Saleha Rizwan, MD

02/14/2025

Updates in ER+ Breast cancer

AHN

Disclosures

None

Objectives

- Ember-3 trial
- Destiny Breast 06
- Impact of Anthracyclines in high genomic risk node negative HR + breast cancer

Thank you!

- Aditya Bardia
- Komal Jhaveri
- Harold Burstein
- Nan Chen

Treatment options in advanced ER+ breast cancer

01

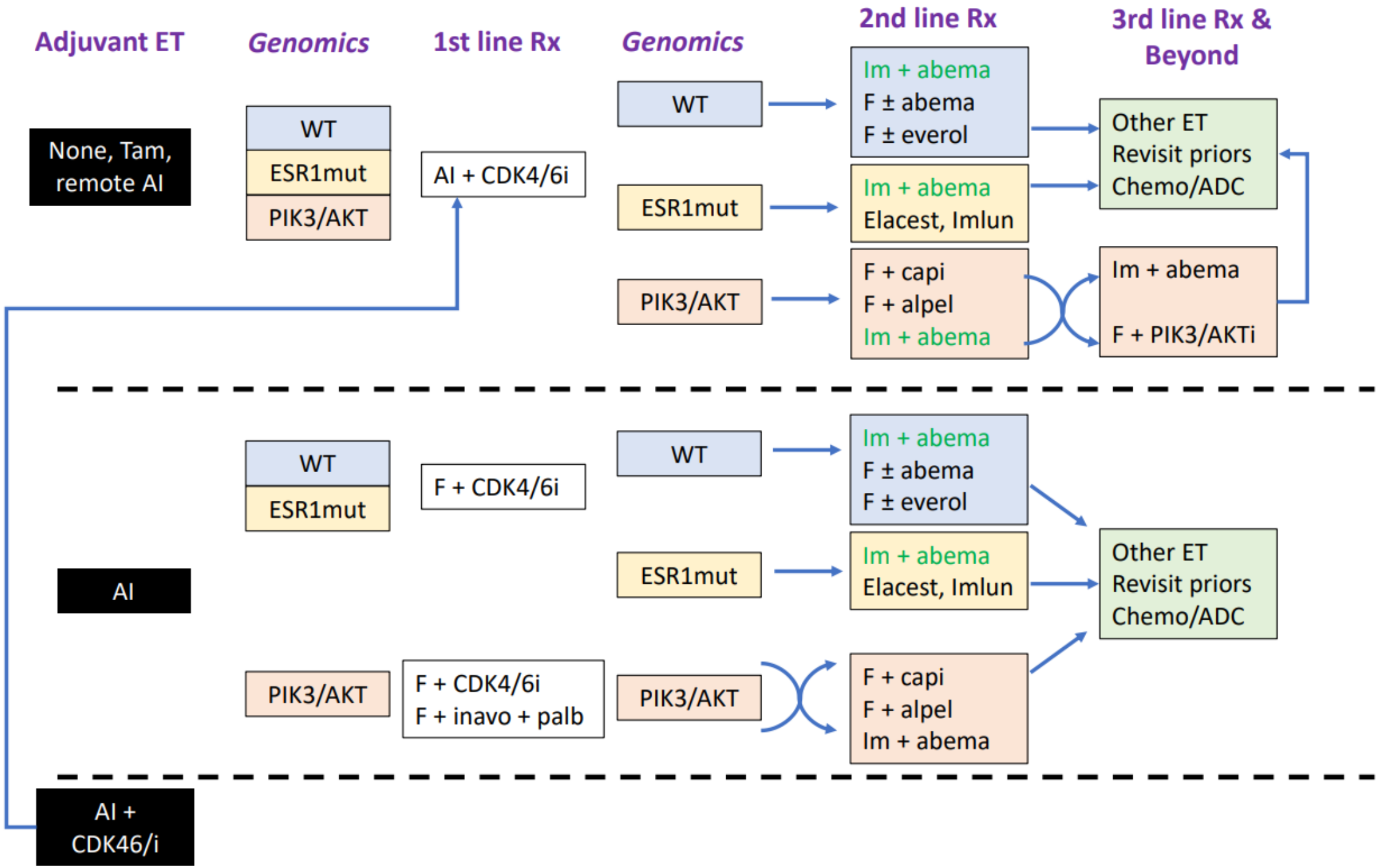
Moving away from chemotherapy

02

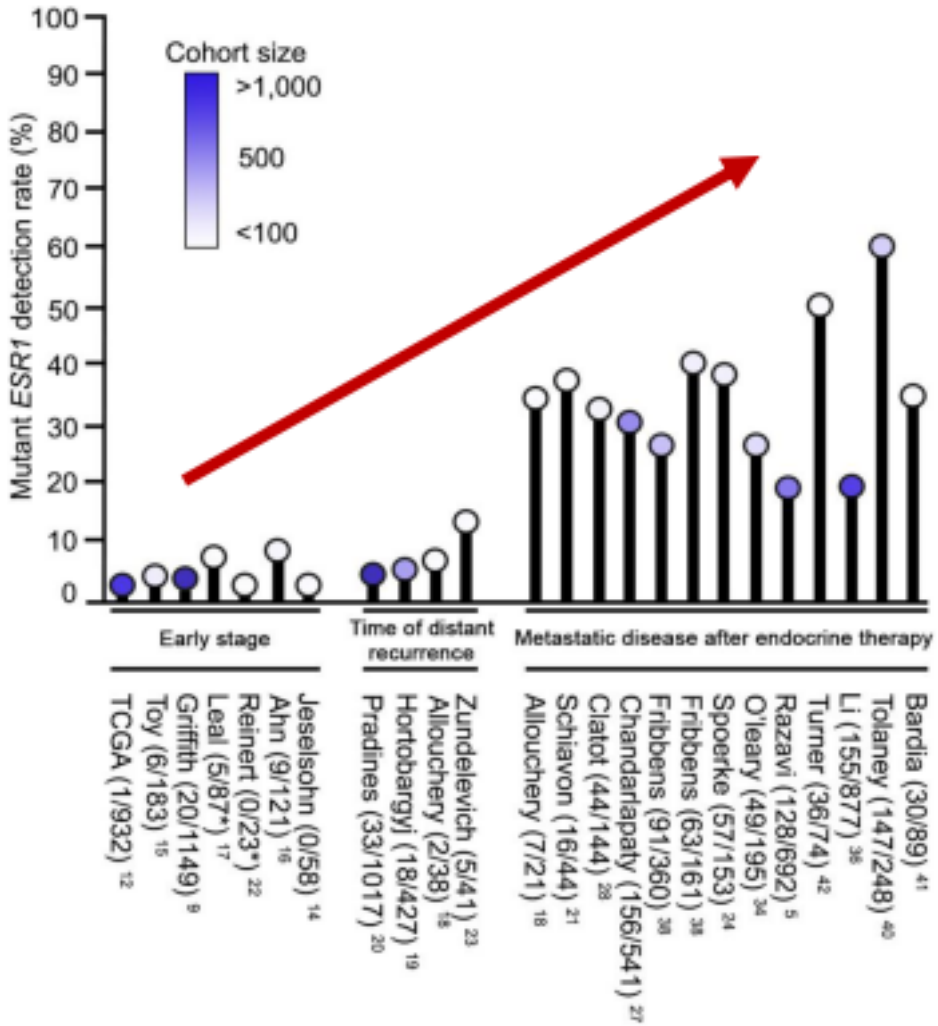
Using targeted therapy

03

Using LIQUID BIOPSY!


Adjuvant ET
Genomics
1st line Rx
Genomics
2nd line Rx
3rd line Rx & Beyond
None, Tam, remote AI
WT
ESR1mut
PIK3/AKT
AI + CDK4/6i
WT
ESR1mut
PIK3/AKT
Im + abema
F ± abema
F ± everol
Im + abema
Elacest, Imlun
F + capi
F + alpel
Im + abema
Other ET
Revisit priors
Chemo/ADC
Im + abema
F + PIK3/AKTi
AI
WT
ESR1mut
F + CDK4/6i
WT
ESR1mut
Im + abema
F ± abema
F ± everol
Im + abema
Elacest, Imlun
Other ET
Revisit priors
Chemo/ADC
PIK3/AKT
F + CDK4/6i
F + inavo + palb
PIK3/AKT
F + capi
F + alpel
Im + abema
AI + CDK46/i

ESR1 Mutations are Enriched in Metastatic Disease Following Endocrine Treatment Especially After AI-exposure



Mutations cluster in ligand binding domain yielding conformational change with clinical consequences

1. constitutive ER activity in absence of estrogen
> AIs not effective

2. decreased binding affinity of SERDs
> higher doses (~2 fold) needed to antagonize/degrade ER

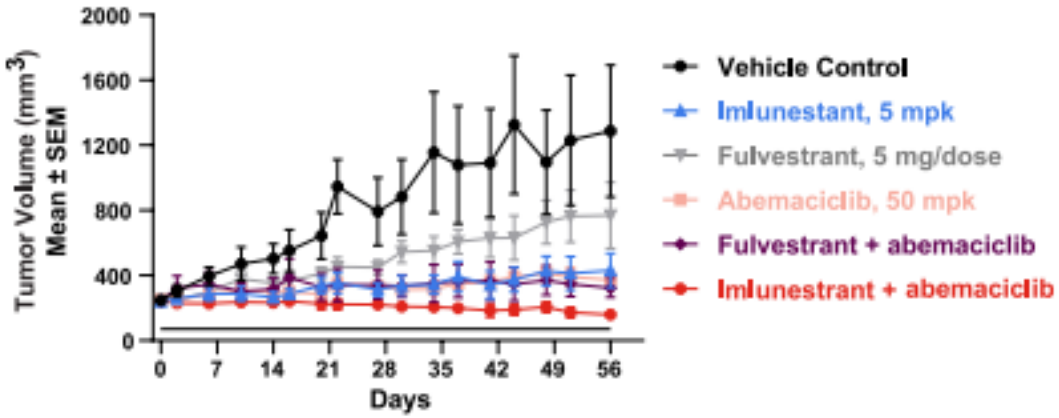
"…the doses at which potent ER inhibition is achieved in the mutant-expressing models may exceed the steady-state, intratumoral levels achieved in patients."
Toy W, et al. Nat Genetics 2013;45:1439.

Grinshpun, Jeselsohn. Heme Onc Clinics 2023;37:169.

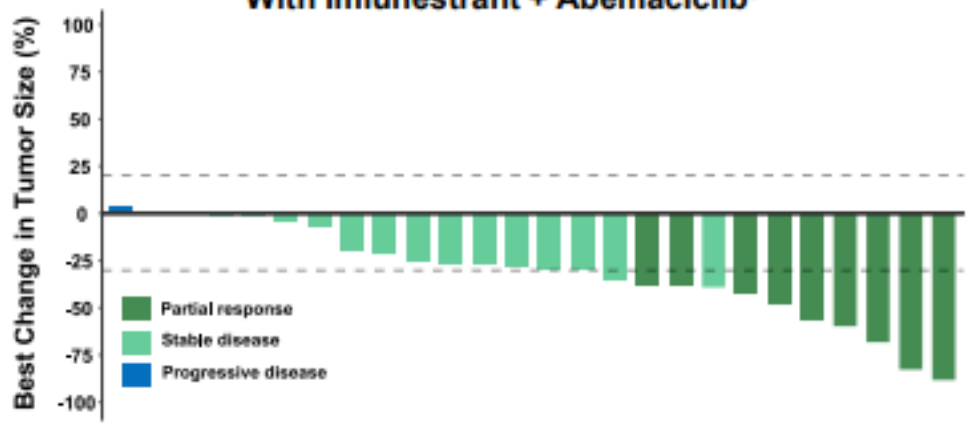
Background

- **ER and CDK4/6 are critical oncogenic pathways of ER+, HER2- ABC**
- **ET + CDK4/6i are essential therapies for ER+, HER2- ABC[1]**
  - Continued suppression of ER and CDK4/6 beyond progression on CDK4/6i + ET may be important for improved patient outcomes, regardless of *PIK3CA* or *ESR1*m
  - Abemaciclib has shown benefit in CDK4/6i-naïve[2] & CDK4/6i-pretreated patients[3]
- **Fulvestrant is the only SERD broadly approved as monotherapy and in combination, but**
  - **Efficacy** is **limited** in patients with *ESR1*m
  - Requires **intramuscular administration[4]**
    - Often painful & burdensome to patients,[5] when oral options are generally preferred[6]
- **Elacestrant is an oral SERD with dose-dependent mixed ER agonist/antagonist activity approved as monotherapy for patients with *ESR1*m[7]**
- **Imlunestrant is a next-generation, brain-penetrant, oral SERD and pure ER antagonist that delivers continuous ER inhibition**

In Vivo Efficacy in CTG-1260 *ESR1 D538G* Model[8]



EMBER Phase 1 trial: Tumor Response in Patients Treated With Imlunestrant + Abemaciclib[9]



ABC, advanced breast cancer; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; SEM, standard error of the mean.

