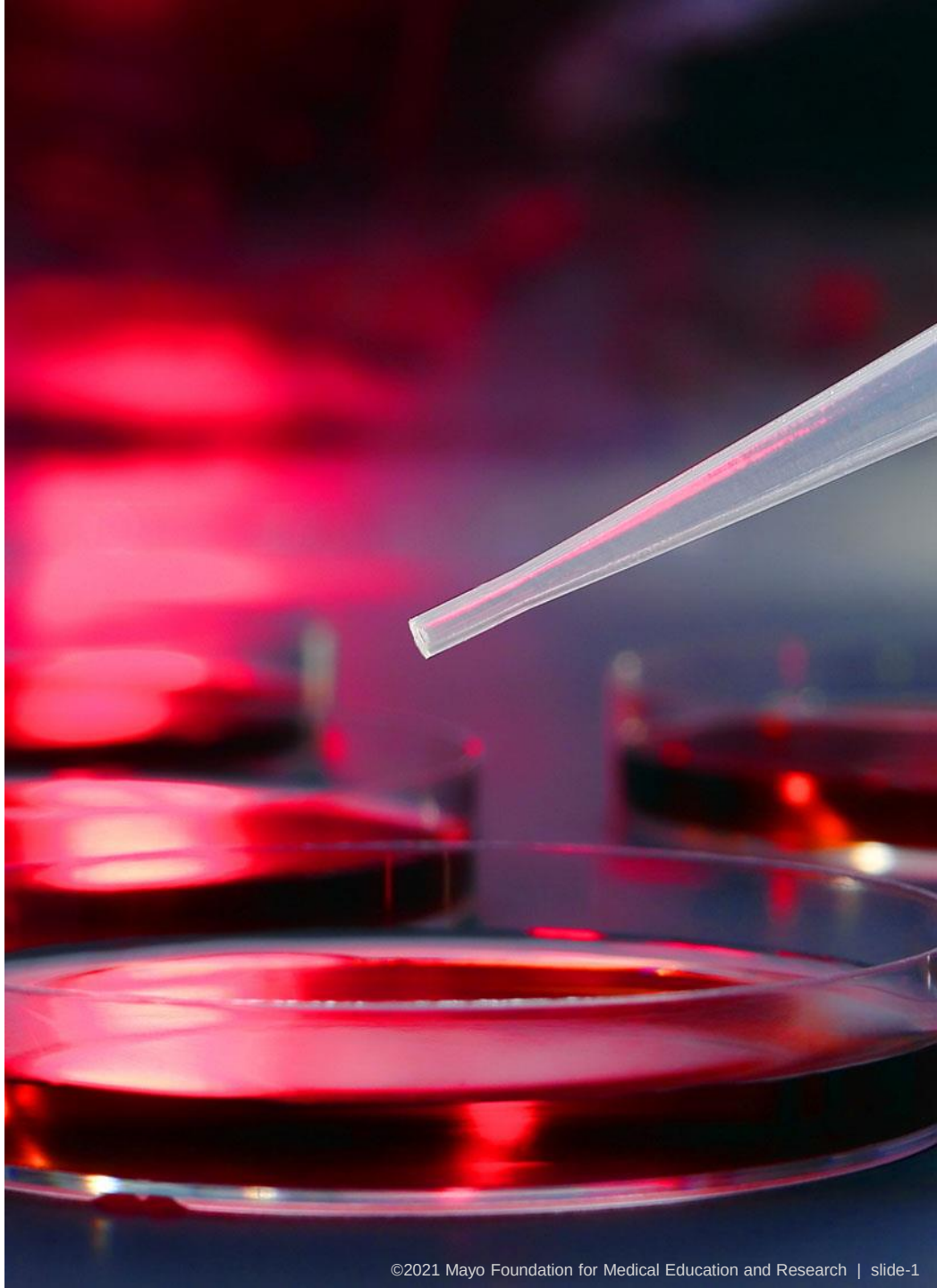
MAYO CLINIC | School of Continuous Professional Development

UPDATES ON EARLY BREAST CANCER

POOJA ADVANI, MD

DIRECTOR, ROBERT AND MONICA JACOBY CENTER FOR BREAST HEALTH

MAYO CLINIC



DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S)

- Research funding (Institution): Ayala, Genentech, Gilead, Agendia, Astra Zeneca, Caris Life Sciences, Seagen, Atossa therapeutics, Modulation therapeutics
- Advisory Board: Puma Biotechnologies, Caris Life Sciences

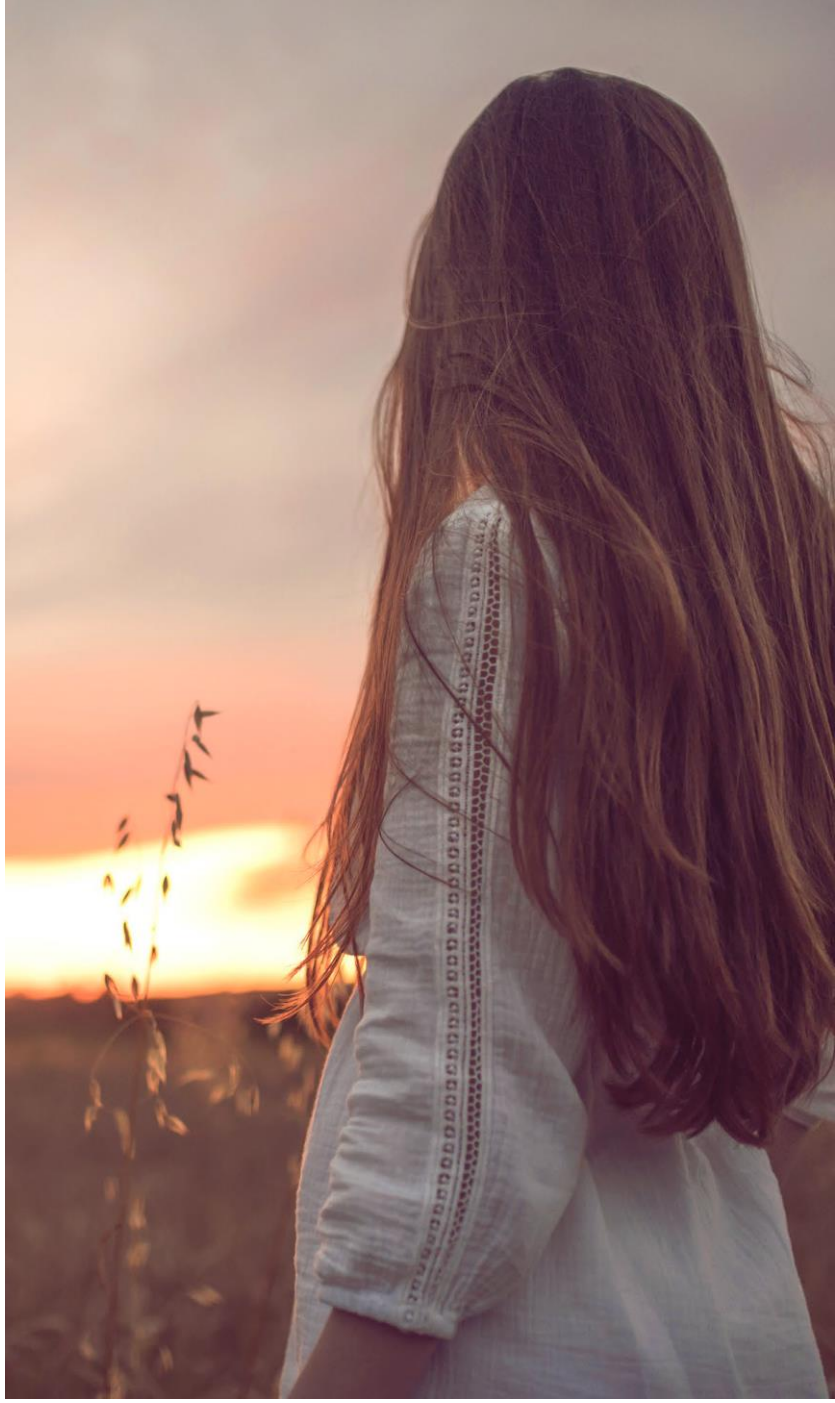
REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

LEARNING OBJECTIVES

- HR positive BC: Discuss updated results from landmark trials-TAILORx, OlympiA, SOFT/TEXT and MonarchE
- Review results of POSITIVE trial in HR+ breast cancer
- HER2 positive BC: Discuss updated results from APT trial
- HER2 positive BC: Discuss neoadjuvant TDXd study
- TNBC: exploratory analysis of KEYNOTE 522
- TNBC: role of carboplatin in NACT and non anthracycline NACT

HR POSITIVE BREAST CANCER



TAILORX TRIAL: AN UPDATE 12-YEAR EVENT RATES

- Main study findings remain unchanged for RS 11-25 with endocrine therapy not inferior to the combination of chemotherapy and endocrine therapy

Endpoint	Event rate	ET	CET
IDFS	5 years	92.8%	93.5%
	12 years	76.8%	77.4%
DRFI	5 years	98.0%	98.2%
	12 years	92.6%	92.8%
RFI	5 years	96.9%	97.0%
	12 years	89.6%	90.5%
OS	5 years	98.0%	98.1%
	12 years	89.8%	89.8%

Sparano J et al SABCS 2022

TAILORX TRIAL: AN UPDATE 12-YEAR EVENT RATES

- Chemotherapy benefit for women≤ 50 yrs with RS 16-25

12-year DRFI rate in women ≤50 years and RS 16-25			
	Chemo benefit **not stratified** by clinical risk	Clinical risk	Chemo benefit **stratified** by clinical risk
RS 16-20	Δ+0.4% (SE 2.1%)	Low	Δ-0.5%
		High	Δ+3.1%
RS 21-25	Δ+7.8% (SE 3.4%)	Low	Δ+5.9%
		High	Δ+11.7%

Sparano J et al SABCS 2022

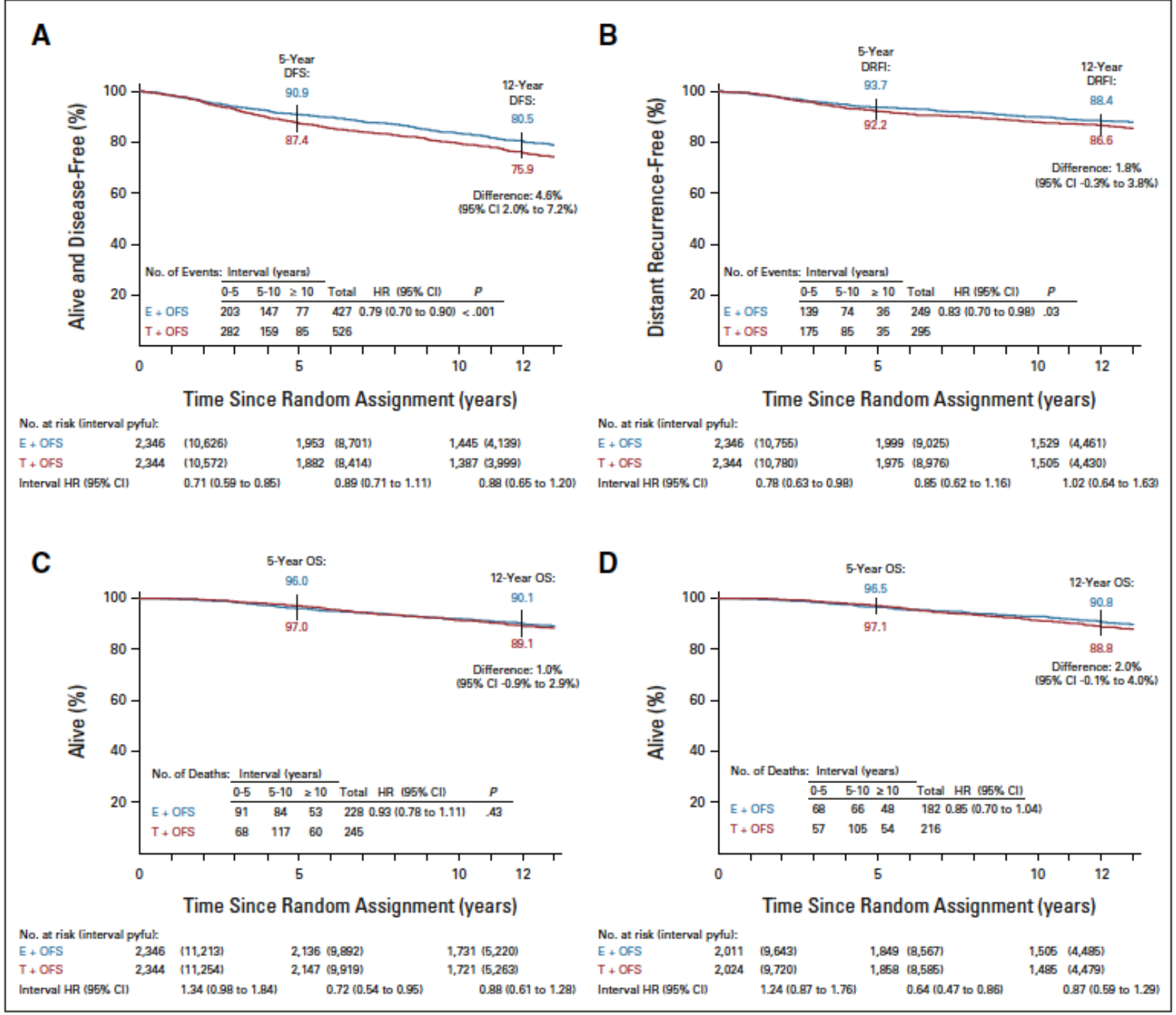
Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials

At 12 yrs, Compared to TAM +OFS, exemestane + OFS in ITT population resulted in:

- 4.6% absolute benefit in DFS
- 1.3% absolute benefit in DRFI
- But not OS!

