Localized Breast Cancer

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CANCER CENTER

Today's Talk

- Hormone receptor positive
- Triple negative
- HER2 positive
- Local treatment

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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

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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].

NATALEE study design: unique features[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo

Anatomical stage IIA[a]
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  - Grade 2 and evidence of high risk:
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    - 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]

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

Rationale for broad population of patients
Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence up to decades after initial diagnosis[3,4]

Rationale for 400 mg RIB
To improve tolerability while maintaining efficacy

Rationale for 3-year treatment duration
Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence[5-7]

tumor ctDNA/ctRNA samples

Randomization stratification
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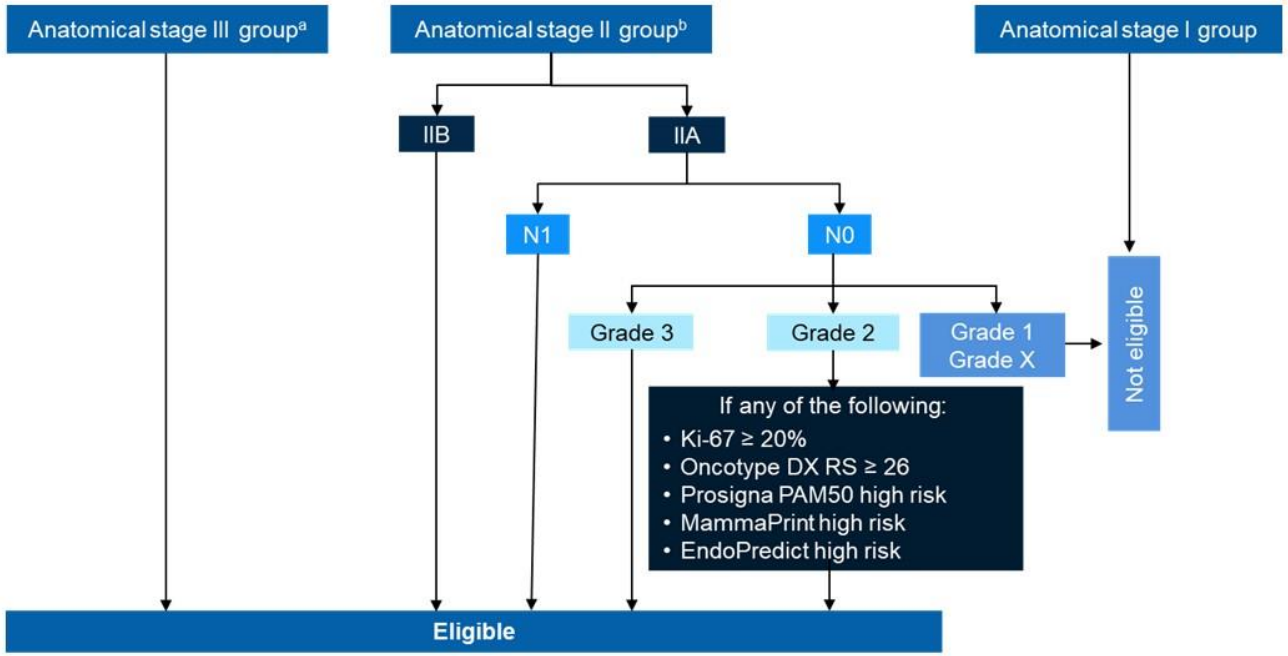
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597]. 3. Gomis RR and Gawrzak S, et al. *Mol Oncol*. 2017;11:62-78. 4. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846. 5. Kovatcheva M, et al. *Oncotarget*. 2015;6:8226-8243; 6. Rader J, et al. *Clin Cancer Res*. 2013;19:6173-6182; 7. Klein ME, et al. *Cancer Cell*. 2018;34:9-20.

NATALEE: eligible patients



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	✓

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or collarbone lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm but less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.
[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% (≈ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, Prosigna PAM50, MammaPrint, or EndoPredict EPclin Risk Score.
1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abstract TPS597]. 3. Data on file. NATALEE CLEE011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020.

Baseline characteristics

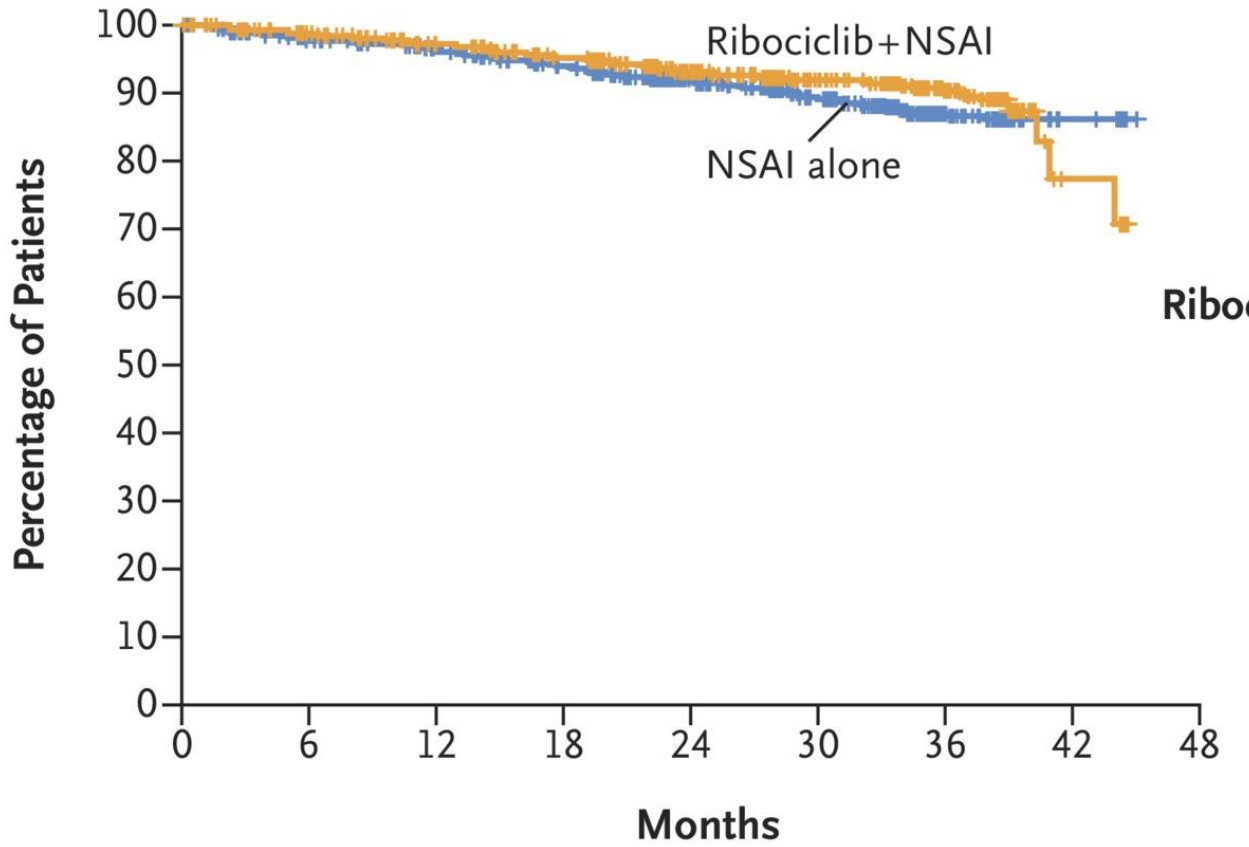
Parameter	RIB + NSAI n = 2549	NSAI Alone n = 2552	All Patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Men[a] and premenopausal women	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomical stage,[b,c] n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)[d]			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; N0, no nodal involvement; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or infra- or supraclavicular lymph nodes; NSAI, nonsteroidal aromatase inhibitor; NX, regional nodes were not assessed; OFS, ovarian function suppression; RIB, ribociclib.

[a] In the RIB + NSAI arm, there were 11 men (0.4%); in the NSAI alone arm, there were 9 men (0.4%). [b] A total of 14 patients with stage I disease were included: 9 (0.4%) in the RIB + NSAI arm and 5 (0.2%) in the NSAI alone arm. [c] Stage is derived using TNM from surgery for patients having not received (neo)adjuvant treatment or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received (neo)adjuvant treatment. [d] Prior OFS was received by 670 patients (26.3%) in the RIB + NSAI arm and 620 (24.3%) in the NSAI alone arm.

PRESENTED BY: Dennis Slamon MD, PhD

Kaplan–Meier Estimates of Invasive Disease–free Survival.



	No. of Patients with Event/ Total No. (%)	3-Yr Invasive Disease–free Survival
		percent
Ribociclib+NSAI	189/2549 (7.4)	90.4
NSAI alone	237/2552 (9.3)	87.1

Hazard ratio for invasive disease, recurrence, or death, 0.75 (95% CI, 0.62–0.91)
Two-sided P=0.003

Median follow-up for invasive disease–free survival, 27.7 mo

No. at Risk

Ribociclib+NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

Slamon D et al. N Engl J Med2024;390:1080-1091

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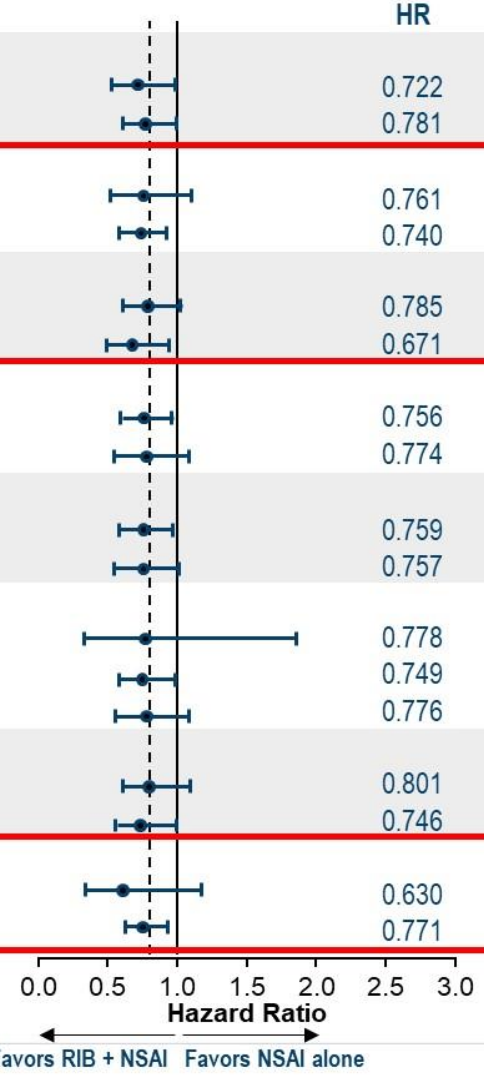
iDFS benefit was consistent across key prespecified subgroups

Subgroup	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559-0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)



AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Adverse Events.

