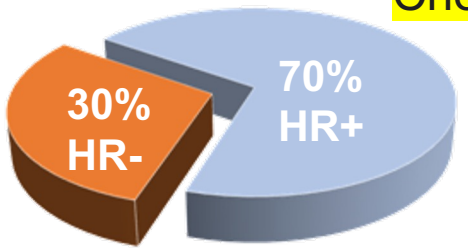
Current and Emerging Treatments for Patients With HR+/HER2– Early Breast Cancer

Lauren Carcas, MD
Breast Medical Oncology

Miami Cancer Institute
BAPTIST HEALTH SOUTH FLORIDA

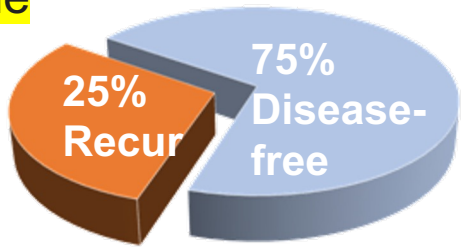
Three Therapeutic Decision Points in Early-Stage HR+ Breast Cancer Patients

Initial diagnosis



Chemotherapy + endocrine or endocrine alone?

5 years post-diagnosis



Cease or extend hormonal therapy?

1.25 million HR+ IDC/ year worldwide
175,000 HR+ IDC/ year in USA

940,000 disease-free HR+ IDC patients/ year worldwide
130,000 disease-free HR+ IDC patients/ year in USA

HR+ breast cancer is a disease of late recurrence with >50% of recurrences and 66% of deaths occurring later than 5yrs after initial diagnosis

High risk patients: adjuvant CDK4/6 inhibitor?

North American Association of Central Cancer Registries (NAACCR), 2019.

Courtesy of Reshma Mahtani, DO

Guideline-Recommended Biomarker Testing for Breast Cancer

HER2 per ASCO/CAP guidelines[1,2]

IHC ± dual-probe ISH assay

ER and PR[2,3]

IHC assay

Gene expression assays

To guide adjuvant chemotherapy

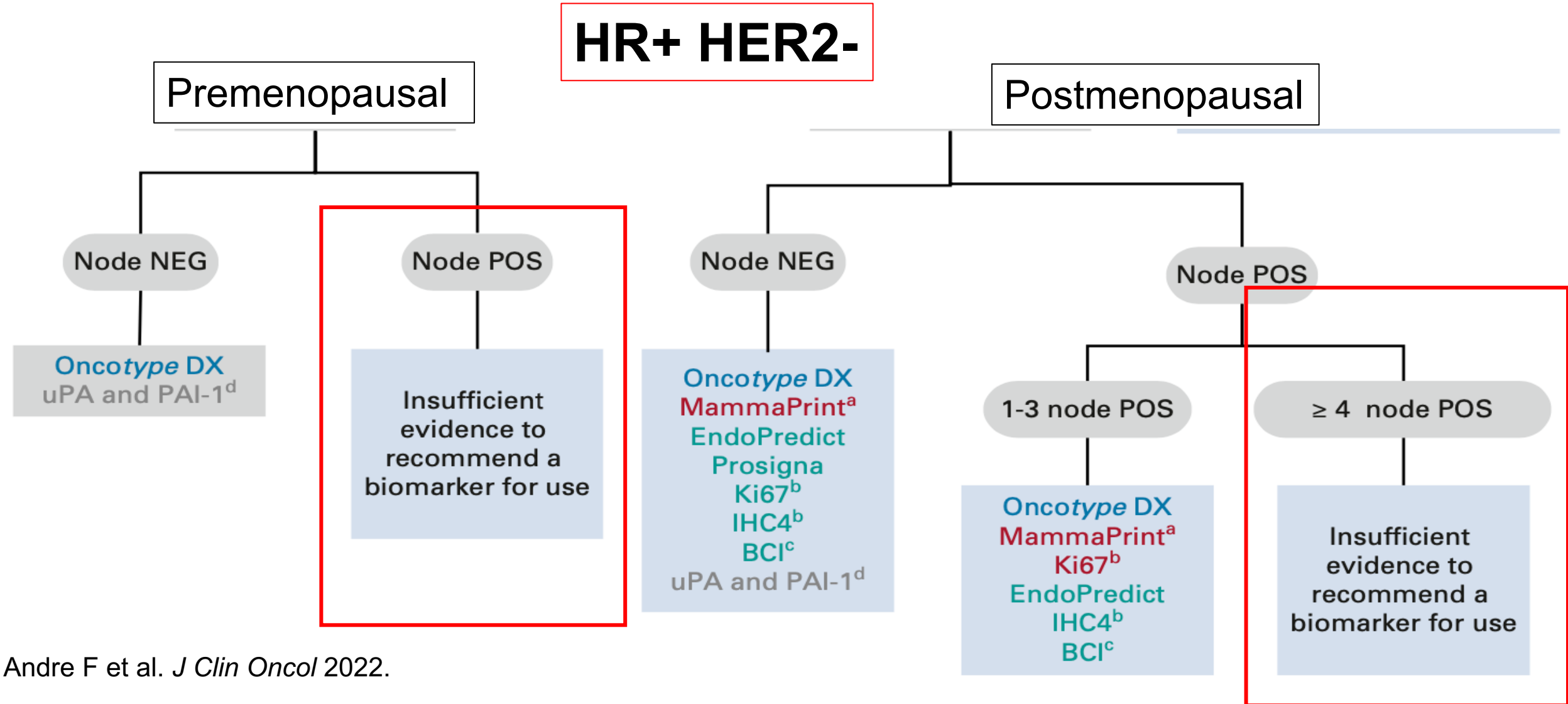
BRCA[4]

For:

- *TNBC (at any age)*
- *Male patients*
- *Meet criteria for personal or family history*
- *When considering olaparib as adjuvant therapy*

1. Wolff. JCO. 2018;36:2105. 2. NCCN. Clinical practice guidelines in oncology: breast cancer. v.4.2023. nccn.org.
3. Allison. JCO. 2020;38:1346. 4. NCCN. Clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast, ovarian, and pancreatic. v.3.2023. nccn.org.

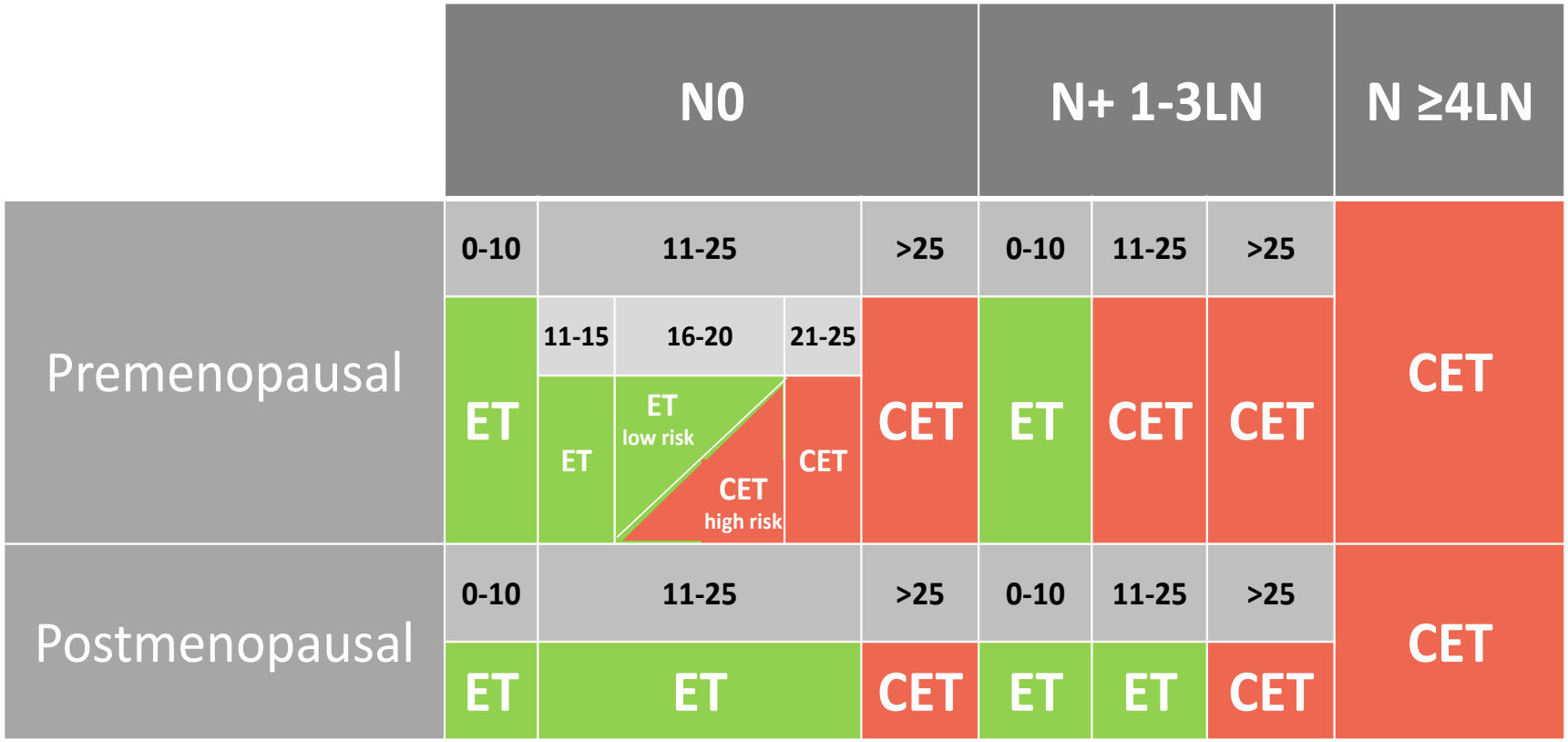
2022 ASCO Guidelines: Biomarkers for Adjuvant Endocrine Therapy and Chemotherapy for Early Breast Cancer



Andre F et al. *J Clin Oncol* 2022.

ER+ EBC: Who benefits from chemotherapy?

Treatment decisions based on Oncotype DX after SABCS 2022



Courtesy of Peter Schmid, FRCP, MD, PhD

Ovarian suppression: Powerful yet underutilized

SOFT-TEXT (n=4690)

OS + exemestane vs OS + Tamoxifen

ITT population 12-year

- DFS (4.6% absolute improvement, HR=0.79; 95%CI 0.70-0.90; P<0.001)
- DRFI (1.8% absolute improvement, HR=0.83; 95%CI 0.70-0.98; P=0.03)
- Overall survival (90.1% versus 89.1%, HR=0.93; 95%CI, 0.78-1.11)

Significant OS improvement in

- women <35 years (4.0%)
- Tumor >2 cm (4.5%)
- Grade 3 tumor (5.5%).

Pagani et al, JCO 2022

SOFT (n=3047)

Tamoxifen vs OS + Tam vs OS + AI

ITT population 12-year DFS

- Tamoxifen 71.9%
- OS + Tam 76.1%
- OS + exemestane 79.0%
- tamoxifen plus OFS versus tamoxifen (HR=0.82; 95%CI 0.69-0.98)

Overall survival

- Tamoxifen 86.8%
- OS + Tam 89.0%
- OS + exemestane 89.4%

Francis et al, JCO 2022

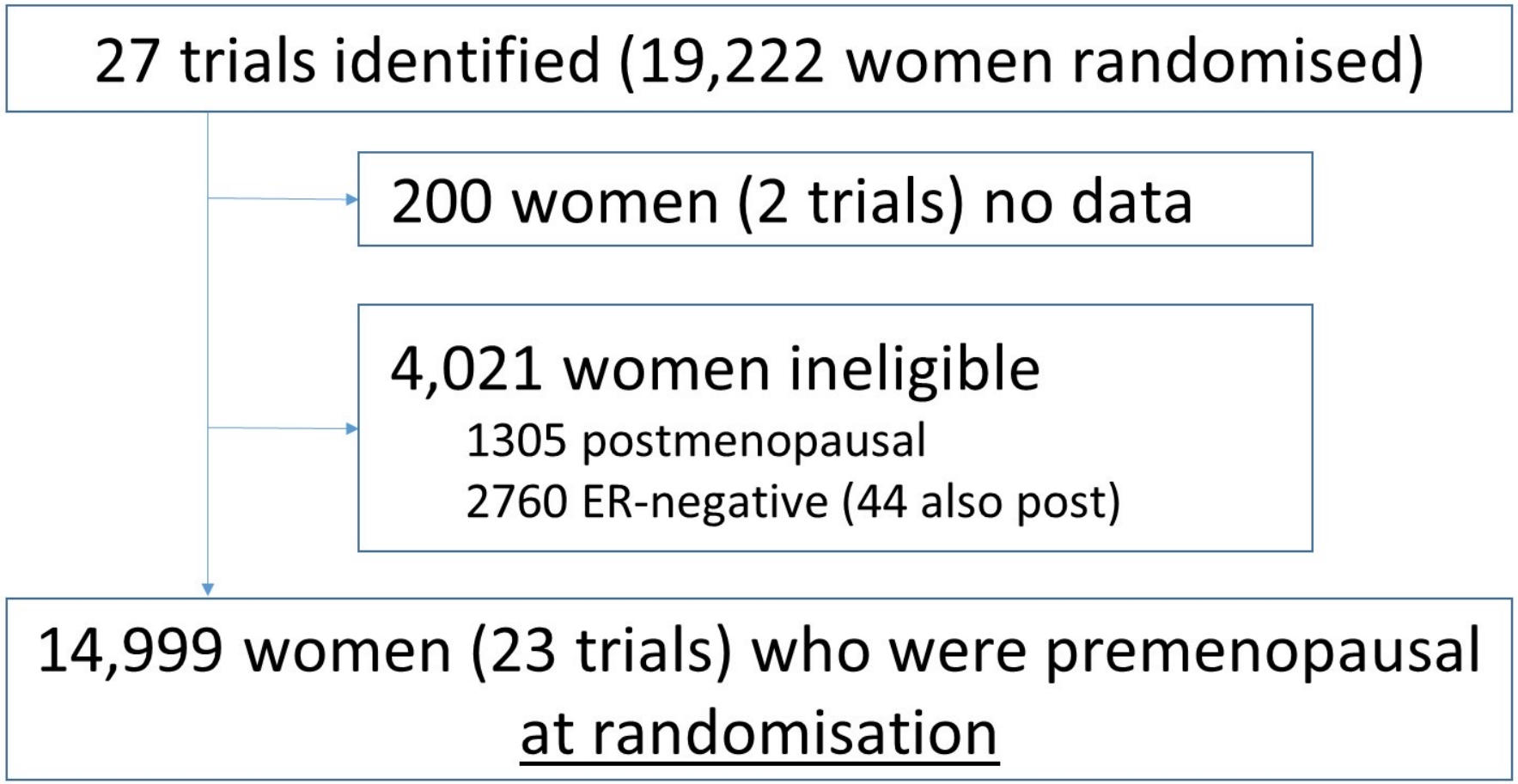
2023 ASCO ANNUAL MEETING

Effects of ovarian ablation or suppression on breast cancer recurrence and survival: patient-level meta-analysis of 14,999 pre-menopausal women in 25 randomized trials

Early Breast Cancer Trialists Collaborative Group (EBCTCG)

Writing Committee: Richard Gray, Rosie Bradley, Jeremy Braybrooke, Mike Clarke, Robert Hills, Richard Peto, Jonas Bergh, Sandra Swain, Rodrigo Arriagada, Judith Bliss, Allan Hackshaw, Hyun-Ah Kim, Woo Chul Noh, John Yarnold, Nancy Davidson, Prudence Francis, Meredith Regan

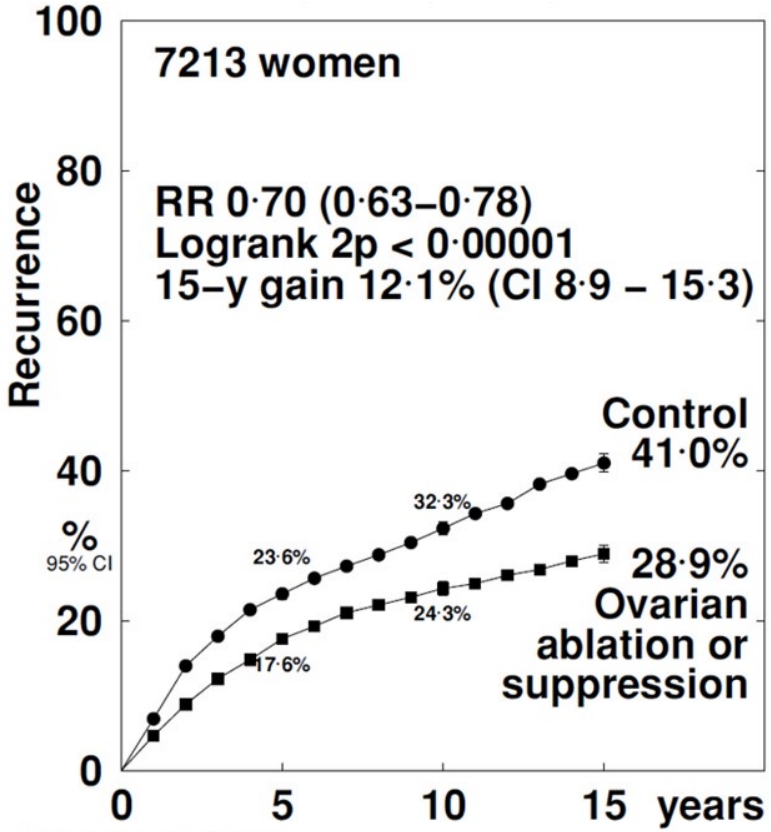
Randomised trials of ovarian ablation/suppression