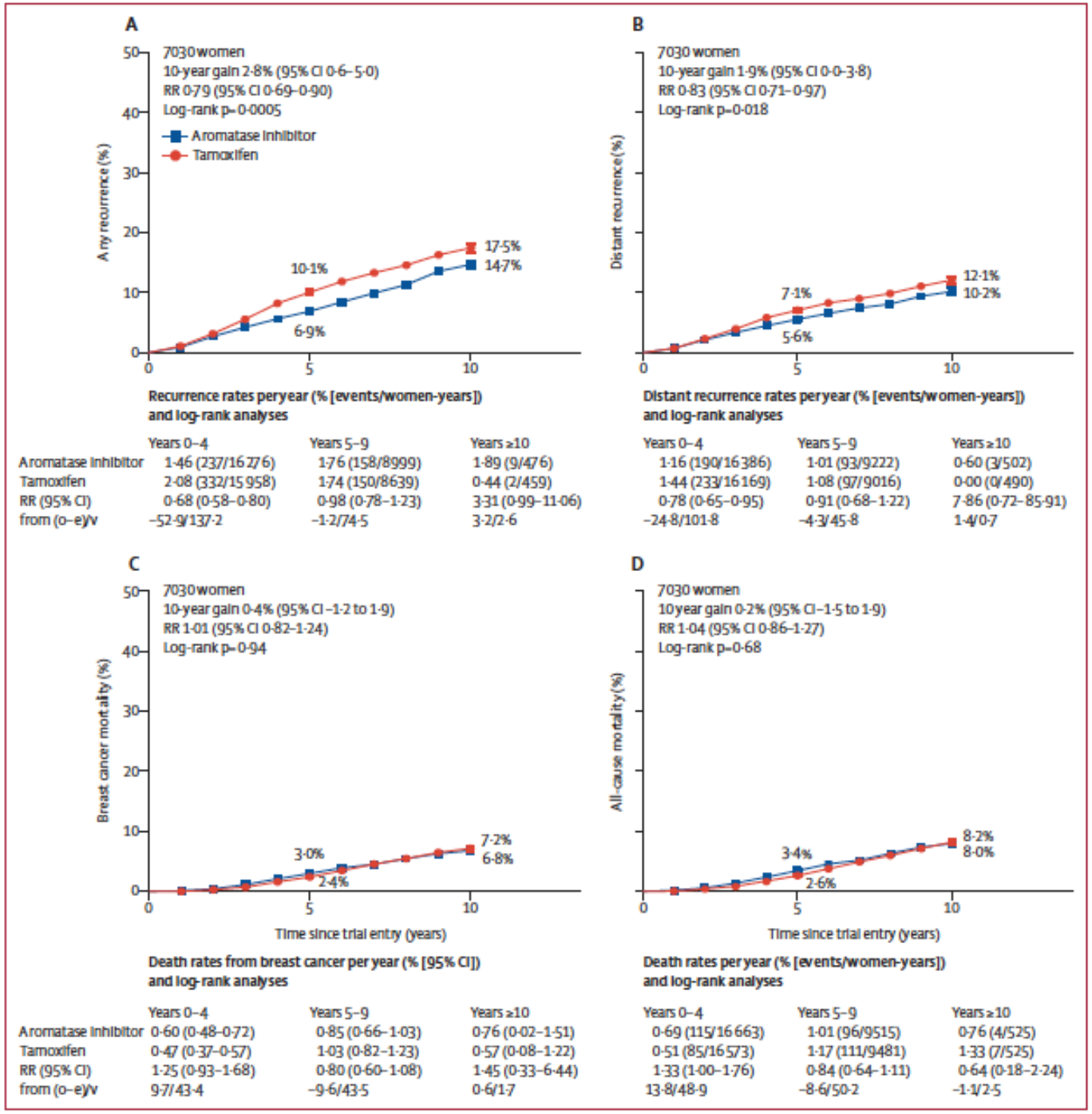
OS improvement seen in HER2 neg tumors (2%) and those that received chemotherapy (3.3%) but this is not statistically significant

HER2 neg tumors with high risk clinicopath characteristics benefit most from OFS + AI



Meta-analyses of TEXT, SOFT, HOBOE, ABCSG XII

- N=7030 women
- Median follow up=8 years
- Rate of recurrence of breast cancer lower for AI c/w tamoxifen RR 0.79
- Most benefit seen in year 0-4, 3.2% absolute reduction in 5 yr recurrence risk
- Distant recurrence risk reduced with AI, RR 0.83
- No benefit in OS
- More bone fracture with AI (RR 1.27)



Recurrence rates per year (% [events/women-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Aromatase inhibitor	1·46 (237/16 276)	1·76 (158/8999)	1·89 (9/476)
Tamoxifen	2·08 (332/15 958)	1·74 (150/8639)	0·44 (2/459)
RR (95% CI)	0·68 (0·58–0·80)	0·98 (0·78–1·23)	3·31 (0·99–11·06)
from (o–e)/v	−52·9/137·2	−1·2/74·5	3·2/2·6

Distant recurrence rates per year (% [events/women-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	1·16 (190/16 386)	1·01 (93/9222)	0·60 (3/502)
	1·44 (233/16 169)	1·08 (97/9016)	0·00 (0/490)
	0·78 (0·65–0·95)	0·91 (0·68–1·22)	7·86 (0·72–85·91)
	−24·8/101·8	−4·3/45·8	1·4/0·7

Death rates from breast cancer per year (% [95% CI]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Aromatase inhibitor	0·60 (0·48–0·72)	0·85 (0·66–1·03)	0·76 (0·02–1·51)
Tamoxifen	0·47 (0·37–0·57)	1·03 (0·82–1·23)	0·57 (0·08–1·22)
RR (95% CI)	1·25 (0·93–1·68)	0·80 (0·60–1·08)	1·45 (0·33–6·44)
from (o–e)/v	9·7/43·4	−9·6/43·5	0·6/1·7

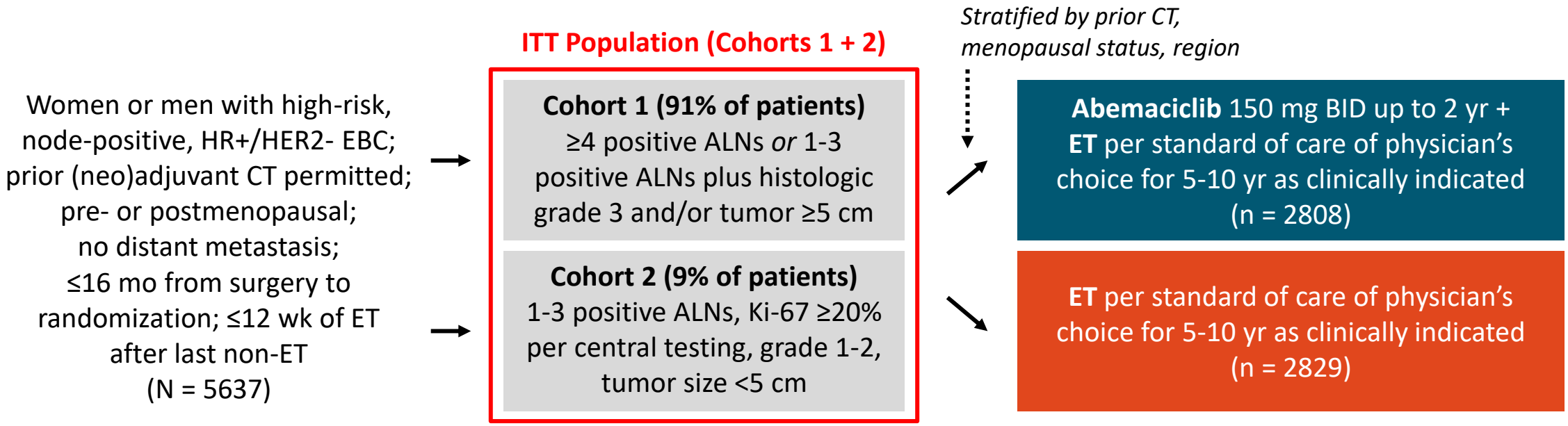
Death rates per year (% [events/women-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	0·69 (115/16 663)	1·01 (96/9515)	0·76 (4/525)
	0·51 (85/16 573)	1·17 (111/9481)	1·33 (7/525)
	1·33 (1·00–1·76)	0·84 (0·64–1·11)	0·64 (0·18–2·24)
	13·8/48·9	−8·6/50·2	−1·1/2·5

EBCTCG group, The Lancet 2022

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

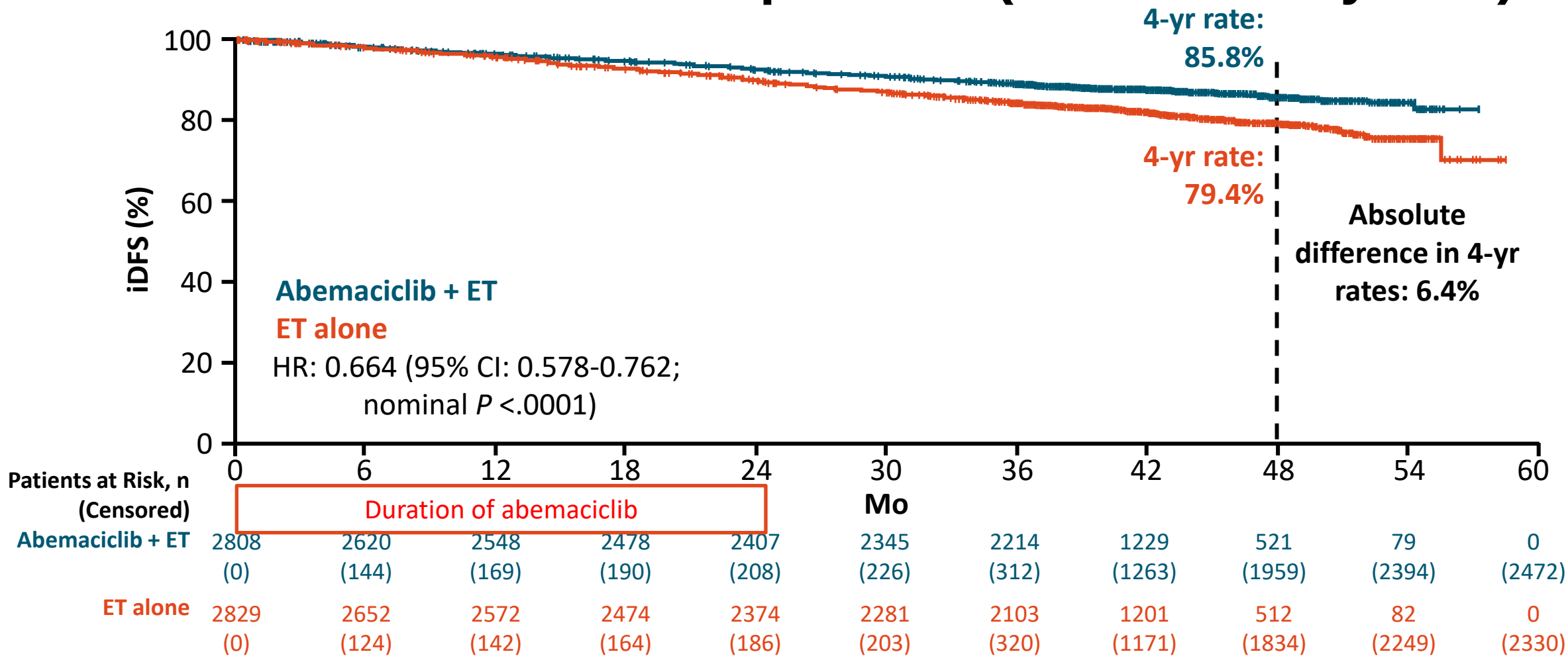
- International, randomized, open-label phase III trial



- **Primary endpoint:** iDFS
- **Key secondary endpoints:** iDFS in Ki-67 high (≥20%) population, DRFS, OS, safety, PROs, PK

Johnston. JCO. 2020;38:3987. Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

monarchE: iDFS in ITT Population (Interim Analysis 2)

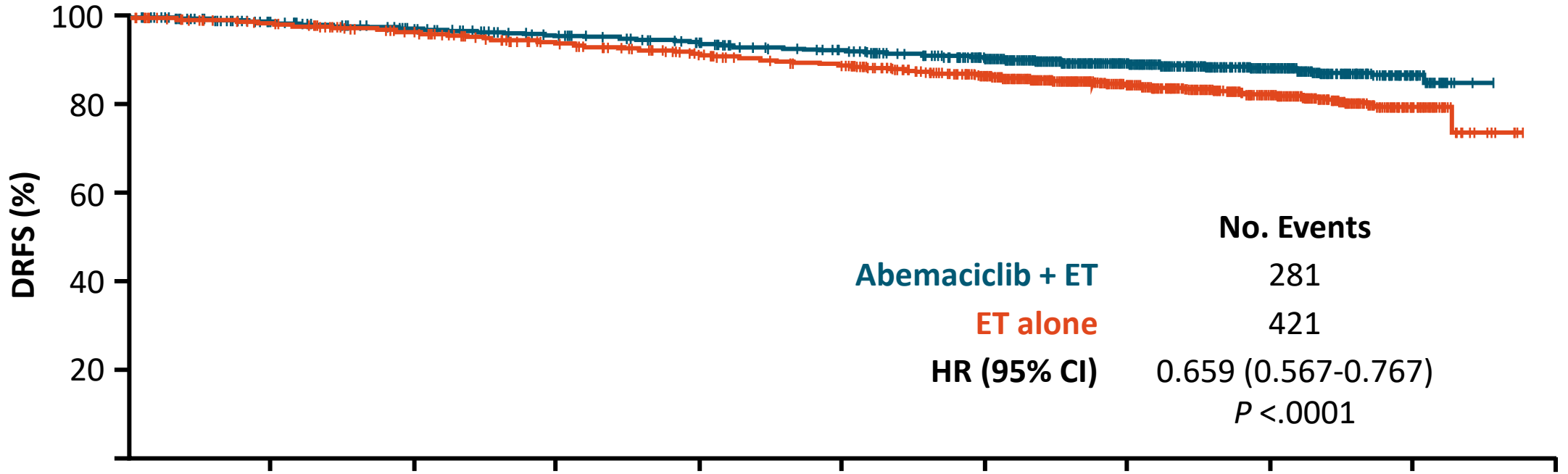


- 3-yr iDFS favored abemaciclib in all evaluated subgroups, including by number of positive LNs, histologic grade, primary tumor size, prior chemotherapy, and menopausal status

Slide credit: clinicaloptions.com

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

monarchE: Distant Relapse–Free Survival



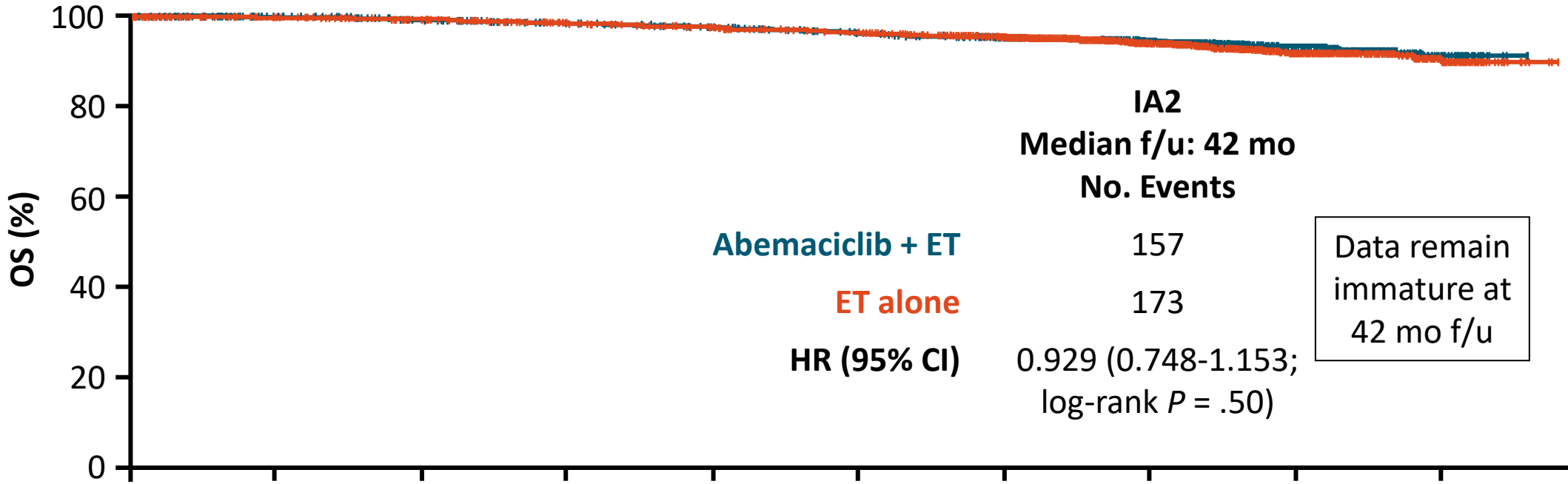
Patients at Risk, n (Censored)	0	6	12	18	24	30	36	42	48	54	60
Abemaciclib + ET	2808 (0)	2629 (147)	2567 (174)	2500 (196)	2434 (217)	2374 (236)	2244 (326)	1251 (1293)	535 (2001)	81 (2447)	0 (2527)
ET alone	2829 (0)	2659 (127)	2589 (148)	2499 (172)	2410 (194)	2327 (213)	2151 (334)	1231 (1210)	526 (1895)	85 (2324)	0 (2408)