Table 2. Adverse Events.*

Event	Ribociclib + NSAI (N = 2524)				NSAI Alone (N = 2444)			
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5
	number of patients (percent)							
Any adverse event	2470 (97.9)	1437 (56.9)	130 (5.2)	12 (0.5)	2128 (87.1)	394 (16.1)	38 (1.6)	4 (0.2)
Adverse events that occurred in ≥15% of patients in either group								
Neutropenia†	1568 (62.1)	1054 (41.8)	52 (2.1)	0	110 (4.5)	17 (0.7)	3 (0.1)	0
Arthralgia	921 (36.5)	24 (1.0)	0	0	1038 (42.5)	31 (1.3)	0	0
Nausea	580 (23.0)	6 (0.2)	0	0	184 (7.5)	1 (<0.1)	0	0
Headache	556 (22.0)	10 (0.4)	0	0	403 (16.5)	4 (0.2)	0	0
Fatigue	554 (21.9)	18 (0.7)	0	0	311 (12.7)	4 (0.2)	0	0
SARS-CoV-2 test positive	487 (19.3)	0	0	0	310 (12.7)	0	0	0
Covid-19	477 (18.9)	18 (0.7)	0	3 (0.1)	314 (12.8)	11 (0.5)	0	1 (<0.1)
Alanine aminotransferase increased	478 (18.9)	154 (6.1)	31 (1.2)	0	128 (5.2)	15 (0.6)	1 (<0.1)	0
Hot flush	473 (18.7)	6 (0.2)	0	0	482 (19.7)	3 (0.1)	0	0
Asthenia	417 (16.5)	15 (0.6)	0	0	273 (11.2)	3 (0.1)	0	0
Aspartate aminotransferase increased	408 (16.2)	96 (3.8)	16 (0.6)	0	131 (5.4)	12 (0.5)	0	0

* Covid-19 denotes coronavirus disease 2019, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Neutropenia is a grouped term that combines the preferred terms neutropenia and neutrophil count decreased.

Slamon D et al. N Engl J Med2024;390:1080-1091

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Adjuvant CDK 4/6is

Trial	Eligibility	Agent and dose	Duration	iDFS	FDA approval
NATALEE	• T2N0 if G3 or G2 and Ki-67 ≥20% or high genomic risk • N1 or greater	Ribociclib 400 mg daily, D1-21 of 28-day cycle	3 years	3-year iDFS 90.4 v 87.1 % p=0.0014	September 2024
MONARCHE	• N1 if T>5cm, G3, or Ki-67 ≥20% • N2 or greater	Abemaciclib 150 mg BID daily	2 years	4-year iDFS 85.8 v 79.4 % P<0.0001	March 2023
PALLAS	Stage II or III	Palbociclib 125 mg daily days 1-21 of 28-day cycle	2 years	4-year iDFS 84.2 v 84.5%	None

2024 ASCO® ANNUAL MEETING

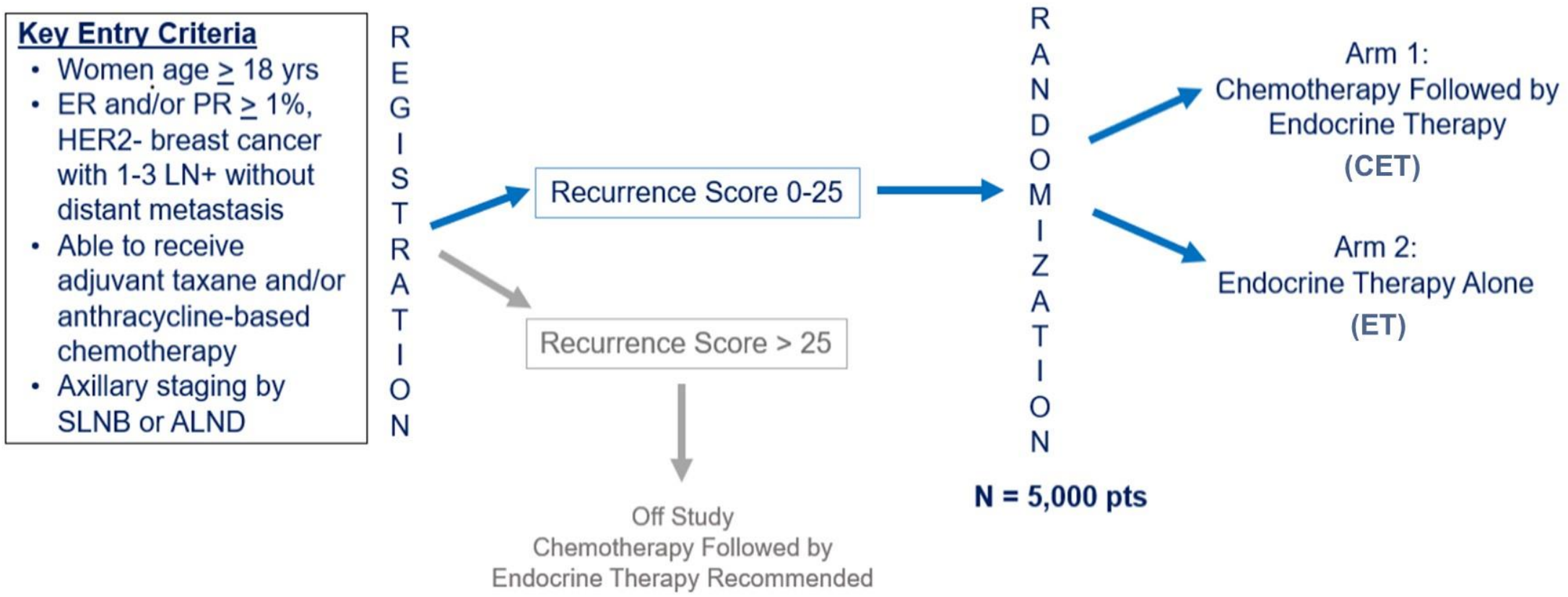
SWOG Leading cancer research. Together.

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

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

PRESENTED BY: Kevin Kalinsky, MD, MS

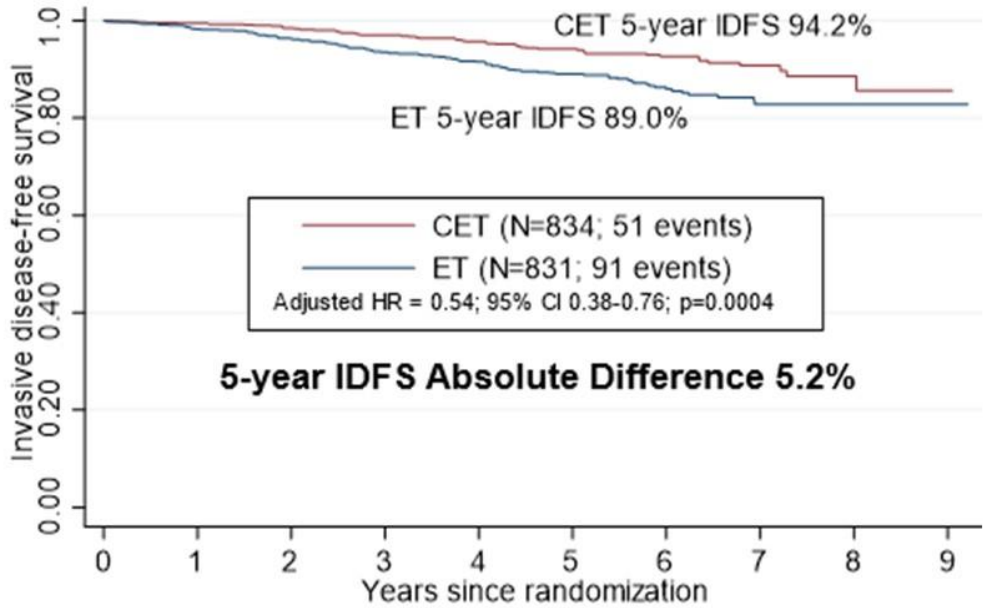
RxPONDER Trial



Kalinsky, et al. NEJM 2021

Chemotherapy benefit differed by menopausal status

"Premenopausal"

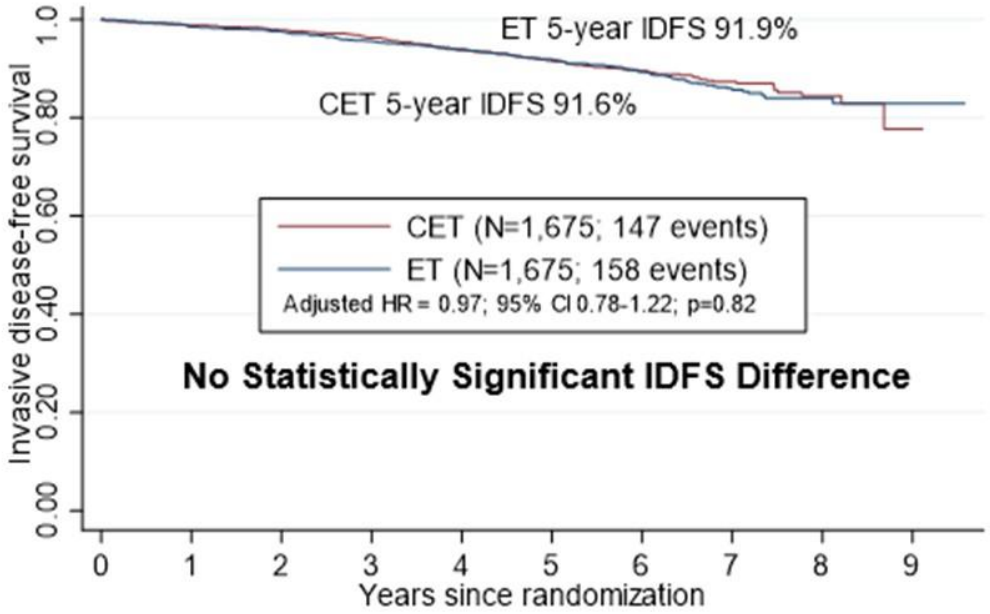


Number at risk

CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

Last menstrual period < 6 mo*

"Postmenopausal"



Number at risk

CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

Last menstrual period > 12 mo or BSO

*If LMP between 6-12 months and age < 50 years were classified as "premenopausal"