1. Gradishar WJ. *J Natl Compr Canc Netw.* 2023;21(5.5):1-4; 2. VERZENIO (abemaciclib) [package insert]. Eli Lilly and Company; 2023; 3. Kalinsky K, et al. *J Clin Oncol.* 2024;42(Suppl 17):abstract LBA1001; 4. Robertson JFR, Harrison M. *Br J Cancer.* 2004;90(Suppl 1):S7-S10; 5. Cox AC, Fallowfield LJ. *Eur J Oncol Nurs.* 2007;11(1):43-48; 6. Eek D, et al. *Patient Prefer Adherence.* 2016;10:1609-1621; 7. Beumer JH, Foldi J. *Cancer Chemother Pharmacol.* 2023;92(2):157-163; 8. VandeKopple M, et al. Poster presented at ESMO Breast Cancer Congress; Berlin, Germany; May 11-13, 2023. Poster 41P; 9. Data on file. March 9, 2023.

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EMBER-3 Study Design

SAN ANTONIO BREAST CANCER SYMPOSIUM®
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AACR American Association for Cancer Research

ER+, HER2- ABC

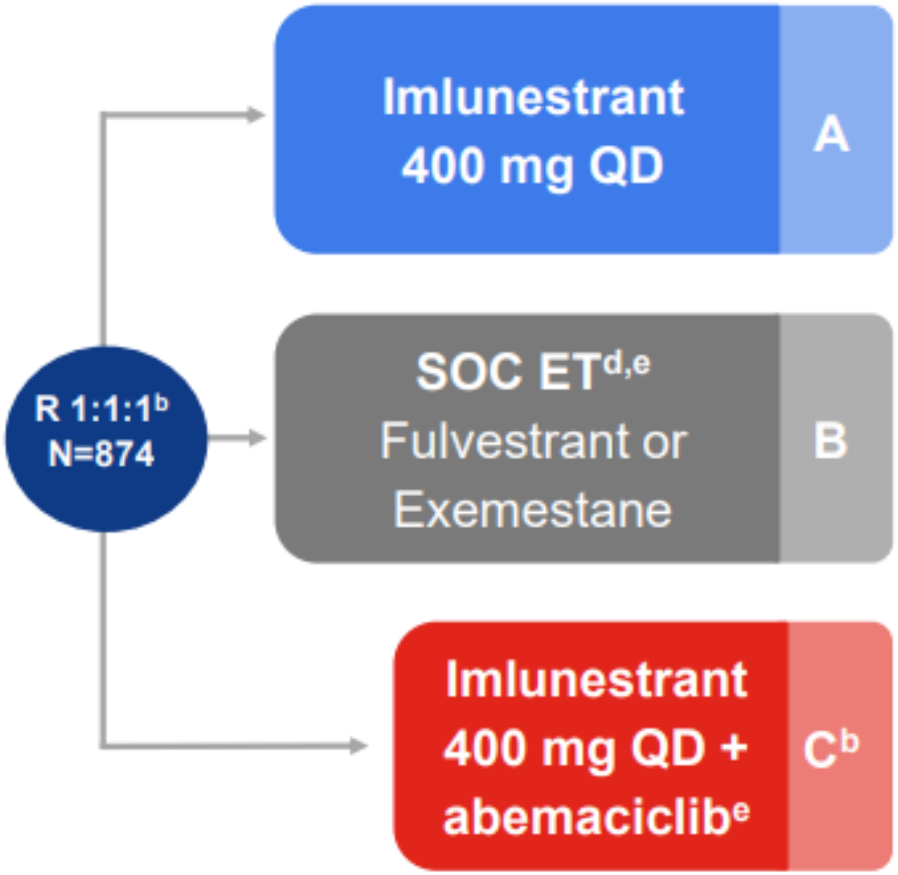
Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

Baseline Demographic and Disease Characteristics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

CDK4/6i, CDK4/6 inhibitor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; PR, progesterone receptor; SOC ET, standard of care endocrine therapy. [a] Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Target assay, Burning Rock Biotech; [b] Includes single nucleotide variants and insertions/deletions of *PIK3CA*, *AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown *ESR1*m status; [c] Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [d] Adjuvant ET = First-line; ABC = Second-line; [e] Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139); [f] Data available in the online supplementary slides.

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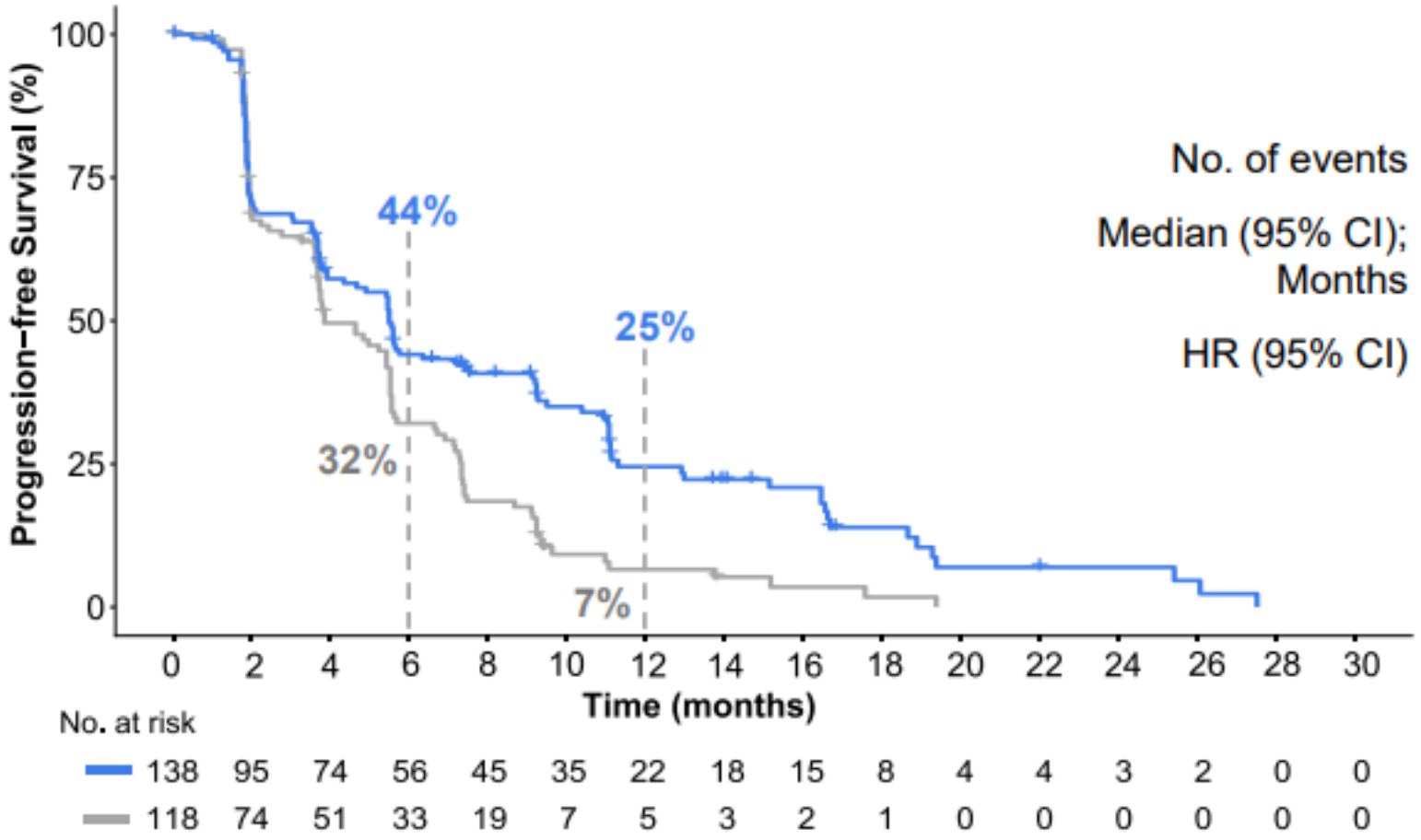
Primary Endpoint: Imlunestrant vs SOC ET Investigator-assessed PFS in Patients with *ESR1*m



	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; RMST, restricted mean survival time; SOC ET, standard of care endocrine therapy. The median follow-up was 16.7 months in the imlunestrant arm and 13.8 months in the SOC ET arm.
[a] Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RSMT at 19.4 months was 7.9 months (95% CI 6.8-9.1) in the imlunestrant arm vs 5.4 months (95% CI 4.6-6.2) in the SOC ET arm [difference 2.6 months (1.2.-3.9)].

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Investigator-assessed PFS by Subgroup: Consistent Imlunestrant Benefit Across Subgroups in Patients with *ESR1*m

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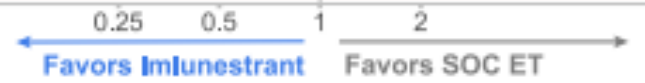
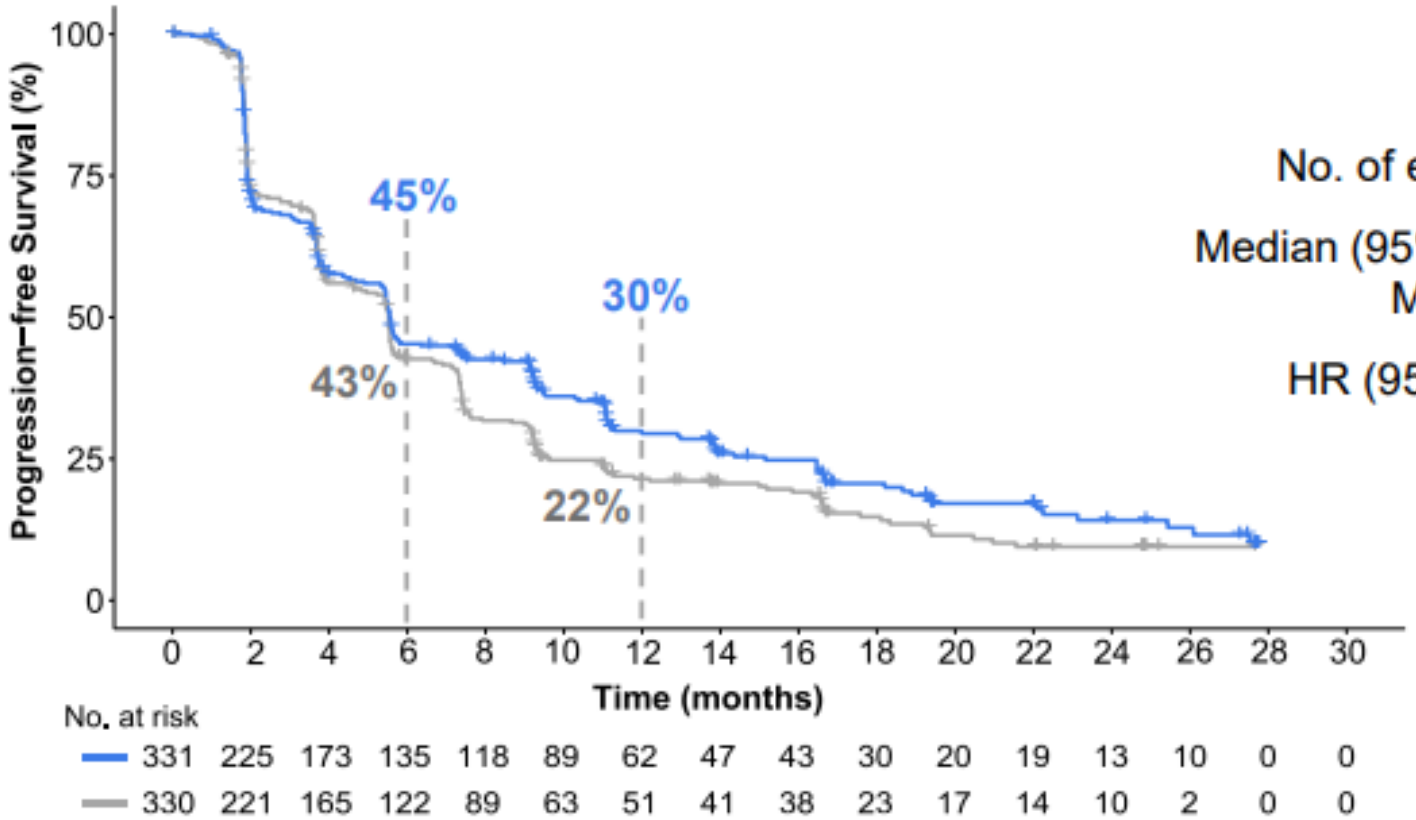
Subgroup		Imlunestrant No. of Events/Total No.	SOC ET No. of Events/Total No.	Hazard Ratio (95% CI)	Interaction *p*-value
Patients with *ESR1* mutation		109/138	102/118	0.62 (0.46, 0.82)	
Investigator's choice of ET	Exemestane	3/4	4/6	0.53 (0.09, 3.00)	**0.950**
	Fulvestrant	106/134	98/112	0.61 (0.46, 0.81)	
Age	<65 years	74/91	69/78	0.61 (0.44, 0.86)	**0.859**
	≥65 years	35/47	33/40	0.57 (0.34, 0.95)	
Region	East Asia	23/30	23/26	0.47 (0.25, 0.89)	**0.284**
	North America/Western Europe	51/63	44/54	0.77 (0.51, 1.17)	
	Other	35/45	35/38	0.50 (0.31, 0.82)	
No. of metastatic sites	1	24/35	26/35	0.53 (0.30, 0.94)	**0.901**
	2	36/45	35/39	0.61 (0.37, 0.99)	
	≥3	49/58	41/44	0.63 (0.41, 0.98)	
Visceral metastasis	No	39/54	42/51	0.51 (0.32, 0.79)	**0.612**
	Yes	70/84	60/67	0.68 (0.47, 0.98)	
Liver metastasis	No	58/81	59/71	0.58 (0.40, 0.83)	**0.679**
	Yes	51/57	43/47	0.64 (0.41, 0.99)	
Bone-only metastasis	No	92/111	79/88	0.65 (0.47, 0.89)	**0.439**
	Yes	17/27	23/30	0.42 (0.22, 0.80)	
Previous CDK4/6 inhibitor	No	29/45	31/33	0.42 (0.25, 0.72)	**0.246**
	Yes	80/93	71/85	0.72 (0.52, 1.01)	
Line of therapy in advanced setting	First-line	19/30	21/23	0.48 (0.25, 0.92)	**0.599**
	Second-line	88/106	81/95	0.66 (0.48, 0.90)	
PI3K pathway mutation status	Detected	59/72	48/57	0.62 (0.41, 0.93)	**0.732**
	Not detected	50/64	54/61	0.61 (0.41, 0.91)	