PRESENTED BY: Richard Gray, Emeritus Professor of Medical Statistics, University of Oxford

Ovarian ablation/suppression vs not: Recurrence

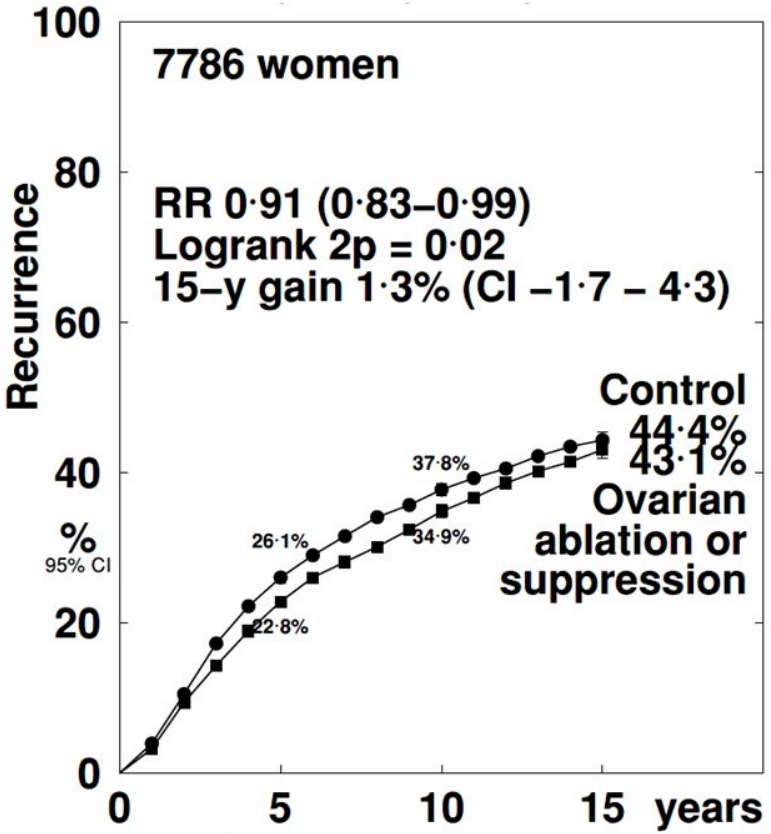
(A) No chemotherapy or premenopausal after chemotherapy



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	4·39 (668 / 15218)	1·90 (162 / 8535)	1·39 (52 / 3729)	1·29 (71 / 5487)
Control	5·12 (739 / 14430)	2·33 (176 / 7541)	2·79 (79 / 2828)	1·40 (54 / 3867)
Rate ratio, from (O–E) / V	0·71 CI 0·62 – 0·81 −77·1 / 226·1	0·74 CI 0·57 – 0·95 −18·5 / 60·6	0·45 CI 0·30 – 0·69 −16·7 / 21·1	0·86 CI 0·52 – 1·43 −2·2 / 15·2

(B) Premenopausal before chemotherapy, uncertain after

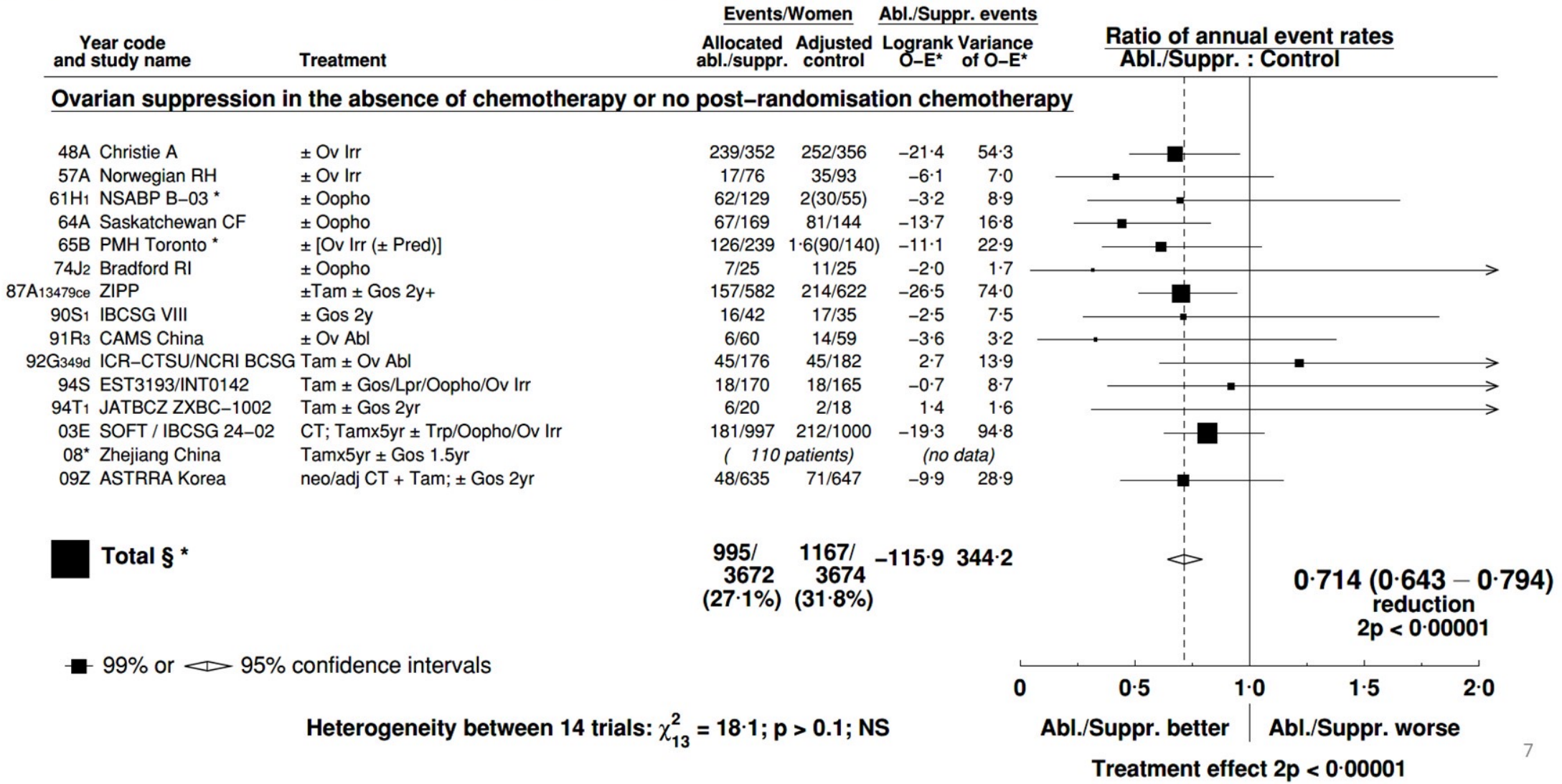


Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	5·29 (848 / 16038)	3·40 (345 / 10156)	2·73 (109 / 3993)	1·20 (21 / 1747)
Control	5·88 (950 / 16170)	3·51 (351 / 9996)	2·33 (91 / 3901)	0·95 (16 / 1676)
Rate ratio, from (O–E) / V	0·85 CI 0·76 – 0·95 −54·4 / 337·3	0·97 CI 0·82 – 1·15 −4·1 / 135·6	1·18 CI 0·86 – 1·61 6·5 / 39·6	1·07 CI 0·53 – 2·18 0·5 / 7·6

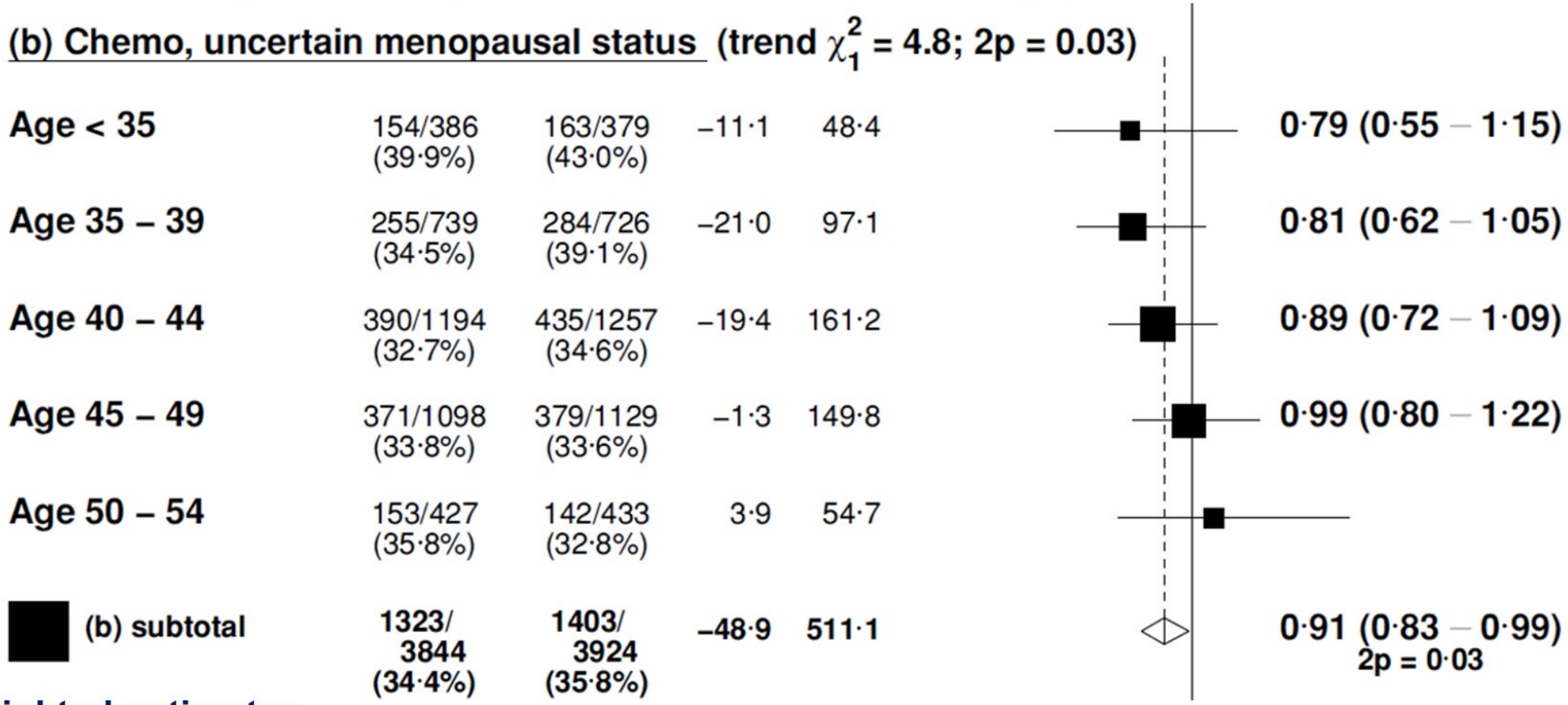
Ovarian ablation/suppression vs not: Recurrence

(A) No chemotherapy or premenopausal after chemotherapy



Ovarian ablation/suppress. vs not: Recurrence by age*

(B) Premenopausal prior to chemotherapy, uncertain after

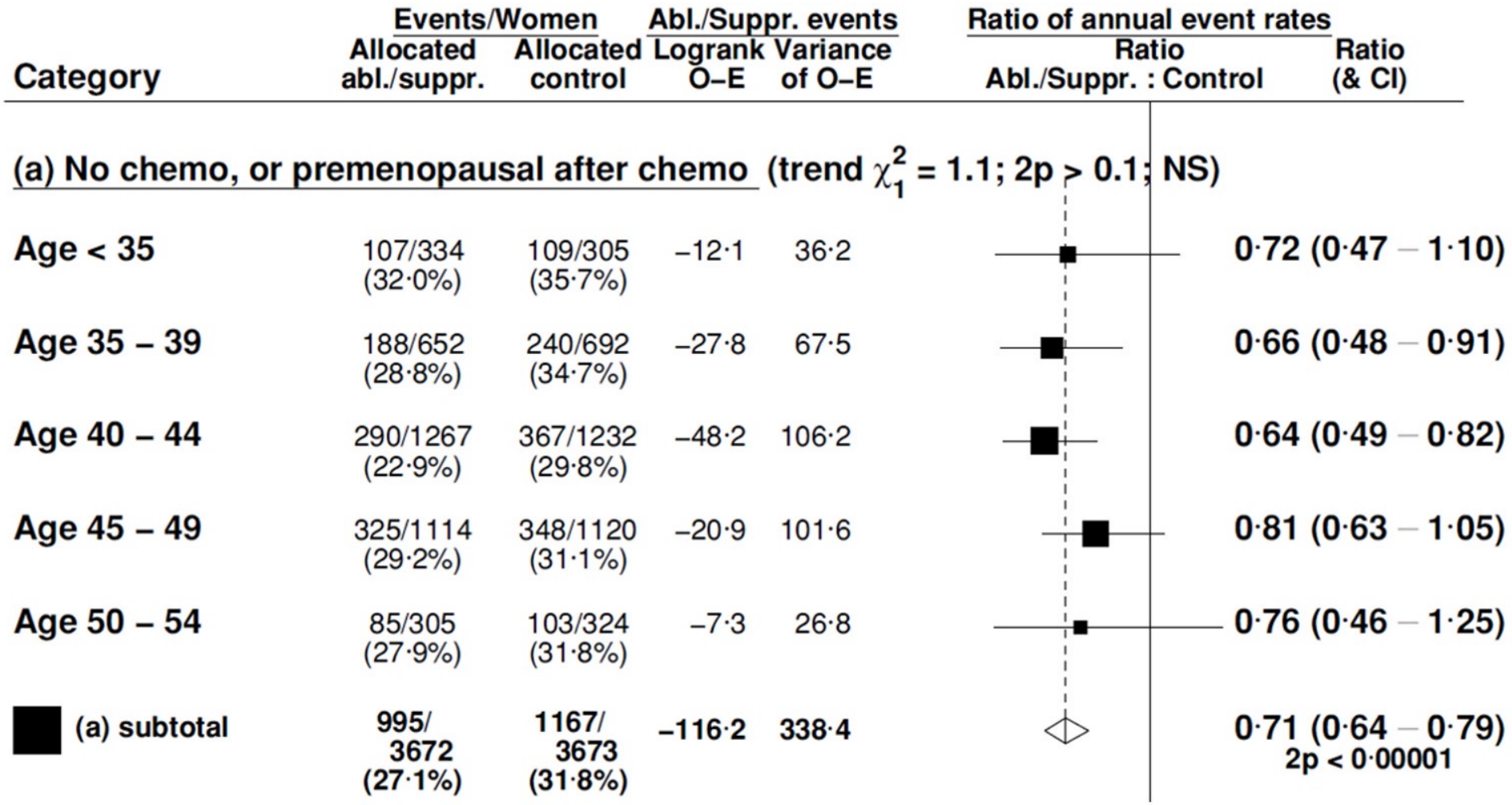


* ER-weighted estimates

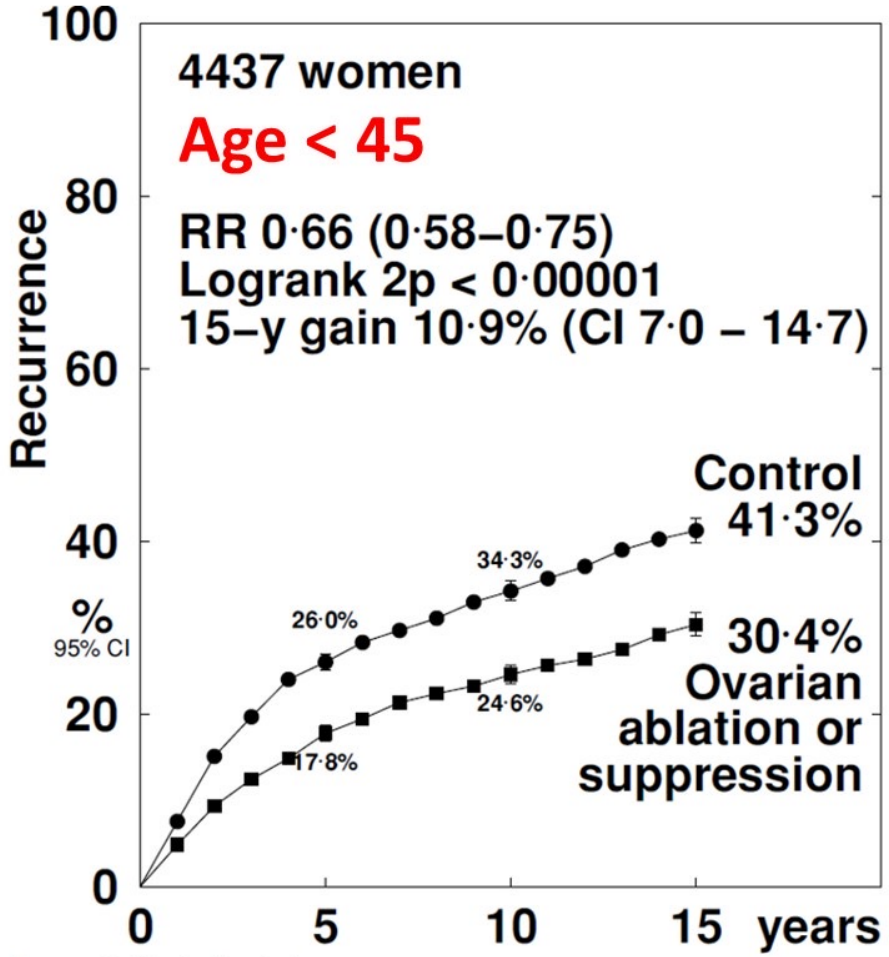
PRESENTED BY: Richard Gray, Emeritus Professor of Medical Statistics, University of Oxford