- 3-yr DRFS favored abemaciclib in all evaluated subgroups, including by number of positive LNs, histologic grade, primary tumor size, prior chemotherapy, and menopausal status

Slide credit: clinicaloptions.com

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

monarchE: Overall Survival (ITT)



IA2
Median f/u: 42 mo

No. Events	
Abemaciclib + ET	157
ET alone	173
HR (95% CI)	0.929 (0.748-1.153; log-rank *P* = .50)

Data remain immature at 42 mo f/u

Patients at Risk, n (Censored)											
Abemaciclib + ET	2808 (0)	2665 (138)	2613 (172)	2564 (201)	2516 (228)	2453 (255)	2343 (339)	1330 (1338)	573 (2089)	87 (2564)	0 (2651)
ET alone	2829 (0)	2704 (114)	2663 (145)	2598 (186)	2544 (215)	2494 (237)	2357 (355)	1361 (1317)	578 (2085)	93 (2563)	0 (2656)

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

Slide credit: clinicaloptions.com

monarchE: Outcomes by Cohort

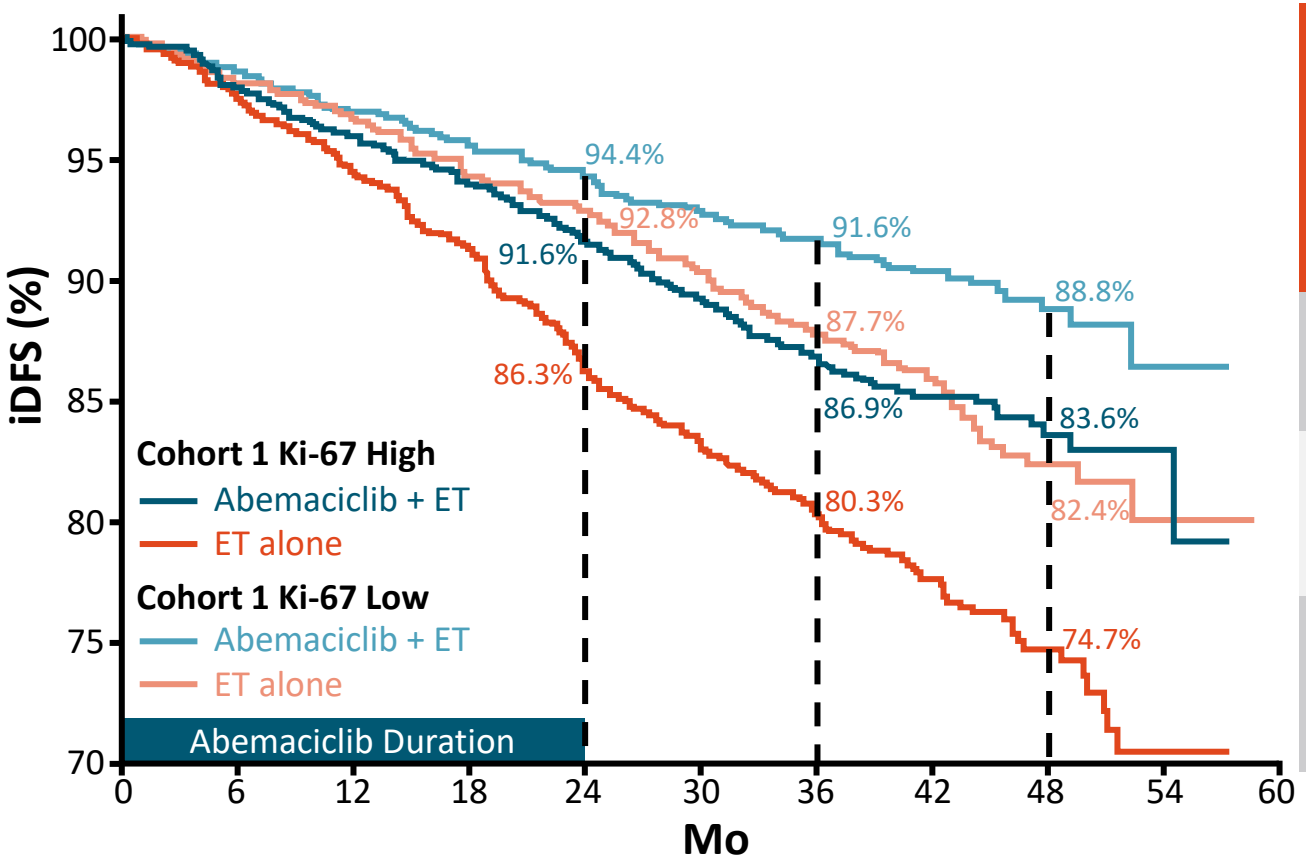
Outcome	Cohort 1		Cohort 2*	
	Abemaciclib + ET (n = 2555)	ET (n = 2565)	Abemaciclib + ET (n = 253)	ET (n = 264)
iDFS events, n	317	474	19	25
HR (95% CI)	0.653 (0.567-0.753)		0.773 (0.420-1.420)	
P value	<.0001		.4048	
4 yr iDFS rate, % (95% CI)	85.5 (83.8-87.0)	78.6 (76.7-80.4)	NR	NR
DRFS events, n	267	402	14	19
HR (95% CI)	0.652 (0.558-0.761)		0.764 (0.383-1.526)	
P value	<.0001		.4448	
4 yr DRFS rate, % (95% CI)	87.9 (86.4-89.3)	81.8 (79.9-83.4)	NR	NR
OS events, n	147	168	10	5
HR (95% CI)	0.890 (0.714-1.111)		NR	

*Enrolled patients with intermediate clinicopathologic features; data remain immature.

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

monarchE: Outcomes by Ki-67 Status

iDFS by Ki-67 Status



- Abemaciclib treatment effects similar in Ki-67–high and Ki-67–low groups within cohort 1

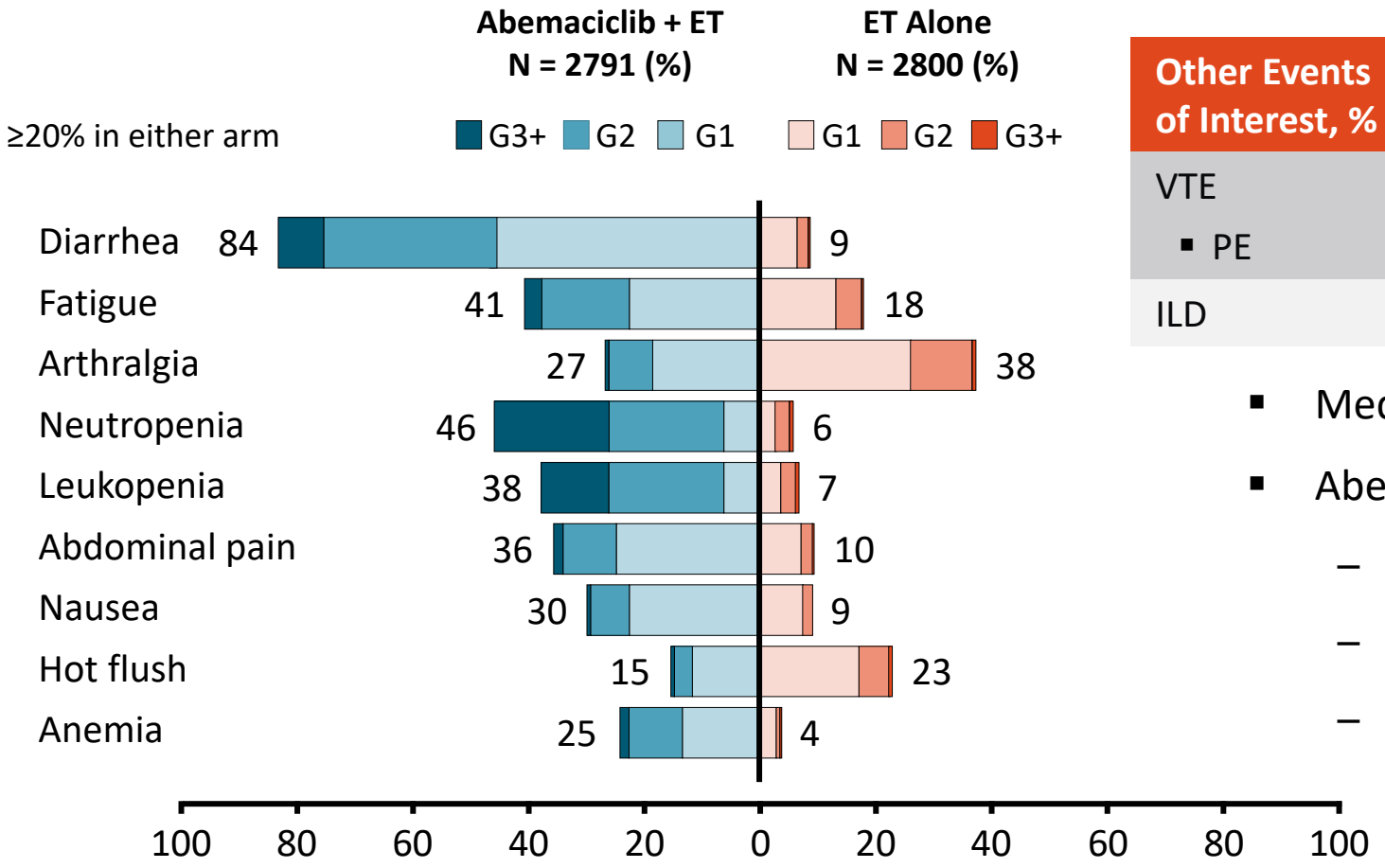
Outcome	Cohort 1*			
	Ki-67 High		Ki-67 Low	
	Abemaciclib + ET (n = 1017)	ET (n = 986)	Abemaciclib + ET (n = 946)	ET (n = 968)
iDFS events, n	147	224	91	141
HR (95% CI)	0.618 (0.501-0.762)		0.624 (0.478-0.814)	
DRFS events, n	126	193	74	119
HR (95% CI)	0.612 (0.488-0.767)		0.613 (0.458-0.821)	
OS events, n	68	88	39	50
HR (95% CI)	0.733 (0.533-1.007)		0.772 (0.506-1.175)	

*Ki-67 missing in 1203 (23.5%) patients.

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09.

Slide credit: clinicaloptions.com

monarchE: Safety



All patients who received ≥1 dose of study treatment were included in the safety population

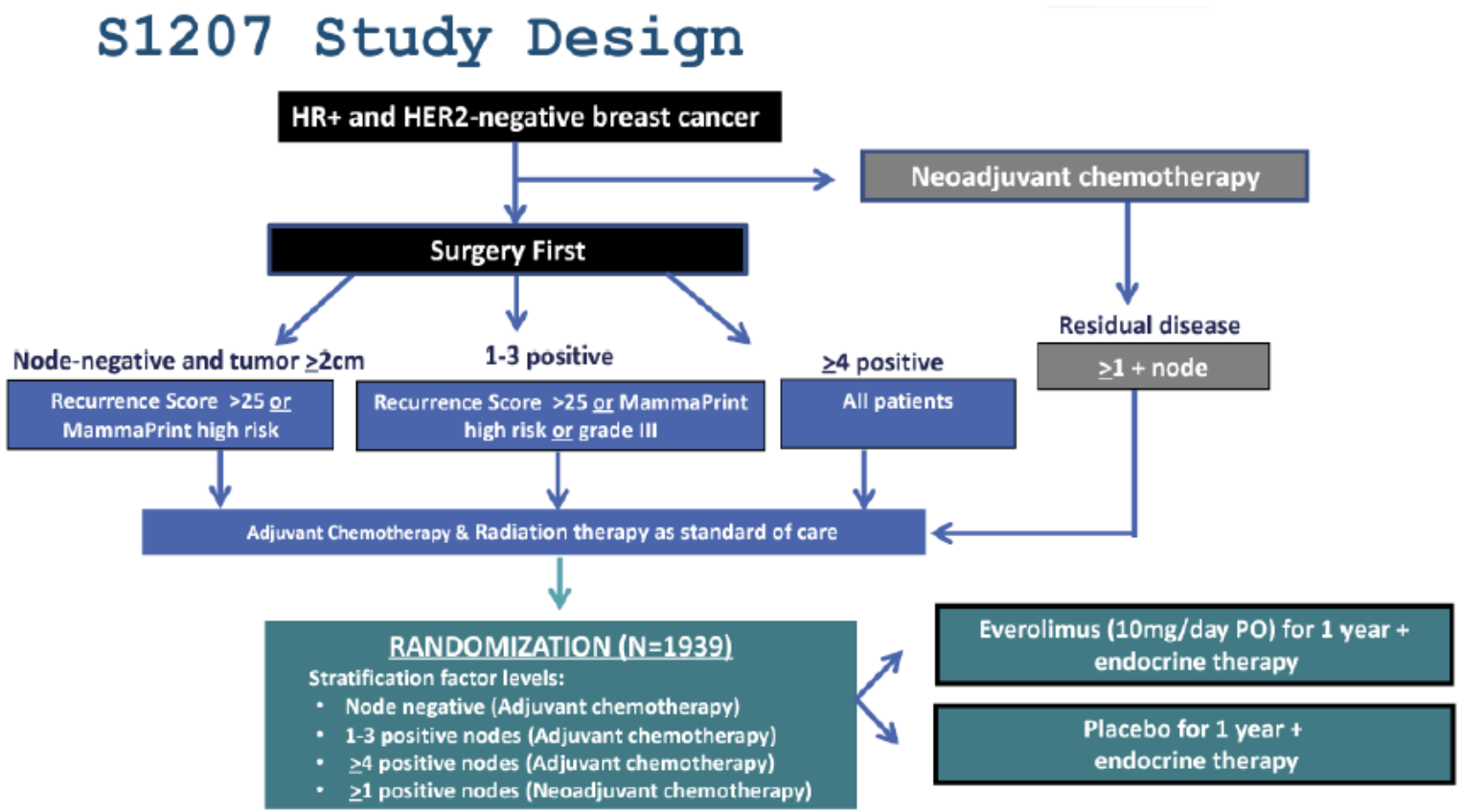
Other Events of Interest, %	Abemaciclib + ET (n = 2791)	ET Alone (n = 2800)
VTE	2.5	0.7
▪ PE	1.0	0.1
ILD	3.3	1.3

- Median duration of abemaciclib: 24 mo
- Abemaciclib dose adjustments due to AE:
  - Dose holds: 61.7%
  - Dose reductions: 43.6%
  - Discontinuations: 18.5% (8.9% after dose reduction)

Johnston. Lancet Oncol. 2022;[Epub]. Johnston. SABCS 2022. Abstr GS1-09. Reproduced with permission.