Primary Endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in All Patients



	Imlunestrant n=331	SOC ET n=330
No. of events	237	253
Median (95% CI); Months	**5.6** (5.3-7.3)	**5.5** (4.6-5.6)
HR (95% CI)	**0.87 (0.72-1.04)** *p*-value 0.12	

Prespecified Critical HR < 0.84[a]

PFS difference of imlunestrant vs SOC ET in all patients did not reach significance

- The majority subgroup of patients without *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79-1.27)[b]

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. The median follow-up was 16.6 months in the imlunestrant arm and 16.8 months in the SOC ET arm.
[a] At full alpha; [b] Data available in the online supplementary slides.

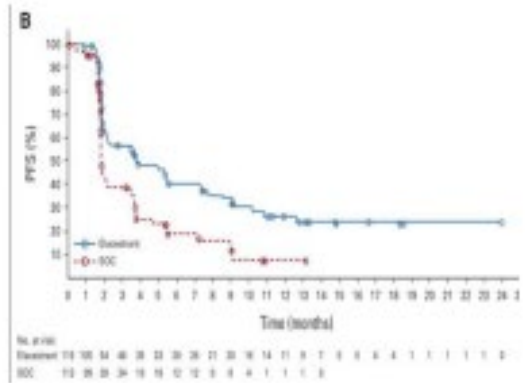
EMERALD
SOC vs Elacestrant

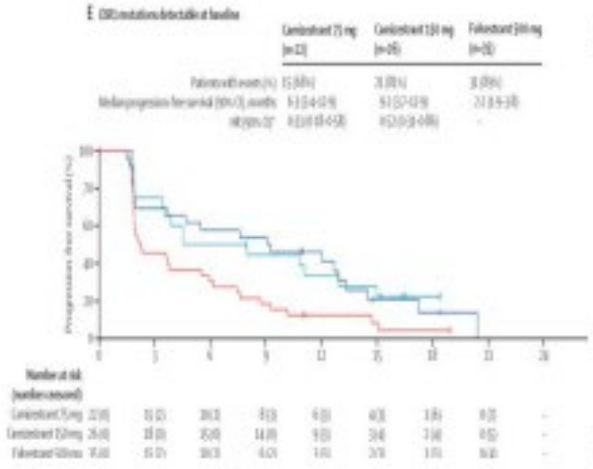
SERENA-2
Fulv vs Camizestrant

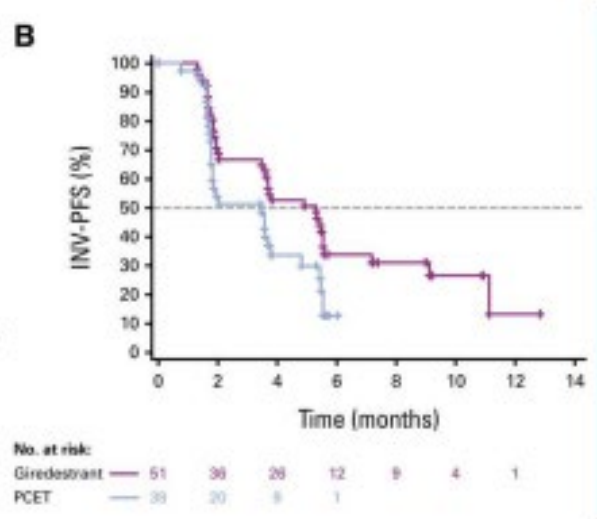
acelERA
PCET vs Giredestrant

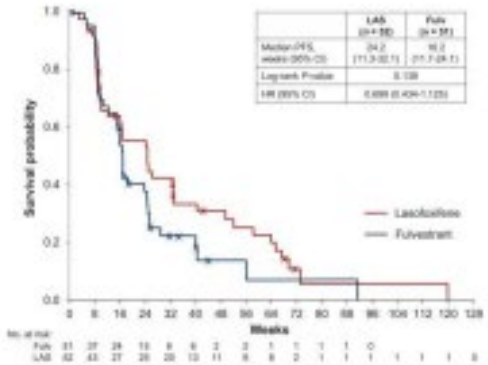
ELAINE 1
Fulv vs Lasofoxifene

ESR1 mut

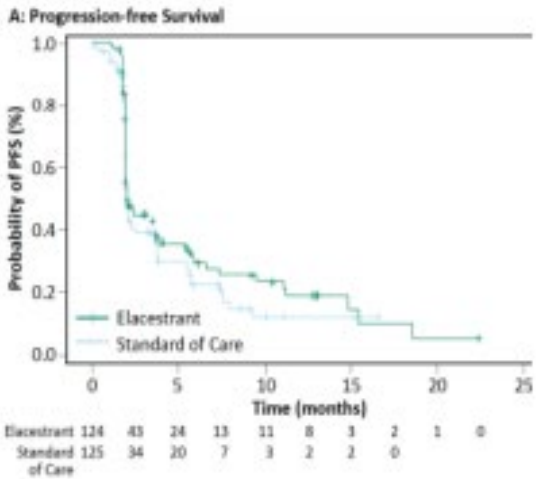


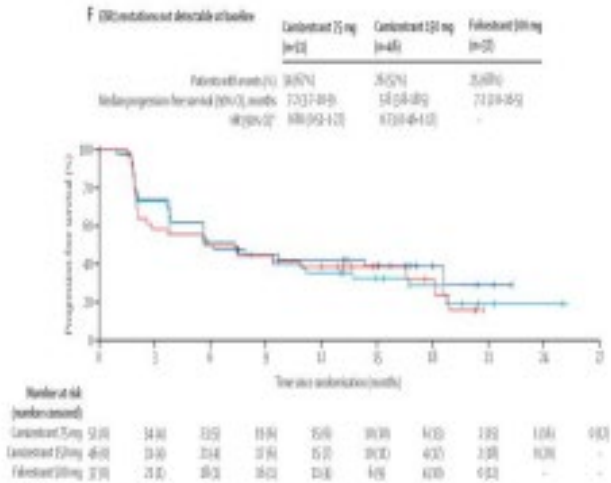


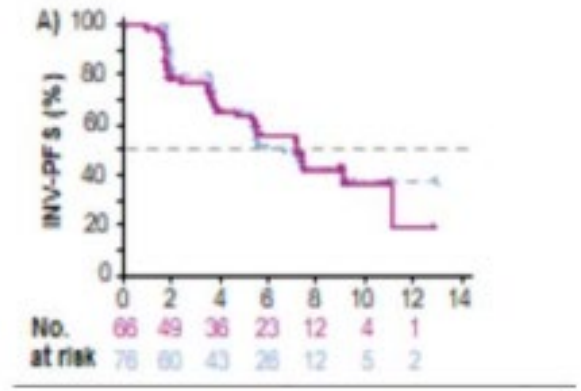




ESR1 wt







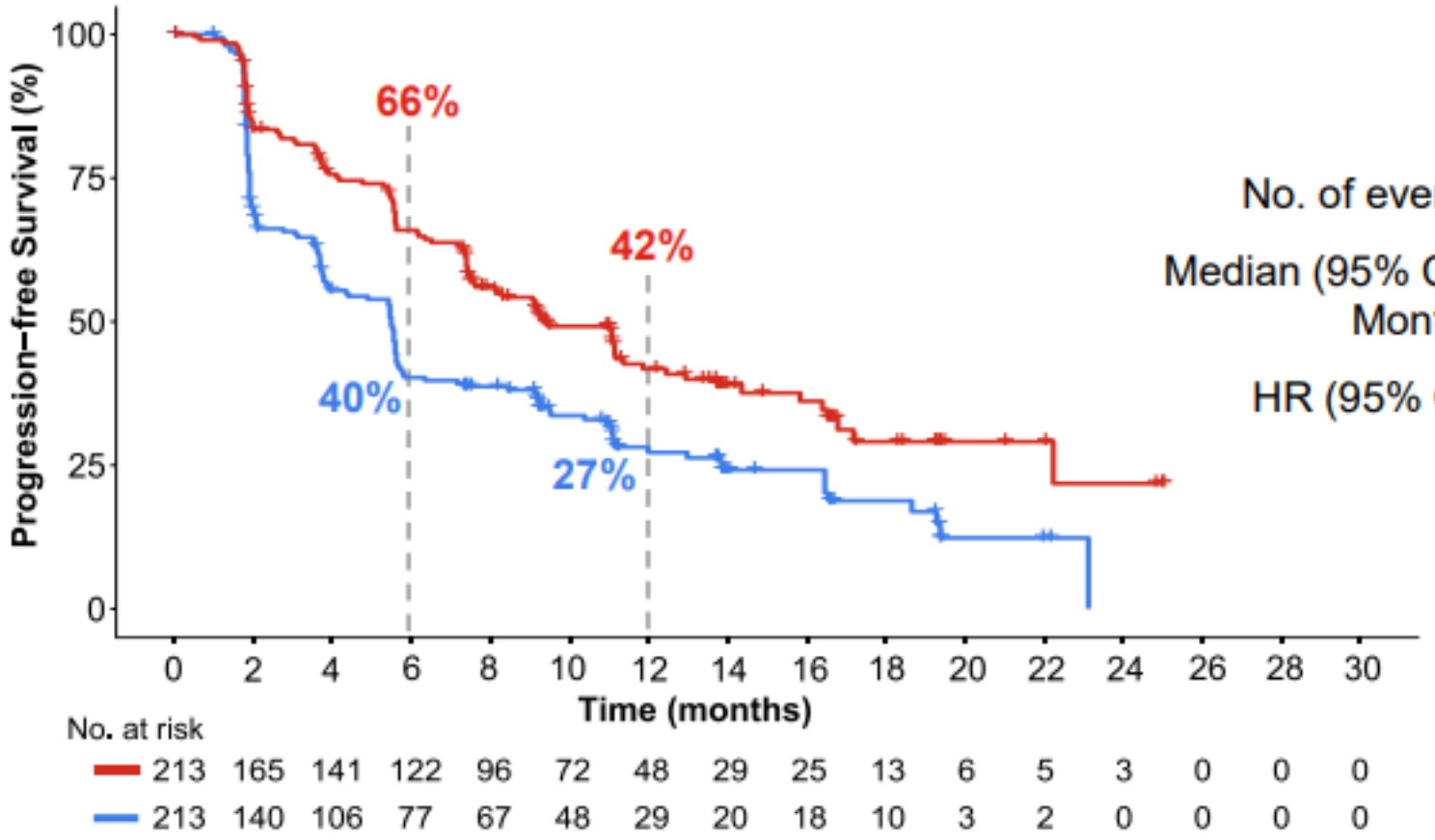
Bidard, FC et al.
J Clin Oncol 2022;40:3246

Oliveira M, et al.
Lancet Oncol 2024;25:1424

Martin M, et al.
J Clin Oncol 2024;42:2149

Goetz MP, et al.
Ann Oncol 2023;34:1141

Primary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in All Patients



	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5-11.9)	**5.5** (3.8-5.6)
HR (95% CI)	**0.57 (0.44-0.73)** *p*-value <0.001	

Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients

CI, confidence interval; HR, hazard ratio. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. The median follow-up was 13.5 months in the imlunestrant + abemaciclib arm and 13.7 months in the imlunestrant arm.

