3.0% difference

Prior analysis: Two year IDFS 92.2% in the abemaciclib + ET arm and 88.7% in the ET arm - 3.5% difference

CA mama com mutação de BRCA1/2: OlympiA



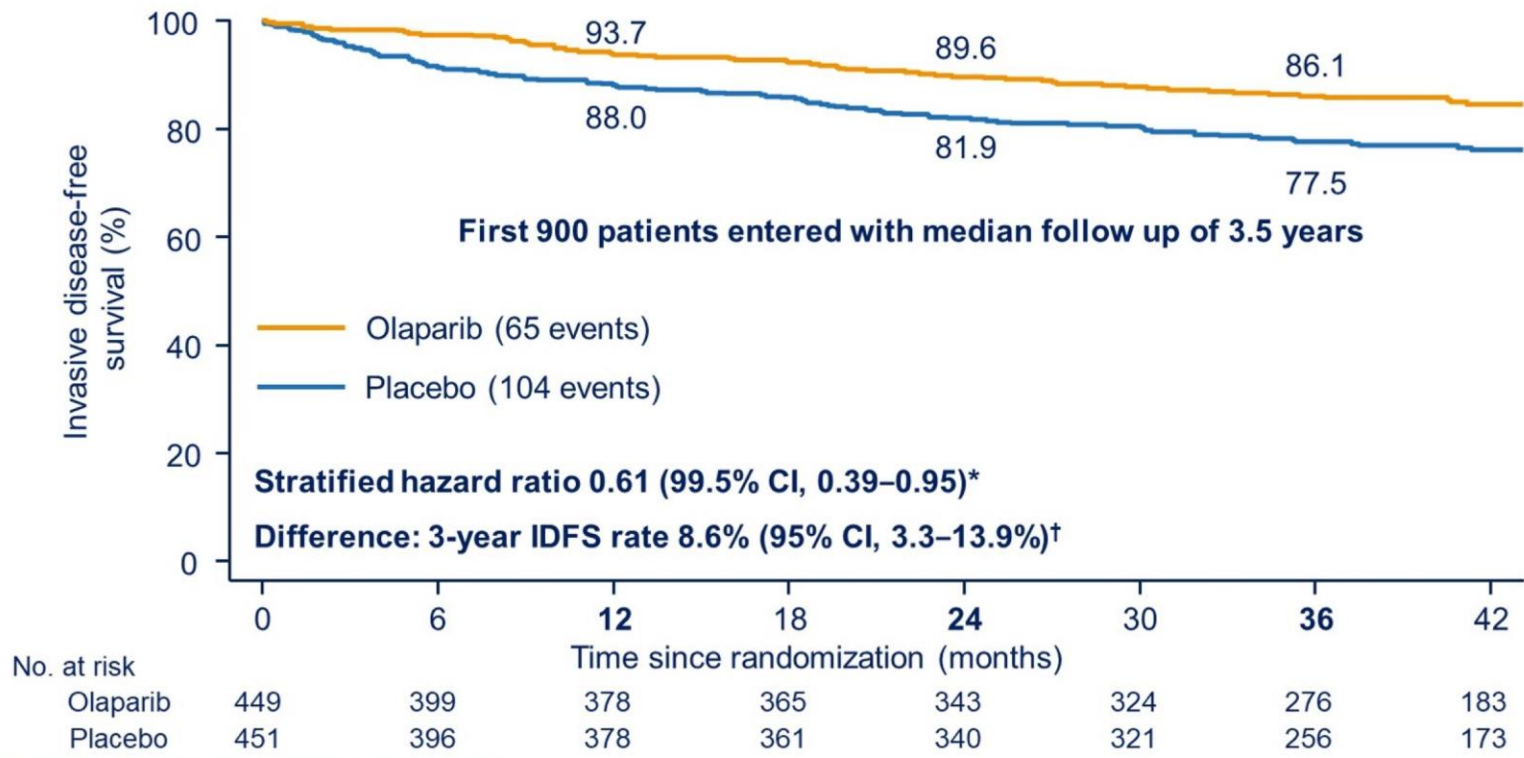
Hormone receptor +ve defined as ER and/or PgR positive (IHC staining $\geq 1\%$)

Triple Negative defined as ER and PgR negative (IHC staining $< 1\%$)