Ovarian ablation/suppression vs not: Recurrence by age*

(A) No chemotherapy or premenopausal after chemotherapy

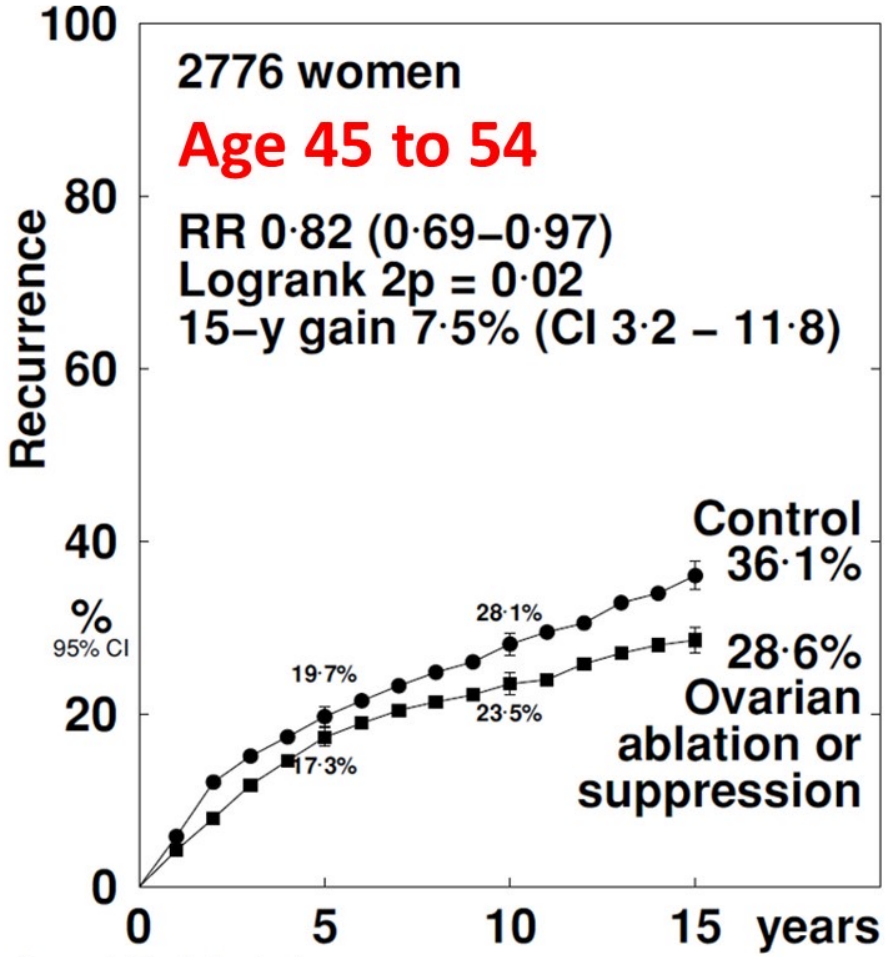


Ovarian ablation/suppression vs not: Recurrence (A) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	4·52 (412 / 9119)	1·86 (100 / 5384)	1·50 (41 / 2736)	1·11 (32 / 2885)
Control	5·77 (498 / 8637)	2·35 (110 / 4678)	2·41 (53 / 2201)	1·40 (30 / 2137)
Rate ratio, from	0·64 CI 0·55 – 0·75	0·75 CI 0·55 – 1·02	0·64 CI 0·40 – 1·01	0·65 CI 0·32 – 1·31
(O–E) / V	–66·8 / 149·9	–11·4 / 39·8	–8·0 / 17·6	–3·4 / 7·7

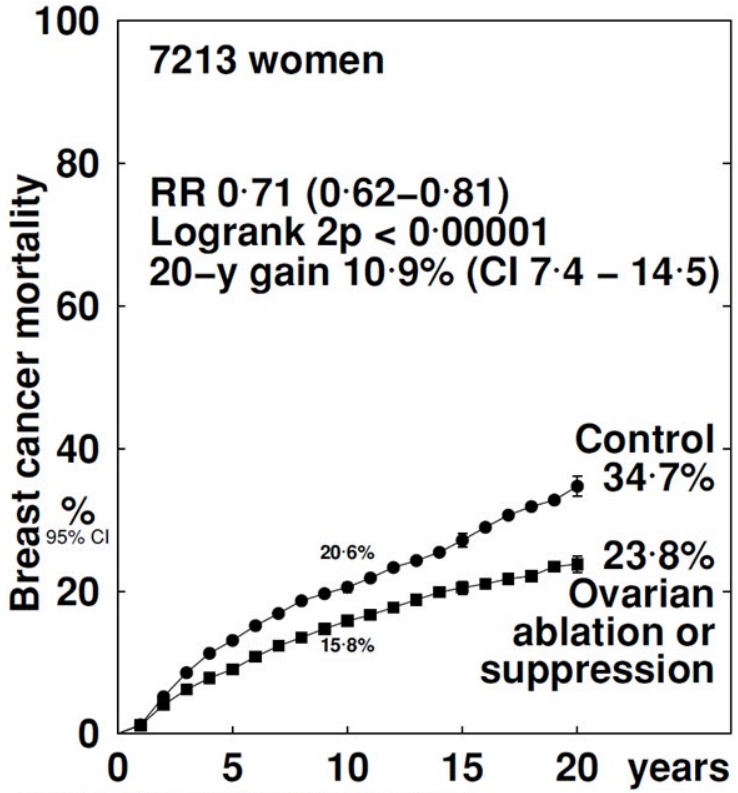


Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	4·17 (255 / 6113)	1·72 (78 / 4548)	1·45 (37 / 2555)	1·52 (40 / 2635)
Control	4·17 (242 / 5807)	2·08 (88 / 4238)	2·27 (47 / 2072)	1·37 (24 / 1756)
Rate ratio, from	0·87 CI 0·69 – 1·08	0·71 CI 0·50 – 1·02	0·63 CI 0·38 – 1·05	1·25 CI 0·62 – 2·52
(O–E) / V	–11·0 / 76·4	–10·1 / 30·1	–6·9 / 15·1	1·7 / 7·7

Ovarian ablation/suppression vs not: Mortality
(A) No chemotherapy or premenopausal after

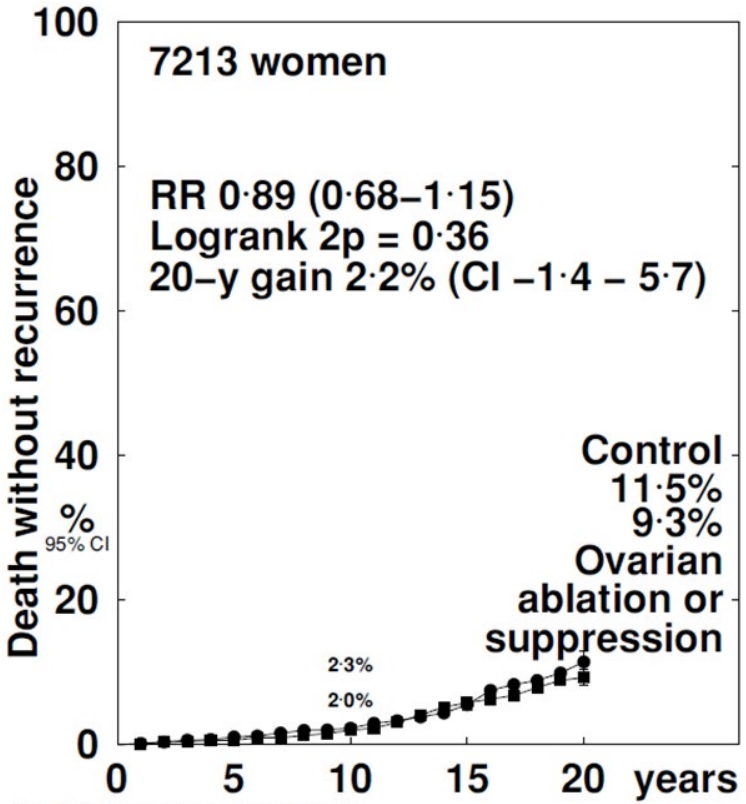
Breast cancer mortality



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	2·01 ci 1·84 – 2·18	1·18 ci 0·95 – 1·41	1·30 ci 0·93 – 1·68
Control	2·19 ci 2·01 – 2·37	1·78 ci 1·47 – 2·09	1·47 ci 1·01 – 1·93
Rate ratio, from	0·74 ci 0·63 – 0·86	0·58 ci 0·42 – 0·81	0·82 ci 0·43 – 1·56
(O–E) / V	–51·7 / 169·2	–19·5 / 35·9	–1·9 / 9·4

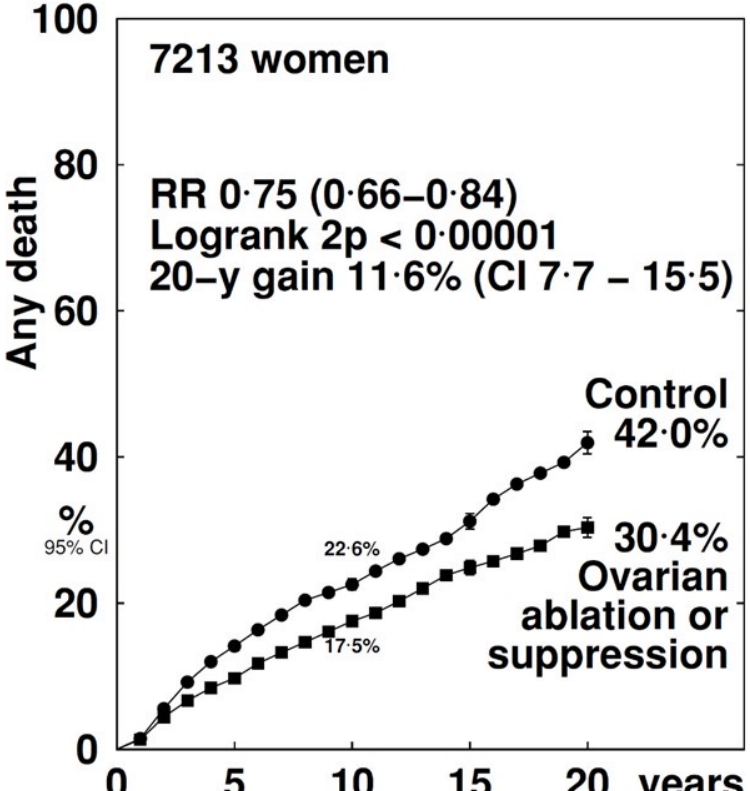
Death without recurrence



Death–without–recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	0·19 (49 / 25166)	0·73 (56 / 7648)	4·32 (146 / 3376)
Control	0·21 (50 / 23362)	0·86 (51 / 5905)	4·32 (106 / 2452)
Rate ratio, from	0·75 ci 0·46 – 1·22	0·89 ci 0·54 – 1·47	0·98 ci 0·67 – 1·44
(O–E) / V	–4·7 / 16·2	–1·8 / 15·4	–0·5 / 26·1

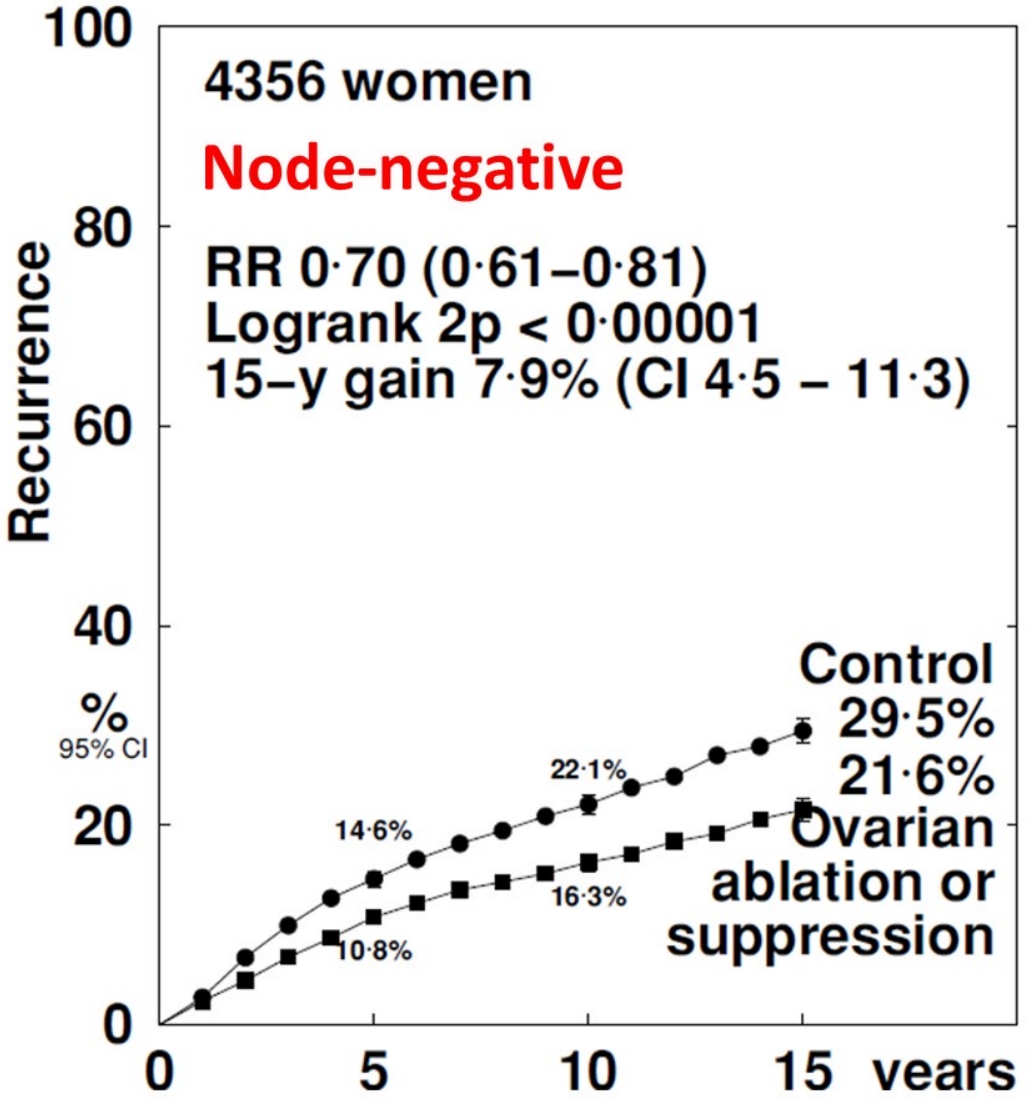
All cause mortality

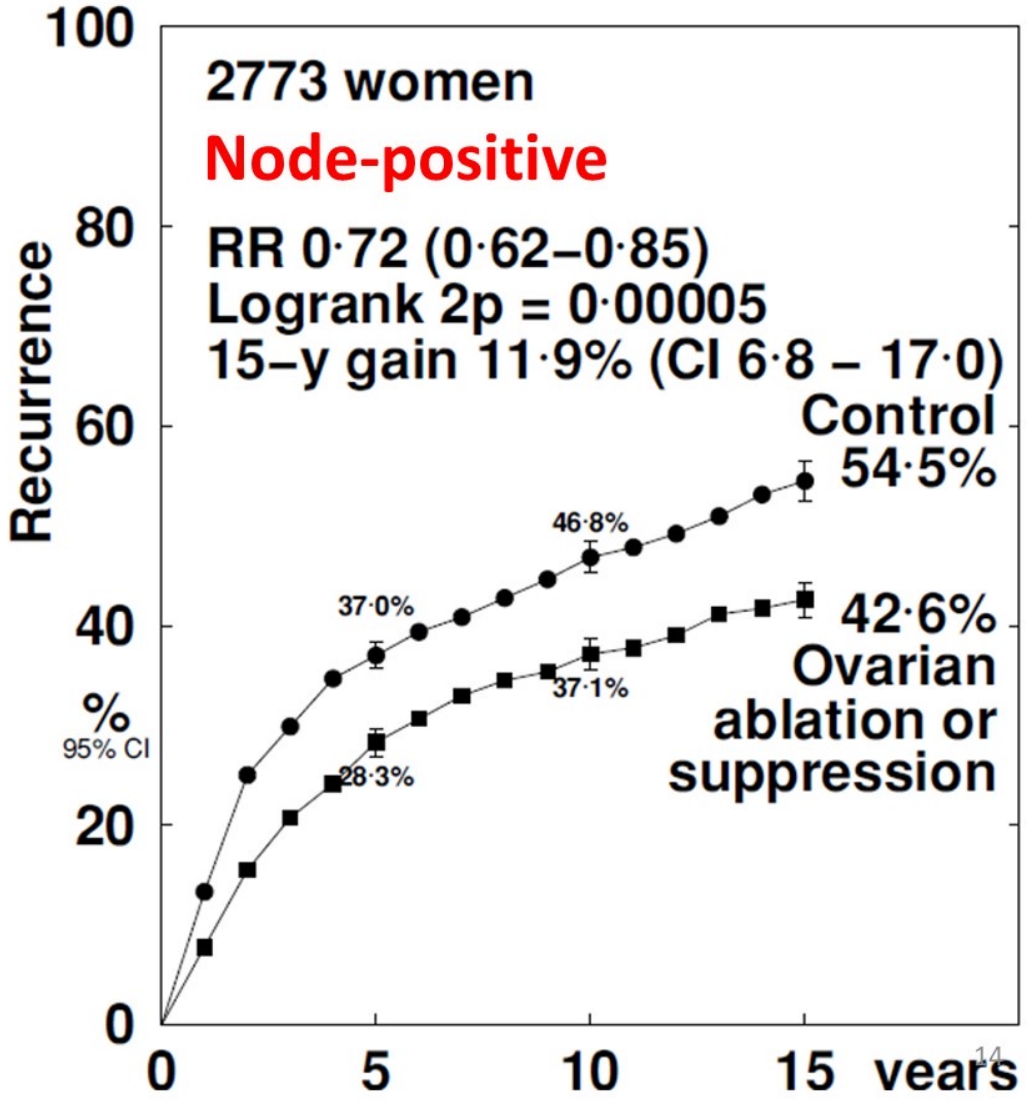


Death rates (% / year) and logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	2·22 (602 / 27161)	1·89 (160 / 8488)	5·40 (193 / 3573)
Control	2·43 (628 / 25843)	2·55 (178 / 6991)	5·52 (145 / 2625)
Rate ratio, from	0·74 ci 0·64 – 0·85	0·66 ci 0·50 – 0·87	0·93 ci 0·67 – 1·30
(O–E) / V	–56·4 / 185·5	–21·3 / 51·3	–2·4 / 35·5