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Investigator-assessed PFS by Subgroup: Consistent Imlunestrant + Abemaciclib Benefit Across Subgroups

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Subgroup		Imlunestrant + abemaciclib No. of Events/Total No.	Imlunestrant No. of Events/Total No.	Hazard Ratio (95% CI)	Interaction *p*-value
All Patients		114/213	149/213	0.57 (0.44, 0.73)	
Age	<65 years	71/122	99/134	0.64 (0.47, 0.87)	**0.705**
	≥65 years	43/91	50/79	0.58 (0.38, 0.87)	
Region	East Asia	35/66	48/67	0.57 (0.36, 0.88)	**0.370**
	North America/Western Europe	51/95	66/92	0.53 (0.37, 0.77)	
	Other	28/52	35/54	0.83 (0.50, 1.37)	
Number of metastatic sites	1	26/76	39/65	0.49 (0.30, 0.81)	**0.744**
	2	34/57	50/74	0.67 (0.43, 1.03)	
	≥3	54/80	60/74	0.58 (0.40, 0.85)	
Visceral metastasis	No	44/94	61/93	0.64 (0.43, 0.94)	**0.439**
	Yes	70/119	88/120	0.55 (0.40, 0.75)	
Liver metastasis	No	78/156	90/144	0.68 (0.50, 0.92)	**0.142**
	Yes	36/57	59/69	0.47 (0.31, 0.73)	
Bone-only metastasis	No	95/162	124/167	0.59 (0.45, 0.78)	**0.849**
	Yes	19/51	25/46	0.55 (0.30, 1.02)	
Previous CDK4/6 inhibitor	No	35/74	40/73	0.82 (0.52, 1.29)	**0.066**
	Yes	79/139	109/140	0.51 (0.38, 0.68)	
Line of therapy in advanced setting	First-line	28/63	40/61	0.55 (0.34, 0.90)	**0.705**
	Second-line	85/149	107/150	0.62 (0.47, 0.83)	
***ESR1* mutation status**	Detected	36/67	71/92	0.53 (0.35, 0.80)	**0.574**
	Not detected	78/146	78/121	0.59 (0.43, 0.81)	
PI3K pathway mutation status	Detected	55/88	70/84	0.61 (0.42, 0.87)	**0.628**
	Not detected	53/109	73/112	0.55 (0.39, 0.79)	
Concurrent *ESR1* mutation and PI3K pathway mutation status	Detected	21/40	38/47	0.48 (0.28, 0.83)	**0.576**
	Not detected	87/157	105/149	0.61 (0.46, 0.81)	

CI, confidence interval. First-line: most recent ET was adjuvant; Second-line: most recent ET was ABC. The total number of patients may not add up due to missing data in certain subgroups. Patients without *ESR1*m include 8 with unknown *ESR1*m status (imlunestrant + abemaciclib, n=1; Imlunestrant, n=7).

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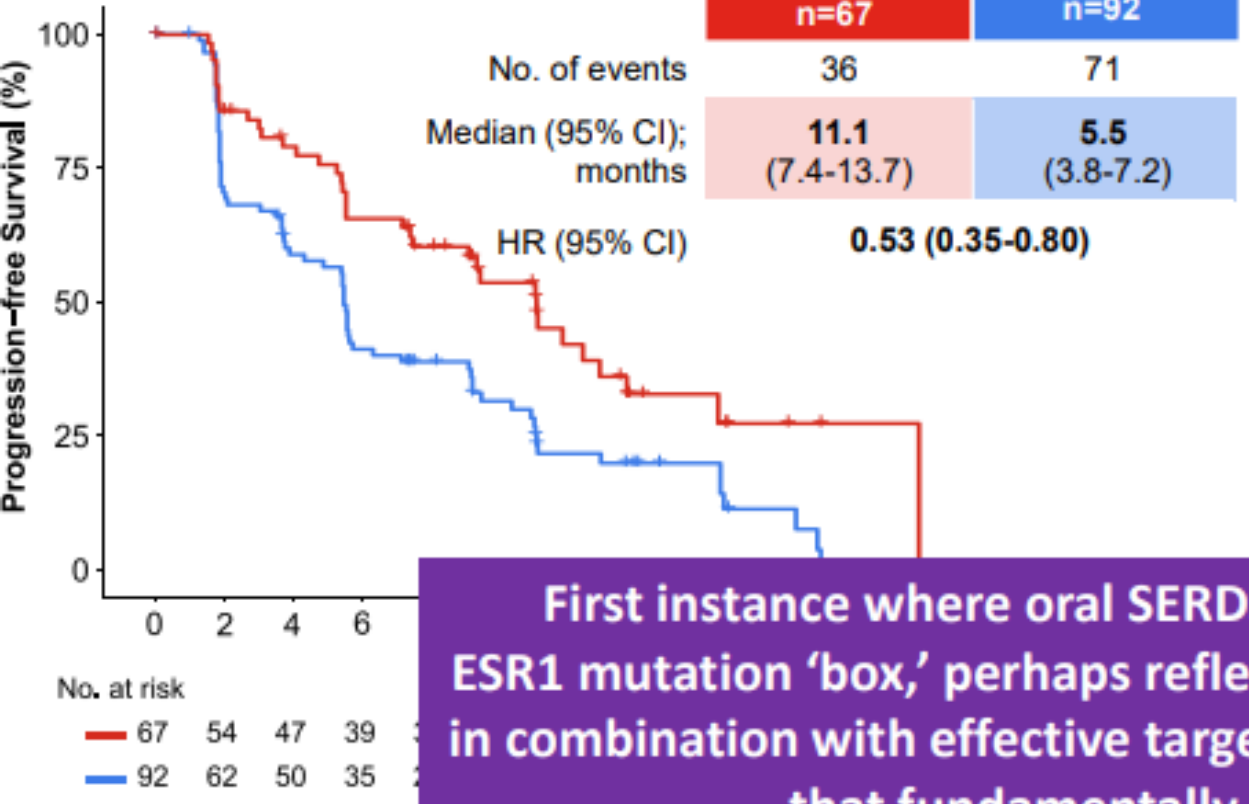
Subgroup Analysis: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS by *ESR1m* status

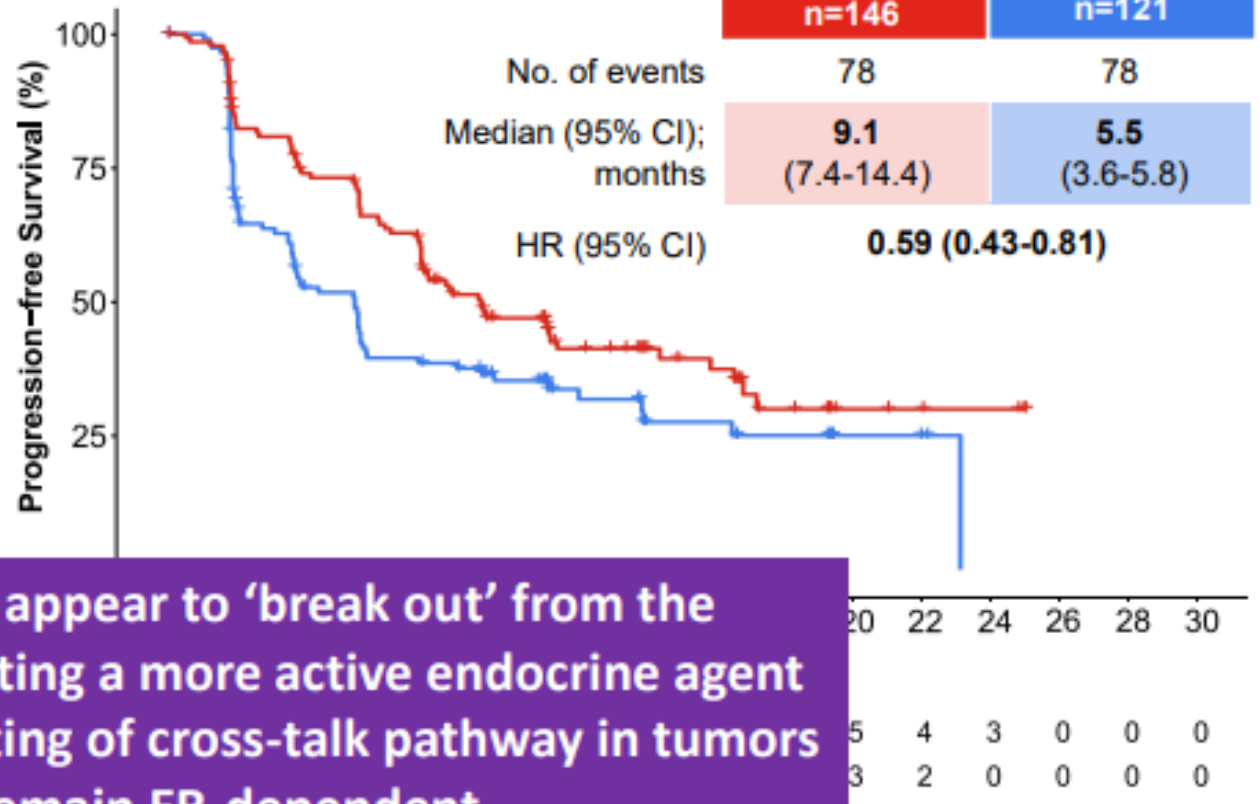
Patients with *ESR1*m

	Imlunestrant + abemaciclib n=67	Imlunestrant n=92
No. of events	36	71
Median (95% CI); months	**11.1** (7.4-13.7)	**5.5** (3.8-7.2)
HR (95% CI)	**0.53 (0.35-0.80)**	