Slide credit: clinicaloptions.com

SWOG S1207



<u>Addition of 1 yr of everolimus did not improve iDFS or OS</u>
5 yr estimate is 74.9% (everolimus +endocrine) vs. 74.4% (placebo+endocrine)

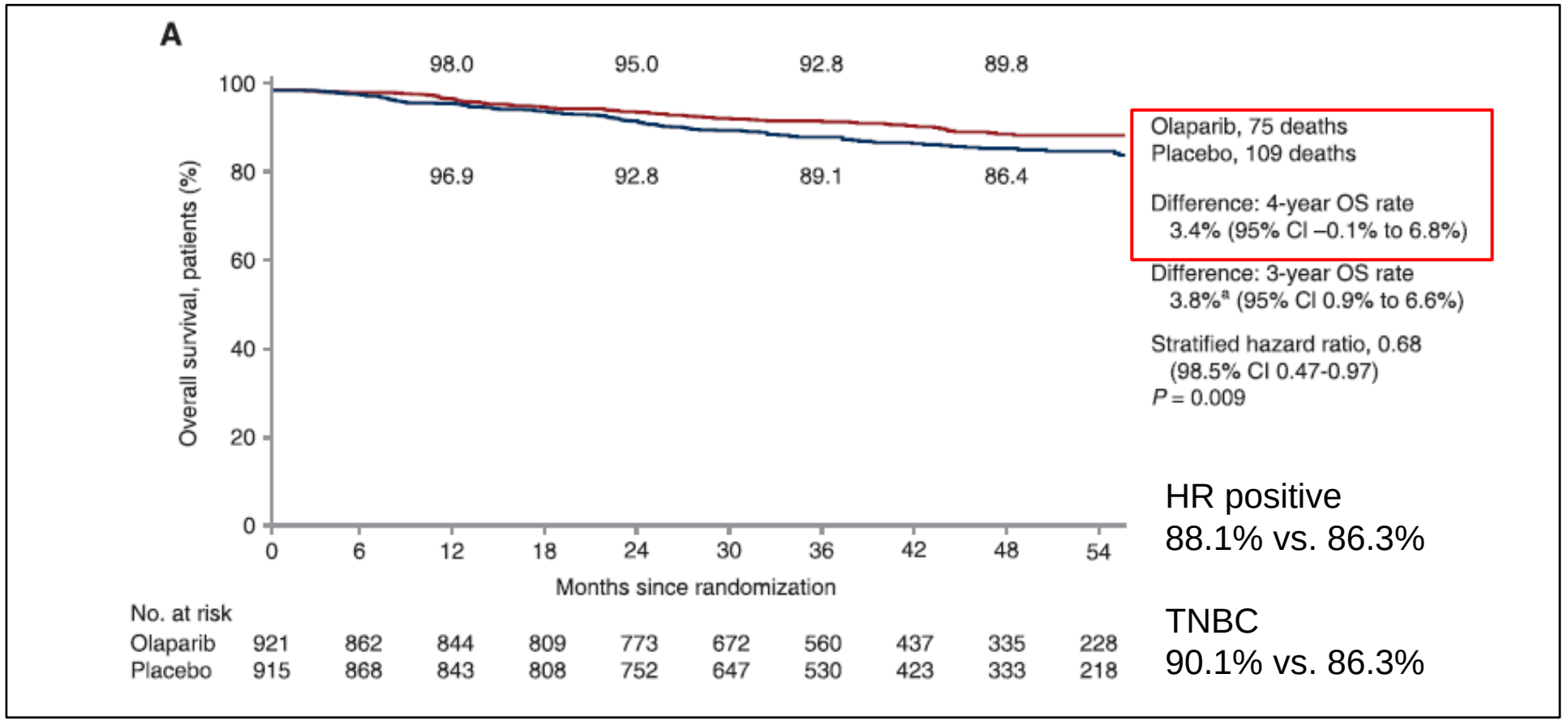
Low completion rate (43%) due to AEs. No new safety signal

A trend in IDFS and OS improvement in premenopausal women for everolimus + endocrine -> hypothesis generating

Chavez-MacGregor M et al, SABCS 2022.

OLYMPIA TRIAL: AN UPDATE ON OS

Median follow up=3.5 years

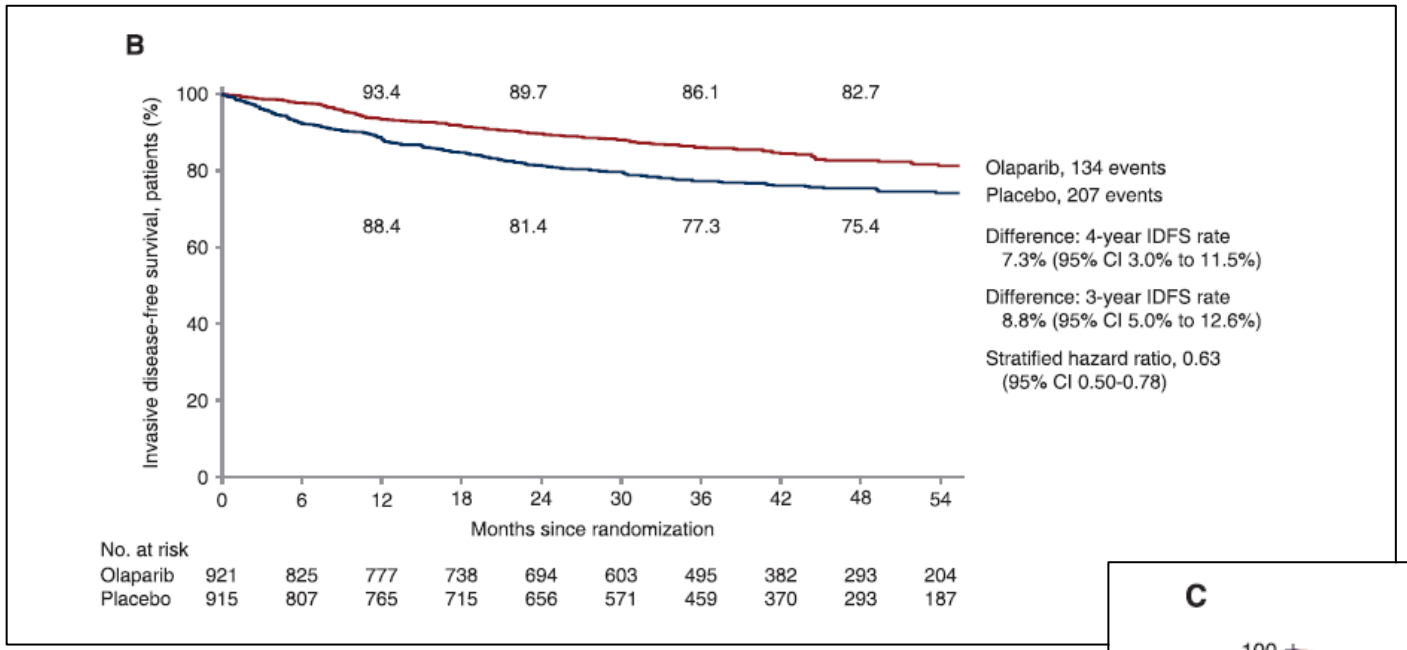


HR positive
88.1% vs. 86.3%

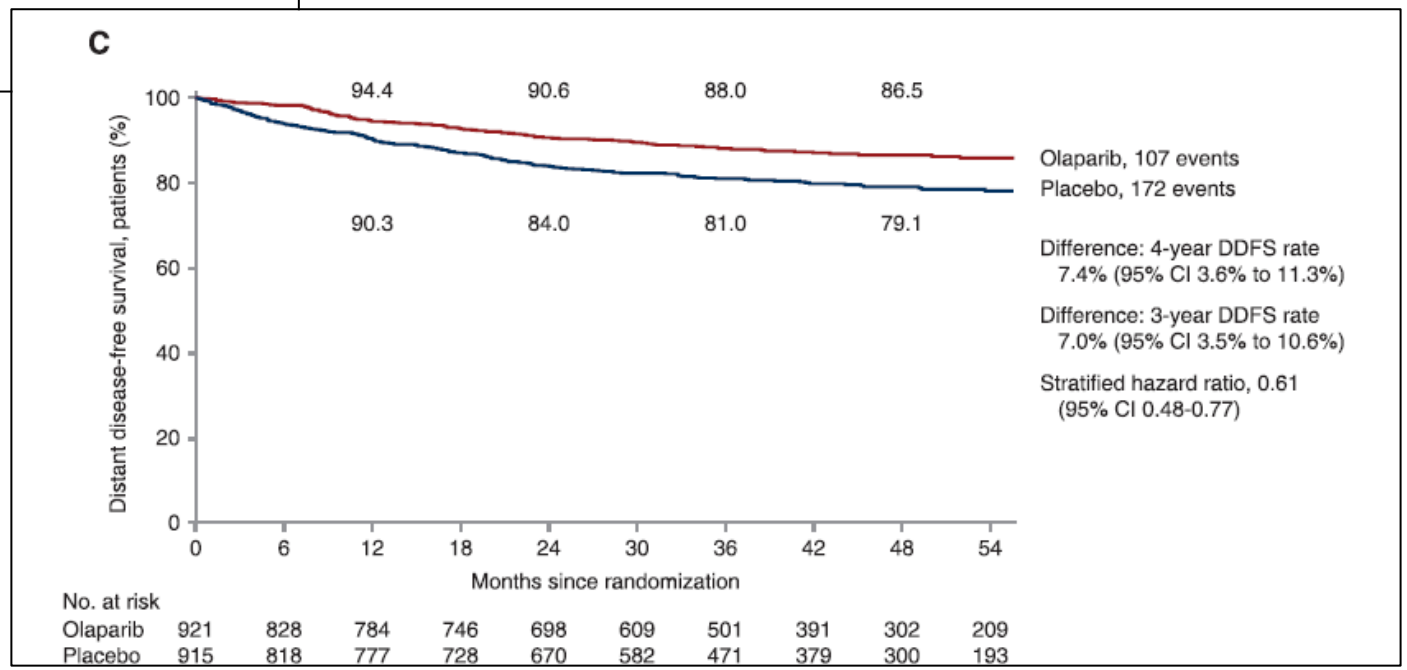
TNBC
90.1% vs. 86.3%

Geyer CE et al, Annals of Oncology 2022

OLYMPIA TRIAL: AN UPDATE ON IDFS AND DDFS



Subset analyses for OS, iDFS and DDFS showed benefit across major subgroups



Geyer CE et al, Annals of Oncology 2022

OLYMPIA TRIAL: AN UPDATE ON SAFETY

- No new safety signals-no new cases of MDS/AML

Table 2. Summary of adverse events in the safety analysis set[a]

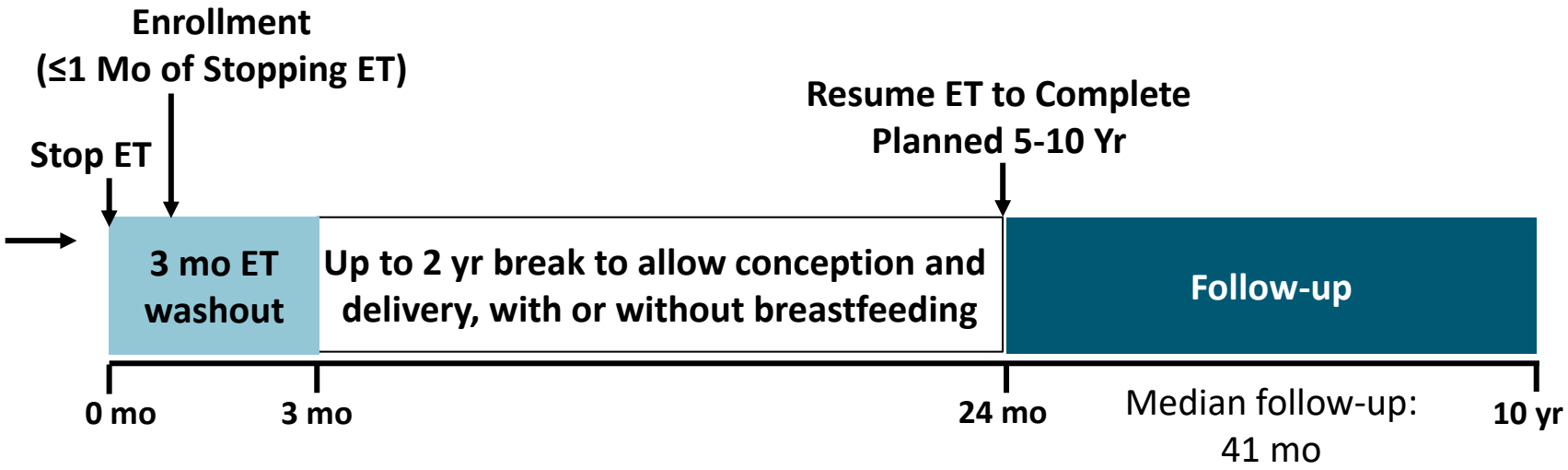
Adverse event, no. of patients (%)	Olaparib (n = 911)	Placebo (n = 904)
Any adverse event	836 (91.8)	758 (83.8)
Serious adverse event	79 (8.7)	78 (8.6)
Adverse event of special interest[b]	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis[c]	9 (1.0)	12 (1.3)
New primary malignancy[d]	21 (2.3)	36 (4.0)
Grade ≥3 adverse event	223 (24.5)	102 (11.3)
Grade 4 adverse event[e]	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of treatment[f]	98 (10.8)	42 (4.6)
Adverse event leading to death[g]	1 (0.1)	2 (0.2)

Geyer CE et al, Annals of Oncology 2022

POSITIVE: Interrupting ET in Women With HR+ Breast Cancer to Attempt Pregnancy

- International, prospective, single-arm trial to study breast cancer relapse after temporarily interrupting ET to attempt pregnancy

Premenopausal women ≤42 yr of age with 18-30 mo prior adjuvant ET (neo/adjuvant CT with or without fertility preservation permitted) for stage I-III HR+ BC; desiring pregnancy; no clinical evidence of recurrence (N = 516)



- **Primary endpoint:** BCFI (defined as time from enrollment to first invasive disease [ipsilateral, contralateral, or locoregional] or distant recurrence)
- **Secondary endpoints:** pregnancy and offspring outcomes, breastfeeding, ART use, adherence to ET, DRFI (defined as time from enrollment to first distant recurrence of BC)
- Cohort of 1499 patients from SOFT/TEXT trials used as external control

Partridge. SABCS 2022. Abstr GS4-09. Sun. Breast. 2020;53:1.