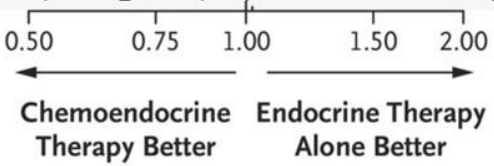
BSO = bilateral salpingo-oophorectomy

Kalinsky et al. NEJM 2021

PRESENTED BY: Kevin Kalinsky, MD, MS

Chemotherapy benefit lower in older "premenopausal" in RxPONDER

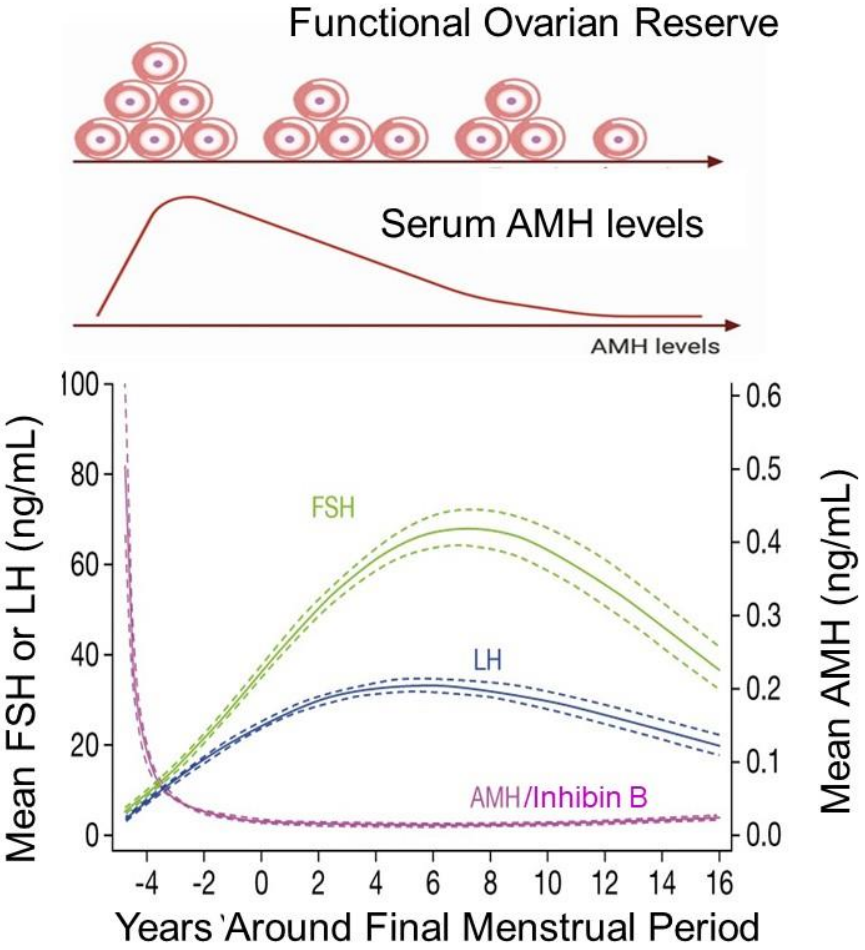
Subgroup	No. of Participants	No. of Events	Hazard Ratio for Invasive Disease Recurrence, New Primary Cancer, or Death (95% CI)
Age			
≥50 yr	509	44	0.98 (0.54–1.78)
45–49 yr	615	46	0.46 (0.25–0.86)
<45 yr	531	59	0.49 (0.28–0.84)
Grade			
Intermediate or high	1280	125	0.58 (0.41–0.84)
Low	357	23	0.67 (0.29–1.55)
Tumor size			
T2 or T3	728	80	0.64 (0.41–0.99)
T1	925	69	0.53 (0.32–0.88)
Nodes			
2 or 3 positive	574	55	0.62 (0.36–1.06)
1 positive	1081	94	0.57 (0.37–0.87)
Sentinel node	556	60	0.61 (0.36–1.02)
Full axillary lymph-node dissection	1099	89	0.60 (0.39–0.91)
Recurrence score			
14–25	1015	113	0.63 (0.43–0.91)
0–13	640	36	0.49 (0.24–0.99)
Overall	1655	149	0.60 (0.43–0.83)



Kalinsky, et al. NEJM 2021

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

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



FSH = Follicular Stimulating Hormone

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

PRESENTED BY: Kevin Kalinsky, MD, MS

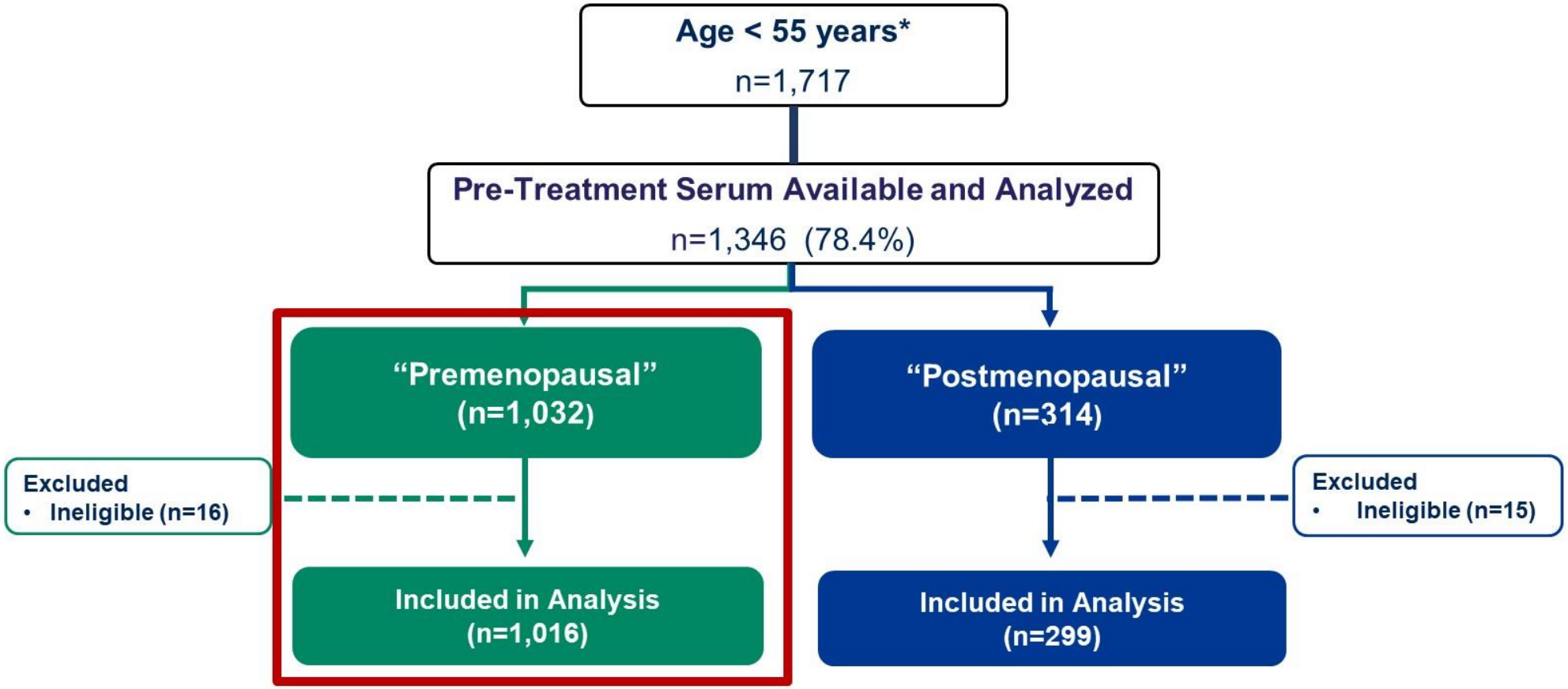
Objective

Objective

- To determine chemotherapy benefit if < 55 years using serum markers of ovarian function or reserve

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

Population in this analysis



*Does not include 235 pts < 55 years from UNICANCER who will serve as validation cohort

"Premenopausal": LMP < 6 months or age < 50 years with no LMP > 12 months and no BSO

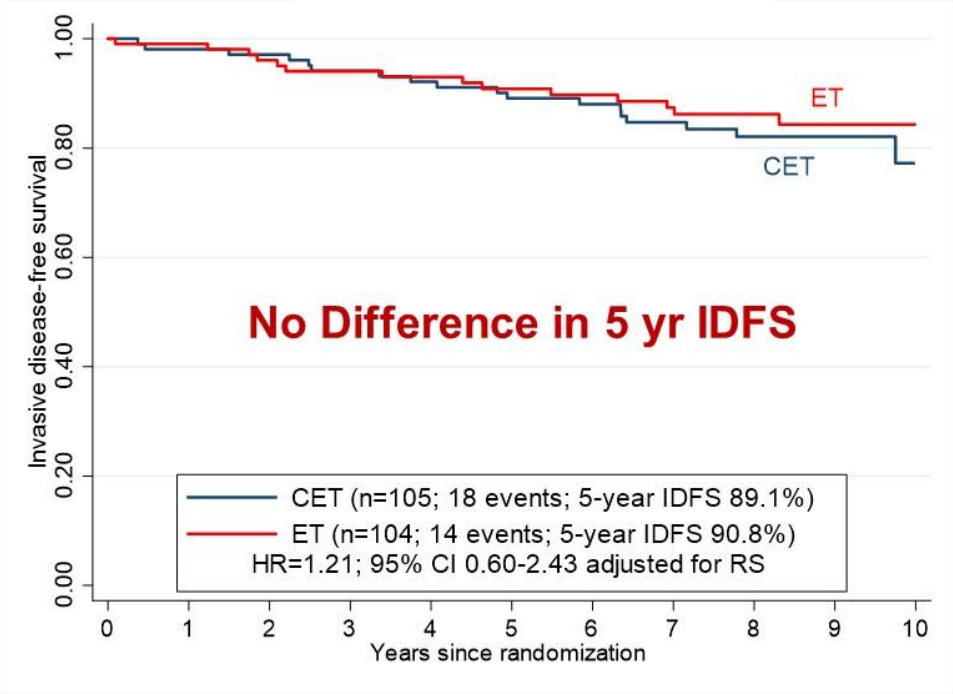
Pre-treatment serum AMH predicts chemotherapy benefit in “premenopausal” women < 55 years

Variable (n=1,016)	Cutoff	Chemo IDFS Benefit*: Variable x Treatment (p-value)
Age	≥ 50 years	0.15
AMH	< 10 pg/mL	0.019*
Inhibin B	≤ 12 pg/mL	0.051
Estradiol	≤ 30 pg/ML	0.88
Progesterone	≤ 0.5 ng/mL	0.78
FSH	>20 mIU/mL	0.13
FSH and Estradiol	> 20 and ≤ 30	0.46
LH	> 7 mIU/mL	0.08

*Adjusted for treatment arm, RS, variable and tested the interaction of the variable and treatment for significance ($p<0.05$)
Continuous age, stage, number of nodes, and grade not predictive; AMH and Inhibin B strongly correlated ($r=0.74$)

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

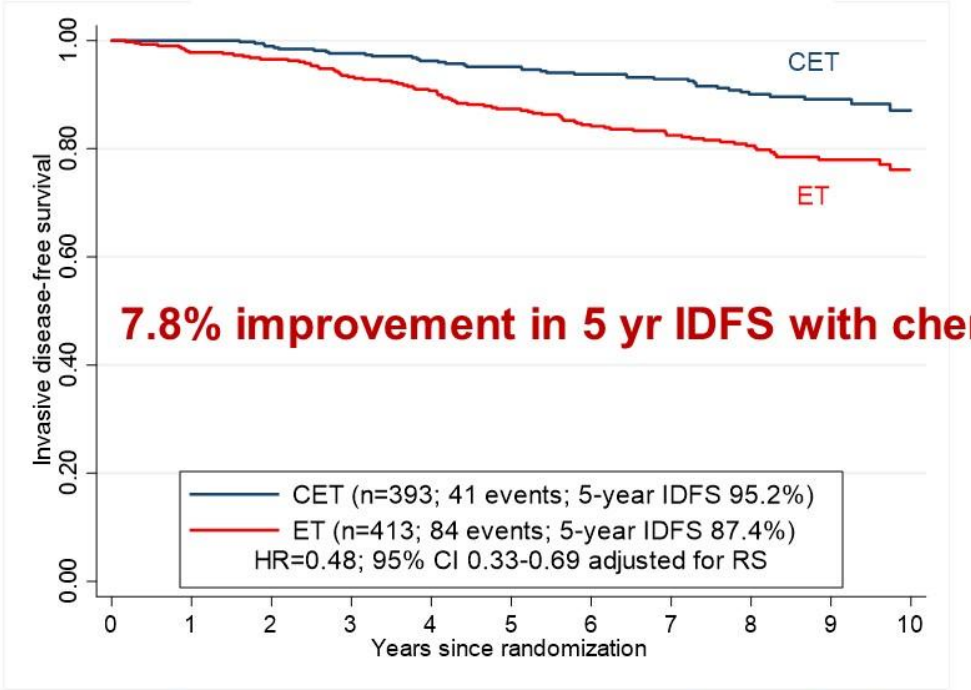
Low AMH (n=209)



No Difference in 5 yr IDFS

Postmenopausal: < 10 pg/mL

Medium/High AMH (n=806)



7.8% improvement in 5 yr IDFS with chemo

Premenopausal: ≥ 10 pg/mL

Significant interaction p=0.019, adjusting for RS

AMH levels in RxPONDER

- 21% of “premenopausal” women <55 years with low pre-treatment AMH levels (<10 pg/ML) did not benefit from adjuvant chemotherapy in addition to ET.