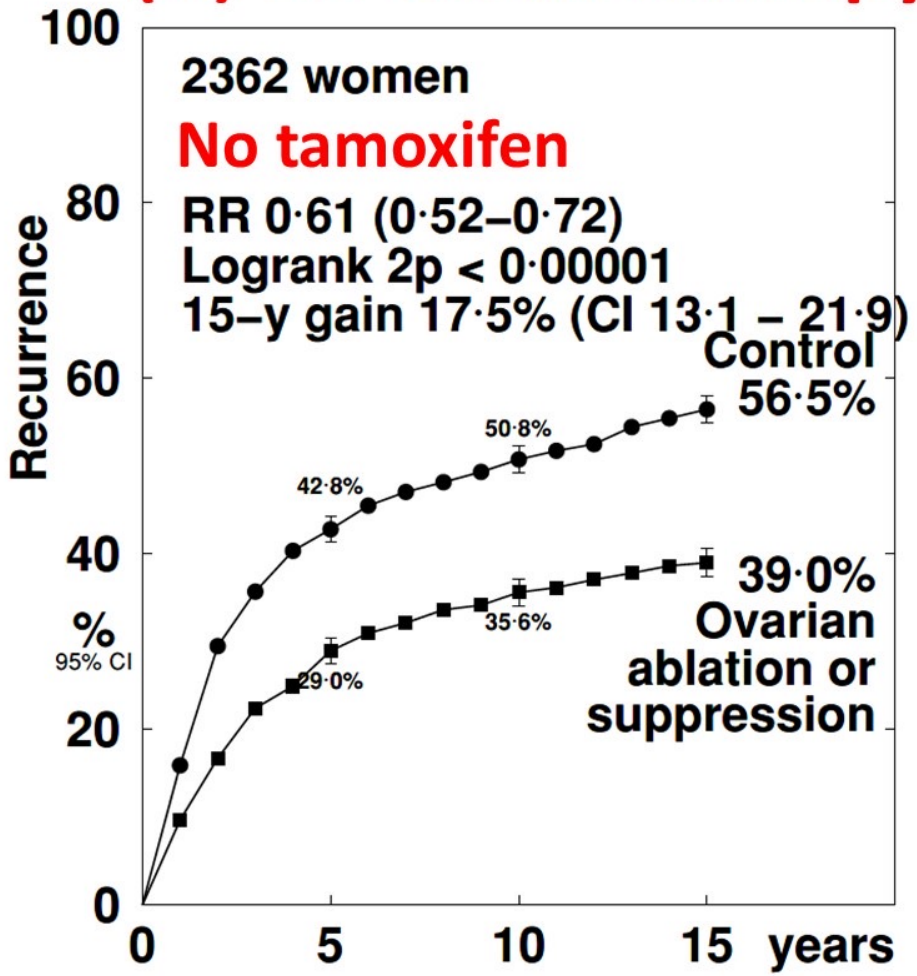
Ovarian ablation/suppression vs not: Recurrence by N-/N+
(A) No chemotherapy or premenopausal after





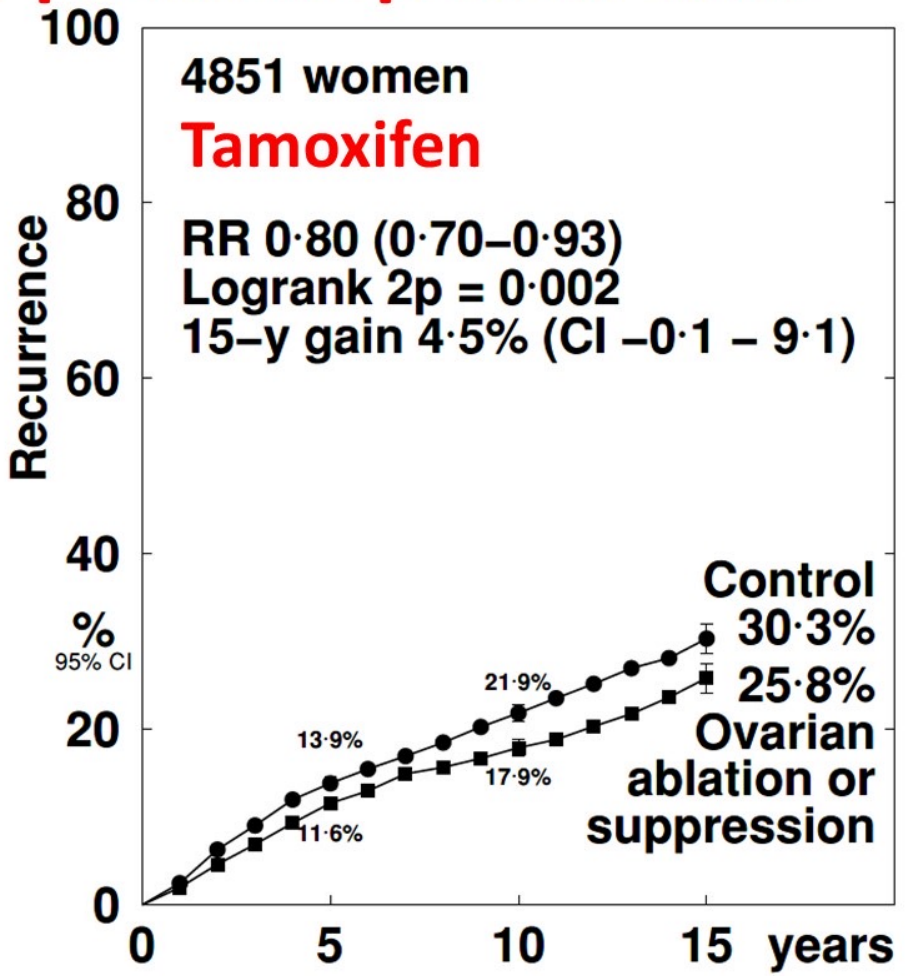
Ovarian ablation/suppress. vs not: Recurrence by tamoxifen use

(A) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

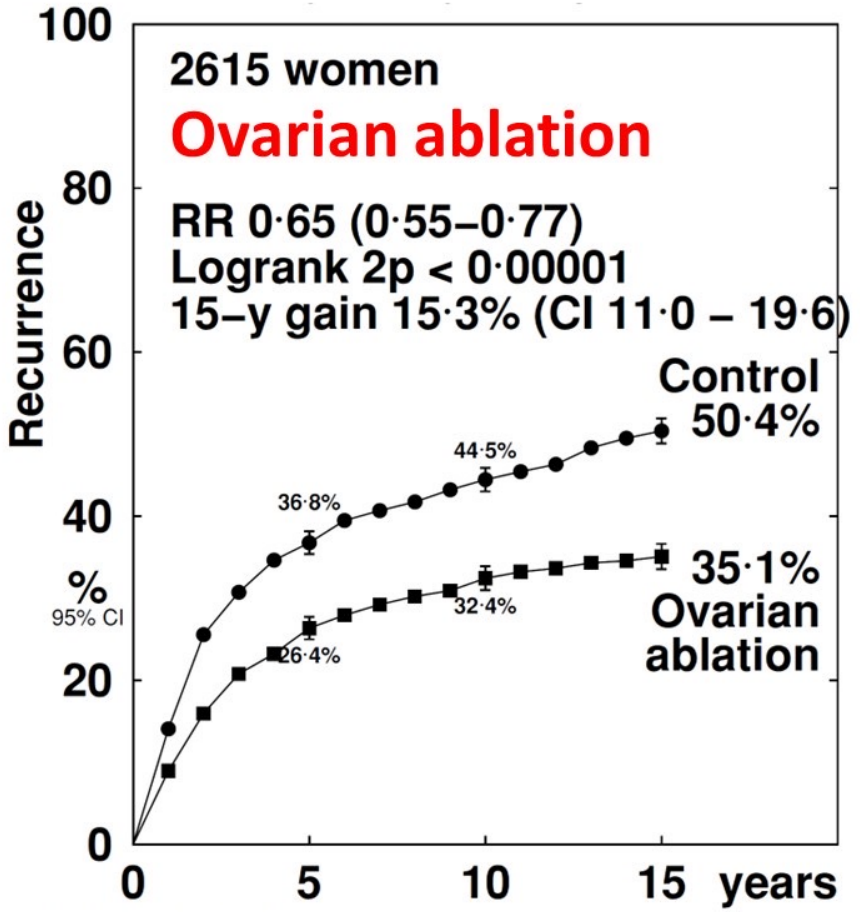
Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	8·37 (412 / 4921)	2·22 (82 / 3691)	1·26 (37 / 2945)	1·28 (69 / 5395)
Control	10·82 (427 / 3945)	2·90 (80 / 2757)	2·47 (52 / 2103)	1·37 (52 / 3785)
Rate ratio, from	0·60 CI 0·49 – 0·72	0·66 CI 0·43 – 0·99	0·47 CI 0·27 – 0·81	0·85 CI 0·51 – 1·42
(O–E) / V	–51·8 / 100·0	–9·6 / 22·8	–9·8 / 12·9	–2·4 / 14·3



Recurrence rates (% / year) and logrank analyses

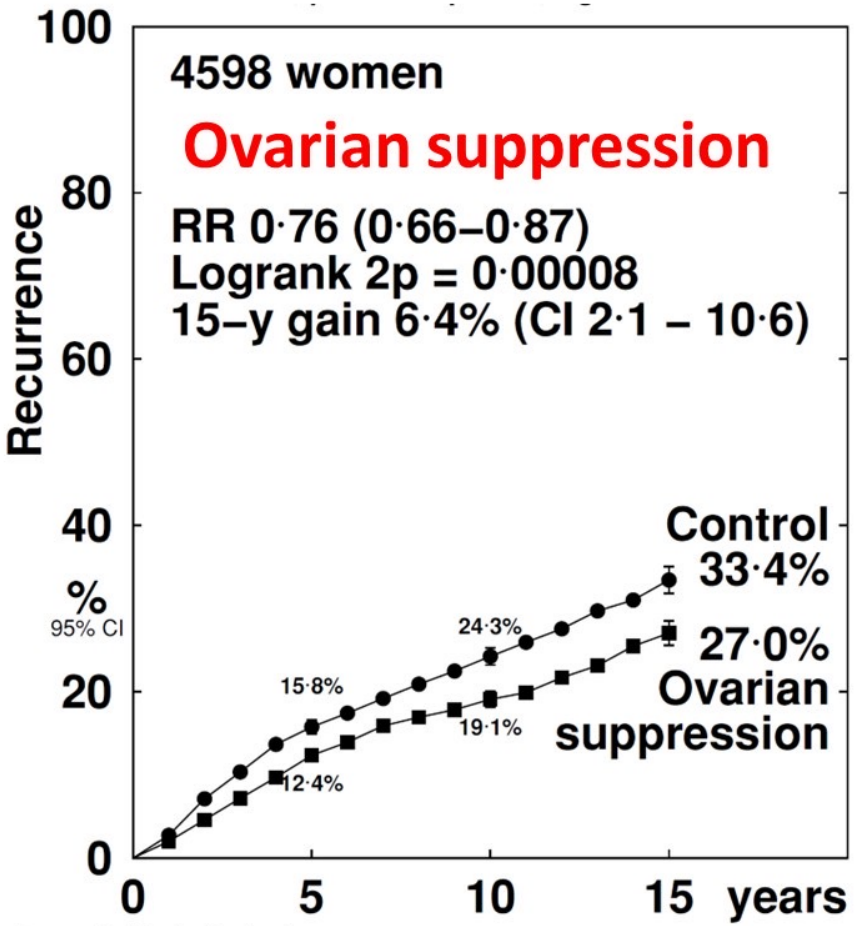
Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	2·47 (255 / 10311)	1·54 (96 / 6242)	1·75 (41 / 2346)	2·40 (3 / 125)
Control	2·98 (313 / 10499)	1·92 (118 / 6159)	2·21 (48 / 2169)	1·85 (2 / 108)
Rate ratio, from	0·81 CI 0·68 – 0·97	0·78 CI 0·58 – 1·03	0·77 CI 0·50 – 1·20	1·94 CI 0·30 – 12·52
(O–E) / V	–26·1 / 126·3	–12·0 / 47·1	–5·0 / 19·7	0·7 / 1·1

Ovarian ablation/suppression vs not: Recurrence by method
(B) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	7·42 (410 / 5529)	1·93 (79 / 4091)	1·13 (30 / 2645)	1·29 (68 / 5267)
Control	8·78 (404 / 4603)	2·50 (82 / 3284)	2·08 (39 / 1879)	1·39 (51 / 3678)
Rate ratio, from	0·65 CI 0·53 – 0·80	0·66 CI 0·43 – 1·01	0·40 CI 0·20 – 0·78	0·85 CI 0·50 – 1·44
(O–E) / V	–40·3 / 94·3	–8·6 / 20·8	–7·8 / 8·5	–2·3 / 13·9



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	2·65 (257 / 9703)	1·69 (99 / 5841)	1·81 (48 / 2646)	1·58 (4 / 253)
Control	3·41 (336 / 9841)	2·06 (116 / 5632)	2·55 (61 / 2393)	1·40 (3 / 215)
Rate ratio, from	0·75 CI 0·63 – 0·89	0·77 CI 0·58 – 1·02	0·75 CI 0·50 – 1·11	1·49 CI 0·31 – 7·13
(O–E) / V	–37·5 / 132·0	–13·0 / 49·1	–7·0 / 24·1	0·6 / 1·6

Summary: ovarian ablation/suppression

- Substantial benefit for premenopausal women with ER+ tumours from ovarian suppression and from ovarian ablation
- Similar benefits in women who received prior chemotherapy, and remained premenopausal after chemo, as in women who received no chemotherapy
- Benefits appear larger for women who received no tamoxifen than for women receiving tamoxifen

PRESENTED BY: Richard Gray, Emeritus Professor of Medical Statistics, University of Oxford

NRG-BR009 (OFSET): Schema

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

Stratification

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

Randomization

N=3,960

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

* Tamoxifen can be used if AI is not tolerated

Slide courtesy of Terry Mamounas, MD

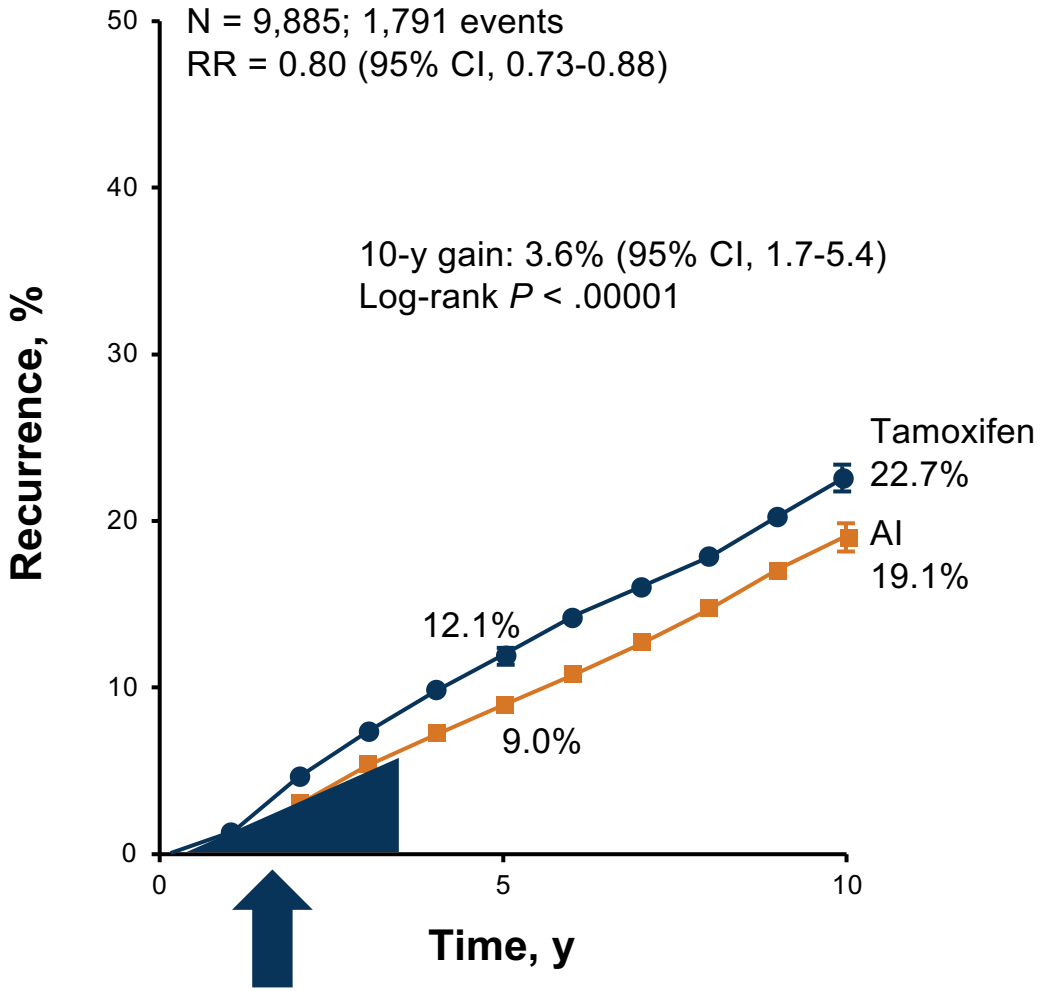
Treatment of HR+/HER2- EBC (2002-2021)

Endocrine therapy

- Tamoxifen
- Aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 years vs 5 years)

Unmet need

- Identifying patients with HR+ BC who have primary endocrine resistance and preventing or delaying recurrence with additional therapy



Cardoso F et al. *Ann Oncol.* 2019;30:1194-1220. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386:1341-1352.