¹Hudis CA, J Clin Oncol 2007

CA mama com mutação de BRCA1/2: OlympiA

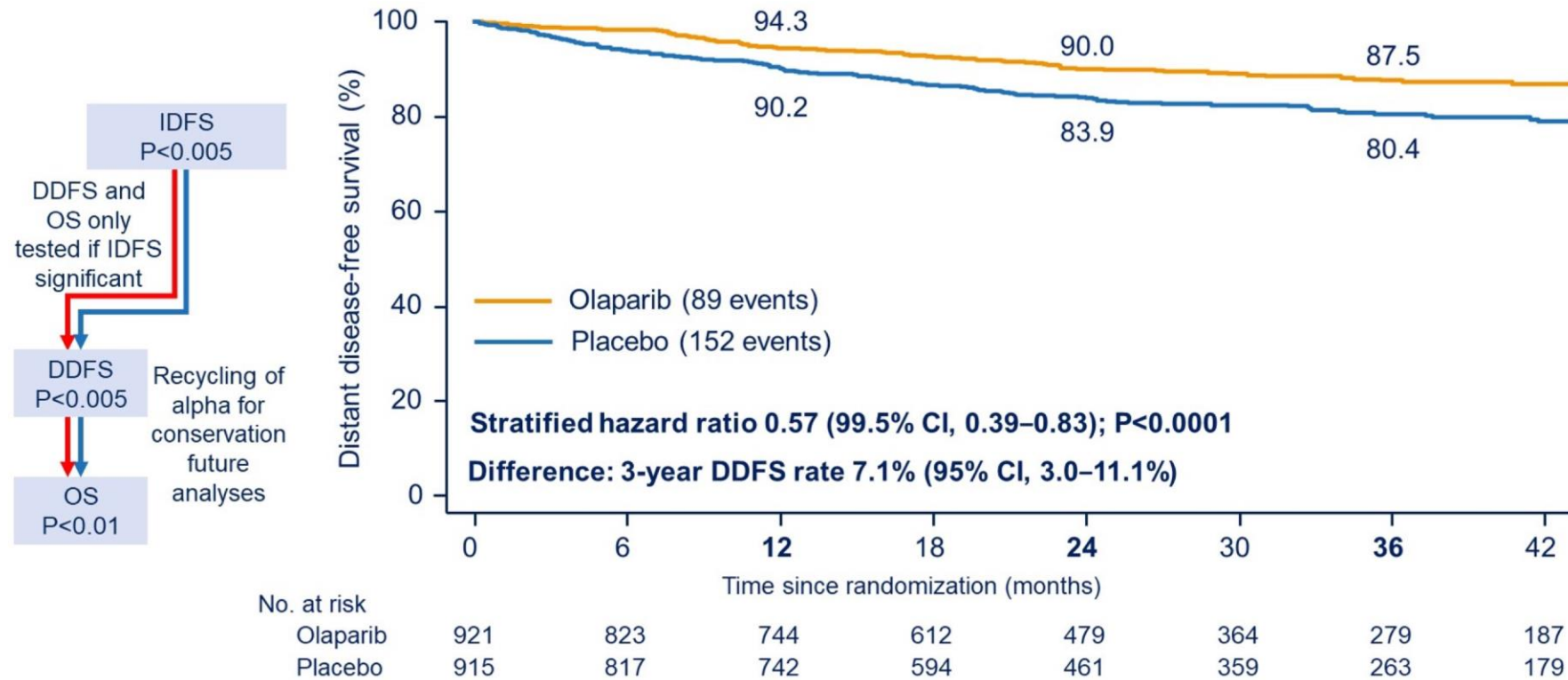
OlympiA: Invasive disease-free survival (mature cohort)



*Stratified Cox proportional hazards model, †Kaplan–Meier estimates

CA mama com mutação de BRCA1/2: OlympiA

OlympiA: Distant disease-free survival



Considerações na paciente pré-menopausa com CA mama luminal e axila (+)

Preservação da fertilidade durante QT

Aderência à HT

Efeitos adversos a longo prazo da HT

TABLE 4. Summary of Select Pharmacologic and Nonpharmacologic Strategies to Mitigate Some of the Most Prevalent and Disturbing Side Effects of Endocrine Therapy

Side Effect	Management Strategy	
	Pharmacologic	Nonpharmacologic
Musculoskeletal symptoms	Switching strategy duloxetine	Physical activity Acupuncture
Vasomotor symptoms (hot flashes)	Antidepressants SSRIs (citalopram, escitalopram, sertraline) SNRIs (venlafaxine) Anticonvulsants (gabapentin and pregabalin) Oxybutynin	Cognitive behavioral therapy Hypnosis
Sexual dysfunction (other than vulvovaginal symptoms)	Switch from AI + OFS to tamoxifen ± OFS Switch from tamoxifen + OFS to tamoxifen alone If patient is on antidepressants that can affect sexual function (e.g., SSRI and SNRI), switch to antidepressants that may be less likely to cause sexual side effects (e.g., mirtazapine)	Cognitive behavioral therapy
Vulvovaginal symptoms (vaginal dryness/dyspareunia)	Moisturizers Lubricants Lidocaine Switch from AI + OFS to tamoxifen + OFS or tamoxifen alone Vaginal low-dose estrogen (estradiol)*	Laser therapy**
Fatigue	—	Physical activity Cognitive behavioral therapy
Weight gain	—	Physical activity Diet Cognitive behavioral therapy

Vaz-Luiz et al. ASCO Educational Book 2021;vol 41.

Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Obrigada!

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