- 52% of premenopausal women 50-54 had low pre-treatment AMH levels .

- AMH levels were a better predictor of chemotherapy benefit than age, reported menopause status or other hormones.

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AMH levels in RxPONDER

- Need validation before widespread uptake of AMH levels.
- AMH not usually followed for menopausal status.

2024 ASCO ANNUAL MEETING

A-BRAVE-TRIAL

A-BRAVE Trial: a phase III randomised trial with Avelumab in early triple negative breast cancer with residual disease after neoadjuvant chemotherapy or at high risk after primary surgery and adjuvant chemotherapy

PierFranco Conte, Maria Vittoria Dieci, Giancarlo Bisagni, Peter Schmid, Vittoria Fotia, Federico Piacentini, Michelino de Laurentiis, Adolfo Favaretto, Stefano Tamberi, Giulia Bianchi, Claudio Zamagni, Saverio Cinieri, Domenico Corsi, Lucia Del Mastro, Antonella Ferro, Alessandra Gennari, Marta Mion, Antonino Musolino, Gian Luca De Salvo, Valentina Guarneri
on behalf of A-BRAVE study team

Medical Oncology 2, Istituto Oncologico Veneto IRCCS
DiSCOG-University of Padova, Italy

PRESENTED BY: Pierfranco Conte, MD

A-BRAVE Trial - Study Design

Investigator-driven study, sponsored by University of Padova.
Drug supply and Grant support by Merck KGaA.

A-BRAVE-TRIAL

High Risk TNBC patients who completed locoregional and systemic treatment with curative intent

Key eligibility criteria:
- Age ≥18 years
- ECOG PS 0-1
- TNBC (ER & PgR <10%, HER2 0-1+ or 2+ FISH-)^
- Anthracycline and taxane (neo)-adjuvant ChemoRx
- Tissue samples for central PD-L1 assessment
- Randomization <10 weeks from last chemo or surgery

- **Stratum A (Adjuvant): pT2N1, pT3-4 N0-3, pN2-3 anyT#**
- **Stratum B (Post-neoadjuvant): residual invasive carcinoma in the breast and/or axillary lymph nodes§***

R 1:1
N=477

Avelumab
10mg/kg, iv, q 2 weeks for 52 weeks

Observation

In case of ER 1-9%, adjuvant HT allowed at discretion of treating physicians.
Whenever indicated, radiotherapy allowed concomitantly with avelumab.

^for patients in the neoadjuvant stratum, TN status required in the preoperative and in the post-surgical specimen
 # trial initially limited to pN≥2; protocol amendment in 10/2017 to include patents with pT2N1 and pT3-4 N0-3 disease stage
§ excluding ypT1micN0, ypT1micN0i+, ypT0N0i+
*** After amendment on 06/2018, patients in stratum B were allowed to receive additional post-operative chemotherapy and were randomized at completion of treatment.**
Randomization balanced for Stratum A and Stratum B.

EUDRACT 2016-000189-45; NCT 02926196

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A-BRAVE Trial – Study Objectives

Primary efficacy objectives
- Disease-free survival (DFS)
- Disease-free survival (DFS) in Stratum B (post-neoadjuvant)

Secondary efficacy objectives
- Overall survival (OS)
- DFS in PD-L1 positive patients*

Safety objectives
- Overall safety of avelumab

Exploratory objectives
- Molecular, soluble and microbiological biomarkers (CD8, Foxp3, MHC-I, PD-L2, gene expression, circulating tumor DNA, cytokines, intestinal microbiota composition) in tumor tissue, plasma and fecal samples.

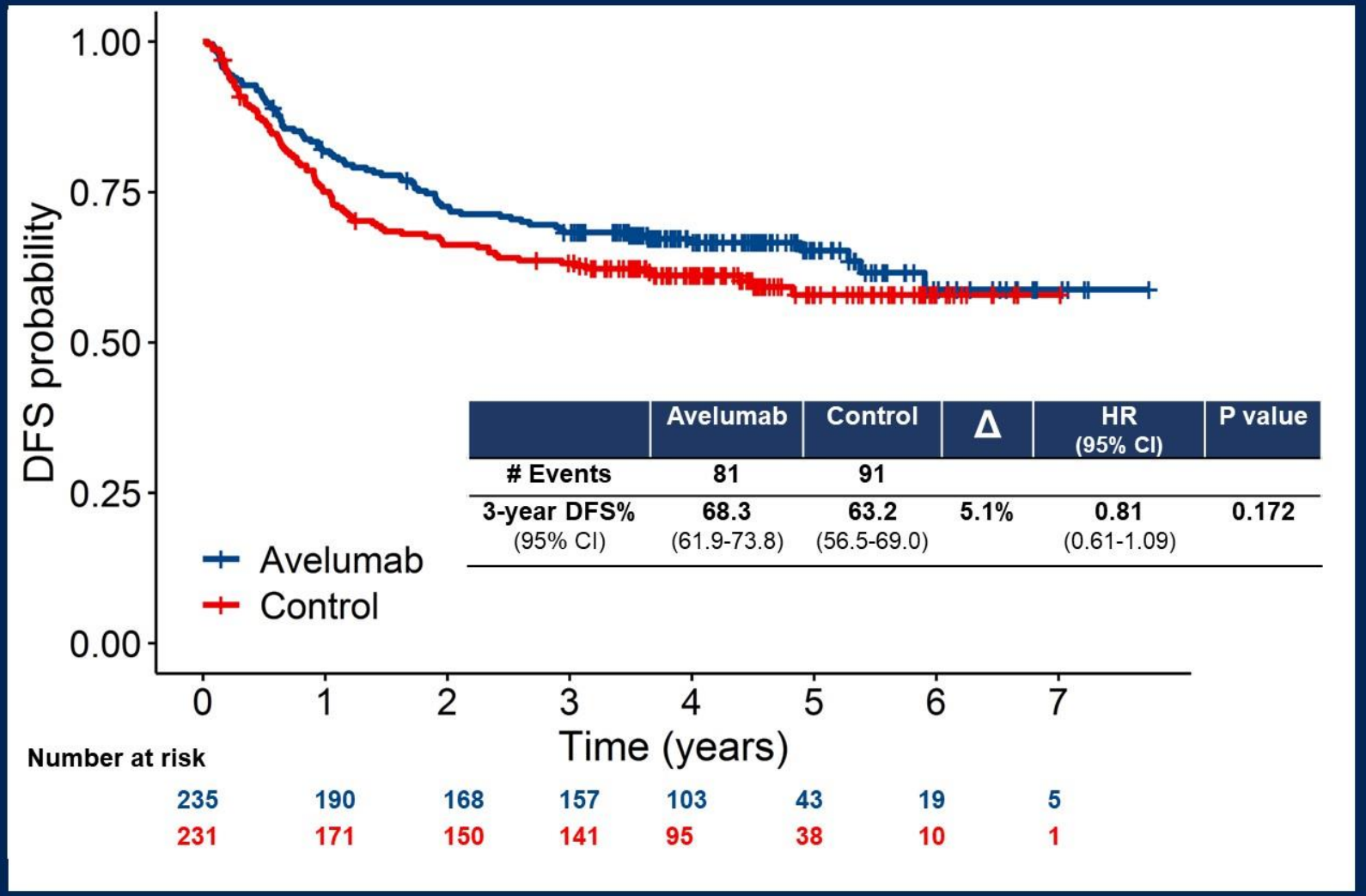
*initially planned as co-primary end point; protocol amended in january 2020

Patient characteristics		Avelumab (n= 235)	Control (n= 231)
Age, median (range)		50.9 (28.3-78.6)	51.9 (28.8-79.9)
ER & PgR <10%, n (%)		231 (98.3)	226 (97.8)
HER2 status, n (%)	0	150 (64.1)	147 (63.9)
	1+/2+ (ISH neg)	84 (35.7)	83 (35.9)
gBRCA status, n (%)	gBRCA mutated	24 (10.2)	27 (11.7)
Adjuvant (Stratum A)		**40 (17.8)**	**43 (18.6)**
AJCC stage at surgery, n (%)	II	20 (50.0)	22 (51.2)
	III	20 (50.0)	21 (48.8)
Post-neoadjuvant (Stratum B)		**195 (83.0)**	**188 (81.4)**
AJCC stage at surgery, n (%)	ypT1 & ypN0	93 (47.7)	85 (45.2)
	≥ypT2 & ypN0	31 (15.9)	38 (20.2)
	any ypT & ypN1	49 (25.1)	42 (22.3)
	any ypT & ≥ ypN2	22 (11.3)	23 (12.2)
RCB, n (%)	RCB 1	8 (4.1)	17 (9.0)
	RCB 2	98 (50.3)	77 (41.0)
	RCB 3	26 (13.1)	18 (9.6)
	Under evaluation	63 (32.3)	76 (40.4)
Adjuvant capecitabine, n(%)*		57 (24.2)	42 (18.2)

* After 06/2018 amendment

A-BRAVE Trial - Disease-Free Survival, ITT (co-primary end point)