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

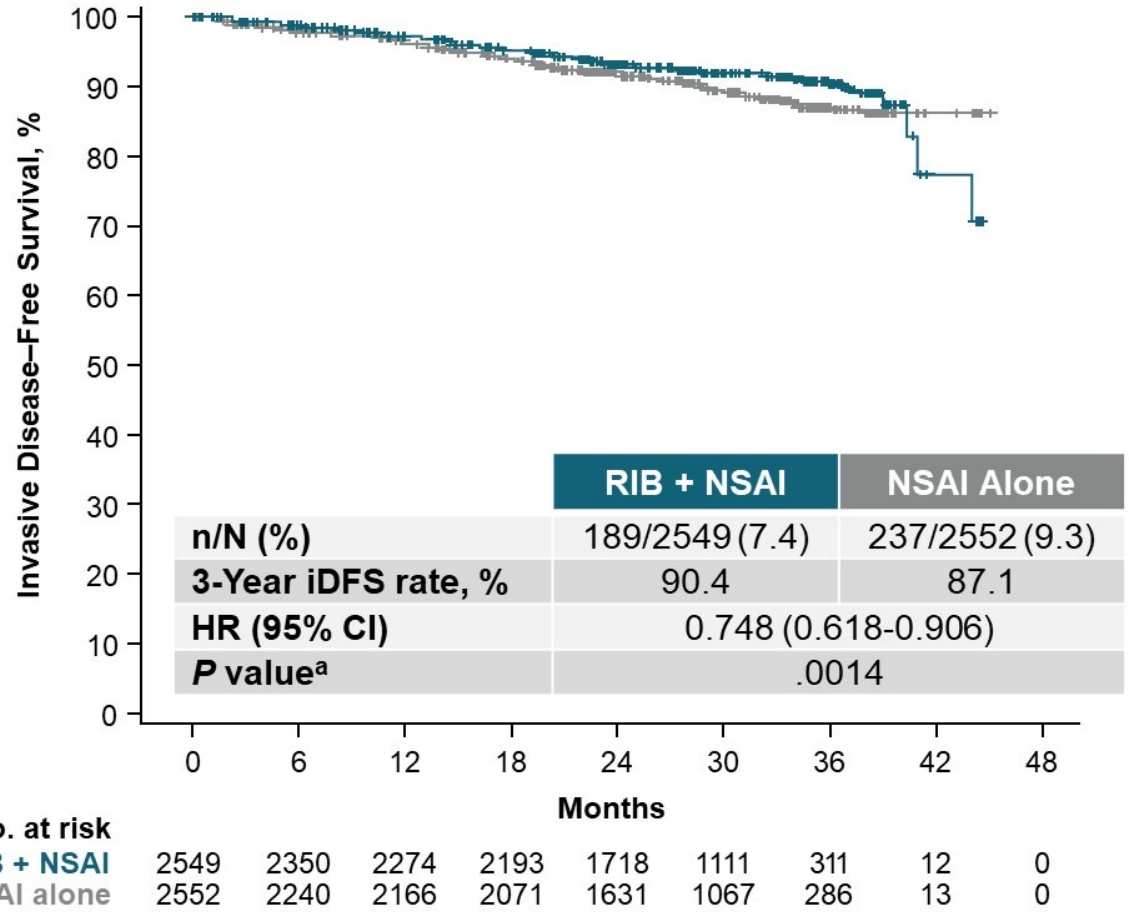
Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

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].

Ribociclib achieved highly significant iDFS benefit



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

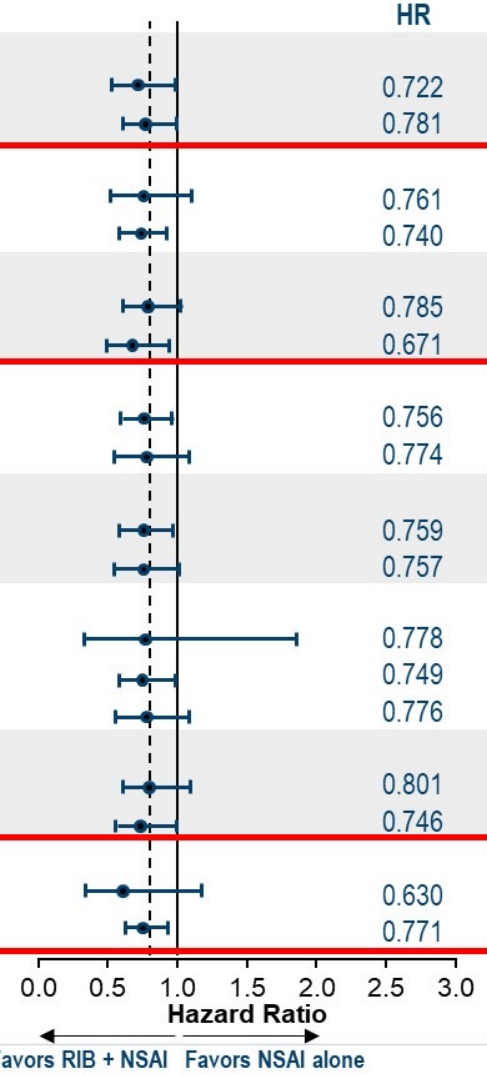
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

- Median follow-up for iDFS was 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

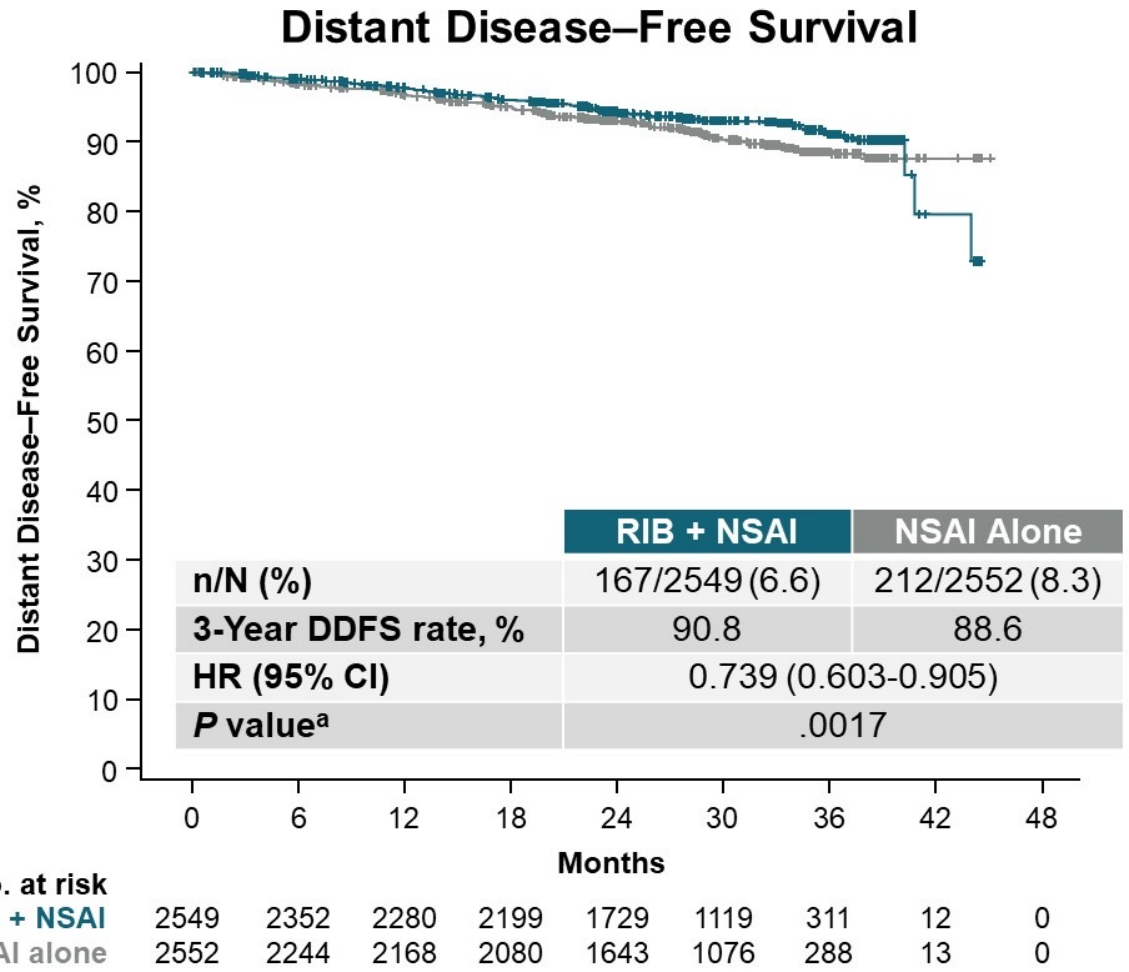
iDFS benefit was consistent across prespecified key subgroups

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 worse stage derived per surgical specimen or at diagnosis.

Consistent improvement in DDFS with ribociclib

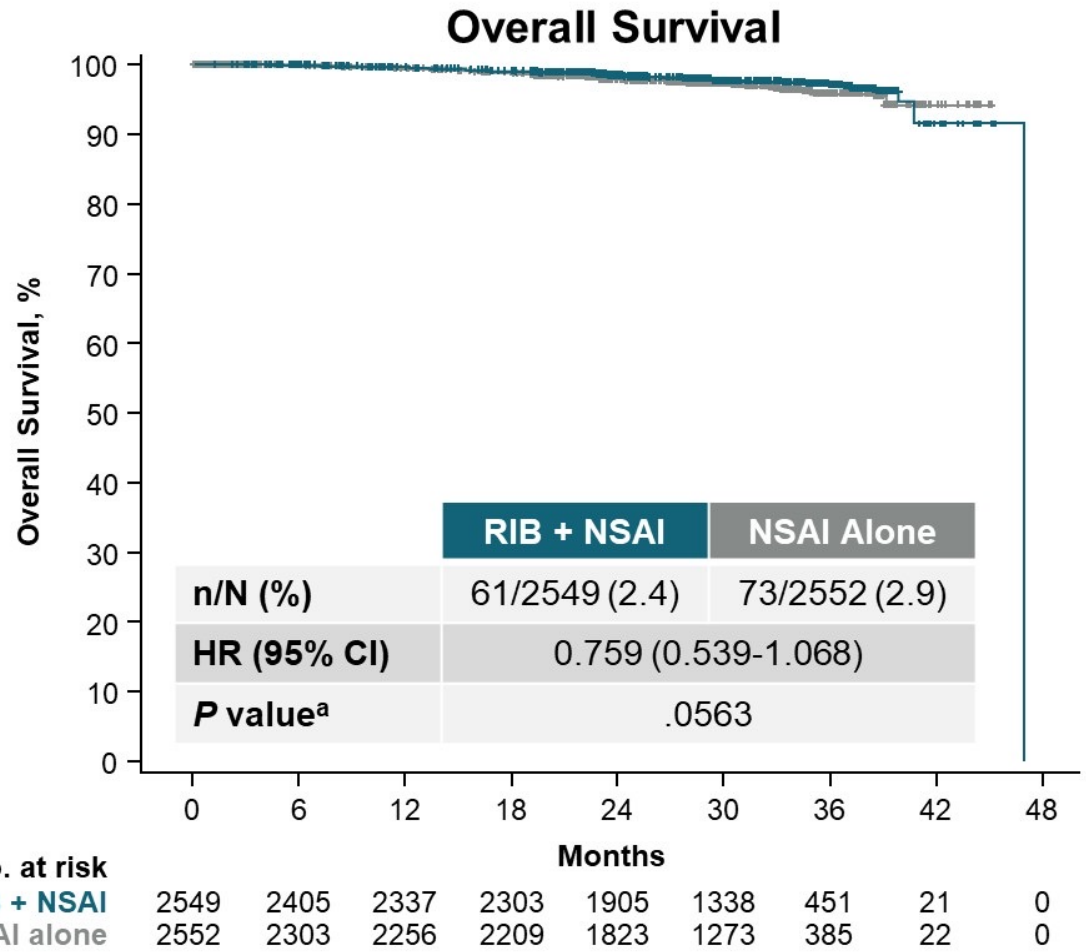


	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

DDFS, distant disease–free survival; ET, endocrine therapy; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value. [b] Excluding basal and squamous cell carcinomas of the skin.

- Distant disease–free survival is defined as the time from date of randomization to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer[b]
- The one-sided nominal *P* value was .0017
- Absolute distant disease–free survival benefit with RIB + NSAI at 3 years was 2.2%
- Risk of distant disease was reduced by 26.1% with RIB + NSAI vs NSAI alone

Ribociclib showed a trend for improved OS



	RIB + NSAI	NSAI Alone
n/N (%)	61/2549 (2.4)	73/2552 (2.9)
HR (95% CI)	0.759 (0.539-1.068)	
P value[a]	.0563	

- Median follow-up for OS was 30.4 months
- Additional follow-up for OS is planned

HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.
[a] One-sided nominal *P* value.

Ribociclib at the 400-mg dose was safe and well tolerated

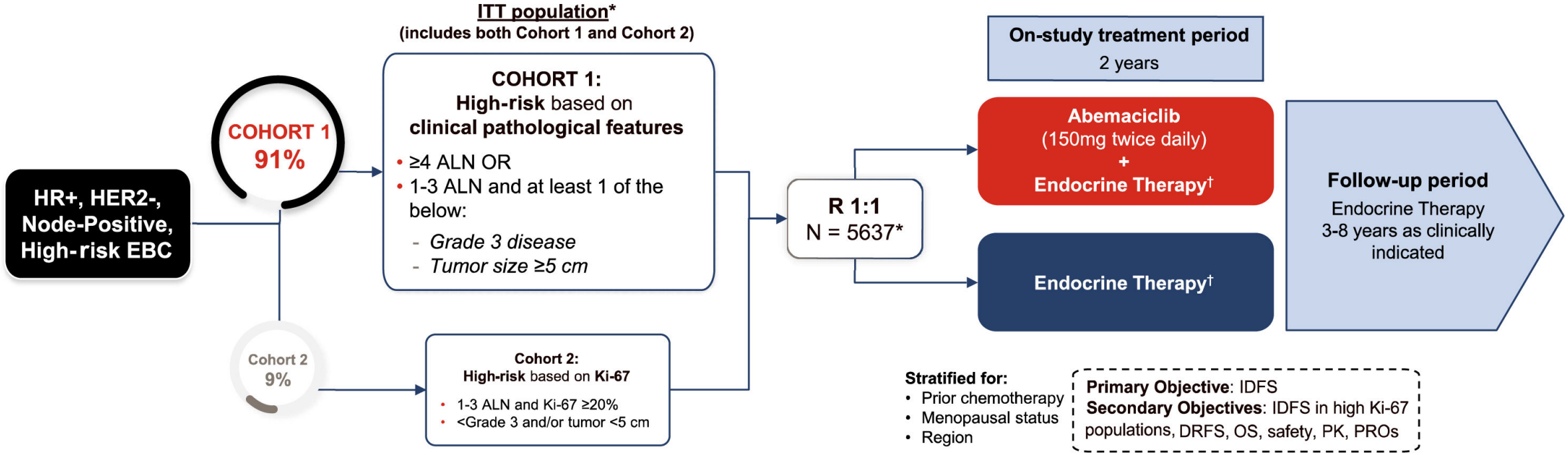
	RIB + NSAI n = 2524		NSAI Alone n = 2444	
AESIs, %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

monarchE Study Design (NCT03155997)

- Patients with node-positive early BC are at high-risk of recurrence (up to 30% at 5 years)
- MonarchE evaluated 2 years of adjuvant abemaciclib + endocrine therapy