Patients without *ESR1*m

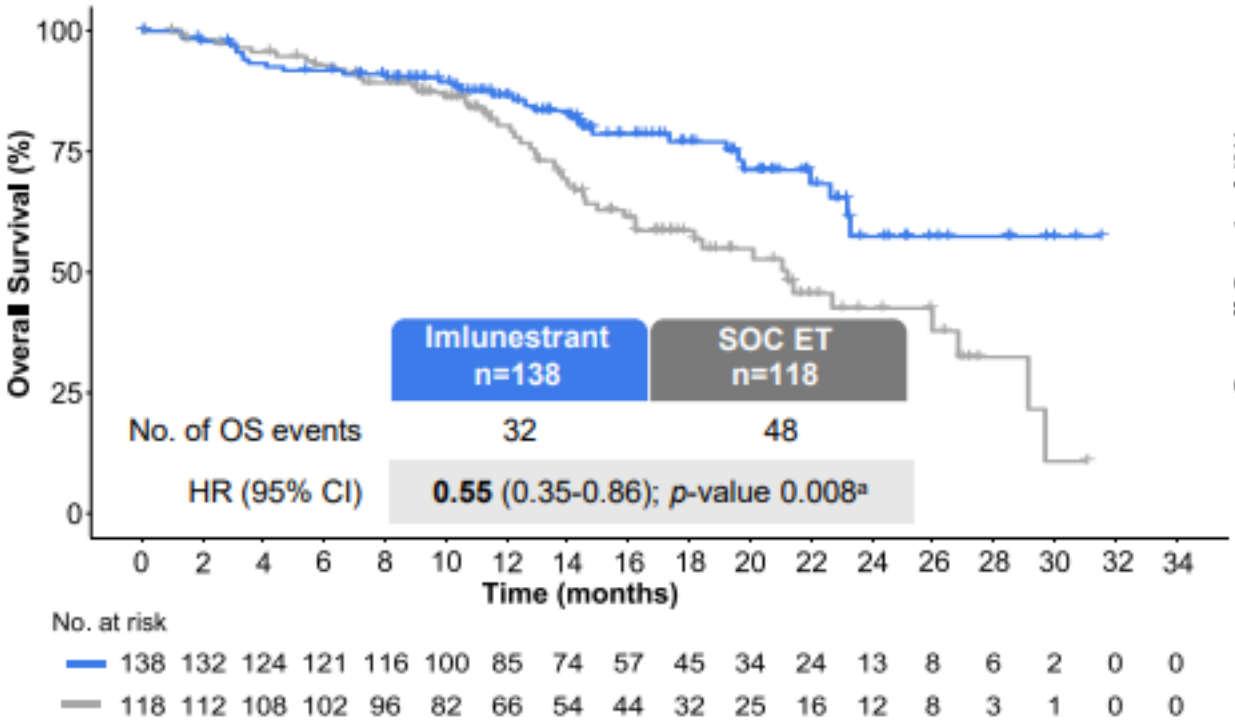
	Imlunestrant + abemaciclib n=146	Imlunestrant n=121
No. of events	78	78
Median (95% CI); months	**9.1** (7.4-14.4)	**5.5** (3.6-5.8)
HR (95% CI)	**0.59 (0.43-0.81)**	



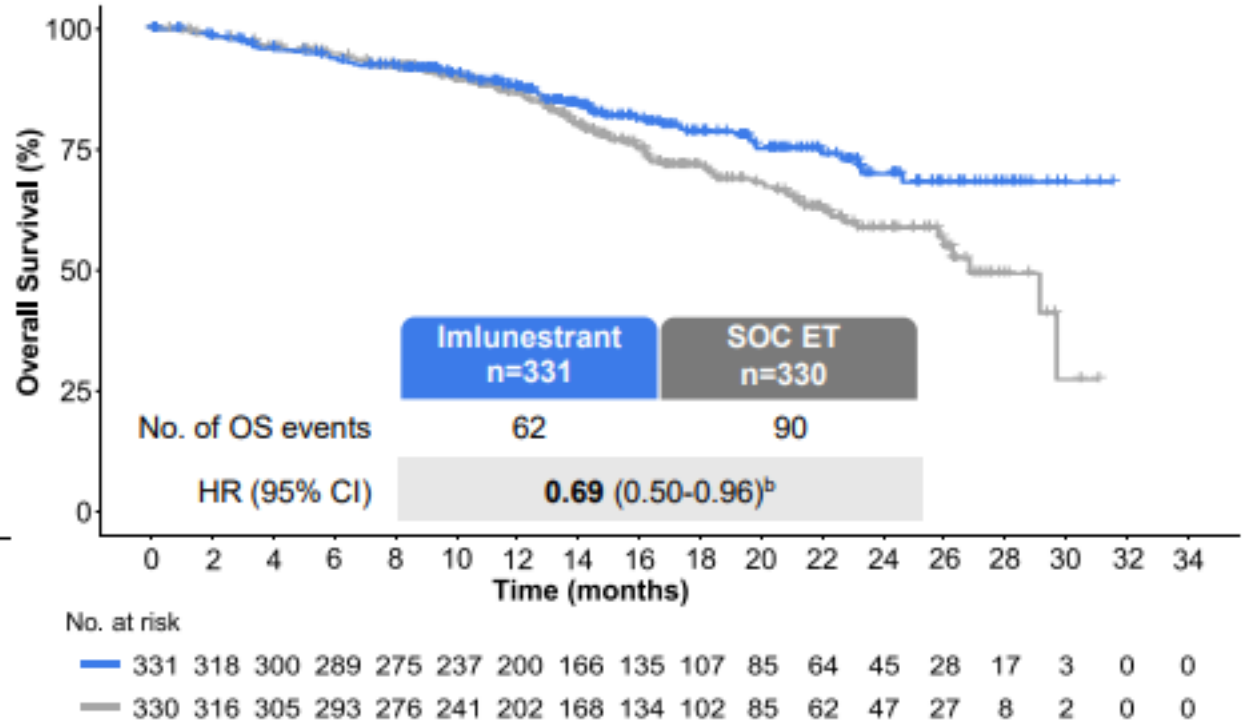
First instance where oral SERDs appear to 'break out' from the ESR1 mutation 'box,' perhaps reflecting a more active endocrine agent in combination with effective targeting of cross-talk pathway in tumors that fundamentally remain ER-dependent

Interim Overall Survival

Patients with *ESR1*m (31% maturity)



All Patients (23% maturity)



- In patients <u>without</u> *ESR1*m: maturity 18% (HR=0.87; 95% CI, 0.54-1.40)[c]
- In all patients within the combination therapy comparison: maturity 15% (HR=1.34; 95% CI, 0.81-2.21)[c]

*ESR1*m, *ESR1* mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival. Maturity is defined as the total number of events divided by the total number of patients. [a] Did not meet prespecified boundary for statistical significance; [b] Statistical significance was not inferentially tested due to not meeting the PFS endpoint; [c] Prespecified subgroup analysis, not inferentially tested, data available in the online supplementary slides.

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Safety and Tolerability

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

Generally favorable safety profile

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

Safety consistent with the known abemaciclib profile

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; PRO-CTAE, Patient Reported Outcomes-Common Terminology Criteria for AEs; SAE, serious AEs; TEAE, treatment-emergent AE. [a] Consolidated term; [b] N is the number of evaluable patients who received fulvestrant; [c] N is the number of evaluable patients who completed the PRO-CTCAE survey (answered "yes" or "no" to injection site pain, swelling, or redness).

[d] Dose reduction of imlunestrant alone: 2%; abemaciclib alone: 23%; both drugs: 14%

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Conclusions

Imlunestrant monotherapy

- **Significantly improved PFS vs SOC ET in patients with *ESR1*m (HR=0.62; 95% CI, 0.46-0.82)** but did not reach statistical significance in the overall population (HR=0.87; 95% CI, 0.72-1.04)
- Consistent benefit across key subgroups, secondary and exploratory endpoints, and sensitivity analyses
- OS analyses were immature and ongoing
- **Favorable safety** profile; no oral SERD specific safety signals (eg, ocular or cardiac)

Imlunestrant + abemaciclib

- **Significantly improved PFS vs imlunestrant in all patients (HR=0.57; 95% CI, 0.44-0.73), regardless of *ESR1*m status, achieving a 9.4-month PFS (95% CI, 7.5-11.9),** with consistent benefit across key subgroups
- **Predictable safety**, comparable to prior studies of fulvestrant + abemaciclib with a **low discontinuation rate (6%)** relative to available combination regimens (13-26%)[1,2]

Imlunestrant, as monotherapy or combined with abemaciclib, provides an all-oral targeted therapy option after progression on ET for patients with ER+, HER2- ABC

1. André F, et al. *Ann Oncol*. 2021;32(2):208-217; 2. Turner NC, et al. *N Engl J Med*. 2023;388(22):2058-2070.

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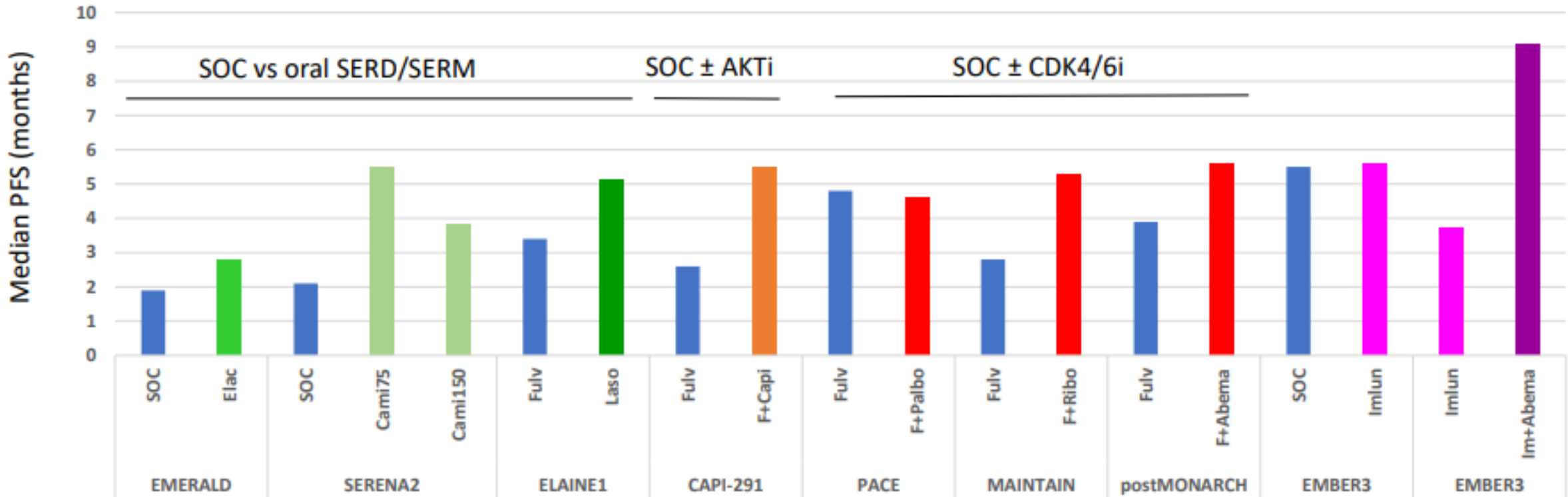
Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy:
*Outcomes among patients with prior CDK4/6 inhibitor treatment**



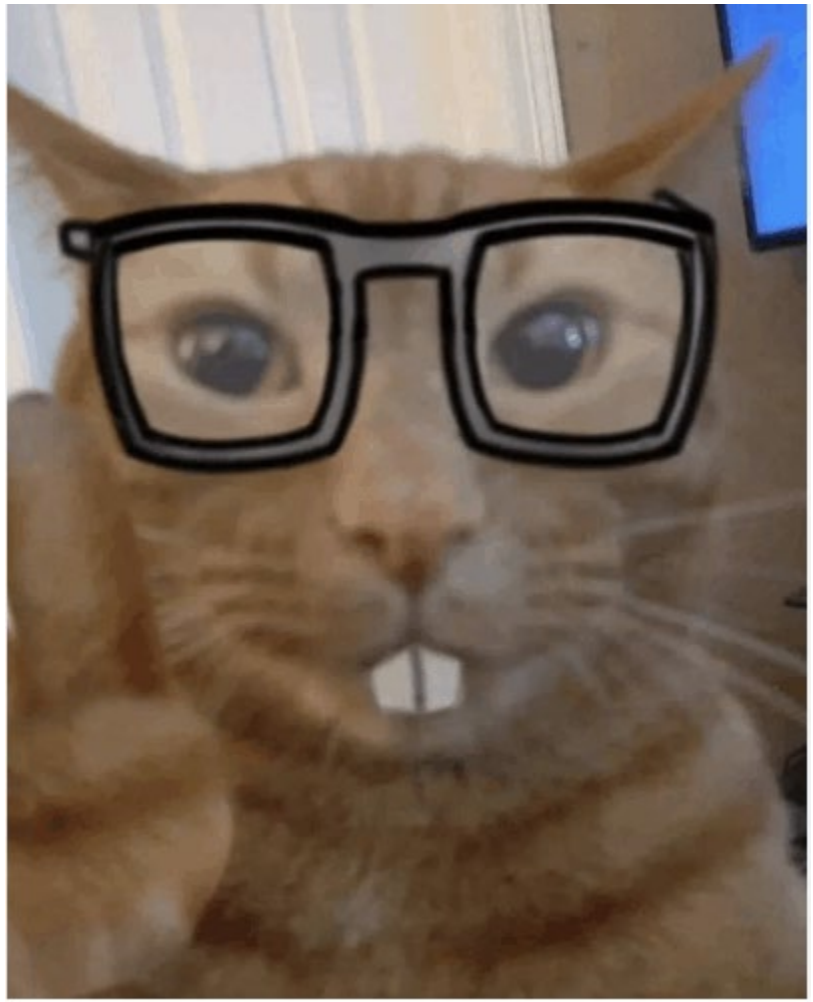
*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

Patient scenario

- 69yo CF presented with a large left sided breast mass eroding through the skin in 09/2018 with PET scan showing multiple metastatic sites to the bones and mediastinal/hilar LAN
- Underwent palliative RT to the Left breast
- Initiated on Ibrance and femara + bisphosphonates
- Did well for over 6 years
- Recently progression noted with progressive LAN and new lung nodules

We are NERDs & MUTATIONS excite US!