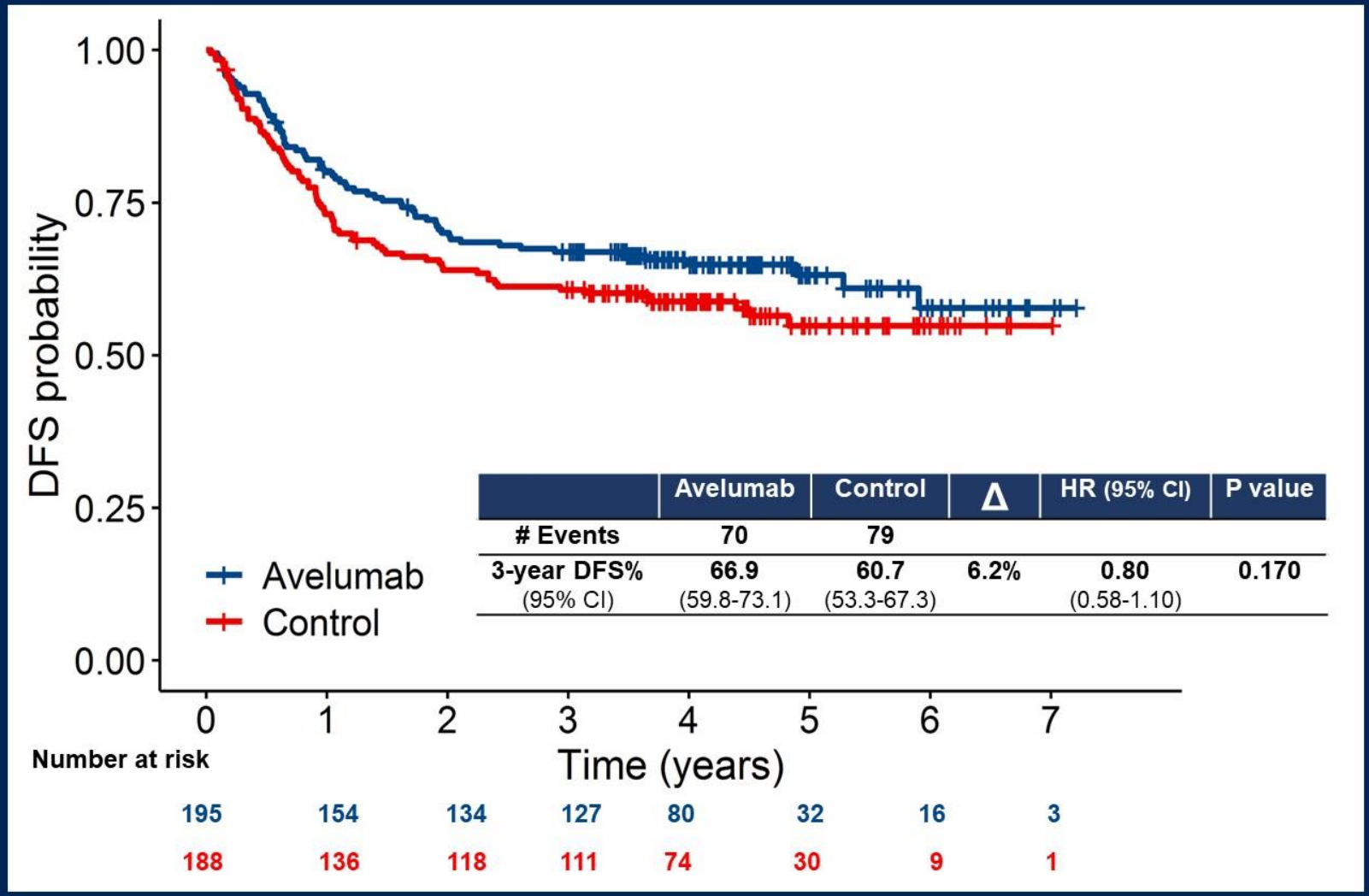
median FUp: 52.1 months (95% CI: 49.8- 53.8)



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	81	91			
3-year DFS% (95% CI)	68.3 (61.9-73.8)	63.2 (56.5-69.0)	5.1%	0.81 (0.61-1.09)	0.172

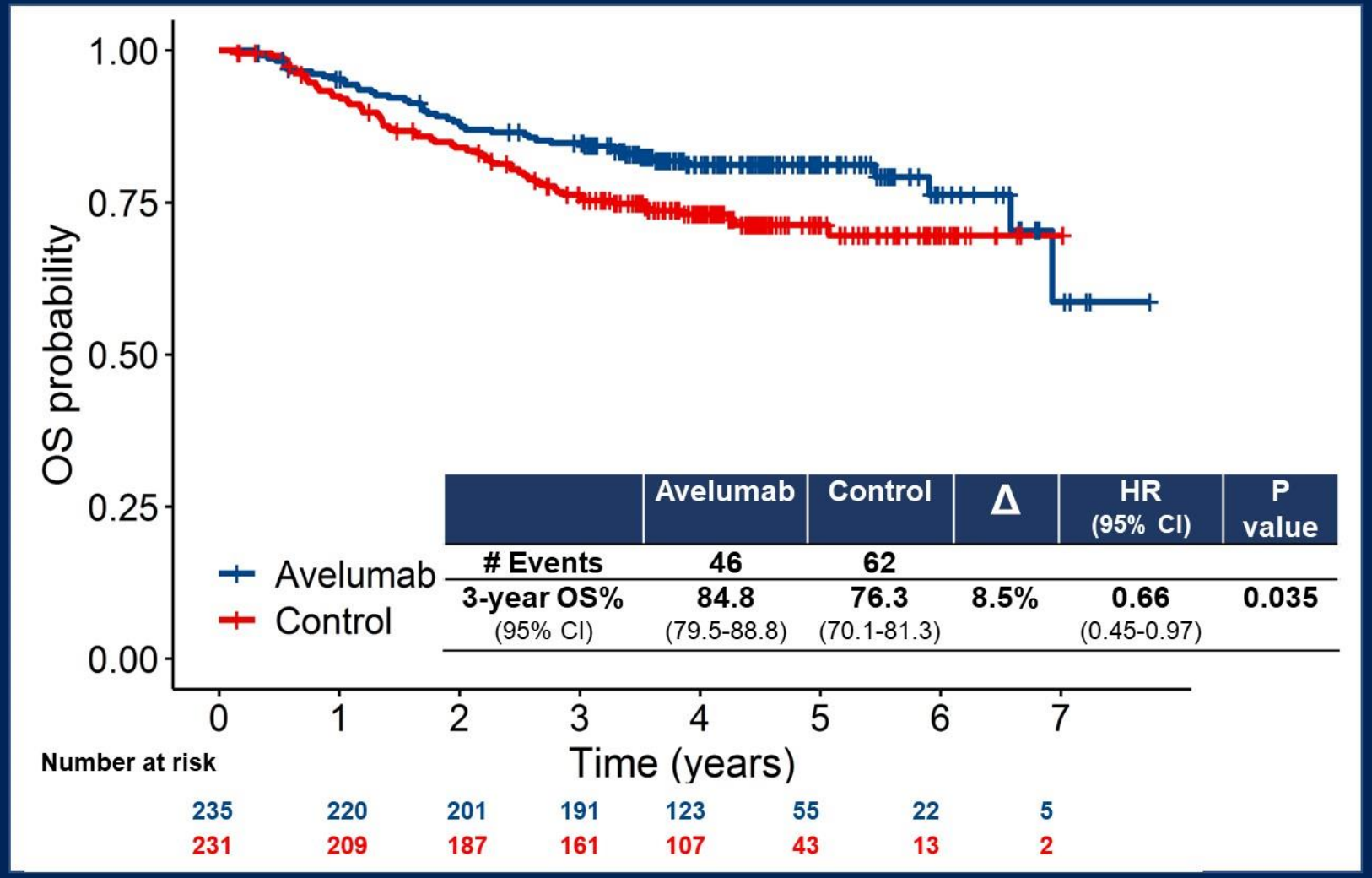
A-BRAVE Trial - Disease-Free Survival, stratum B (post-neoadjuvant)

(co-primary endpoint)



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	70	79			
3-year DFS% (95% CI)	66.9 (59.8-73.1)	60.7 (53.3-67.3)	6.2%	0.80 (0.58-1.10)	0.170

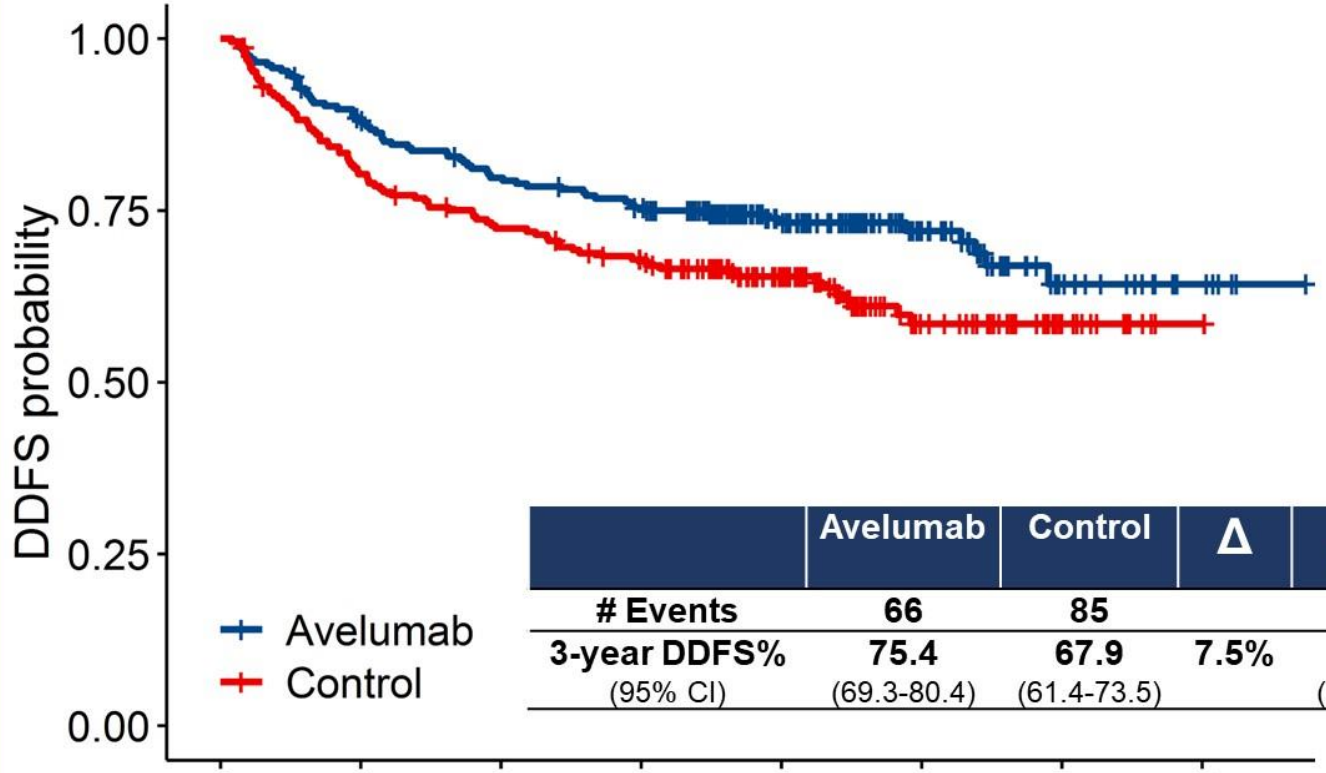
A-BRAVE Trial - Overall Survival, ITT (secondary endpoint)



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	46	62			
3-year OS% (95% CI)	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035

A-BRAVE Trial – Distant disease-free survival, ITT

(post-hoc exploratory analysis)



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	66	85			
3-year DDFS% (95% CI)	75.4 (69.3-80.4)	67.9 (61.4-73.5)	7.5%	0.70 (0.50-0.96)	0.0277

Defined according to updated STEEP 2.0 criteria [Tolaney SM, et al., J Clin Oncol. 2021 Aug 20;39(24):2720-2731].