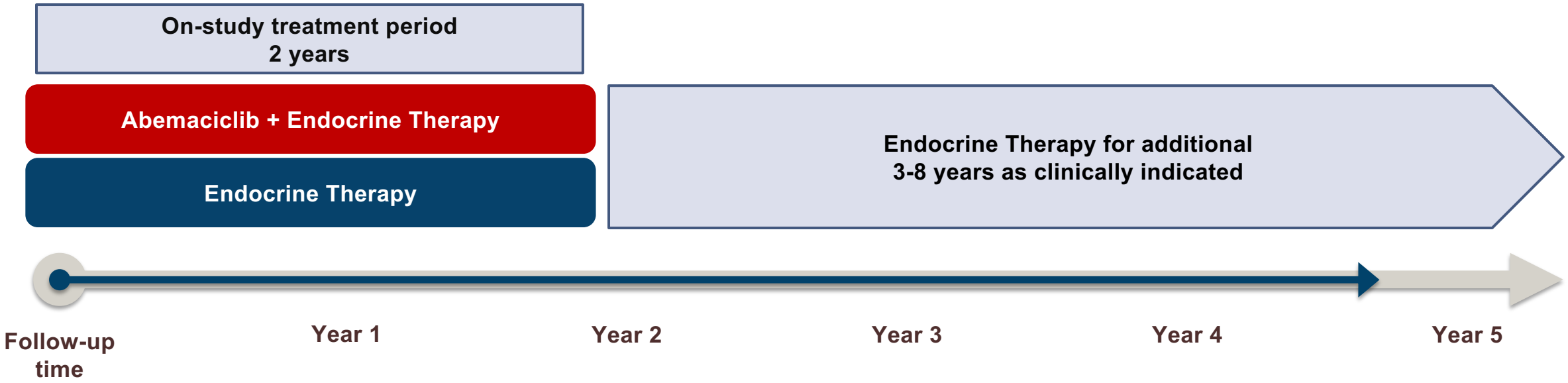
*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

All patients are off abemaciclib; median follow-up, 54 months

Year 1 Year 2 Year 3 Year 4 Year 5

Presented by Nadia Harbeck, MD

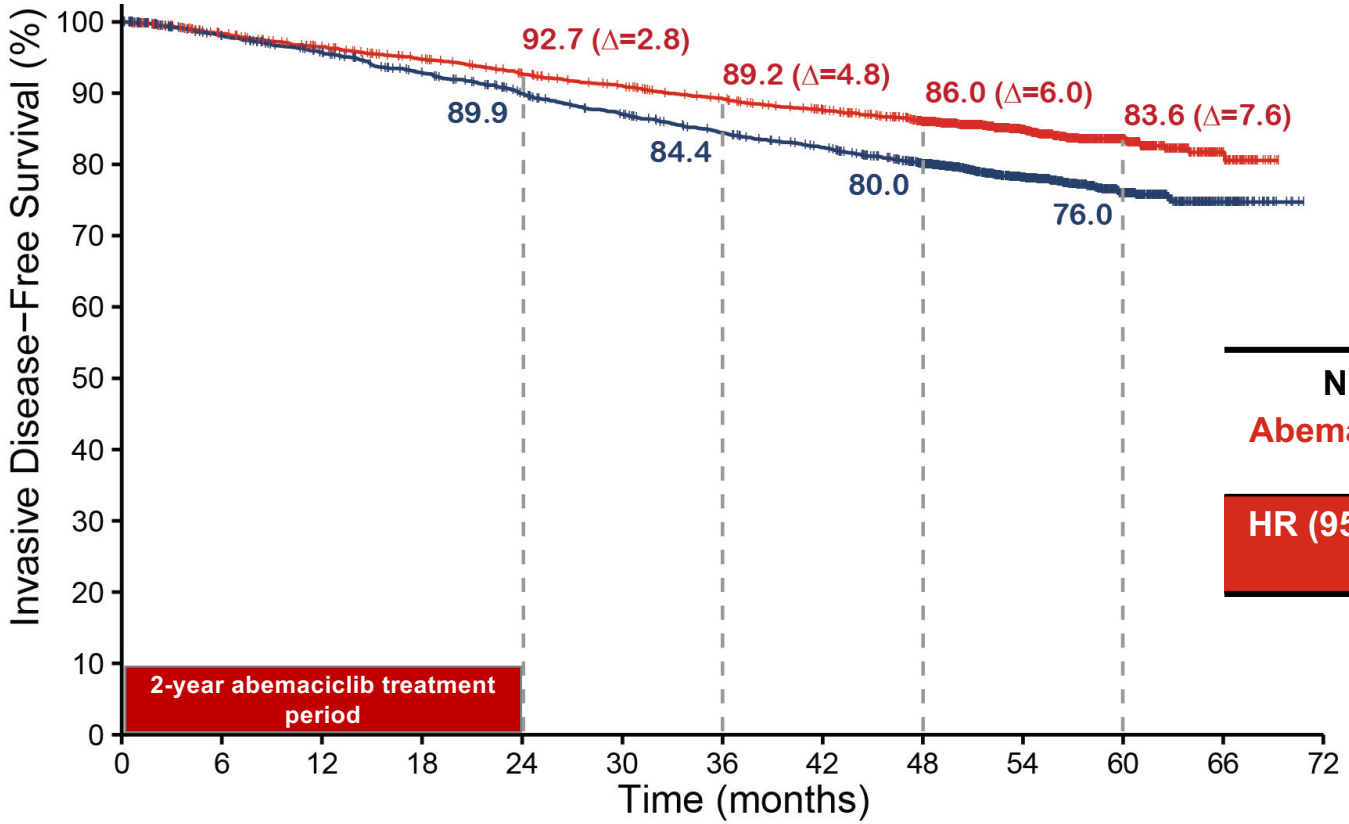
Overall Survival Interim Analysis 3 (OS IA3)



- Here, we report 5-year efficacy results from a prespecified monarchE analysis
  - Data cutoff July 3rd, 2023
- Extent of follow-up at OS IA3 allows for robust estimation of IDFS and DRFS at the critical 5-year landmark
- Median follow-up time is 4.5 years (54 months)
- All patients are off abemaciclib
  - More than 80% of patients have been followed for at least 2 years since completing abemaciclib

Presented by: Nadia Harbeck, MD

Sustained IDFS Benefit in ITT



Number of IDFS events

Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

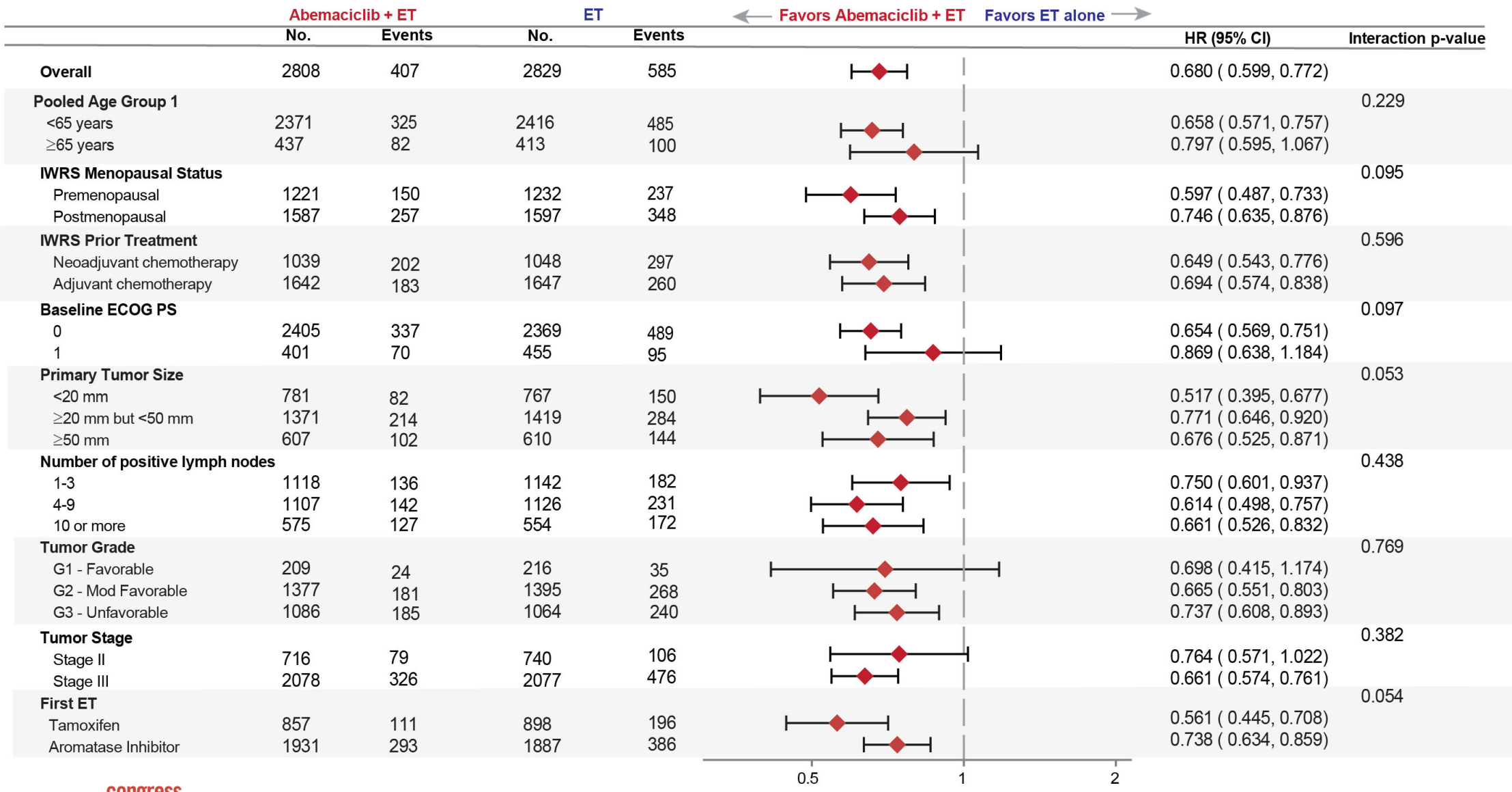
Number at risk

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

32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

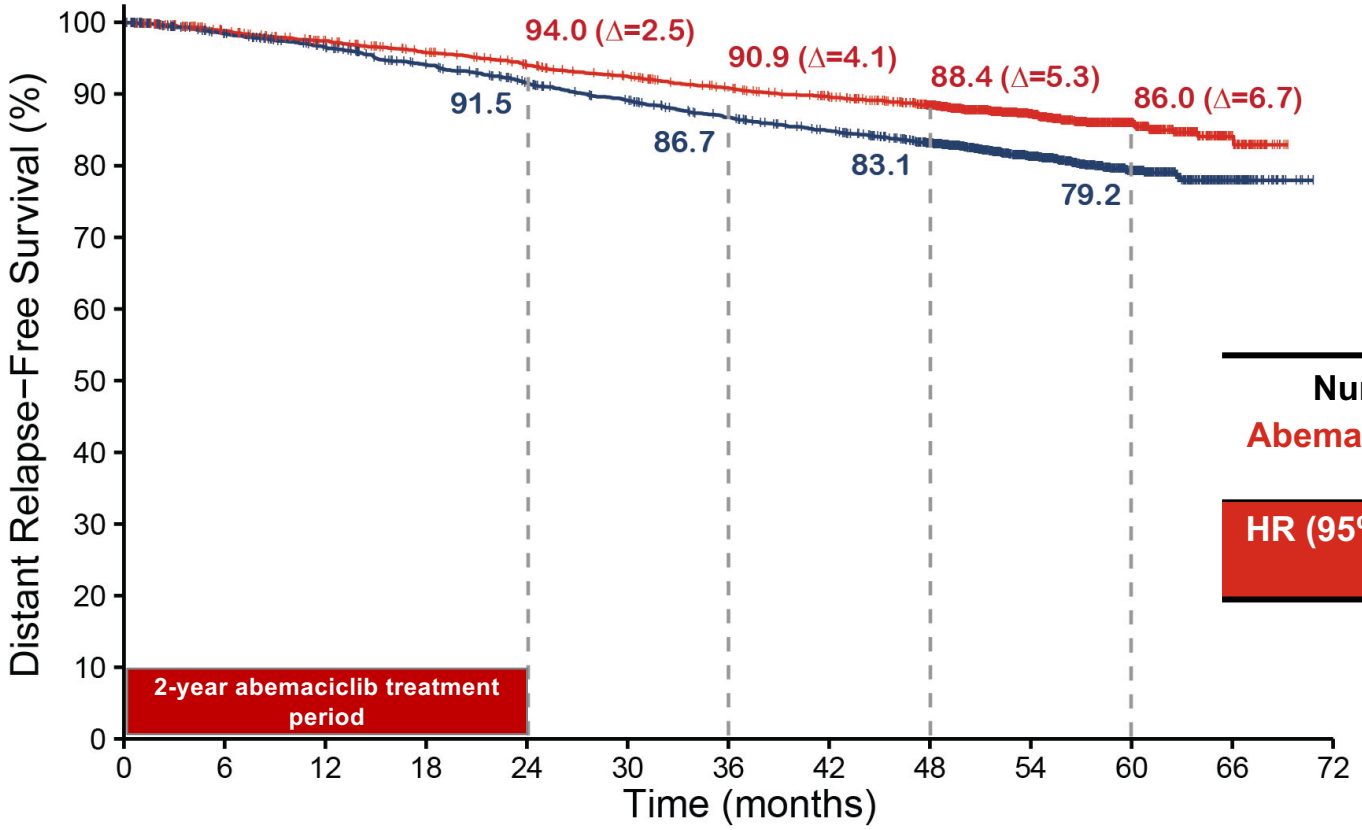
Presented by Nadia Harbeck, MD

Consistent IDFS Benefit Observed in Selected Subgroups*



*Region of enrollment and Progesterone status data not shown

Sustained DRFS Benefit in ITT



Number of DRFS events	
Abemaciclib + ET	ET Alone
345	501

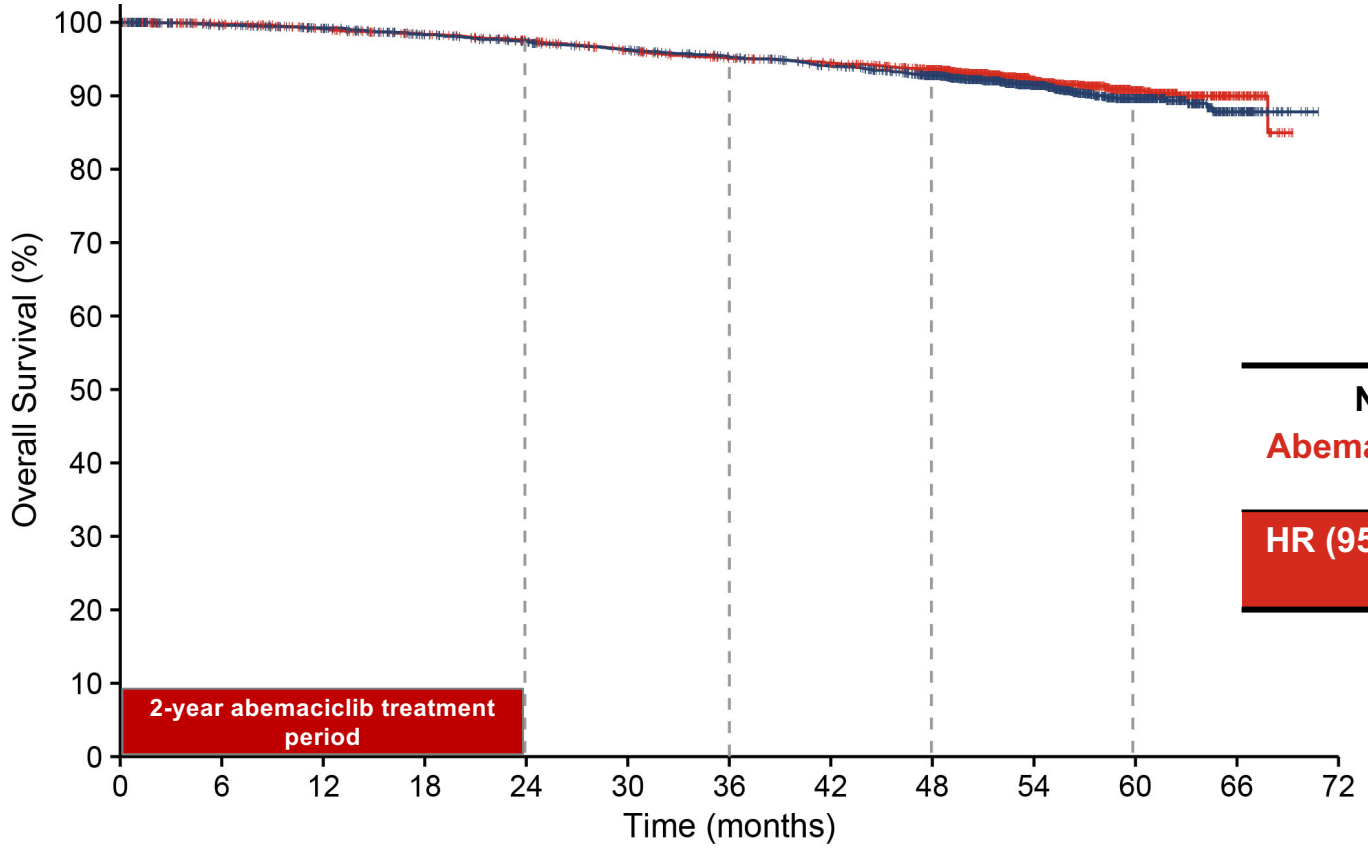
HR (95% CI): 0.675 (0.588, 0.774)
Nominal p <0.001

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.
The KM curves continue to separate and the absolute difference in DRFS rates between arms was 6.7% at 5 years