Slide credit: clinicaloptions.com

POSITIVE: Patient Characteristics and Treatment Patterns

Characteristic	Patients (N = 516)
Age at enrollment in yr, median (range)	37 (27-43)
▪ <35, n (%)	177 (34)
▪ 35-39, n (%)	221 (43)
▪ 40-42, n (%)	118 (23)
Number of prior births, n (%)	
▪ 0	387 (75)
▪ 1	107 (21)
▪ ≥2	22 (4)
TNM stage, n (%)	
▪ I	242 (47)
▪ II	240 (47)
▪ III	31 (6)
▪ Unknown	3 (1)

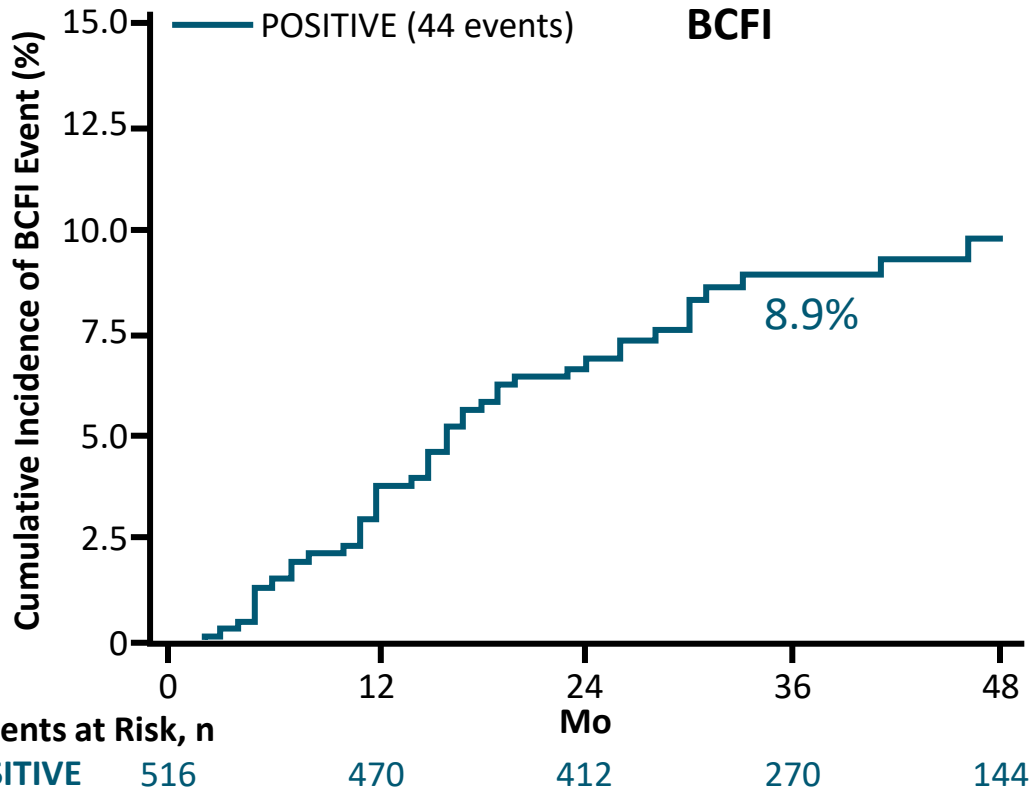
Treatment	Patients (N = 516)
Median duration of ET prior to enrollment, mo	23.4
▪ SERM alone, n (%)	215 (42)
▪ SERM + OFS, n (%)	184 (36)
▪ AI + OFS, n (%)	82 (16)
▪ Other, n (%)	35 (7)
Prior (neo)adjuvant CT, n (%)	
▪ No	196 (38)
▪ Yes	320 (62)
Breast surgery, n (%)	
▪ Mastectomy	233 (45)
▪ Breast-conserving procedure	283 (55)

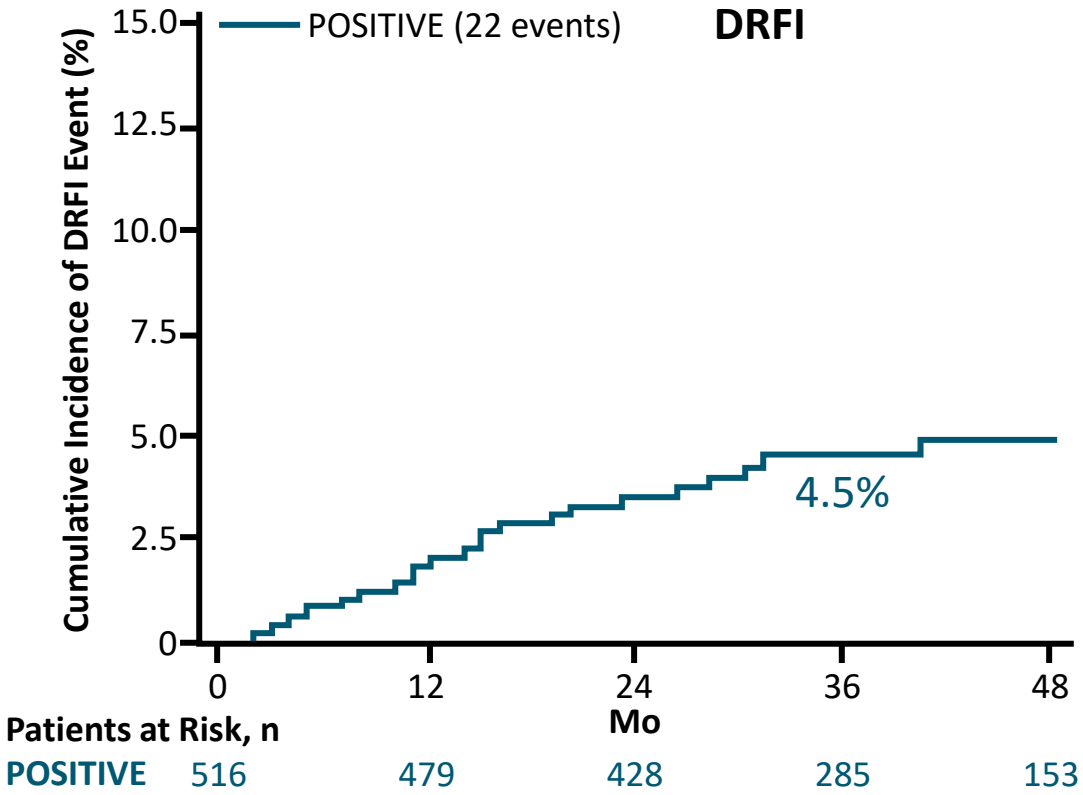
Partridge. SABCS 2022. Abstr GS4-09.

Slide credit: clinicaloptions.com

POSITIVE: BCFI and DRFI

- Follow-up: 1638 patient-yr (median follow-up: 41 mo)



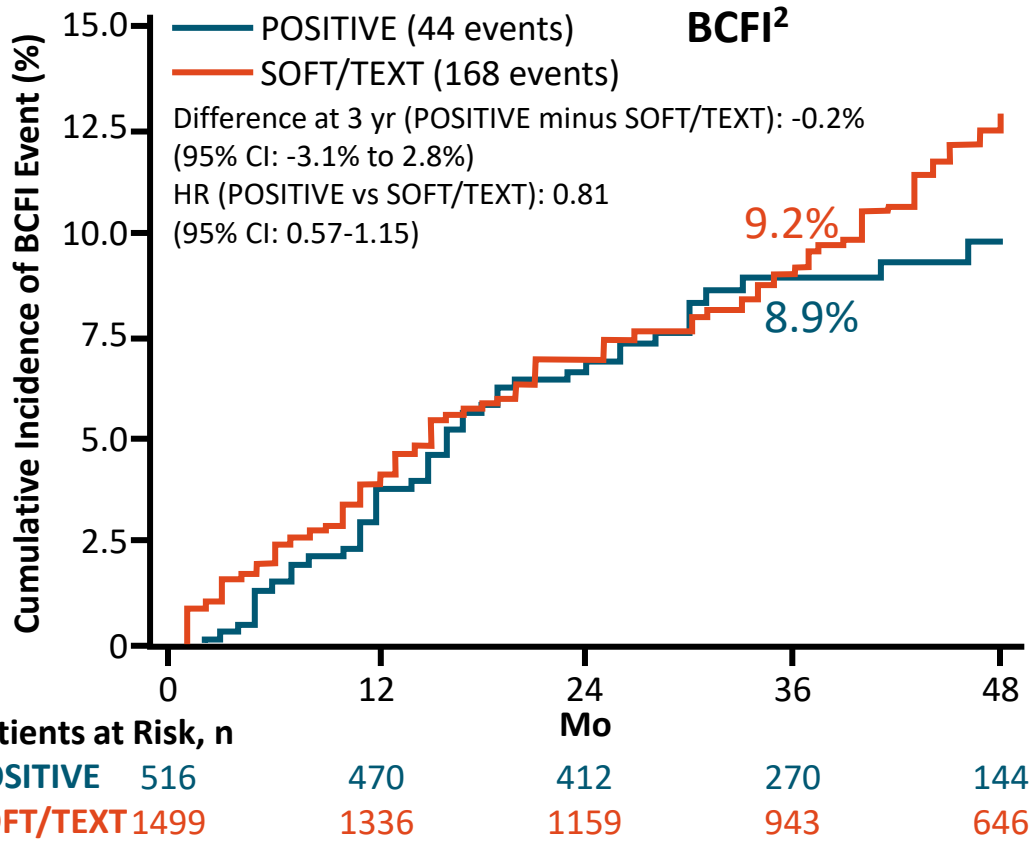


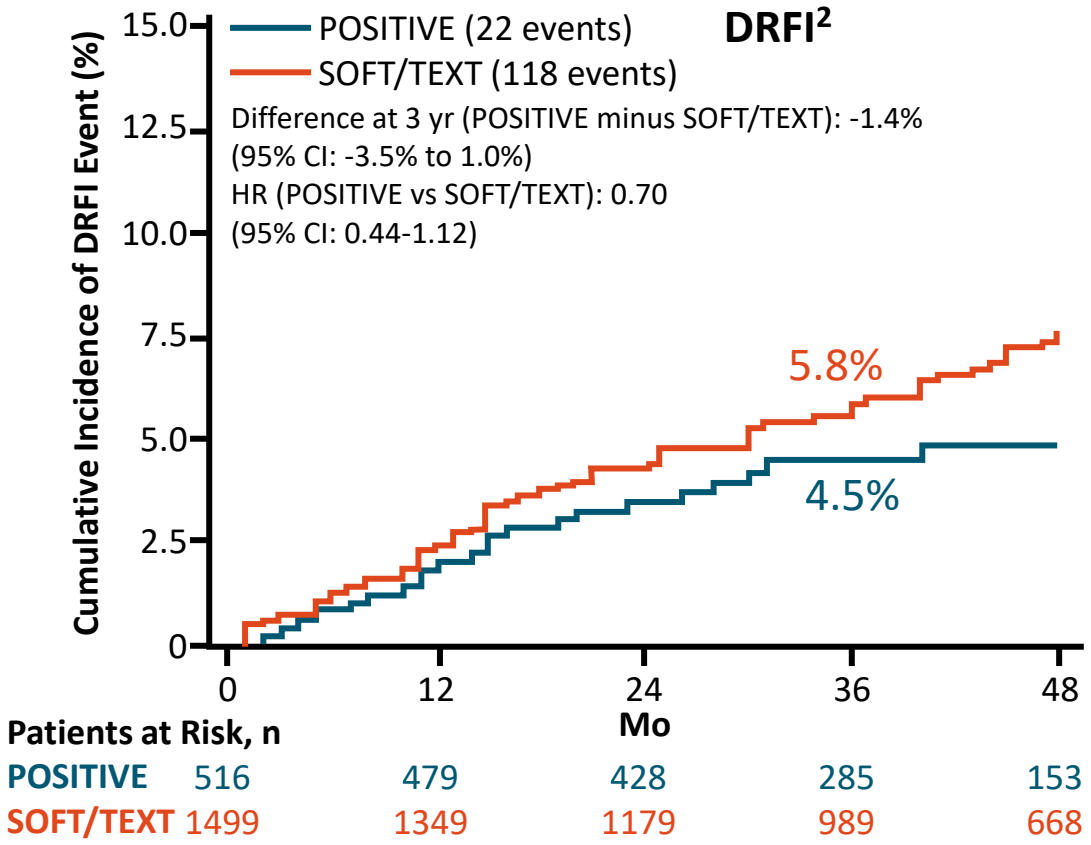
Partridge. SABCS 2022. Abstr GS4-09. Reproduced with permission.

Slide credit: clinicaloptions.com

POSITIVE: BCFI and DRFI Compared With SOFT/TEXT Studies

- SOFT/TEXT: 1499 matched patients with no ET interruption (external cohort)[1]

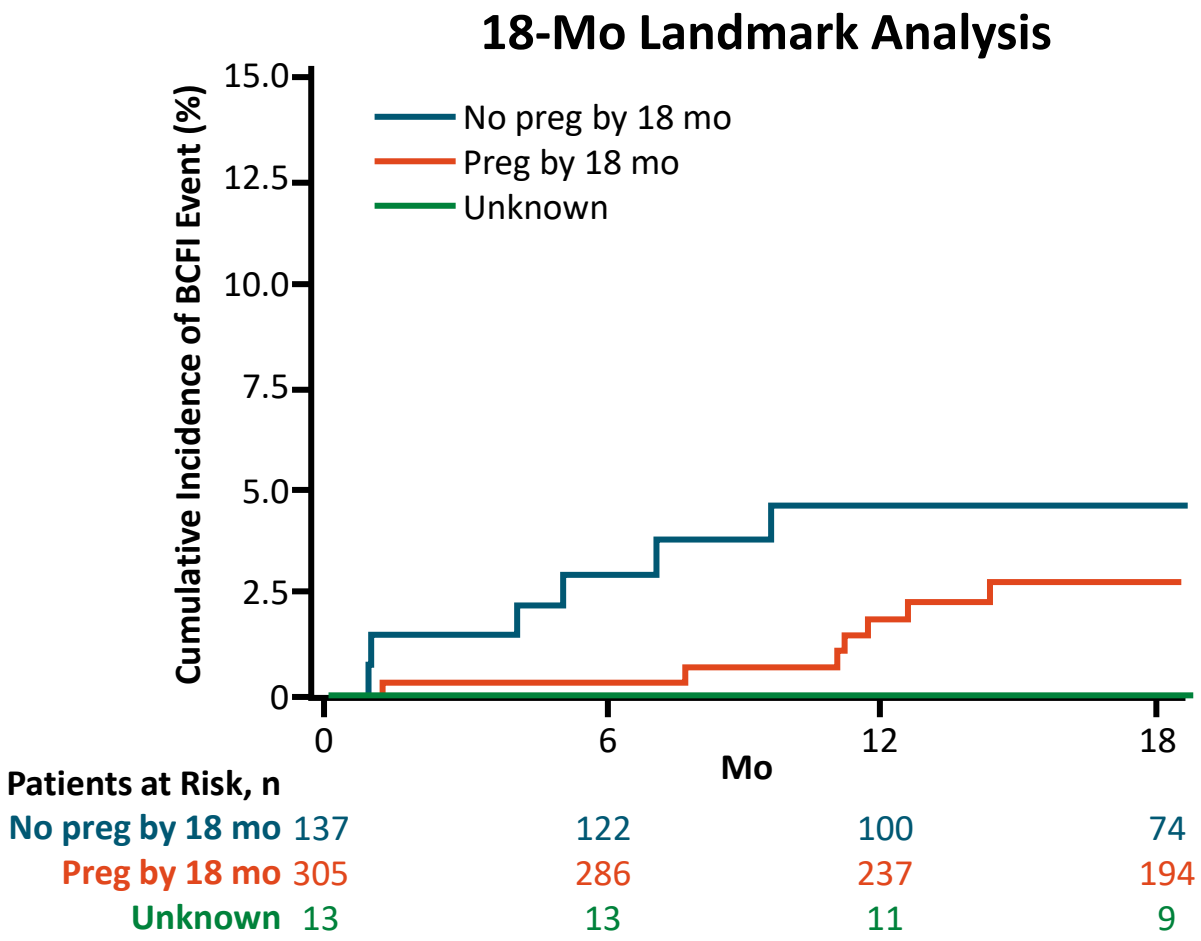




1. Sun. Breast. 2020;53:1. 2. Partridge. SABCS 2022. Abstr GS4-09. Reproduced with permission.

Slide credit: clinicaloptions.com

POSITIVE: BCFI in Pregnant vs Nonpregnant Women



BCFI HR	Pregnant vs Nonpregnant
Univariable HR (95% CI)	0.55 (0.28-1.06)
Multivariable* HR (95% CI)	0.53 (0.27-1.04)

*Comprising BMI, lymph node status, age, prior AI, prior CT.