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A-BRAVE Trial - Treatment exposure (Avelumab Arm)

Patients with treatment data		# 233
Treatment	Completed	168 (72.1%)
	Discontinued	65 (27.9%)
Reasons for Discontinuations	Adverse Events	20 (30.8%): *17/20 irAEs*
	Disease recurrence	33 (50.8%)
	Patient decision	7 (10.8%) 2 after 2 cycles; 1 each after 8,10,11,16, 23 cycles
	Others	5 (7.7%) 1 lung cancer, 1 covid emergency, 1 lost to Fup, 2 medical decision (after 18 and 24 cycles)

A-BRAVE Trial - Safety

irAEs				
	Avelumab		Control	
irAE	Any grade N. of patients (%)	Grade ≥ 3 N. of patients (%)	Any grade N. of patients (%)	Grade ≥ 3 N. of patients (%)
Hypothyroidism	31 (13.2)	-	5 (2.2)	-
Hyperthyroidsm	11 (4.7)	-	1 (0.4)	-
Adrenal insufficiency	2 (0.8)	-	-	-
Colitis/diarrhea	17 (7.2)	1 (0.4)	1 (0.4)	-
Hypertransaminases	11 (4.7)	3 (1.3)	2 (0.9)	-
Lipase increase	5 (2.1)	3 (1.3)	-	-
Amilase increase	4 (1.7)	3 (1.3)	-	-
Myocarditis	1 (0.4)	-	-	-
Uveitis	1 (0.4)	-	-	-

A-BRAVE

- Primary endpoint of DFS not met; secondary endpoint OS met.
- Avelumab is not FDA approved for breast cancer.
- Await results of SWOG S1418 with adjuvant pembrolizumab.

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Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis

Sibylle Loibl, Max S. Mano, Michael Untch, Chiun-Sheng Huang, Eleftherios P. Mamounas, Norman Wolmark, Adam Knott, Asna Siddiqui, Thomas Boulet, Beatrice Nyawira, Eleonora Restuccia, Charles E. Geyer, Jr.

Presenting author: Prof. Dr. Sibylle Loibl, M.D., Ph.D

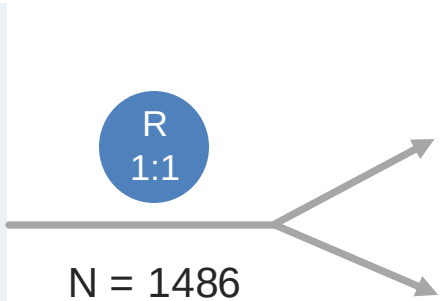
German Breast Group, Neu-Isenburg; Centre for Haematology and Oncology Bethanien, Goethe University, Frankfurt, Germany

GBG GERMAN BREAST GROUP
NSABP Foundation, Inc.

IDFS, invasive disease-free survival; OS, overall survival.

KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

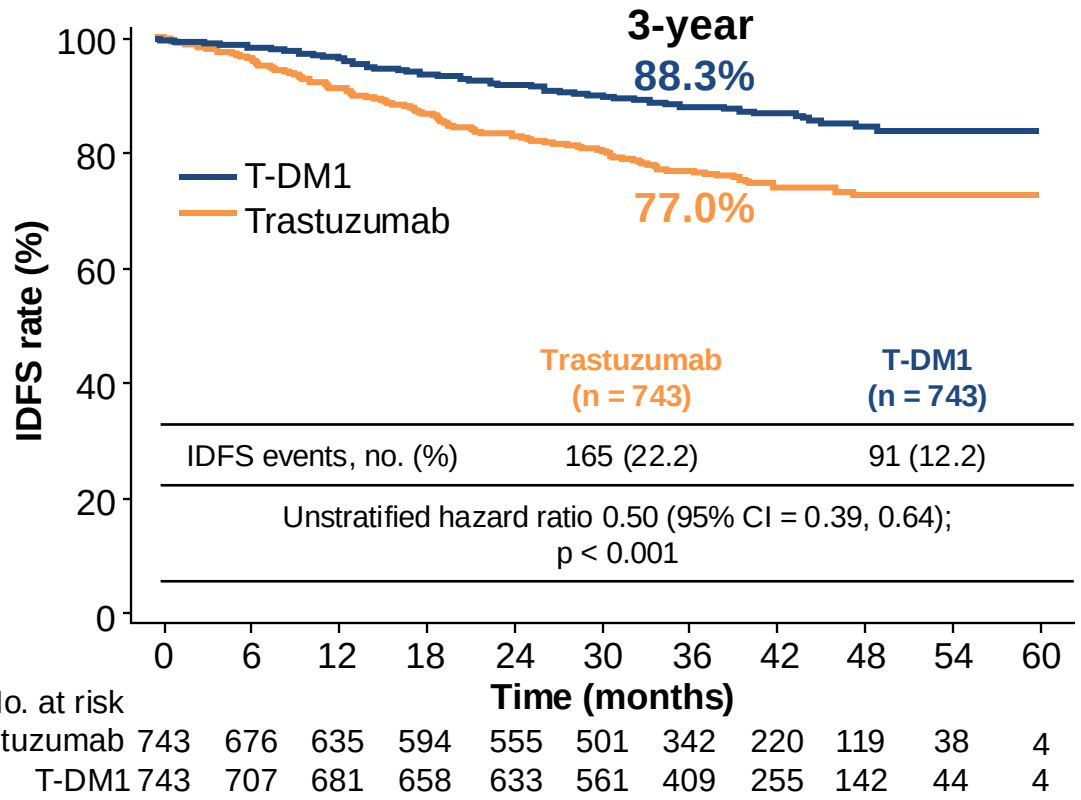
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

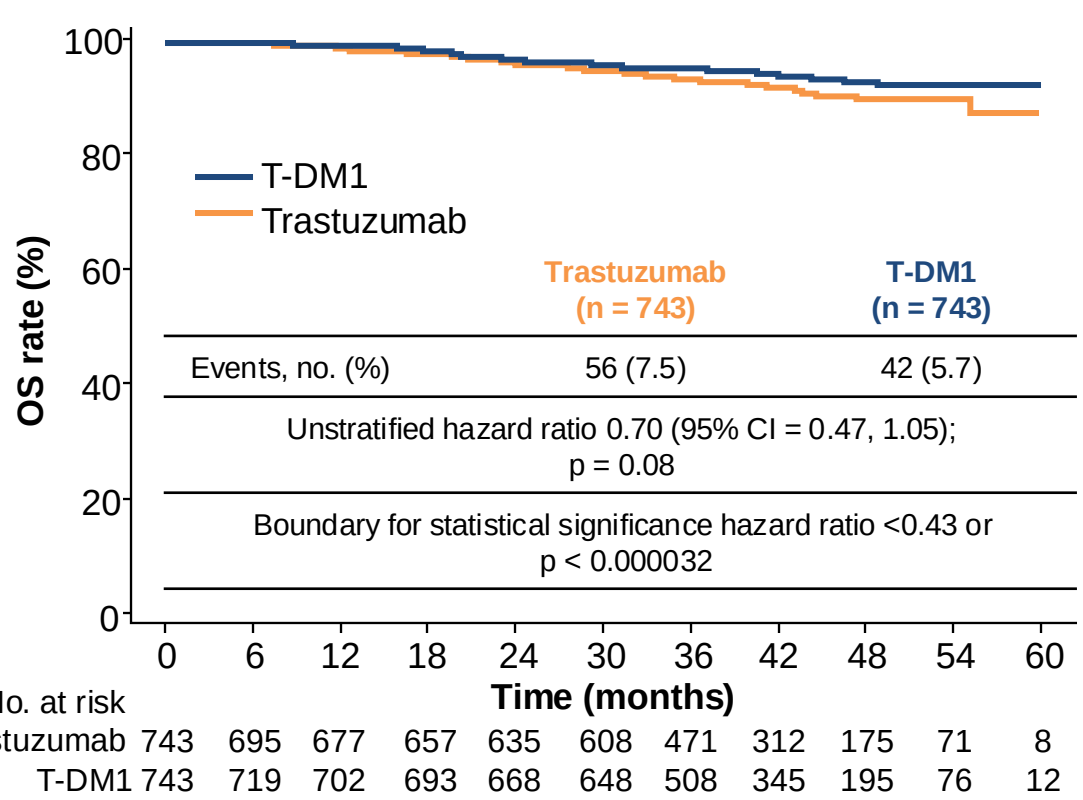
Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

KATHERINE primary analysis (2018)

IDFS



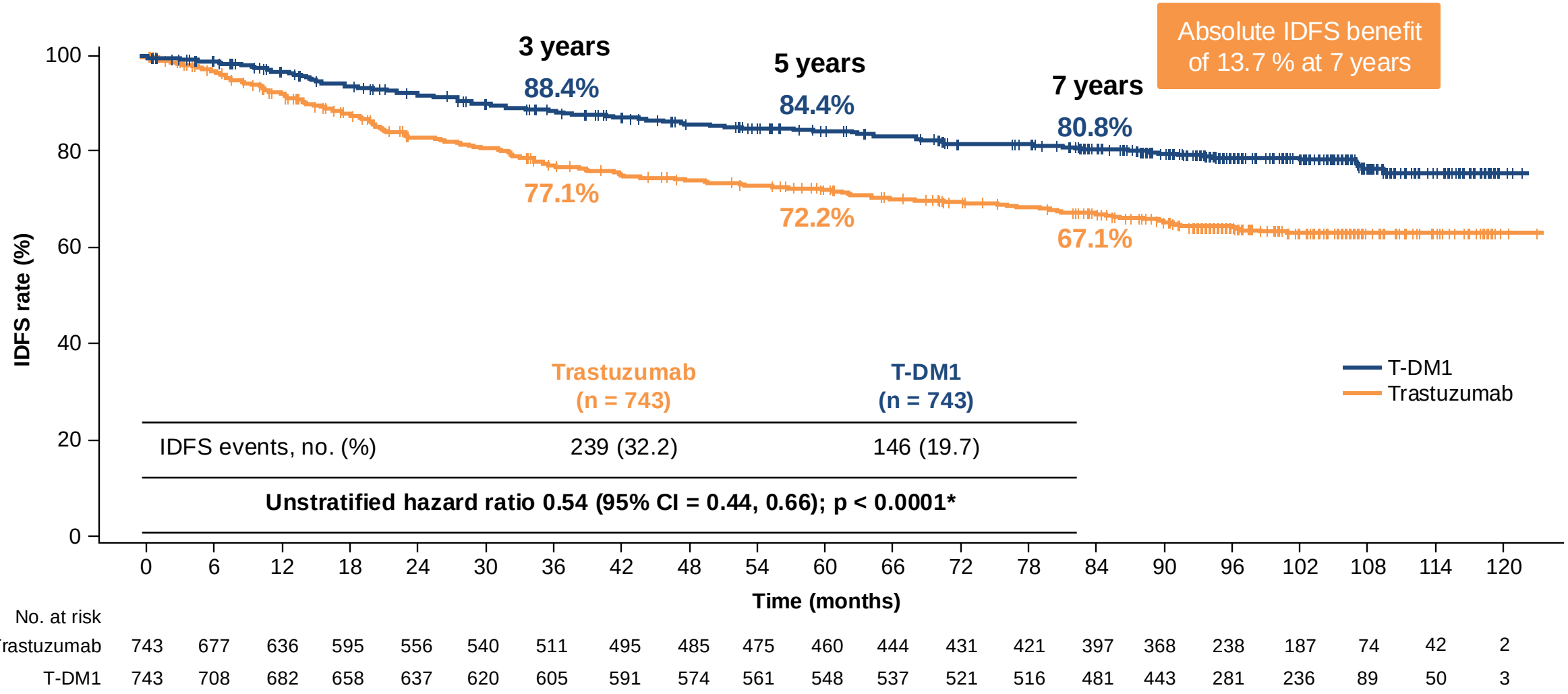
OS



CCOD: July 25, 2018; median follow-up: 41.4 months (T-DM1) and 40.9 months (trastuzumab).
CCOD, clinical cutoff date; CI, confidence interval; IDFS, invasive disease-free survival; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