Fewer deaths in the Abemaciclib Arm in ITT



Number of OS events

Abemaciclib + ET	ET Alone
208	234

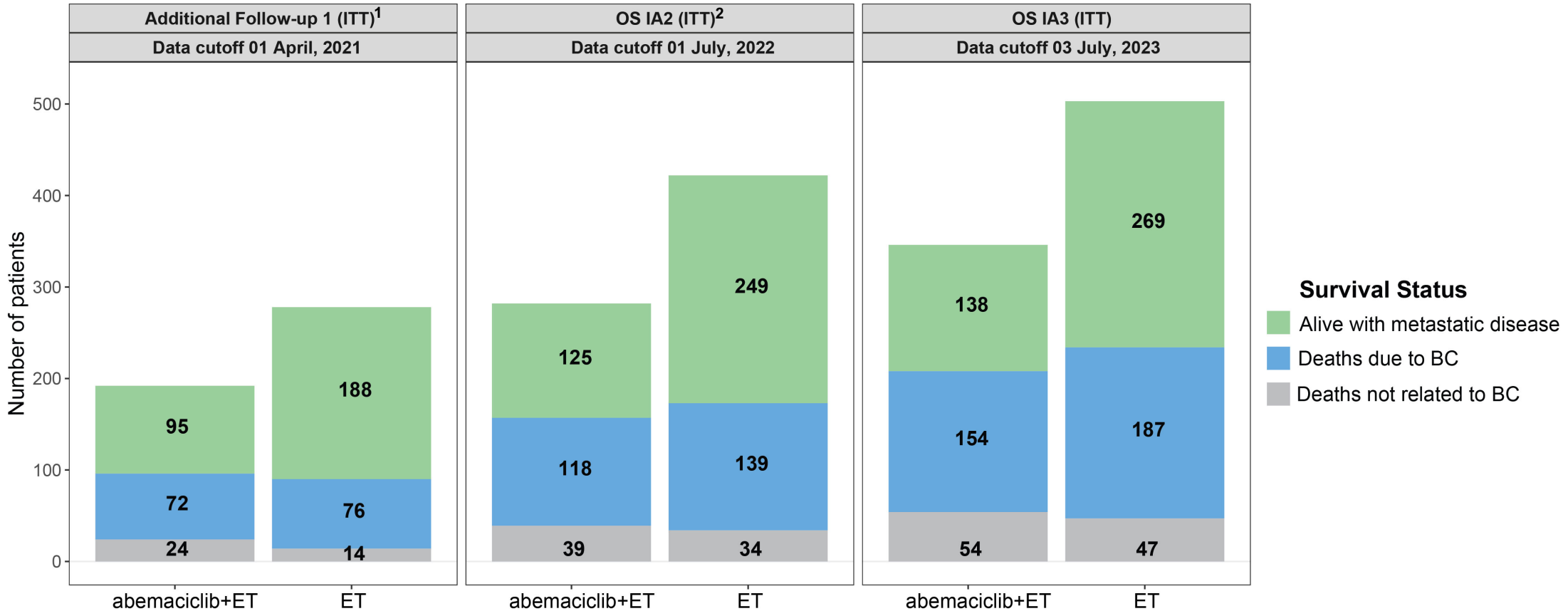
HR (95% CI): 0.903 (0.749, 1.088)
p=0.284

Number at risk

Abemaciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0

At OS IA3 statistical significance was not reached for OS

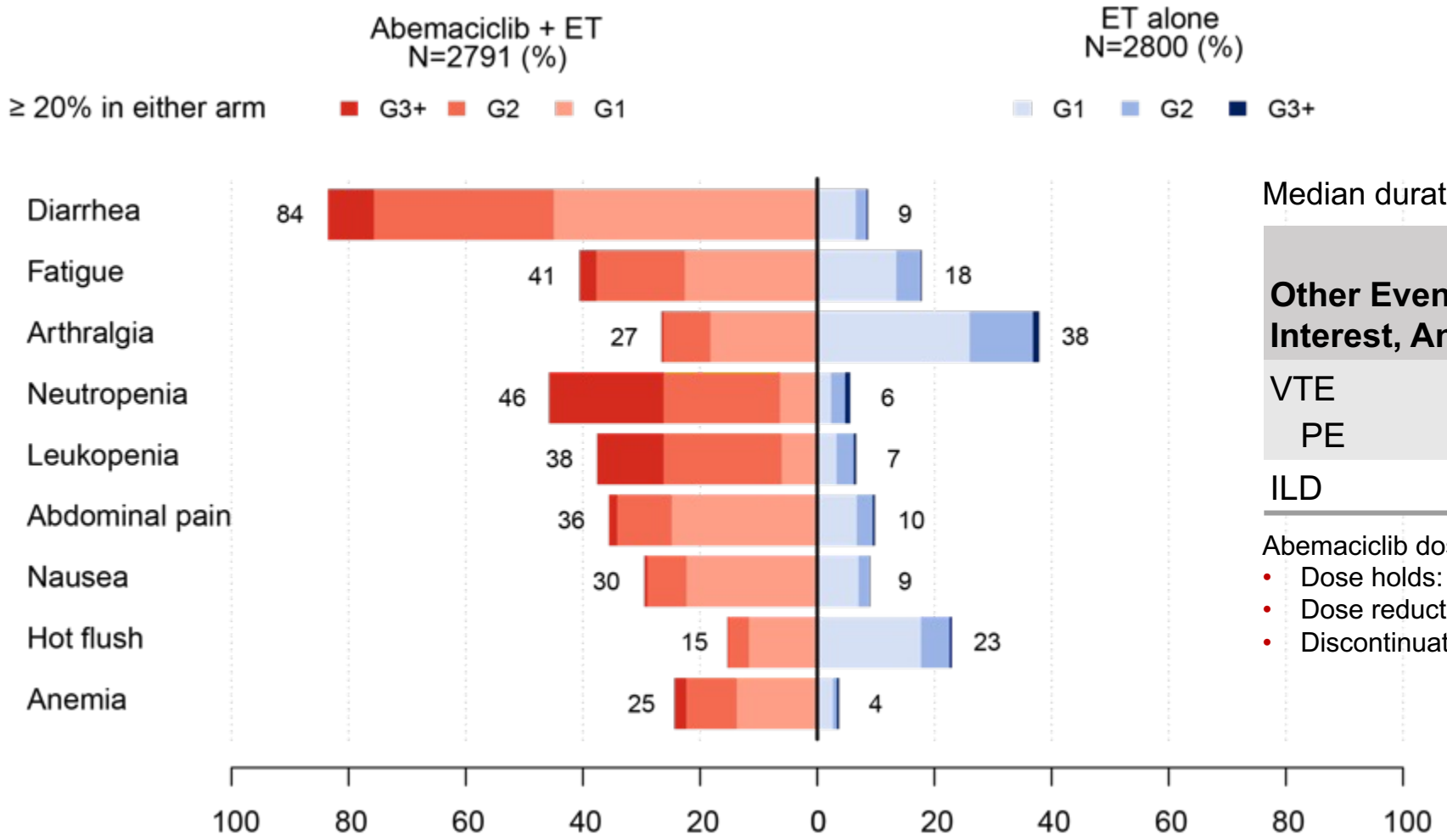
Fewer Patients with Metastatic Disease in the Abemaciclib Arm



The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3

[1]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581 *co-first authors
[2]Johnston SRD, et al. Lancet Oncol. 2023;24:77-90

Safety Findings Consistent With Previous Analyses



Median duration of abemaciclib: 23.7 months.

Other Events of Interest, Any Grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs
- Dose holds: 61.7%
- Dose reductions: 43.6%
- Discontinuations 18.5% (8.9% after dose reduction)

VTE by first endocrine therapy
- 1.7% with AI
- 4.1% with tamoxifen

All patients who received at least 1 dose of study treatment were included in the safety population.

Toi M, et al. ESMO BC 2021. Abstract 440; Rugo HS, et al. *Ann Oncol.* 2022;33(6):616-627.

The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population

Safety

	Abemaciclib + ET n=2791, n (%)		ET n=2800, n (%)	
	OS IA2	OS IA3	OS IA2	OS IA3
Patients with ≥1 TEAE	2746 (98.4)	2746 (98.4)	2488 (88.9)	2488 (88.9)
Patients with ≥1 Grade ≥3 TEAE	1393 (49.9)	1395 (50.0)	472 (16.9)	474 (16.9)
Patients with ≥1 SAE	433 (15.5)	435 (15.6)	256 (9.1)	258 (9.2)

- **SAEs regardless of causality reported for patients in long-term follow-up are higher in ET alone arm (7.3%) compared to abemaciclib plus ET (6.5%)**

Consistent safety results from prior analyses, as all treated patients have completed treatment

Ki-67 Requirement Dropped From Abemaciclib Indication for High-Risk, Node-Positive, HR+/HER2- EBC

Indication Before March 3, 2023

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence ~~and a Ki-67 score ≥20% as determined by an FDA approved test.~~ (1.1, 2.1, 14.1)

Indication After March 3, 2023

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence. (1.1, 14.1)

monarchE: Efficacy by Cohorts and Ki-67 Index in Cohort 1

	Cohort 1 vs Cohort 2				Cohort 1: Ki-67 high vs Ki-67 low			
	Cohort 1		Cohort 2		Cohort 1 Ki-67 High		Cohort 1 Ki-67 Low	
	Abemaciclib + ET	ET	Abemaciclib + ET	ET	Abemaciclib + ET	ET	Abemaciclib + ET	ET
	n=2555	n= 2565	n=253	n=264	n=1017	n= 986	n=946	n=968
IDFS								
Number of events, n	382	553	25	32	176	251	116	171
HR (95% CI)	**0.670 (0.588, 0.764)**		**0.827 (0.484, 1.414)**		**0.643 (0.530, 0.781)**		**0.662 (0.522, 0.839)**	
Nominal p-value	p<0.001		p=0.488		p<0.001		p<0.001	
5-year IDFS rate, % (95% CI)	83.2 (81.5, 84.7)	75.3 (73.4, 77.2)	NR	NR	81.0 (78.1, 83.4)	72.0 (68.7, 75.0)	86.3 (83.6, 88.6)	80.2 (77.2, 82.9)
DRFS								
Number of events, n	325	477	20	24	152	221	96	143
HR (95% CI)	**0.665 (0.577, 0.765)**		**0.892 (0.485, 1.643)**		**0.634 (0.515, 0.781)**		**0.664 (0.512, 0.861)**	
Nominal p-value	p<0.001		p=0.714		p<0.001		p=0.002	
5-year DRFS rate, % (95% CI)	85.6 (84.0, 87.1)	78.5 (76.6, 80.3)	NR	NR	83.4 (80.7, 85.8)	75.2 (72.1, 78.0)	88.6 (86.1, 90.7)	83.5 (80.7, 86.0)
OS (immature)								
Number of events, n	197	223	11	11	92	121	56	62
HR (95% CI)	**0.894 (0.738, 1.084)**		**1.078 (0.465, 2.501)**		**0.717 (0.546, 0.941)**		**0.911 (0.633, 1.309)**	
Nominal p-value	p=0.254		p=0.861		p=0.016		p=0.613	

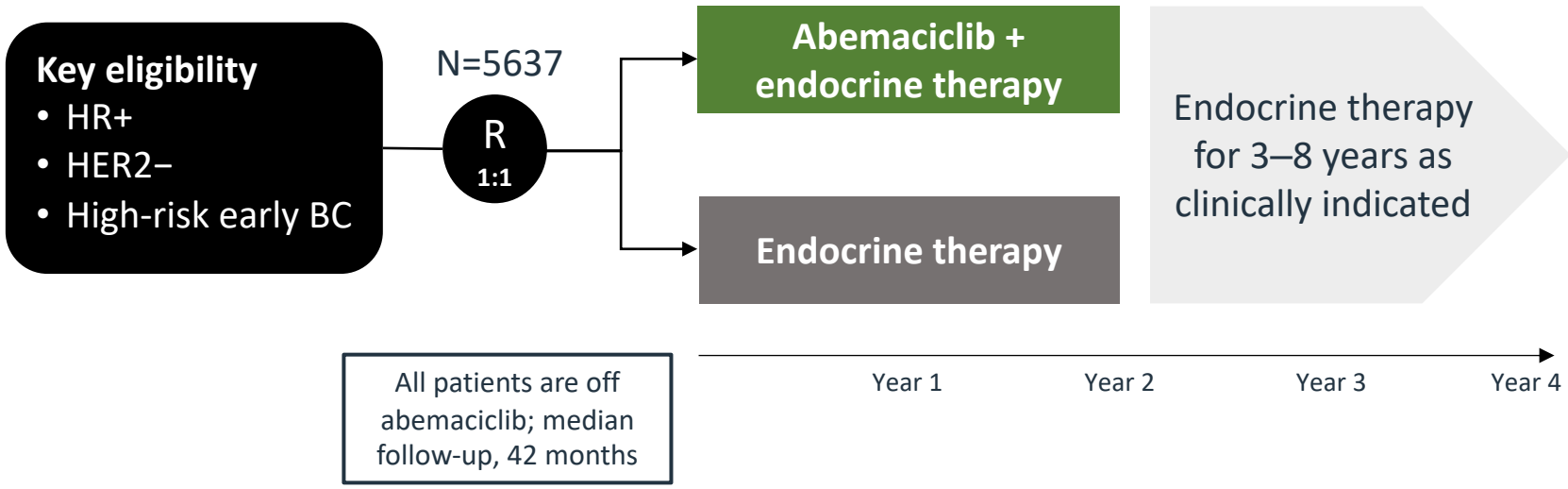
- Treatment benefit in Cohort 1 was consistent with ITT. Cohort 2 data remain immature

- Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Harbeck N, et al. ESMO 2023. Abstract LBA17

monarchE: Impact of dose reductions on efficacy of adjuvant abemaciclib for patients with high-risk early breast cancer

- Dose reductions are commonly used to manage treatment related toxicity with the goal of maximizing treatment adherence.
- In monarchE, many patients treated with abemaciclib underwent dose adjustments to manage AEs



Analyses

- Up to 2 abemaciclib dose reductions (100 or 50mg) were permitted prior to discontinuation
- Analysis population: Patients treated with abemaciclib (N = 2791)
- Efficacy outcome: Invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS)

- Objective: Investigate the impact of dose modifications, specifically dose reductions on the efficacy of abemaciclib in the EBC setting

O'Shaughnessy J, et al. ESMO 2023. Abstract 274P

monarchE: Exposure by Dose Reductions

Summary of abemaciclib exposure by patients with or without dose reductions

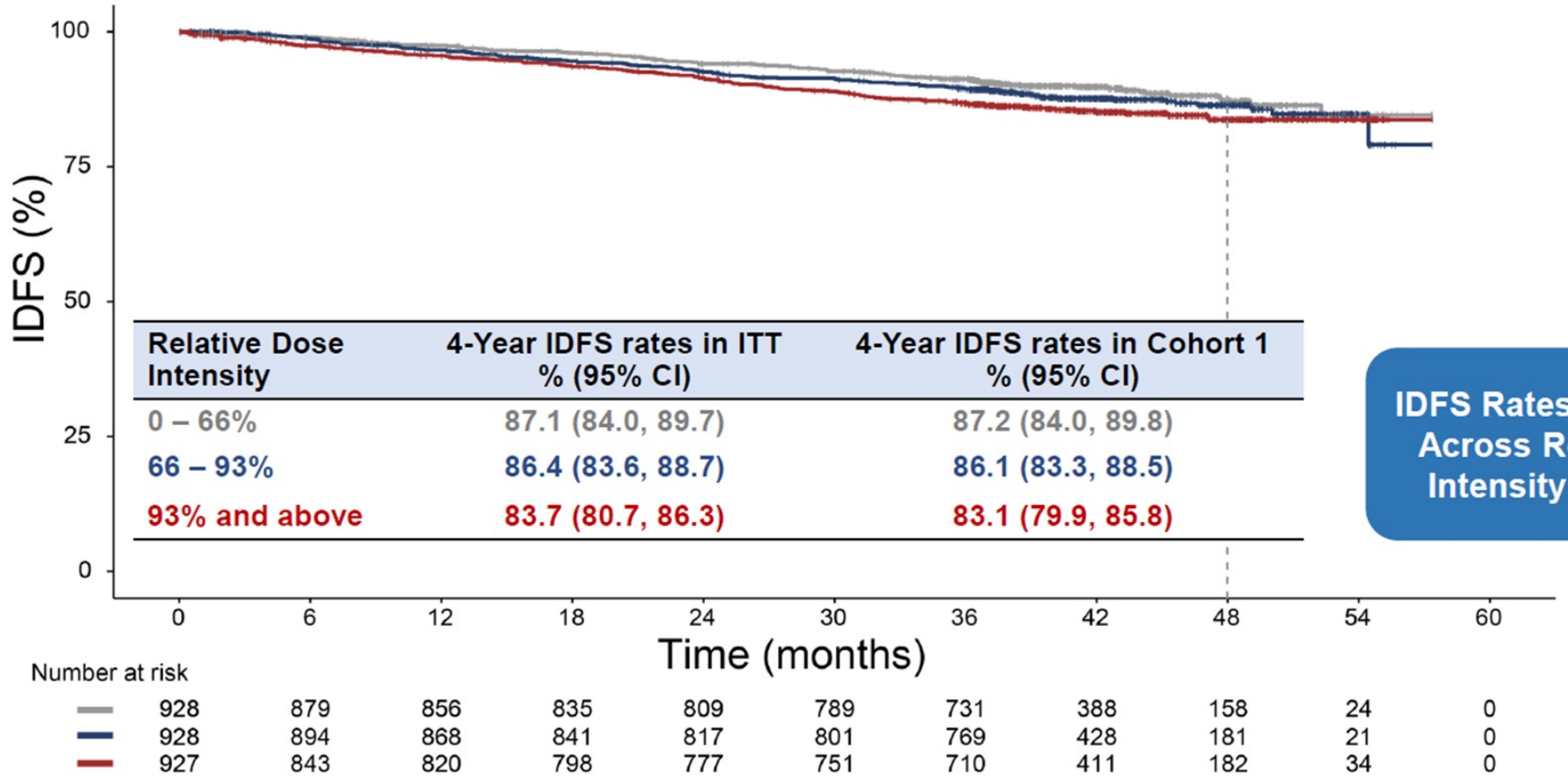
	No Dose Reduction N = 1570	1 Dose Reduction N = 832	2 Dose Reductions N = 389
Treatment Duration			
Median (Q1 – Q3), months	23.7 (14.9 – 23.8)	23.7 (20.6 – 23.8)	23.7 (13.2 – 23.8)
> 3 months, n (%)	1349 (86)	787 (95)	367 (94)
> 6 months, n (%)	1276 (81)	750 (90)	333 (86)
Cumulative Dose, mg			
Median (Q1 – Q3)	192450 (112900 – 210900)	137475 (98825 – 151950)	77200 (50100 – 96500)
Relative Dose Intensity (RDI), %			
Median (Q1 – Q3)	94.6 (83.4 – 99.0)	66.5 (59.5 – 74.4)	40.2 (34.5 – 50.7)