Summary of Detected Somatic Alterations & Biomarkers with Associated Treatment Options

✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 6)	% CFDNA OR COPY NUMBER
ESR1 D538G	✓ Elacestrant ⊗ Anastrozole, Exemestane, Letrozole	Yes	3.4%
PIK3CA N345K	✓ Capivasertib+fulvestrant ~ Alpelisib+fulvestrant	Yes	6.2%
TP53 A347T	None	Yes	0.8%
TP53 R175H	None	No	0.7%
TP53 G245S	None	No	0.2%
GATA3 F431fs	None	No	3.6%
RB1 c.2209_2211+3del (Splice Site Indel)	None	No	0.2%

Variants of uncertain clinical significance listed on following pages.

Treatment options

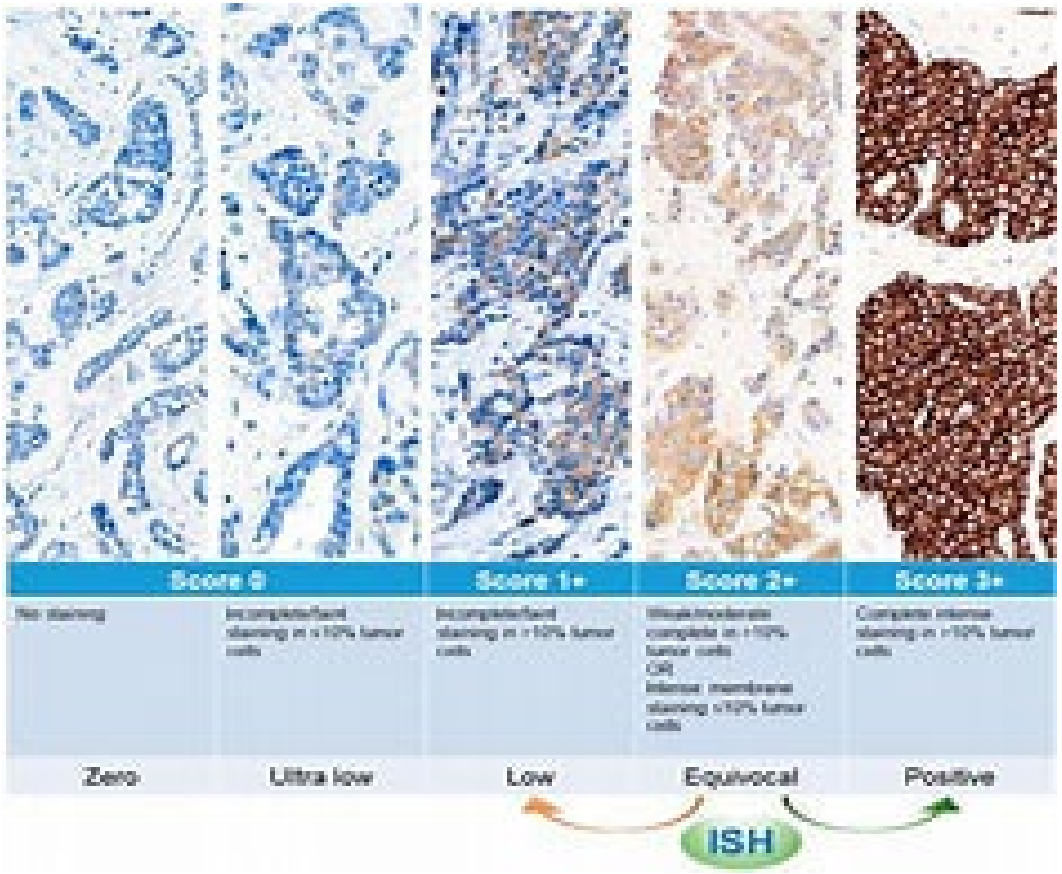
- Fulvestrant
- Elacestrant
- Fulvestrant + alpelisib
- Fulvestrant + capivasertib
- Fulvestrant + abemaciclib
- Imlunestrant + abemaciclib

Destiny Breast06

- Trastuzumab Deruxtecan (T-DXd) after Endocrine therapy in Metastatic Breast Cancer

- Presented at ASCO 2024

What is HER-2 Ultra-low ?



- IHC 0 with some membrane staining

DESTINY-Breast06 study design and primary results

Phase 3, randomized, multicenter, open-label study[1,2]

Data cutoff: March 18, 2024

Patient population

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) **OR** HER2-ultralow (IHC 0 with membrane staining) status
- Chemotherapy naïve in the mBC setting

Prior lines of therapy

- ≥2 lines ET ± targeted therapy for mBC

  OR
- 1 line for mBC AND
  - Progression ≤6 mo of starting first-line ET + CDK4/6i

    OR
  - Recurrence ≤24 mo of starting adjuvant ET

R 1:1

T-DXd 5.4 mg/kg Q3W (n=436)

HER2-low = 713
HER2-ultralow = 153

TPC (n=430)

Capecitabine, 59.8%; nab-paclitaxel, 24.4%; paclitaxel, 15.8%

Baseline characteristics*

- Median age **58 years**; ECOG PS ≥1 **~42%**
- De-novo mBC ~31%; liver metastases ~67%; visceral disease ~85%; primary endocrine resistance ~31%

Primary endpoint

- PFS (BICR) in HER2-low
  - Median **13.2 mo T-DXd** vs 8.1 mo TPC (hazard ratio 0.62; P<0.0001)†

Secondary endpoints

- PFS (BICR) in ITT (HER2-low + HER2-ultralow)
  - Median **13.2 mo T-DXd** vs 8.1 mo TPC (hazard ratio 0.64; P<0.0001)‡
- OS
  - Data maturity ~40% at first IA; early trend favoring T-DXd in ITT
- PFS2 (INV)
- Safety and tolerability

*As averaged across treatment groups in the ITT population; †the hazard ratio and its CI was estimated from a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs no) and HER2 IHC expression (IHC 1+ vs IHC 2+/ISH−); ‡the hazard ratio and its CI was estimated from an unstratified Cox proportional hazards model

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IA, interim analysis; IHC, immunohistochemistry; INV, investigator; ISH−, in situ hybridization–negative; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival / time from randomization to second progression or death; Q3W, every 3 weeks; R, randomization; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, physician's choice of chemotherapy

1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. NCT04494425. Updated. October 17, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed October 23, 2024)

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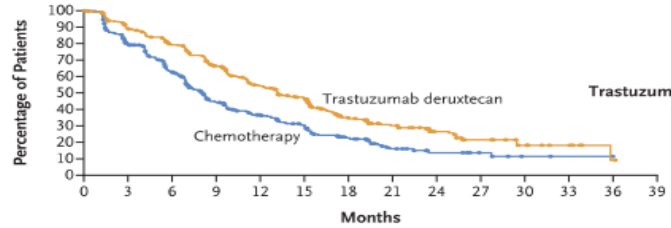
A Progression-free Survival in the HER2-Low Population



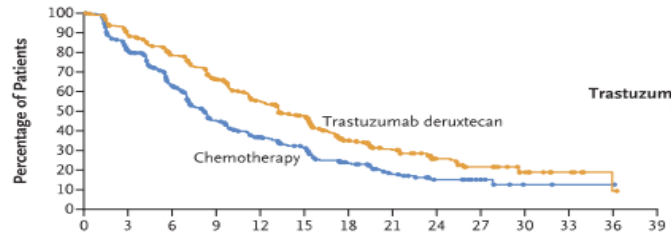
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	359	13.2 (11.4–15.2)
Chemotherapy	354	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, 0.62 (95% CI, 0.52–0.75)
P<0.001

No. at Risk

Trastuzumab deruxtecan	359	310	265	213	163	131	72	49	28	17	10	6	1	0
Chemotherapy	354	254	192	118	85	65	37	19	10	6	2	1	1	0

B Progression-free Survival in the Intention-to-Treat Population



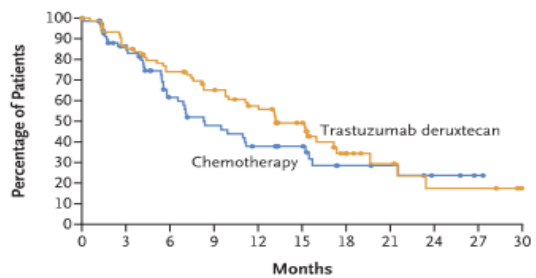
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	436	13.2 (12.0–15.2)
Chemotherapy	430	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, 0.64 (95% CI, 0.54–0.76)
P<0.001

No. at Risk

Trastuzumab deruxtecan	436	375	319	258	199	156	82	56	32	21	11	6	1	0
Chemotherapy	430	306	224	142	103	79	44	25	13	7	2	1	1	0

C Progression-free Survival in the HER2-Ultralow Population



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	76	13.2 (9.8–17.3)
Chemotherapy	76	8.3 (5.8–15.2)

Hazard ratio for disease progression or death, 0.78 (95% CI, 0.50–1.21)

No. at Risk

Trastuzumab deruxtecan	76	64	53	44	35	24	9	6	3	3	0
Chemotherapy	76	52	32	24	18	14	7	6	3	1	0

Efficacy and safety of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) by pace of disease progression on prior endocrine-based therapy: additional analysis from DESTINY-Breast06

LB1-04

Tuesday, December 10, 2024

Aditya Bardia, MD, MPH

University of California Los Angeles,
Jonsson Comprehensive Cancer Center,
Los Angeles, CA, US

Additional authors: Xichun Hu, Rebecca Dent, Kan Yonemori, Carlos H Barrios, Jean-Yves Pierga, Fabio Puglisi, Jean-Marc Ferrero, Kyung Hae Jung, Nusayba A Bagegni, Joëlle Collignon, Miguel Gil-Gil, Xiaoling Wu, Aleksandra Andrzejuk-Ćwik, Maria Schwaederle, Giuseppe Curigliano

On behalf of the DESTINY-Breast06 investigators

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Objectives

Investigate the benefit of T-DXd in patients with different responses to ET*

Time to progression on 1L ET + CDK4/6i; primary/secondary endocrine resistance

Assess the efficacy of subsequent therapies post progression on T-DXd/TPC

Time from randomization to second progression or death (PFS2)

Understand the benefit of T-DXd in patients with varying disease burdens*

Baseline tumor extent and location

*Exploratory post-hoc analyses
1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; PFS2, second progression-free survival / time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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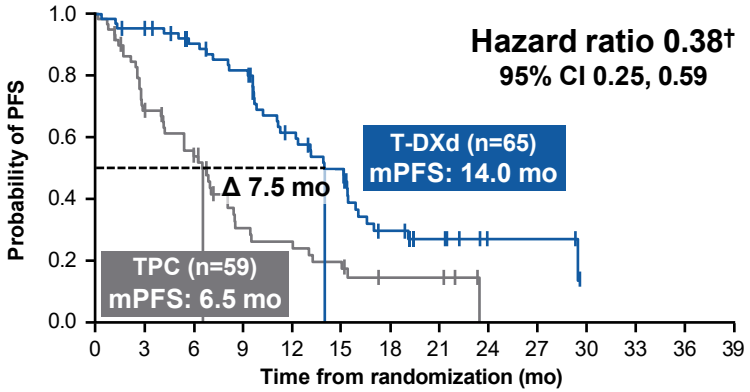
PFS by time to progression on 1L ET + CDK4/6i and endocrine resistance