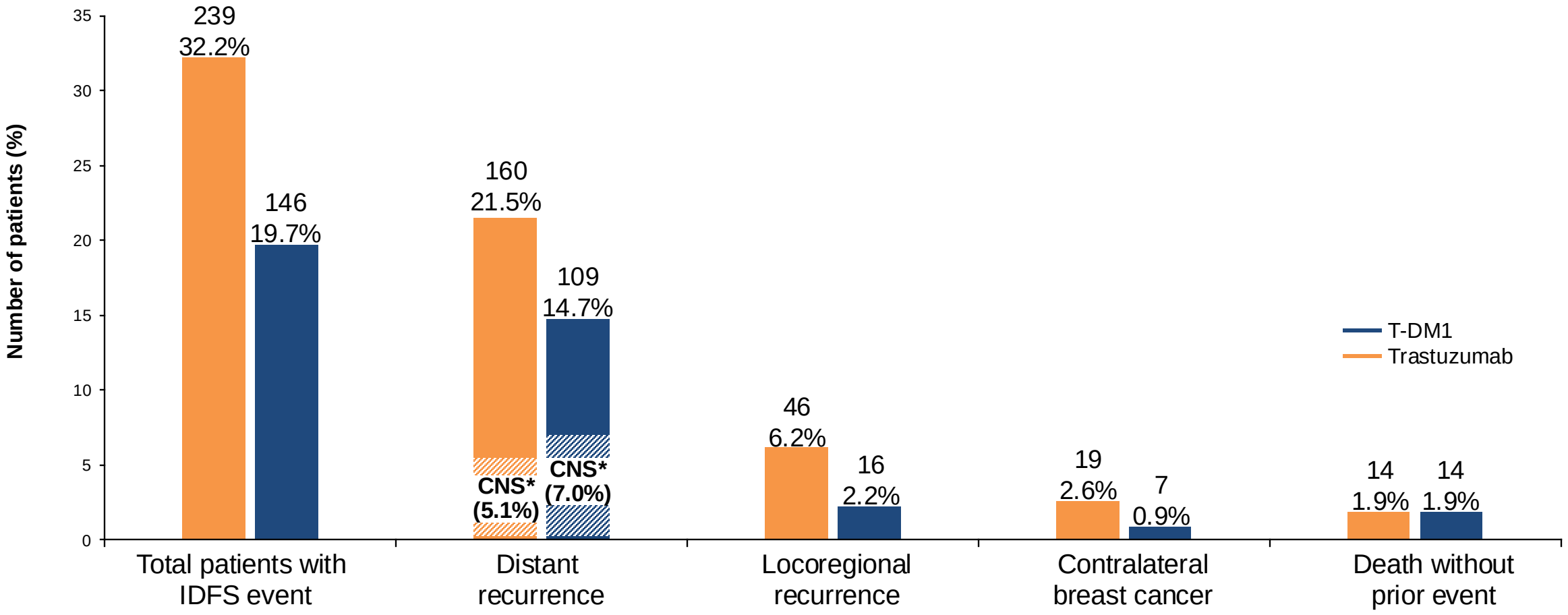
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

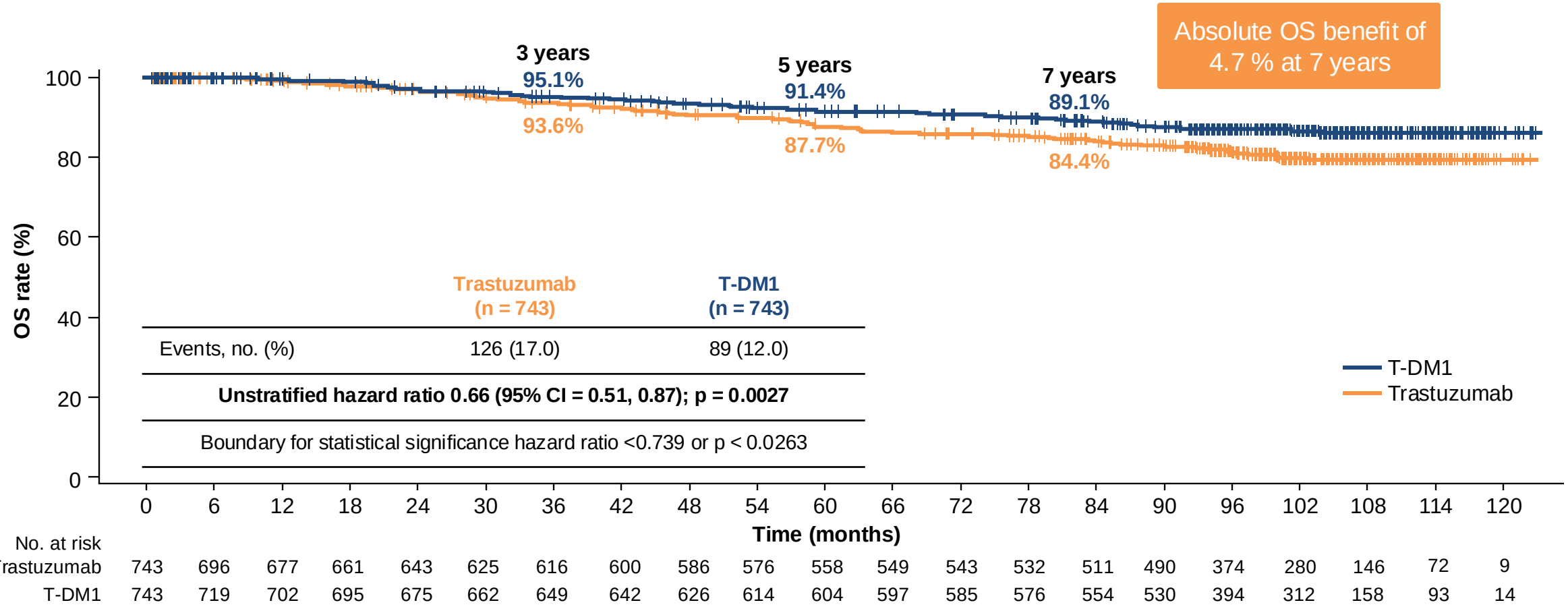
* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Site of first occurrence of an IDFS event



* **CNS metastases as component of distant recurrence (isolated or with other sites).**
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE

- Reassuring OS data on a regimen that has been FDA-approved since 2019.
- Although small numbers, patients who received pertuzumab and those with small volume residual disease benefitted.
- More toxicities with TDM-1 so the approach should be individualized and monitored.

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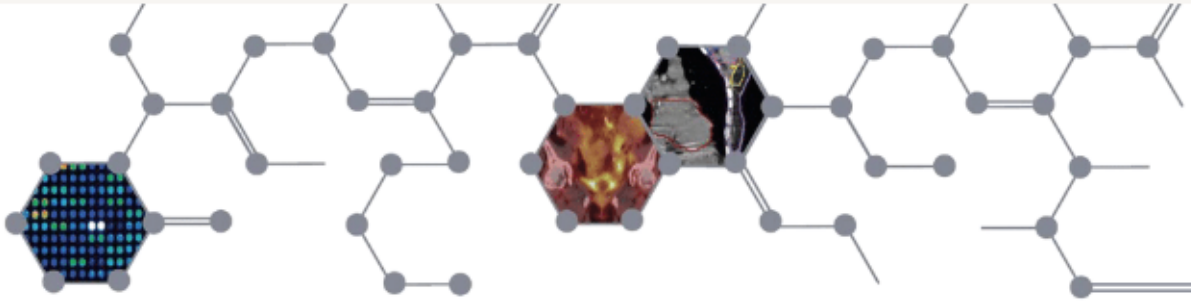


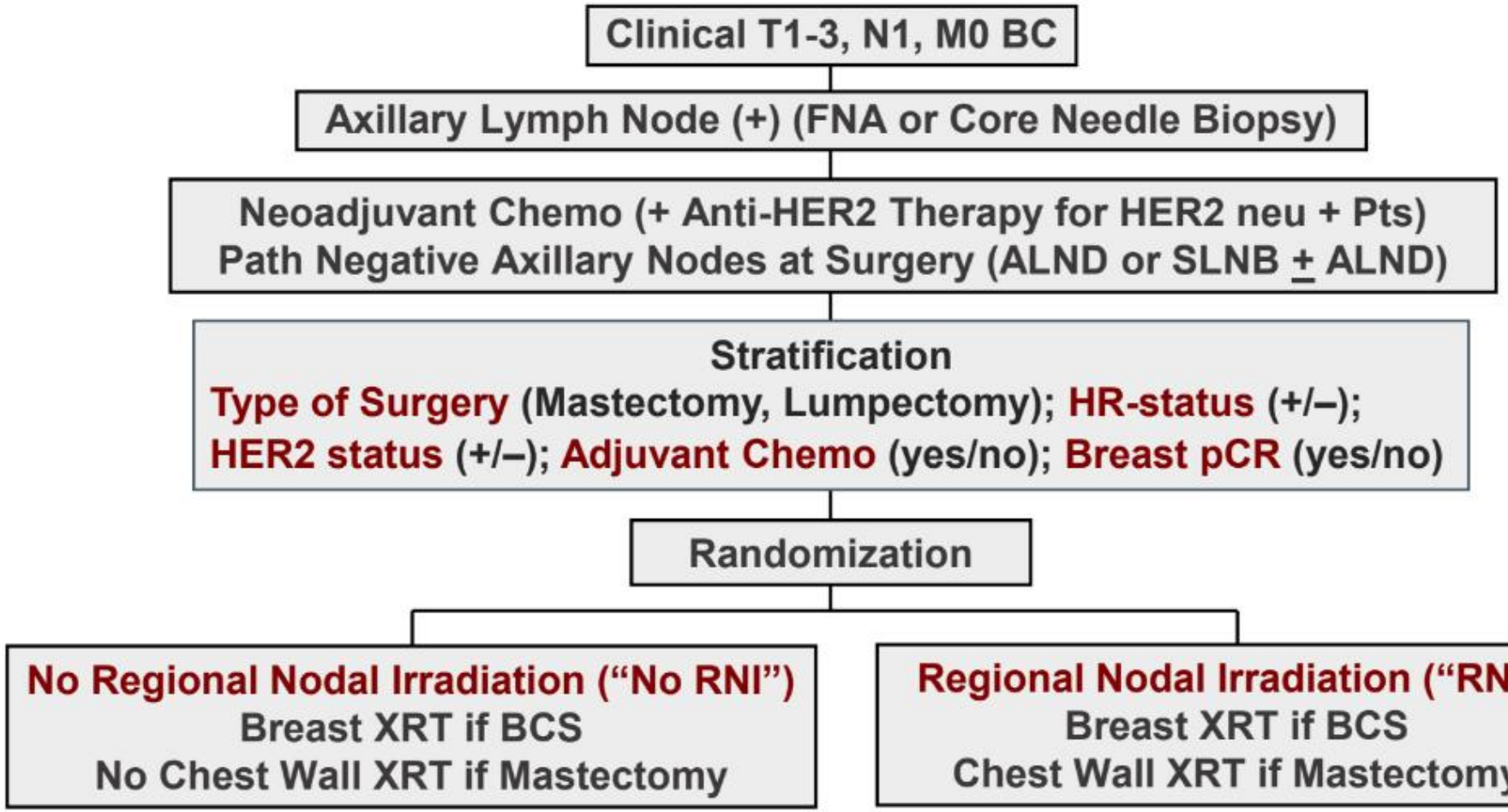
DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Loco-regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