Patients with dose reductions had lower cumulative dose and lower RDI, but were more likely to remain on abemaciclib treatment

O'Shaughnessy J, et al. ESMO 2023. Abstract 274P

monarchE: IDFS by Relative Dose Intensity

IDFS according to RDI in patients treated with abemaciclib in ITT population



Relative Dose Intensity	4-Year IDFS rates in ITT % (95% CI)	4-Year IDFS rates in Cohort 1 % (95% CI)
0 – 66%	87.1 (84.0, 89.7)	87.2 (84.0, 89.8)
66 – 93%	86.4 (83.6, 88.7)	86.1 (83.3, 88.5)
93% and above	83.7 (80.7, 86.3)	83.1 (79.9, 85.8)

IDFS Rates Were Similar Across Relative Dose Intensity Subgroups

- Abemaciclib efficacy is not compromised by dose reductions

O'Shaughnessy J, et al. ESMO 2023. Abstract 274P

monarchE: Exposure by Dose Reductions

Summary of abemaciclib exposure by patients with or without dose reductions

	No Dose Reduction N = 1570	1 Dose Reduction N = 832	2 Dose Reductions N = 389
Treatment Duration			
Median (Q1 – Q3), months	23.7 (14.9 – 23.8)	23.7 (20.6 – 23.8)	23.7 (13.2 – 23.8)
> 3 months, n (%)	1349 (86)	787 (95)	367 (94)
> 6 months, n (%)	1276 (81)	750 (90)	333 (86)
Cumulative Dose, mg			
Median (Q1 – Q3)	192450 (112900 – 210900)	137475 (98825 – 151950)	77200 (50100 – 96500)
Relative Dose Intensity (RDI), %			
Median (Q1 – Q3)	94.6 (83.4 – 99.0)	66.5 (59.5 – 74.4)	40.2 (34.5 – 50.7)

Patients with dose reductions had lower cumulative dose and lower RDI, but were more likely to remain on abemaciclib treatment

O'Shaughnessy J, et al. ESMO 2023. Abstract 274P

Comparing the NATALEE and MonarchE Patient Populations

AJCC anatomical staging	TN (M0)	NATALEE	MONARCH-E *Node Negative NOT allowed*
Stage IIA	T0N1	NA (no primary tumor)	
	T1N1	Eligible	Only if G3 or Ki67≥20%
	T2N0	Only if G3, or G2 with Ki67≥20% or high risk on Oncotype DX /Prosigna/ MammaPrint/EndoPredict	**NA**
Stage IIB	T2N1	Eligible	Only if G3 or Ki67≥20%
	T3N0	Eligible	**NA**
Stage IIIA	T0N2	Eligible	Eligible
	T1N2	Eligible	Eligible
	T2N2	Eligible	Eligible
	T3N1	Eligible	Eligible (Tumor size ≥5cm [T3])
	T3N2	Eligible	Eligible
Stage IIIB	T4N0	Eligible	**NA**
	T4N1	Eligible	Only if tumor size ≥5cm or G3 or Ki67≥20%
	T4N2	Eligible	Eligible
Stage IIIC	Any T N3	Eligible	Eligible

In MonarchE, minimal patients with stage II were allowed:

- Only N1 that are also Gr3 or Ki67≥20%

In MonarchE, within stage III,

- N0 not allowed (in IIIB)
- N1 (whether in IIIA or IIIB) allowed only if G3 or Ki67≥20%

Patients were eligible | **Patients were eligible IF certain criteria were met** | **Patients were NOT eligible**

An Approach for High-Risk HR+/HER2- EBC

OlympiA[1]

- After neoadjuvant CT

HR+/HER2-

No pCR and CPS + EG ≥3[3]

- After adjuvant CT

HR+/HER2-

≥4 positive lymph nodes

monarchE[2]

- ≥4 positive nodes
- 1-3 positive nodes + 1 of the following
  - Tumor size ≥5 cm
  - Histologic grade 3
  - Ki-67 ≥20%

NATALEE[3]

- Stage IIA (either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1)
- Stage IIB
- Stage III

g*BRCA* Wild Type

- Tamoxifen or AI ± ovarian suppression and abemaciclib

g*BRCA* Mutated

- Olaparib ± tamoxifen or AI ± ovarian suppression
- ***Consider*** starting ET + abemaciclib after olaparib completed

1. Geyer. Ann Oncol. 2022;33:1250. 2. Johnston. Lancet Oncol. 2023;24:77. 3. Slamon. ASCO 2023. Abstr LBA 500.

Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer

Initial Results from the **POSITIVE Trial**
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

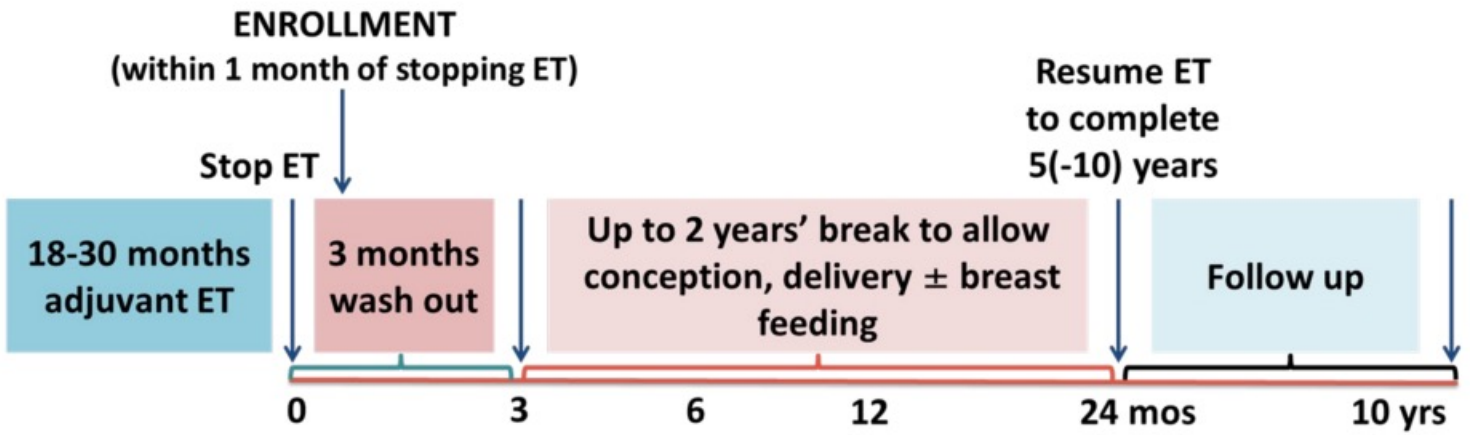
Ann Partridge on behalf of the POSITIVE Consortium

A H Partridge, S M Niman, M Ruggeri, F A Peccatori, H A Azim Jr, M Colleoni, C Saura, C Shimizu, A Barbro Sætersdal, J R Kroep, A Mailliez, E Warner, V F Borges, F Amant, A Gombos, A Kataoka, C Rousset-Jablonski, S Borstnar, J Takei, J Eon Lee, J M Walshe, M Ruíz Borrego, H CF Moore, C Saunders, V Bjelic-Radisic, S Susnjar, F Cardoso, K L Smith, T Ferreiro, K Ribi, K J Ruddy, S El-Abed, M Piccart, L A Korde, A Goldhirsch†, R D Gelber, O Pagani

TRIAL PROCEDURES

IBCSG

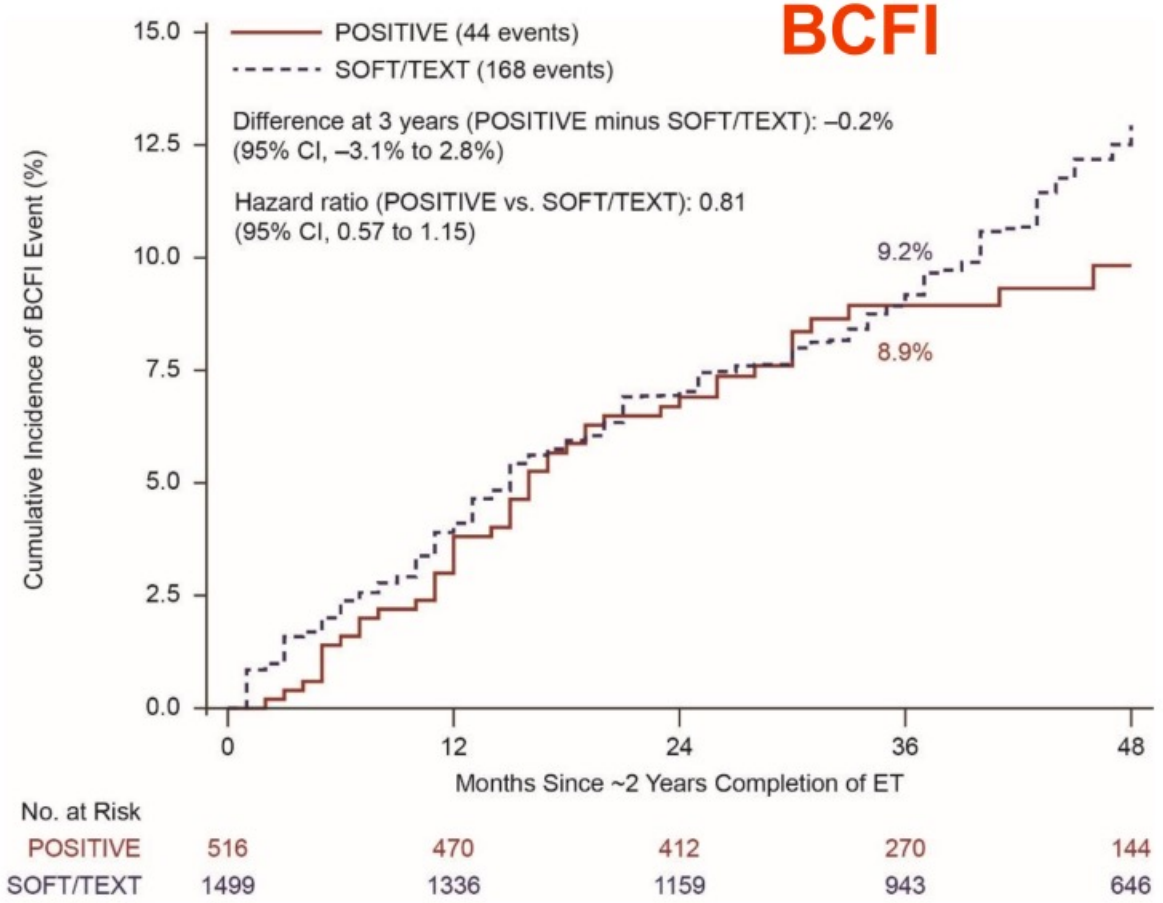
- Planned ET interruption (within 1 month of trial enrollment):
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including 3-months washout period
  - If no pregnancy by 1 year, fertility assessment strongly recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs
- Long-term follow-up



BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT

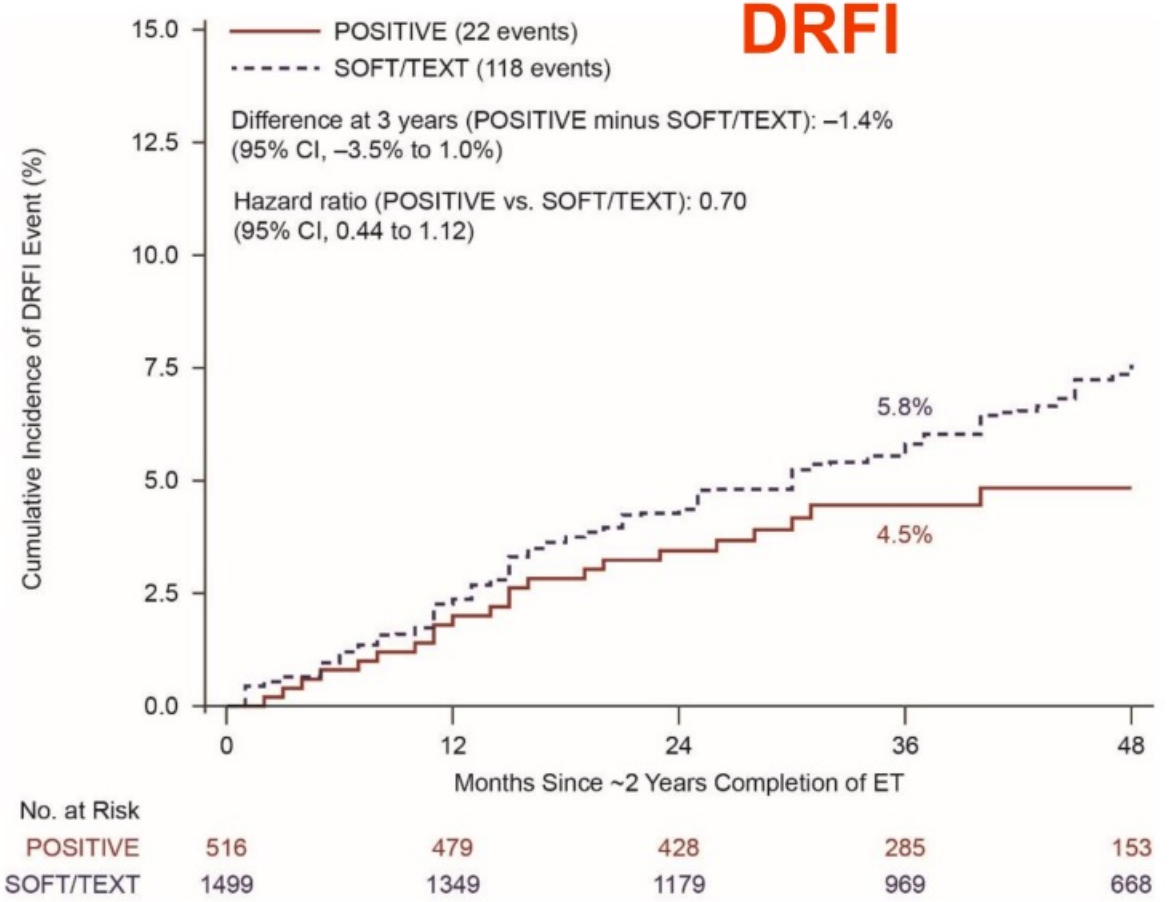
IBCSG

BCFI



No. at Risk					
POSITIVE	516	470	412	270	144
SOFT/TEXT	1499	1336	1159	943	646

DRFI



No. at Risk					
POSITIVE	516	479	428	285	153
SOFT/TEXT	1499	1349	1179	969	668

CONCLUSIONS

IBCSG

- In POSITIVE, temporary interruption of ET to attempt pregnancy among women who desire pregnancy does not impact short-term disease outcomes
- 74% of women had at least one pregnancy, most (70%) within 2 years
- Birth defects were low (2%), not clearly associated with treatment exposure
- Follow-up to 2029 planned to monitor ET resumption and disease outcomes
- **These data stress the need to incorporate patient-centered reproductive healthcare in the treatment and follow-up of young women with breast cancer**

Conclusions on EBC data in HR+/HER2-:

- Genomic testing in HR+/HER2- EBC is the current standard for post menopausal patients with up to 3 lymph nodes and for node-negative premenopausal women to inform chemotherapy treatment decisions
- Emerging data seems to show a trend for aggressive hormone blockade with OS+AI therapy to perhaps reduce the risk of recurrence in the premenopausal, high-risk patients. It begs the question of whether we are overtreating with chemotherapy currently, especially with the availability of CDK4/6 inhibition in the adjuvant setting
- Abemaciclib plays an important adjuvant role for patients with N2 disease or N1 with grade 3 and/or a tumor >/=5cm, regardless of Ki-67. Ki-67 not currently a predictor of response or benefit of therapy
- We await the FDA approval indications for adjuvant Ribociclib based on the Natalee trial which may offer an augmented adjuvant therapy for node negative high-risk men and women with breast cancer
- The BR009 will ultimately help us either confirm or rebuke these inclinations
- Pregnancy after a diagnosis of HR+/HER2- EBC appears to not be associated with early recurrence in women who held ET to achieve pregnancy. We await long-term follow-up data from the POSITIVE trial