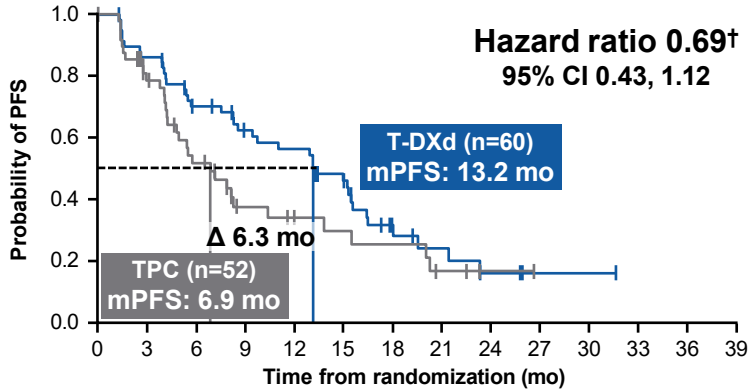
<6-mo 1L TTP*



Number at risk

T-DXd	65	61	53	47	32	25	12	8	3	3	0
TPC	59	38	30	14	12	9	4	4	0	0	0

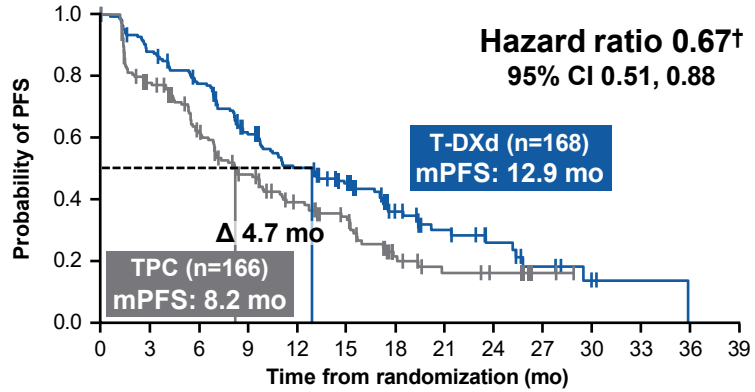
6–12-mo 1L TTP*



Number at risk

T-DXd	60	50	38	31	28	20	9	6	3	1	1	0
TPC	52	34	21	11	8	7	6	3	1	0	0	0

>12-mo 1L TTP*



Number at risk

T-DXd	168	146	125	94	74	59	28	17	11	6	2	1	0
TPC	166	114	86	62	44	33	14	8	6	2	0	0	0

	Primary endocrine resistance‡		Secondary endocrine resistance‡	
	T-DXd (n=128)	TPC (n=140)	T-DXd (n=308)	TPC (n=288)
mPFS, mo (95% CI)	12.4 (10.3, 15.2)	6.6 (5.4, 7.4)	13.2 (12.0, 15.5)	9.5 (8.0, 11.1)
PFS hazard ratio (95% CI)	0.57 (0.42, 0.77)†		0.68 (0.55, 0.84)†	

T-DXd improved PFS vs TPC regardless of time to progression on 1L ET + CDK4/6i or type of endocrine resistance

*TTP analysis included 570 patients with PD on prior 1L ET + CDK4/6i (65.8% of the ITT population); †the hazard ratio and its CI were estimated from an unstratified Cox proportional hazards model; ‡endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC[1]

1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; (m)PFS, (median) progression-free survival; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

1. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–1649

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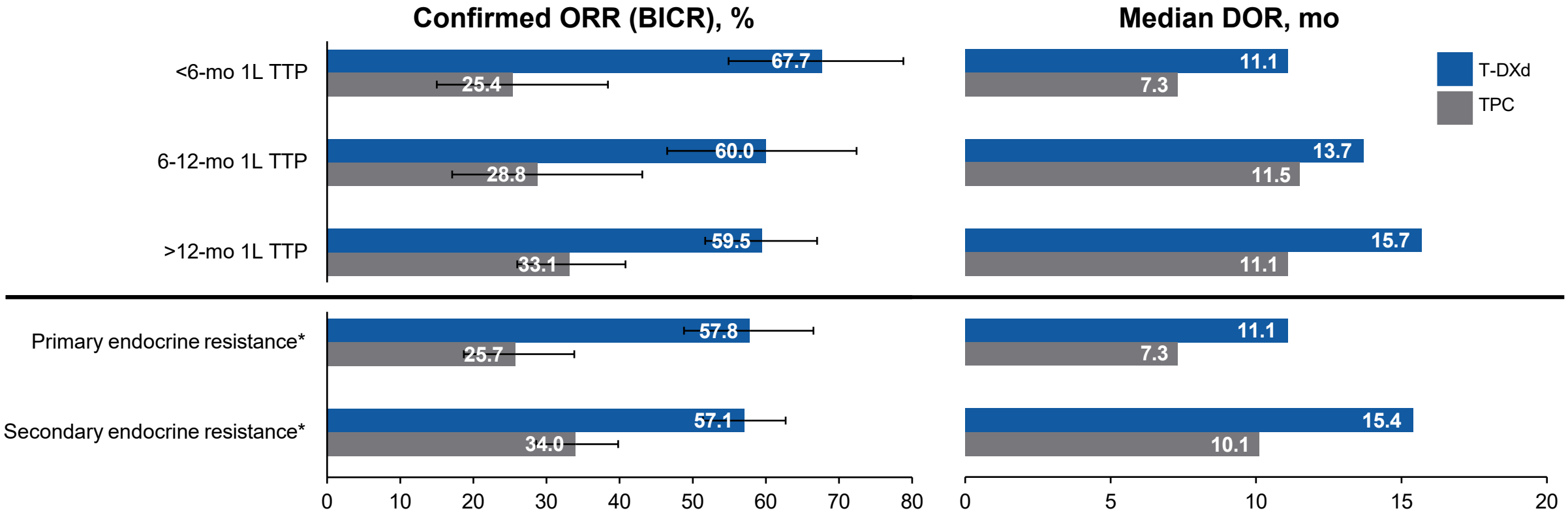
ORR and DOR by time to progression on 1L ET + CDK4/6i and endocrine resistance



T-DXd improved ORR and DOR vs TPC across all TTP subgroups and in patients with primary and secondary endocrine resistance

Error bars represent 95% confidence intervals

*Endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC[1]

1L, first line; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; mBC, metastatic breast cancer; mo, months; ORR, objective response rate; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

1. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–1649

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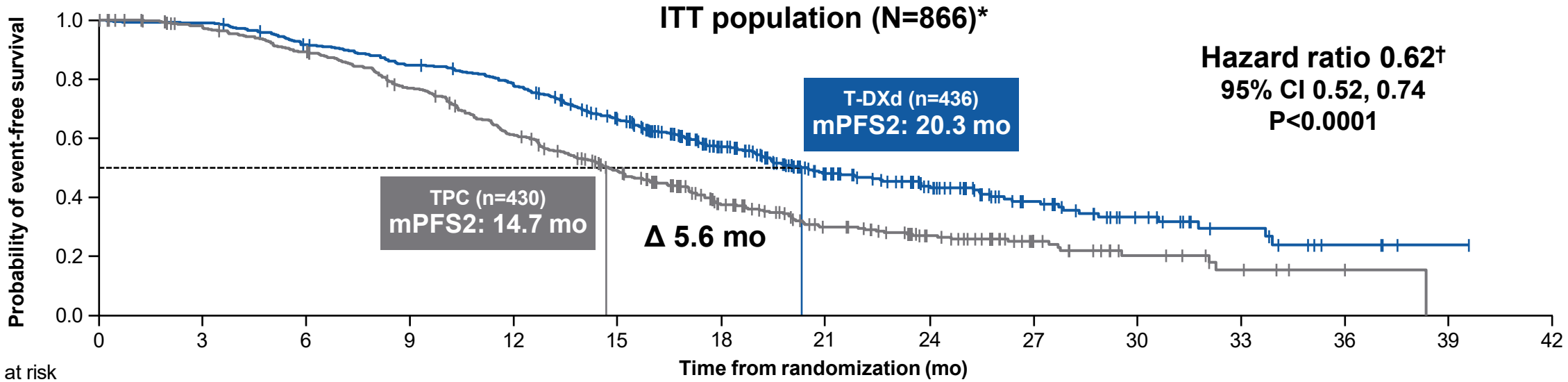
PFS2 in the overall ITT population and time-to-progression subgroups



Number at risk

T-DXd	436	431	396	365	322	268	176	115	78	43	23	11	4	1	0
TPC	430	399	365	311	244	183	109	69	48	26	12	6	2	0	0

	<6-mo 1L TTP		6–12-mo 1L TTP		>12-mo 1L TTP	
	T-DXd (n=65)	TPC (n=59)	T-DXd (n=60)	TPC (n=52)	T-DXd (n=168)	TPC (n=166)
mPFS2, mo (95% CI)	18.9 (14.4, 24.0)	15.2 (10.9, 17.5)	17.1 (13.9, 31.8)	13.7 (10.3, 17.1)	20.0 (18.6, 25.3)	14.3 (12.6, 15.9)
PFS2 hazard ratio (95% CI)	0.73 (0.46, 1.14)†		0.59 (0.37, 0.94)†		0.57 (0.43, 0.75)†	

Delay in PFS2‡ was clinically meaningful in favor of T-DXd in the ITT population and TTP subgroups

*Of patients who received immediate post-discontinuation therapy (n=608), regimens included chemotherapy (66.7%), endocrine-based therapy (26.0%), ADC (7.8%), and targeted therapy alone (2.5%); †the hazard ratio and its CI was estimated from an unstratified Cox proportional hazards model; ‡PFS2 was defined by investigators according to local standard clinical practice as time from randomization to second progression (earliest progression event following first subsequent therapy) or death
ADC, antibody-drug conjugate; CI, confidence interval; ET, endocrine therapy; ITT, intent-to-treat; mo, months; (m)PFS2, (median) second progression-free survival / time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

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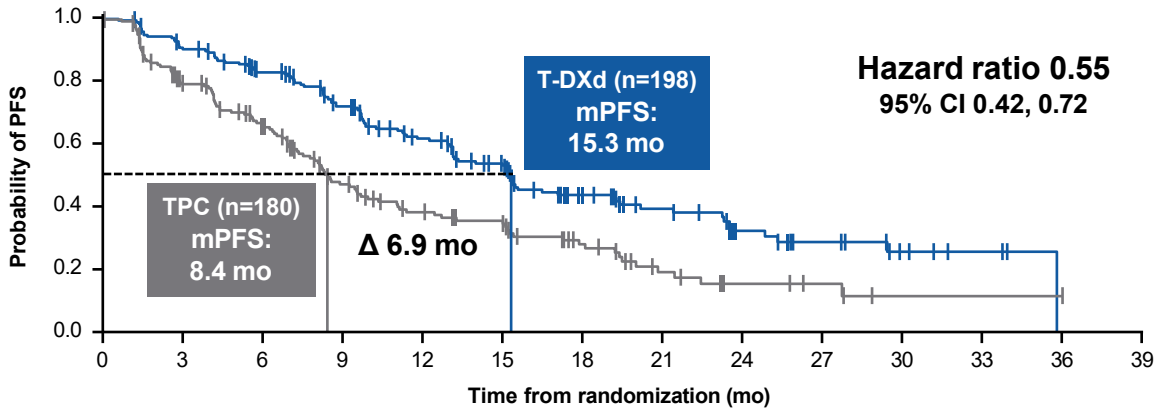
PFS by measures of disease burden

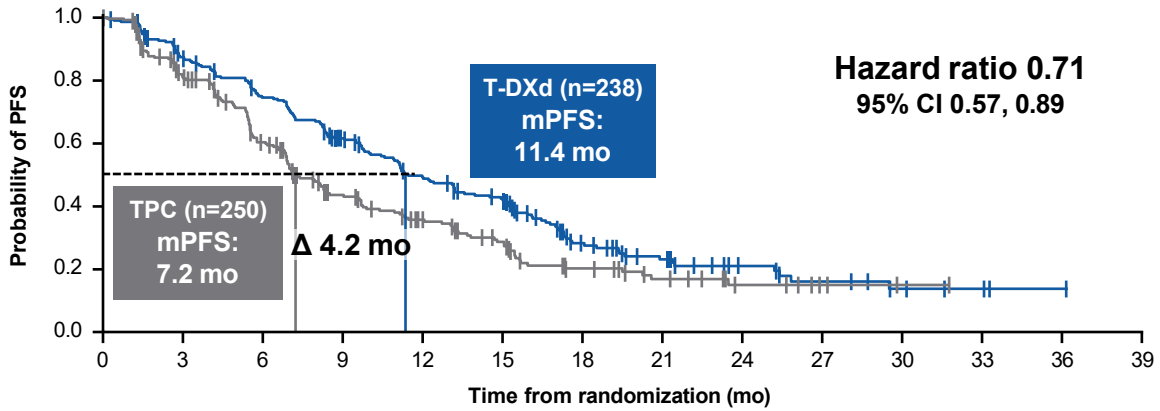
<3 local/metastatic sites at baseline



Number at risk

T-DXd	198	175	152	125	97	76	45	32	18	12	6	3	0	0
TPC	180	125	99	62	45	37	22	11	6	4	1	1	1	0

≥3 local/metastatic sites at baseline

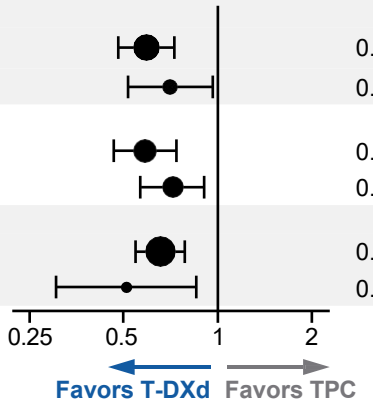


Number at risk

T-DXd	238	200	167	133	102	80	37	24	14	9	5	3	1	0
TPC	250	181	125	80	58	42	22	14	7	3	1	0	0	0

PFS benefit with T-DXd was observed regardless of disease burden, with notable efficacy in patients with lower disease burden

	mPFS, mo (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	
Liver metastases			
Yes (n=579)	12.2 (10.4, 13.5)	7.0 (6.4, 8.1)	0.59 (0.48, 0.72)
No (n=287)	16.5 (13.2, 19.4)	11.3 (8.3, 15.2)	0.70 (0.51, 0.96)
Baseline tumor size*			
>Median (n=432)	12.0 (9.9, 15.2)	7.1 (6.5, 8.3)	0.57 (0.45, 0.72)
≤Median (n=434)	15.0 (13.1, 16.1)	9.7 (7.5, 13.2)	0.71 (0.55, 0.90)
Visceral disease			
Yes (n=740)	13.1 (11.1, 15.1)	7.9 (6.9, 8.5)	0.65 (0.55, 0.78)
No (n=126)	23.3 (13.1, NE)	11.3 (6.9, 15.7)	0.51 (0.30, 0.85)