Eleftherios P. Mamounas[1*], Hanna Bandos[2], Julia R. White[3*], Thomas B. Julian[4], Atif J. Khan[5], Simona F. Shaitelman[6], Mylin A. Torres[7], Frank A. Vicini[8], Patricia A. Ganz[9], Susan A. McCloskey[10], Peter C. Lucas[11,12], Nilendu Gupta[3],
X. Allen Li[13], Beryl McCormick[5], Saumil Gandhi[6], Rahul D. Tendulkar[14], Vivek S. Kavadi,[15], Masahiko Okamoto[16], Samantha Andrews Seaward[17], William J. Irvin, Jr.[18], Jolinta Lin [7], Robert Mutter[19], Thierry M. Muanza[20], Andrew A. Muskovitz[21], Reshma Jagsi[22], Anna C. Weiss[23,24], Walter J. Curran, Jr.[7], and Norman Wolmark[12]

*These authors contributed equally.

Study Schema



FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Bi

Primary endpoint: IBCRFI
Invasive breast cancer recurrence free interval

Dec 5-9, 2023

Baseline Characteristics (1)

Characteristic		No RNI (%) n=821	RNI (%) n=820
Age	**Median**	52 years	52 years
	≤ 49 yrs	40	41
	50-59 yrs	32	33
	≥ 60 yrs	28	26
Race	Asian	8	6
	Black/African American	17	18
	White	69	69
	Unknown/Other	6	6
Ethnicity	Hispanic or Latino	14	14
	Not Hispanic or Latino	83	82
	Unknown	3	3
Clinical Tumor Size	T1	21	21
	T2	59	61
	T3	20	18

Baseline Characteristics (2)

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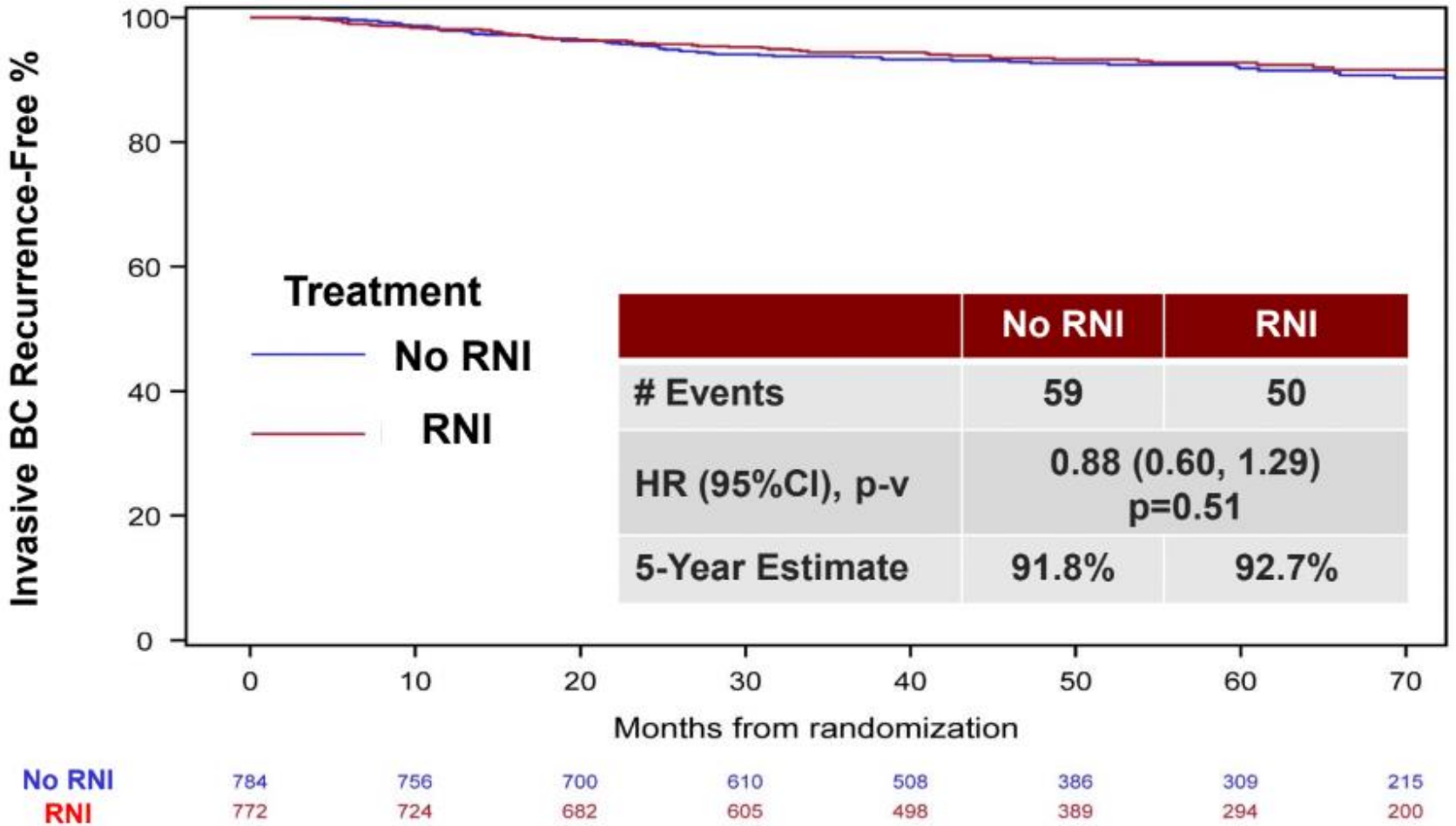
Characteristic		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative ER+ and/or PR+/HER2- ER- and PR-/HER2+ ER+ and/or PR+/HER2+	21 22 25 31	23 20 24 33
Breast Surgery	Lumpectomy Mastectomy	58 42	58 42
Axillary Surgery	SLNB ALND (+/-SLNB)	55 45	56 44
pCR in Breast	No Yes	22 78	21 79
Adjuvant Chemotherapy	No Yes	100 <1	99 1

Primary Endpoint

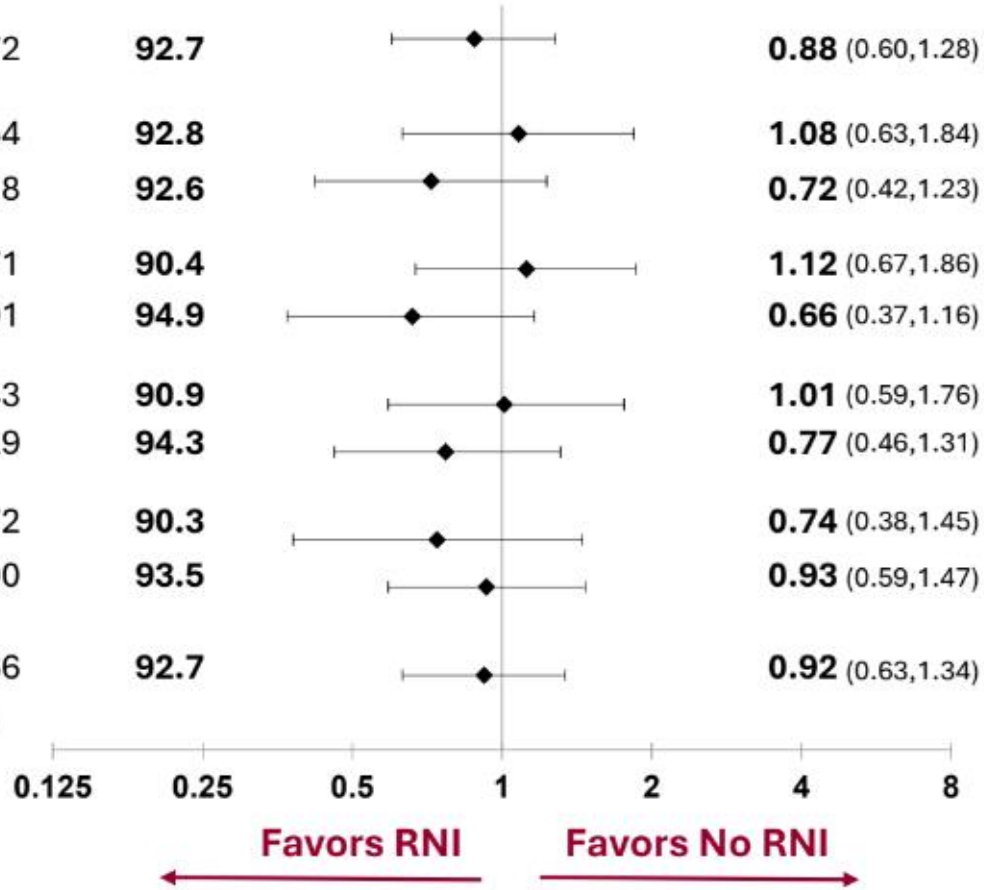
Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

IBCRFI – Subgroup Analysis by Stratification Factors

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	*P*-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Surgery	Lumpectomy	26/454	**93.5**	28/454	**92.8**	**1.08** (0.63,1.84)	**0.28**
	Mastectomy	33/330	**89.5**	22/318	**92.6**	**0.72** (0.42,1.23)	
ER/PR	Negative	28/367	**91.7**	31/371	**90.4**	**1.12** (0.67,1.86)	**0.17**
	Positive	31/417	**92.1**	19/401	**94.9**	**0.66** (0.37,1.16)	
HER2	Negative	25/342	**92.6**	26/343	**90.9**	**1.01** (0.59,1.76)	**0.47**
	Positive	34/442	**91.3**	24/429	**94.3**	**0.77** (0.46,1.31)	
pCR breast	No	20/173	**87.8**	15/172	**90.3**	**0.74** (0.38,1.45)	**0.59**
	Yes	39/611	**93.0**	35/600	**93.5**	**0.93** (0.59,1.47)	
Adjuvant Chemotherapy	No	57/780	**92.1**	50/766	**92.7**	**0.92** (0.63,1.34)	
	Yes	2/4		0/6			



Dec 5-9, 2023

NSABP B51

- At median follow up of 59.5 months, RNI after mastectomy or lumpectomy did not improve IBCRFI, ILRRFI, DRFI, DFS or OS.
- Pre-specified subgroups did not clearly favor omission of RNI but patients with nodal involvement who are downstaged by neoadjuvant chemotherapy appear to do well without RNI.

Thank you!

Questions?

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