Partridge. SABCS 2022. Abstr GS4-09. Reproduced with permission.

Slide credit: clinicaloptions.com

POSITIVE: Pregnancy and Offspring Outcomes

Pregnancy Outcome, n (%)	Secondary Endpoint Population (n = 497)	Patients With ≥1 Pregnancy on Trial (n = 368)
≥1 on-trial pregnancy	368 (74)	368 (100)
≥1 live birth (full or pre term)	317 (64)	317 (86)
≥1 miscarriage	93 (19)	93 (25)
≥1 elective abortion	16 (3)	16 (4)
≥1 stillbirth/ neonatal death	1/1 (0.2/0.2)	1/1 (0.3/0.3)

Offspring Outcome, n (%)	Total Offspring (N = 365)
Low birth weight (<2500 g)	
▪ Yes	29 (8)
▪ No	334 (92)
▪ Missing/unknown	2 (0.5)
Birth defects	
▪ Yes	8 (2)
▪ No	350 (96)
▪ Missing/unknown	7 (2)

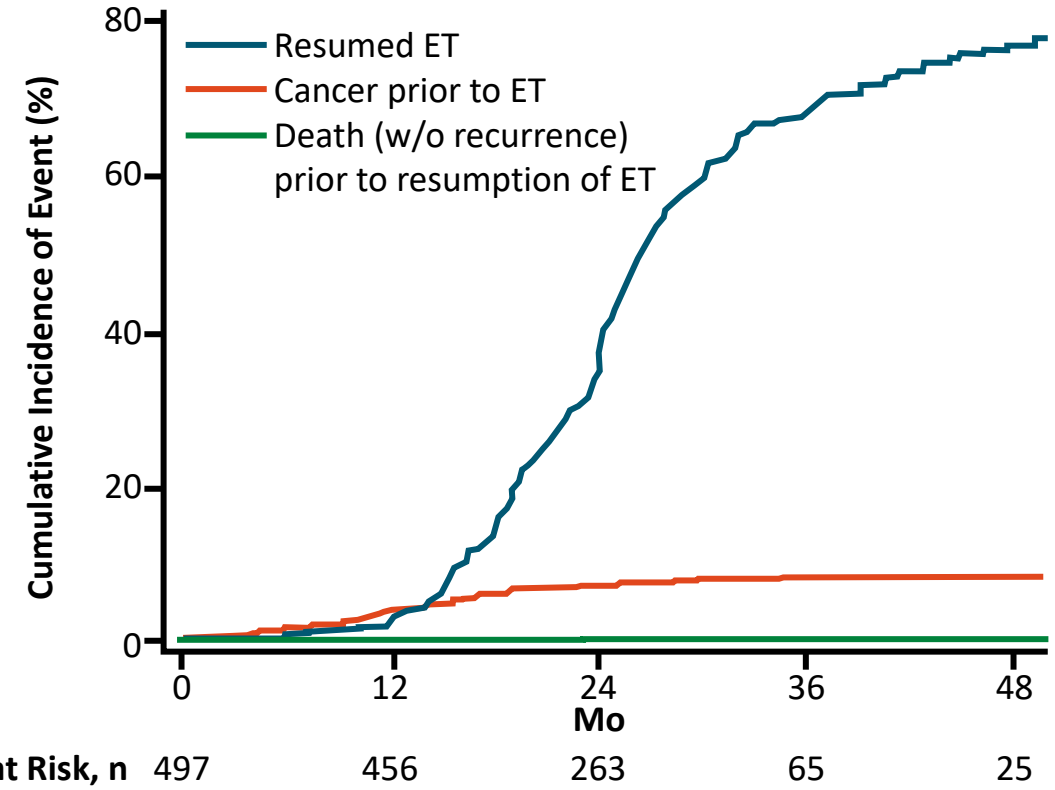
- Delivery: 66% vaginal, 34% cesarean section
- Complications in 11% of pregnancies (most common: hypertension/preeclampsia in 3%, diabetes in 2%)

- 350 live births among 317 women with ≥1 live birth
  - 62% of women reported breastfeeding
- 335 singleton births, 15 sets of twins

Partridge. SABCS 2022. Abstr GS4-09.

Slide credit: clinicaloptions.com

POSITIVE: Competing Risk Analysis of ET Resumption



- Cumulative incidence at 48 mo
  - 8% experienced cancer recurrence/death prior to ET resumption
  - 76% resumed ET
  - 15% had not yet resumed ET
- 79% of women who were disease free at 2 yr had not yet resumed ET, stating active or recent pregnancy, breastfeeding, or in pursuit of pregnancy

Partridge. SABCS 2022. Abstr GS4-09. Reproduced with permission.

Slide credit: clinicaloptions.com

SUMMARY-I

- TAILORx 12 yr event rate follow up shows that endocrine therapy is not inferior to the combination of chemotherapy and endocrine therapy in all pts with RS 11-25
- IDFS benefit in premenopausal patients with RS 21-25, less so for 16-20
- TEXT/SOFT: HER2 neg tumors with high risk clinicopathological characteristics benefit most from OFS + AI
- Meta-analyses: Using an aromatase inhibitor rather than tamoxifen in premenopausal women receiving ovarian suppression reduces the risk of breast cancer recurrence
- Longer follow-up is needed to assess any impact on breast cancer mortality
- Adjuvant abemaciclib + ET continues to show favorable survival benefit at 4 yr in high-risk HR+ HER2- EBC. OS data is not mature
- Adjuvant everolimus + ET did not improve IDFS or OS vs. ET in high risk EBC

SUMMARY-II

- OS benefit is maintained with adjuvant olaparib at 4 yrs in gBRCA pts with EBC-
- TNBC: residual disease after NACT or in adjuvant setting-tumor ≥2cms or positive lymph nodes
- HR+ BC: ≥4 positive lymph nodes or residual disease after NACT with a CPS+EG of 3 or higher
- POSITIVE trial showed that temporary interruption if ET to attempt pregnancy does not impact short term disease outcomes
- Majority of women (74%) had at least one pregnancy, most within the 2 years (70%)
- Incidence of birth defects and low birth weight was low, not clearly associated with treatment exposure

HER2 POSITIVE AND HER2 LOW BREAST CANCER

APT TRIAL: AN UPDATE 10-YEAR EVENT RATES

- After a median follow-up of 10.2 years (122 months)
- 10-year iDFS of 89.7% (86.3%-93.1%) in overall population
- Ten-year iDFS was 90.2% (86.3%-94.3%) and 88.5% (82.4%-95.1%) for patients with HR-positive and HR-negative tumors at baseline, respectively
- 10-year RFI was 96.8% (95.0%-98.7%)
- 10-year OS was 94.2% (91.6%-96.8%)
- 10-year BCSS was 99.1% (, 98.1%-100.0%)
- Among patients experiencing an iDFS event:

✓7 patients (1.7%) had distant recurrences, including 1 with a T2 tumor, 3 with a T1c tumor and 3 with a T1b tumor

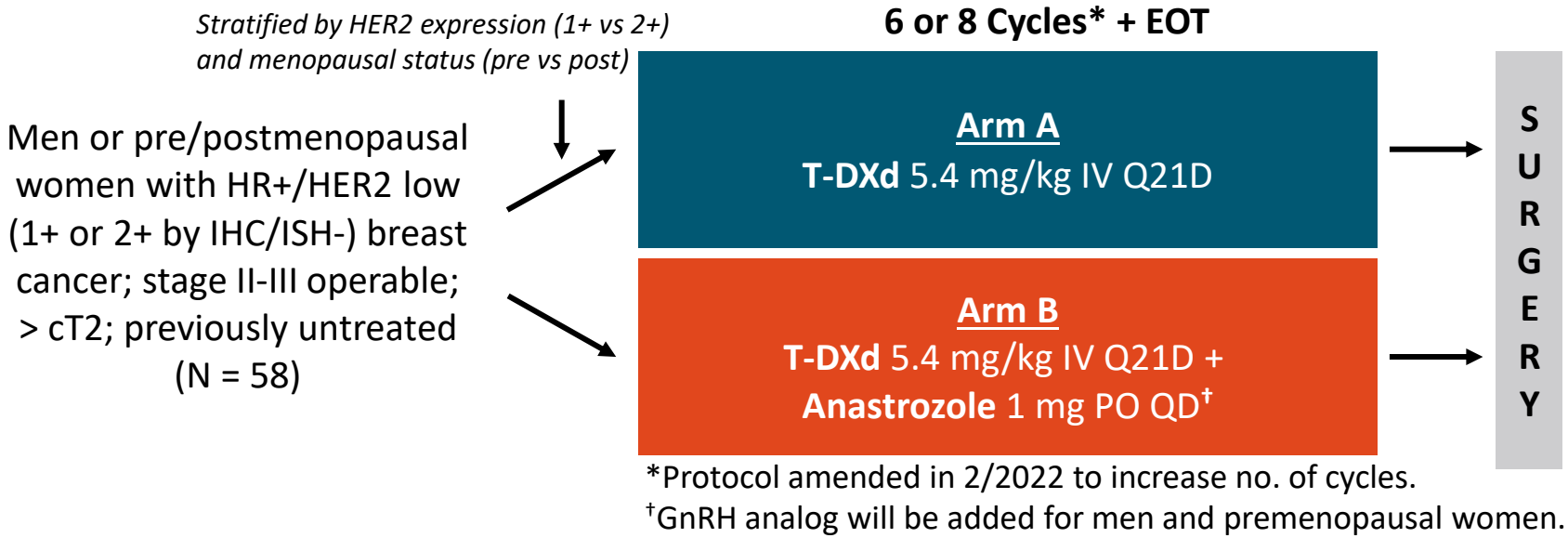
✓At baseline, 6 of them had HR-positive disease, 1 had HR-negative disease, and 6 had high-grade disease

✓Upon biopsy of metastatic lesions, 5 of the 7 distant recurrences were locally found to be HER2+, 1 was HER2-negative and 1 had unknown HER2 status

Tolaney S et al, SABCS 2022

TRIO-US B-12 TALENT: Neoadjuvant T-DXd ± Anastrozole for HR+/HER2-Low EBC

- Investigator-initiated multicenter, randomized, open-label phase II trial with Simon's minimax 2-stage design
  - No formal comparison between arms
  - Statistical benchmark of pCR ≤5%



- **Primary endpoint:** pCR rate in breast and LNs (ypT0/is ypTN0; RCBI = 0)
- **Secondary endpoints:** ORR, tumor biomarkers, safety

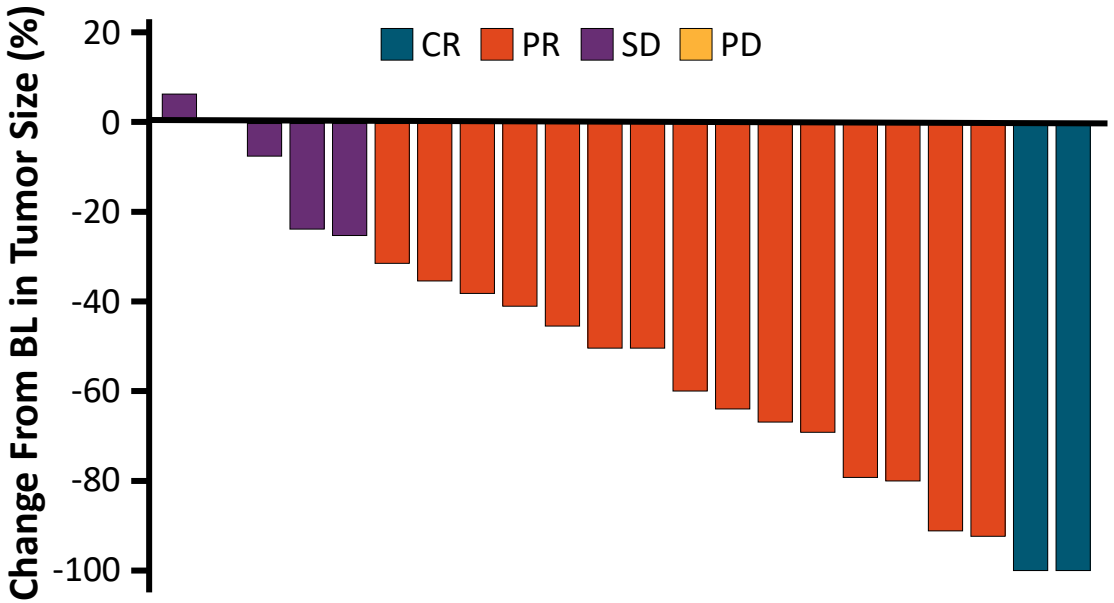
For both arms, tissue will be acquired from archival tissue or biopsy at baseline, at cycle 1 Days 17-21, and at surgery.

- Arms generally well balanced, with most having baseline HER2 IHC 1+ and approximately half with LN+ disease

Hurvitz. SABCS 2022. Abstr GS2-03. NCT04553770

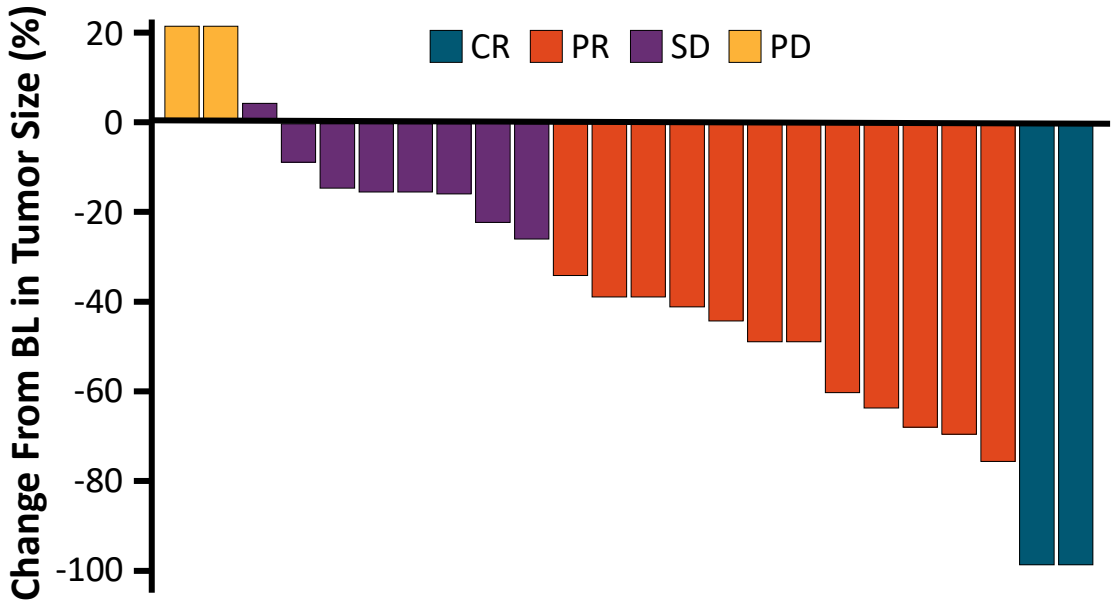
TRIO-US B-12 TALENT: ORR in ITT Population

Arm A: T-DXd (n = 25*)



Response, n (%)	Arm A: T-DXd (n = 25)
ORR	17 (68)
▪ CR	2 (8)
▪ PR	15 (60)

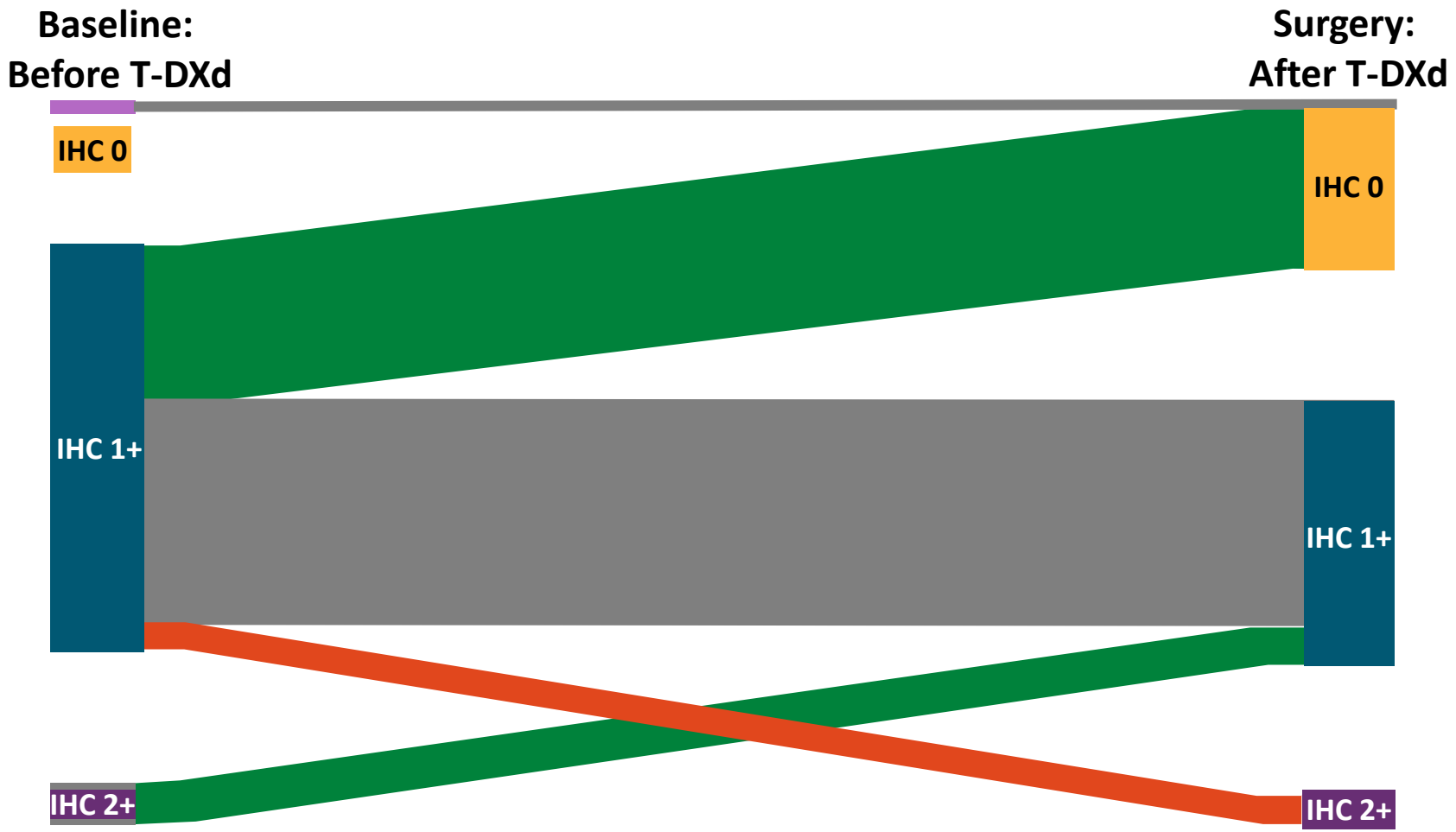
Arm B: T-DXd + Anastrozole (n = 24†)



Response, n (%)	Arm B: T-DXd + Anastrozole (n = 24)
ORR	14 (58)
▪ CR	2 (8)
▪ PR	12 (50)

*n = 4 still on tx; n = 3 discontinued prematurely but still had imaging and included in ORR analysis per protocol. †n = 5 still on tx.

TRIO-US B-12 TALENT: Change in HER2 IHC With T-DXd by Central Review



- HER2 IHC changed in 17/35 patients (49%) after T-DXd
- 88% with changed HER2 had decrease in HER2 expression by IHC

Change From BL to Surgery in HER2 IHC Staining

- Decreased
- Remained stable
- Increased

Hurvitz. SABCS 2022. Abstr GS2-03. Reproduced with permission.

Slide credit: clinicaloptions.com

TRIO-US B-12 (TALENT): RCB After T-DXd

RCB by Cycle and BL Stage, n (%)	Arm A: T-DXd (n = 22*)				Arm B: T-DXd + Anastrazole (n = 20†)			
	RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	***pCR/near pCR***				***pCR/near pCR***			
IIA	0	1 (5)	2 (9)	0	0	1 (5)	6 (30)	0
IIB	0	1 (5)	4 (18)	2 (9)	0	0	3 (15)	1 (5)
IIIA	0	0	1 (5)	2 (9)	0	0	1 (5)	1 (5)
IIIB	0	0	1 (5)	0	0	0	0	0
8 Cycles								
IIA	0	0	2 (9)	0	0	1 (5)	1 (5)	0
IIB	0	0	1 (5)	1 (5)	0	0	2 (10)	0
IIIA	1 (5)	0	0	0	0	1 (5)	0	0
IIIB	0	0	0	0	0	0	0	0

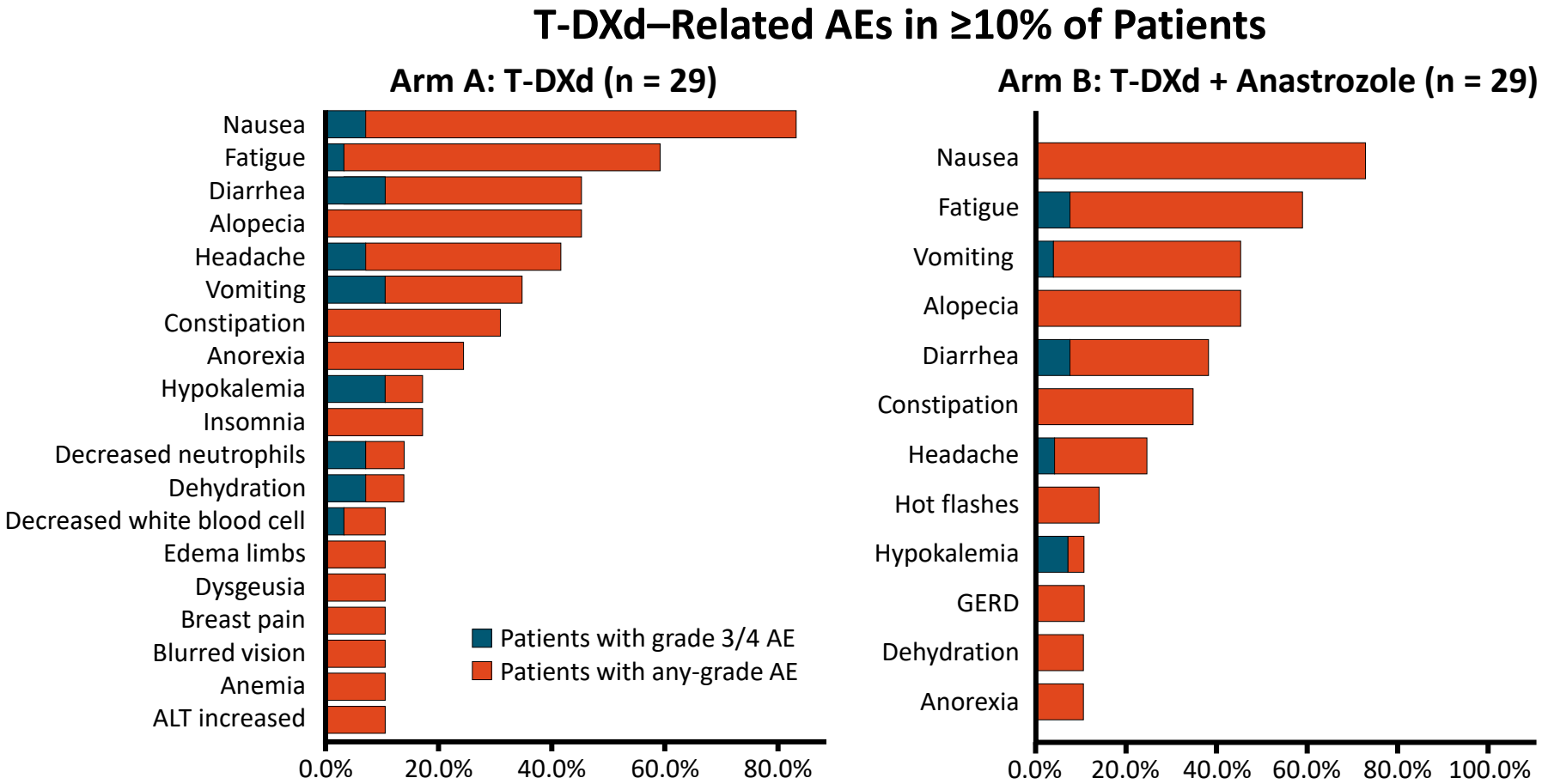
*n = 4 discontinued early. †n = 3 discontinued early but included in ITT analysis.

- Surgical outcomes pending for 24% in arm A and 31% in arm B (data cutoff: 11/25/22)

Hurvitz. SABCS 2022. Abstr GS2-03.

Slide credit: clinicaloptions.com

TRIO-US B-12 (TALENT): Safety



- n = 1 death possibly tx related (MI after severe GI toxicity in arm A)
- n = 3 (5%) had dose reductions due to AEs
- n = 3 discontinued due to AEs (all in arm B; 1 each for grade 4 hypokalemia, small bowel obstruction, and PD)
- n = 1 case of grade 2 pneumonitis, no grade 3/4
- No cardiomyopathy

- Incidence of T-DXd–related GI AEs decreased over time, potentially as supportive therapy improved

Slide credit: clinicaloptions.com

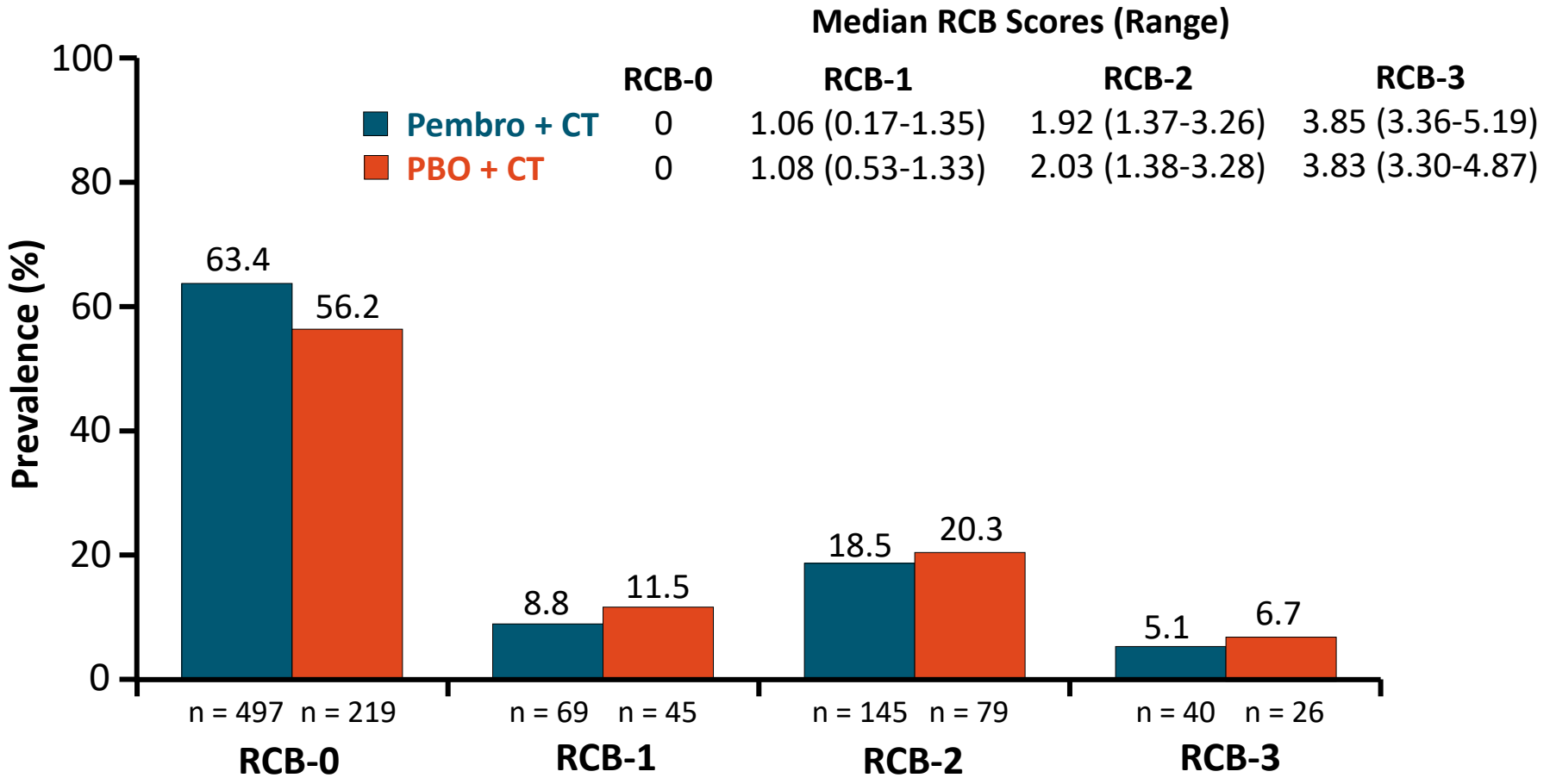
Hurvitz. SABCS 2022. Abstr GS2-03. Reproduced with permission.

SUMMARY-III

- Long term follow up (10 yr) survival outcomes continue to be excellent with the APT regimen supporting de-escalation of adjuvant therapy in HER2 positive breast cancer pts
- Only 7 distant recurrences seen at 10 year follow up
- Neoadjuvant TDXd showed signs of activity in neoadjuvant setting in HER2 low population
- Addition of ET to TDXd did not appear to enhance efficacy
- Results of this small study need to be validated in larger trials
- These trials will provide opportunity to explore/validate biomarkers predictive of response and resistance in this setting

TRIPLE NEGATIVE BREAST CANCER

KEYNOTE-522 Exploratory Analysis: Prevalence of Residual Cancer Burden Categories (ITT)



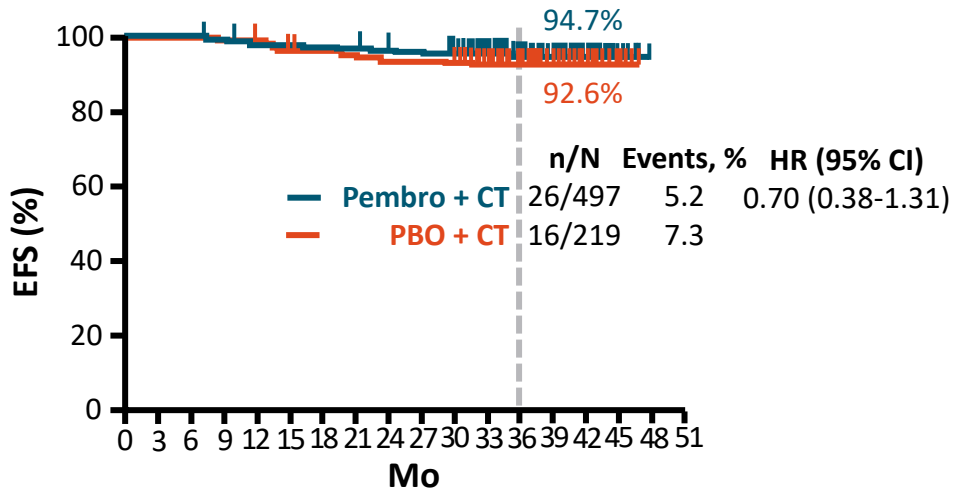
n = 54 (4.6%) missing RCB categorical data; n = 33 (4.2%) in pembrolizumab arm, n = 21 (5.4%) in PBO arm.

Pusztai. ASCO 2022. Abstr 503. Reproduced with permission.

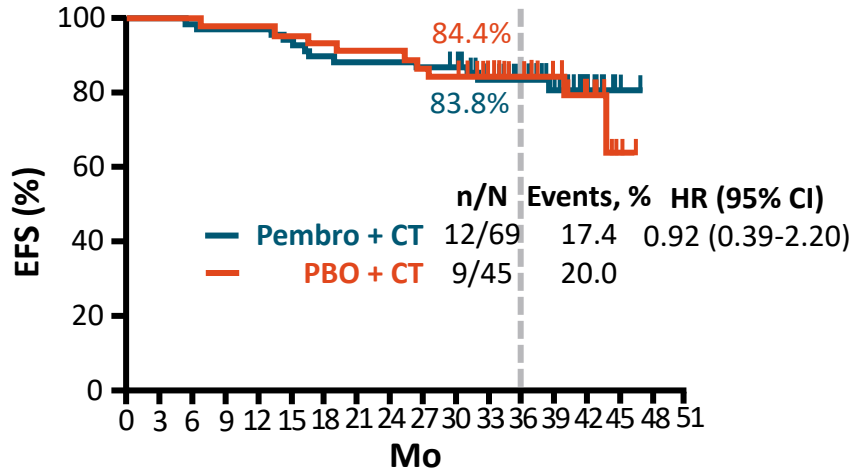
Slide credit: clinicaloptions.com

KEYNOTE-522 Exploratory Analysis: EFS by RCB Category

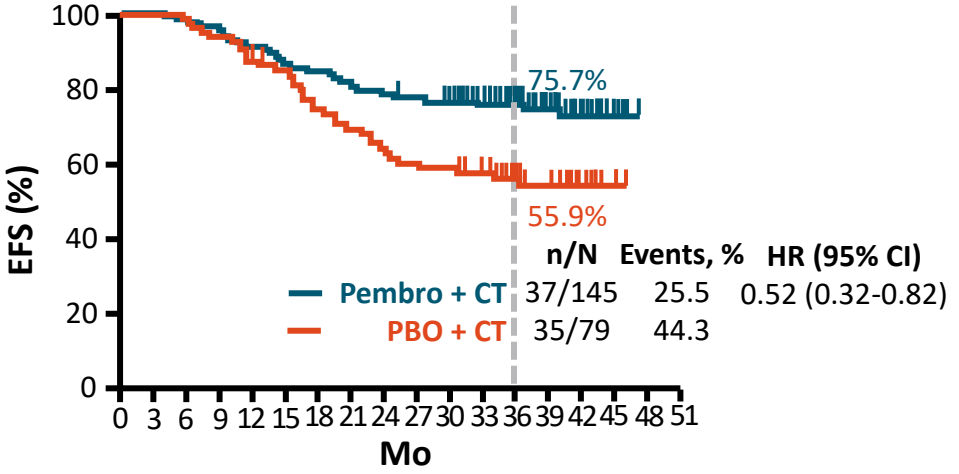
EFS in RCB-0



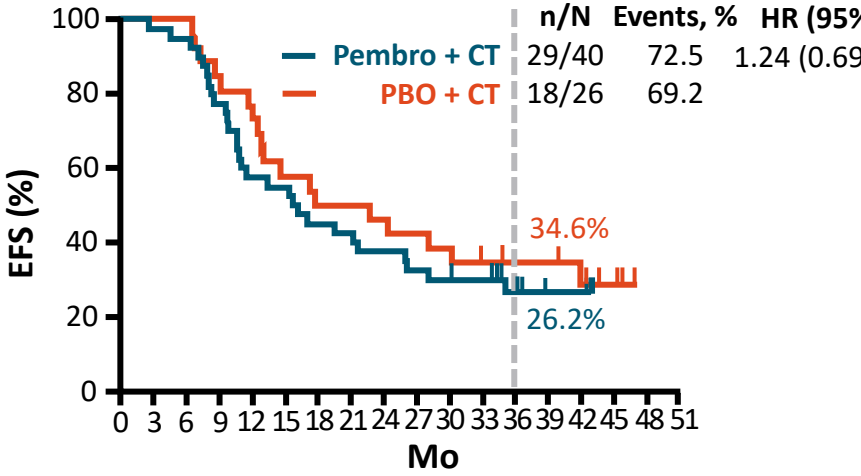
EFS in RCB-1



EFS in RCB-2



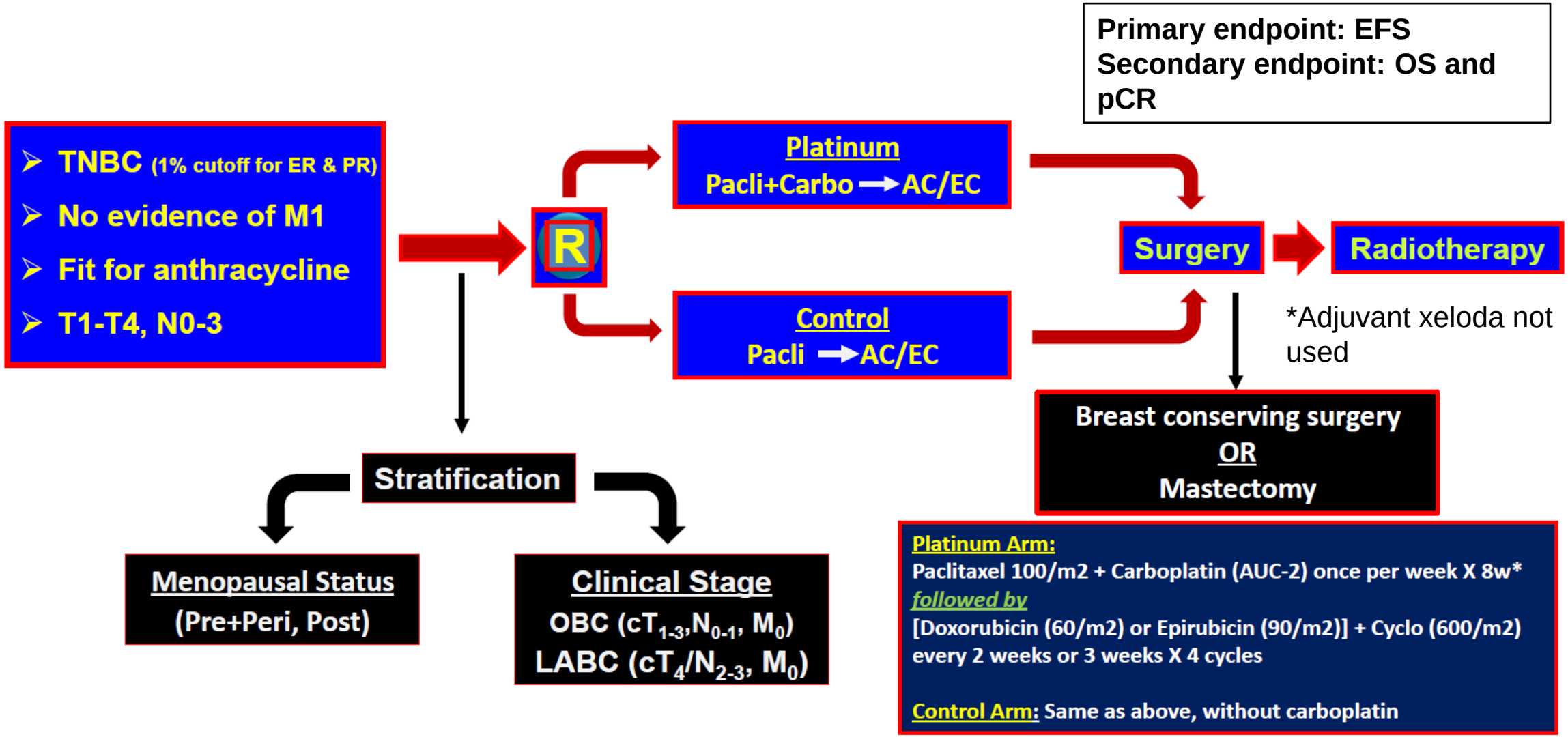
EFS in RCB-3



Pusztai. ASCO 2022. Abstr 503. Reproduced with permission.

Slide credit: clinicaloptions.com

TMC NEOADJUVANT PLATINUM TNBC STUDY



Gupta S et al SABCS 2022

TMC NEOADJUVANT PLATINUM TNBC STUDY

- ITT population: 717 , both arms were well balanced
- Pre/perimenopausal women: 58.3%
- 70% of patient younger than 50 years of age
- 60% of patients had locally advanced cT4/N2-N3 disease
- 77.7% of patients had tumor size greater than 5 cms at diagnosis
- 88% of patients clinically lymph node positive

Path CR	Control	Platinum	P value
Breast and nodes	40.3%	54.5%	<0.001
Breast	43.8%	61.9%	<0.001
Nodes	71.6%	77.7%	0.075

- No new safety signals
- Compliance to NACT was similar in both control vs. platinum, approx. 77-80%

Gupta S et al SABCS 2022

PCR AND EFS BY AGE AND TREATMENT ARM

Breast And Nodes Path CR	Control	Platinum	P value	EFS	Control	Platinum	P value
Age ≤ 50 yrs	41.5%	61.0%	<0.001	Age ≤50 yrs	61.7%	74.2%	0.004
Age >50 yrs	37.5%	38.1%	1.0	Age >50 yrs	62.0%	69.3%	0.253

OS in pts <50 yrs: 65.9% control vs. 77.1% platinum (p=0.003)
OS in pts >50 yrs: 68.9% control vs. 68% platinum (p=0.615)

Gupta S et al SABCS 2022

Phase II NeoPACT: Neoadjuvant Pembrolizumab + Carboplatin/Doxorubicin in TNBC

- Multicenter phase II trial evaluating de-intensified, anthracycline-free neoadjuvant tx for TNBC

Patients with stage I-III TNBC; T >1 cm or N+; ER/PR ≤10%; HER2 negative per ASCO/CAP guidelines (N = 115)

→ **Carboplatin** AUC 6 + **Docetaxel** 75 mg/m^2 + **Pembrolizumab** 200 mg Q21D x 6 → **Surgery** → *Follow-up; adjuvant therapy permitted (no pembrolizumab)*

Primary Endpoint: pCR, %		Patients (N = 115)
All, % (95% CI)		58 (48-67)
TNM	▪ I ▪ II ▪ III	69 59 43
Nodal status	▪ Negative ▪ Positive	65 46
PD-L1 status	▪ Negative ▪ Positive	39 76

Secondary Efficacy Endpoints, %	Patients (N = 115)
RCB 0+1	69
2-yr EFS ▪ With pCR ▪ Without pCR	89 98 78
2-yr OS ▪ With pCR ▪ Without pCR	90 100 76

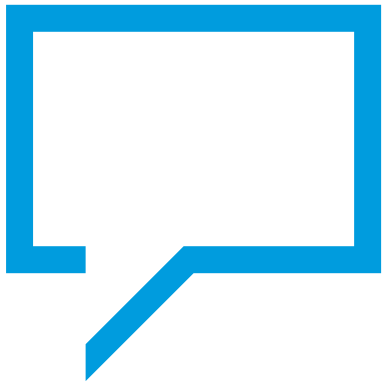
Sharma. ASCO 2022. Abstr 513.

Slide credit: clinicaloptions.com

SUMMARY-IV

- Exploratory analysis of the KEYNIOTE 522 trial suggests that achieving chemo-immunotherapy is associated with high incidence of pCR compared to chemo only
- Higher RCB score associated with worse EFS in patients with early-stage TNB independent of treatment group
- Addition of pembrolizumab to chemotherapy reduced EFS events in most RCB categories, with largest benefit in RCB-2 category
- Addition of carboplatin to neoadjuvant anthracycline-taxane improves pCR, EFS and OS primarily in patients < 50yrs of age, reason is unclear
- pCR continues to be a strong prognostic indicator of survival outcomes in the TMC study
- NeoPACT trial evaluated non-anthracycline neoadjuvant regimen and showed promising results
- Studies are ongoing to define optimal management of patients after neoadjuvant therapy –escalate therapy for residual disease and de-escalate for pCR. Can we use biomarkers and/or ctDNA in this setting

QUESTIONS & DISCUSSION



Multidisciplinary Update in Breast Disease 2023

November 9-11, 2023

MAKE PLANS TO ATTEND

Naples Grande Beach Resort
Naples, Florida

Save the Date