*Median baseline tumor size in the ITT population (per BICR) was 48.6 mm, considering '0' as baseline tumor size for patients without target lesion at baseline
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; ET, endocrine therapy; HR, hazard ratio; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; NE, not evaluable; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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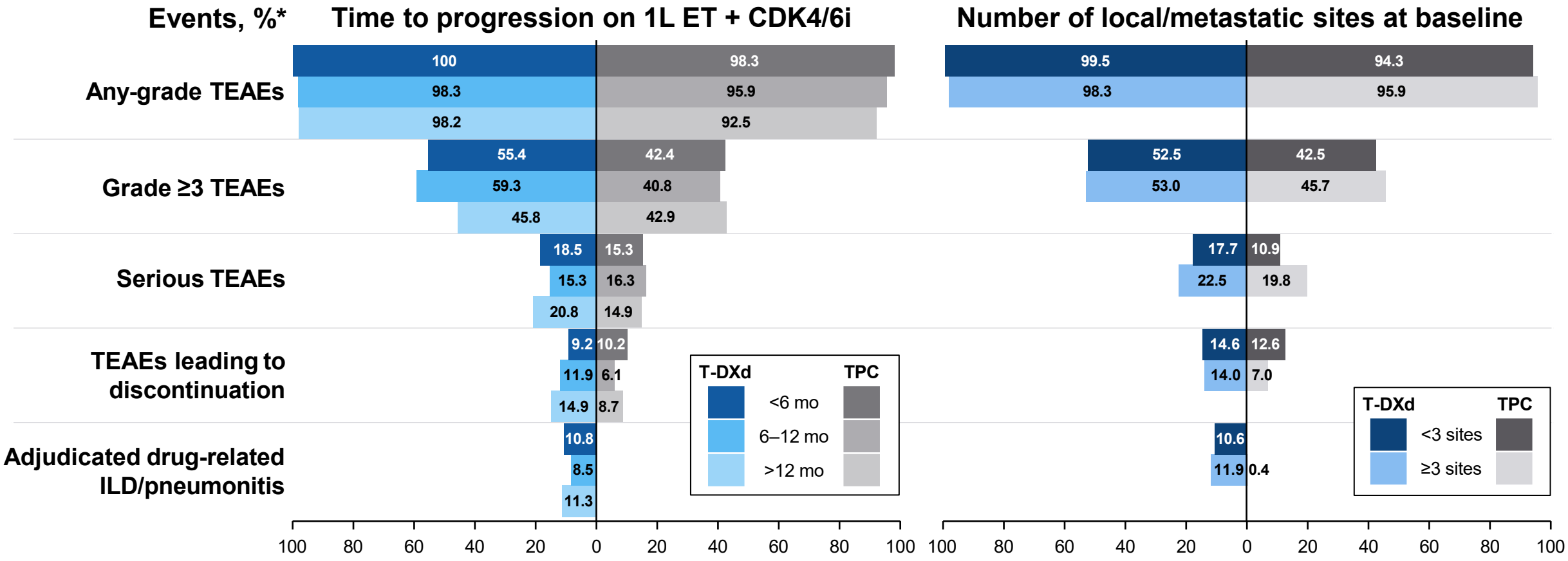
Safety in time-to-progression and disease burden subgroups



Safety profiles for T-DXd and TPC in time-to-progression and disease burden subgroups were in line with the overall safety population†

*Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first). Includes ILD/pneumonitis with an onset date or worsening on or after the date of first dose; †overall safety population (T-DXd vs TPC): any TEAEs, 98.8% vs 95.2%; Grade ≥3 TEAEs, 52.8% vs 44.4%; serious TEAEs, 20.3% vs 16.1%; TEAEs leading to discontinuation, 14.3% vs 9.4%; adjudicated drug-related ILD/pneumonitis, 11.3% vs 0.2%[1,2]

1L, first line; AE, adverse event; ET, endocrine therapy; ILD, interstitial lung disease; mo, months; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, physician's choice of chemotherapy; TTP, time to progression

1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. Bardia A, et al. *N Engl J Med.* 2024;391:2110–2122

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Conclusions

- T-DXd demonstrated a clinically meaningful efficacy benefit vs TPC regardless of TTP on 1L ET + CDK4/6i (**mPFS 12.9–14.0 mo with T-DXd**)
  - This included patients with rapid (<6-mo) progression on 1L ET + CDK4/6i
- Efficacy outcomes were consistent in patients with primary and secondary endocrine resistance (**mPFS 12.4–13.2 mo with T-DXd**)
- PFS2 favored T-DXd over TPC in the overall population (**mPFS2 20.3 mo with T-DXd**) and in all TTP subgroups (**mPFS2 17.1–20.0 mo with T-DXd**), indicating a sustained benefit with T-DXd beyond initial disease progression
- T-DXd demonstrated efficacy regardless of disease burden, with efficacy also in patients with low disease burden (**mPFS 15.0–23.3 mo with T-DXd**)
- Safety profiles in subgroups were consistent with the overall safety population

T-DXd is an effective treatment option in patients with HR+, HER2-low/-ultralow mBC following ≥1 endocrine-based therapy

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This study was sponsored and designed by AstraZeneca, in collaboration with Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201)
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1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; (m)PFS2, (median) second progression-free survival / time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

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Clinical implications of the study/ Take aways

- Consider using in earlier lines of treatment
- Will have to be an individualized patient decision given safety profile
- Pathologists will have to separate the current HER-2 IHC 0 category (with and without membrane staining)
- Will need to work closely with our pathologists in determining the Her-2 ultra low population

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Impact of Anthracyclines in High Genomic Risk Node-Negative HR+/HER2- Breast Cancer

Nan Chen MD[a], Jincong Q Freeman MPH MS, Sudha Yarlagadda MD, Aishwarya Atmakuri, Kevin Kalinsky MD, Lajos Pusztai MD DPhil, Dezheng Huo MD PhD, Rita Nanda MD, Frederick M Howard MD[a]

Presentation ID: GS3-03

[a] Department of Internal Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA

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Key Conclusions:

- TAILORx study demonstrated benefit of chemotherapy in hormone receptor positive (HR+)/ HER2-negative, lymph-node negative breast cancers with recurrence scores (RS) ≥ 26

- This post-hoc analysis of TAILORx demonstrates benefit from the addition of anthracyclines to a taxane-based regimen in cancers with RS ≥ 31
  - Benefit is limited to tumors > 2cm in size

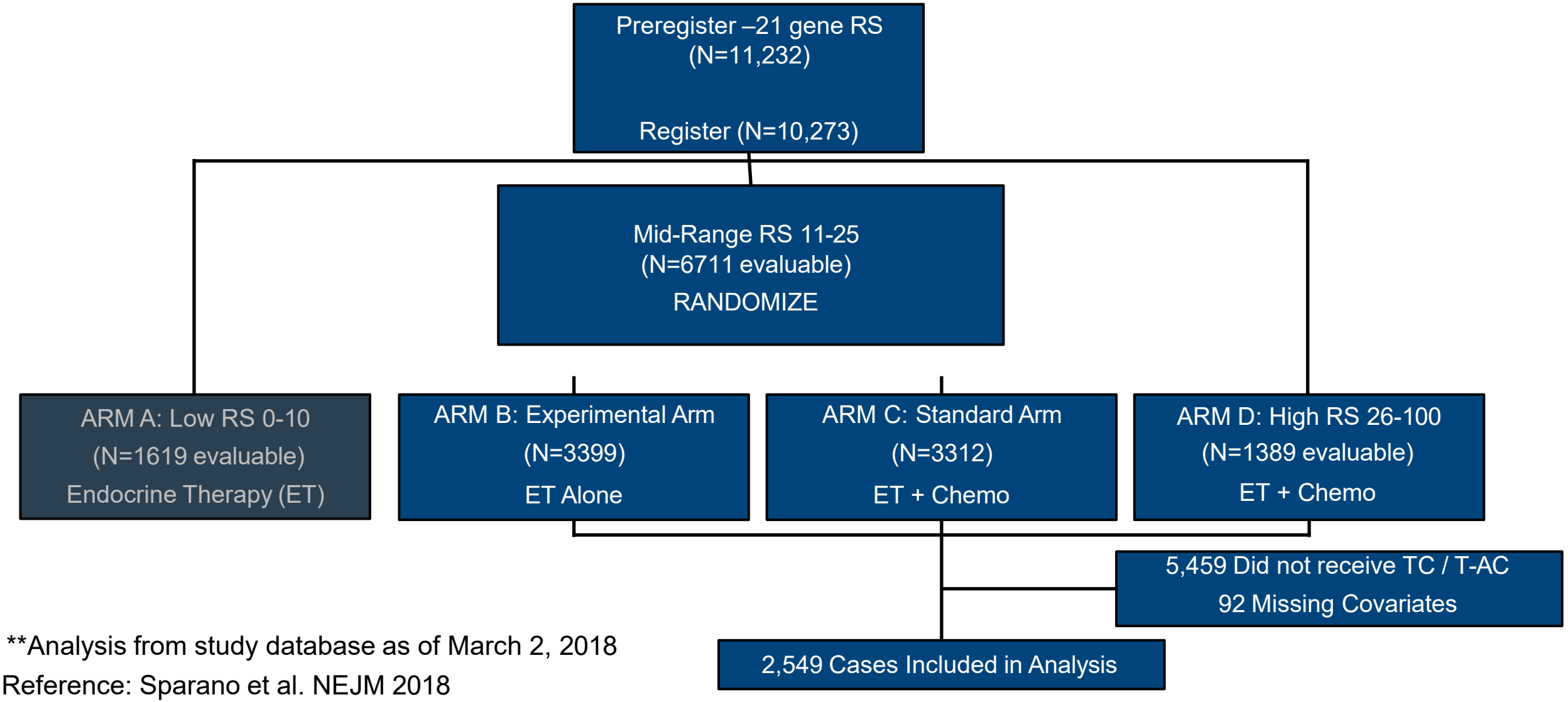
- This benefit increases with increasing RS above 31

Anthracyclines in Early HR+ Breast Cancer

- The role of chemotherapy in the adjuvant treatment of high-risk, early-stage HR+/HER2- breast cancer has evolved
- Anthracyclines in Early Breast Cancer (ABC) trials evaluated the potential non-inferiority of taxane plus cyclophosphamide (TC) for 6 cycles vs taxane plus anthracycline based therapy (T-AC) with a primary endpoint of invasive disease-free survival (IDFS) in early-stage HER2- breast cancer
  - No benefit of anthracyclines in overall subset of HR+ cancers
  - Poor correlation between number of LN and benefit of anthracycline (hazard ratio 0.95 in LN-, HR+ population)
- RS cutoffs of 26 and 31 have been previously evaluated for benefit of chemotherapy

Reference: Blum et al. JCO 2017; Geyer et al. JCO 2024

Study Design



**Analysis from study database as of March 2, 2018

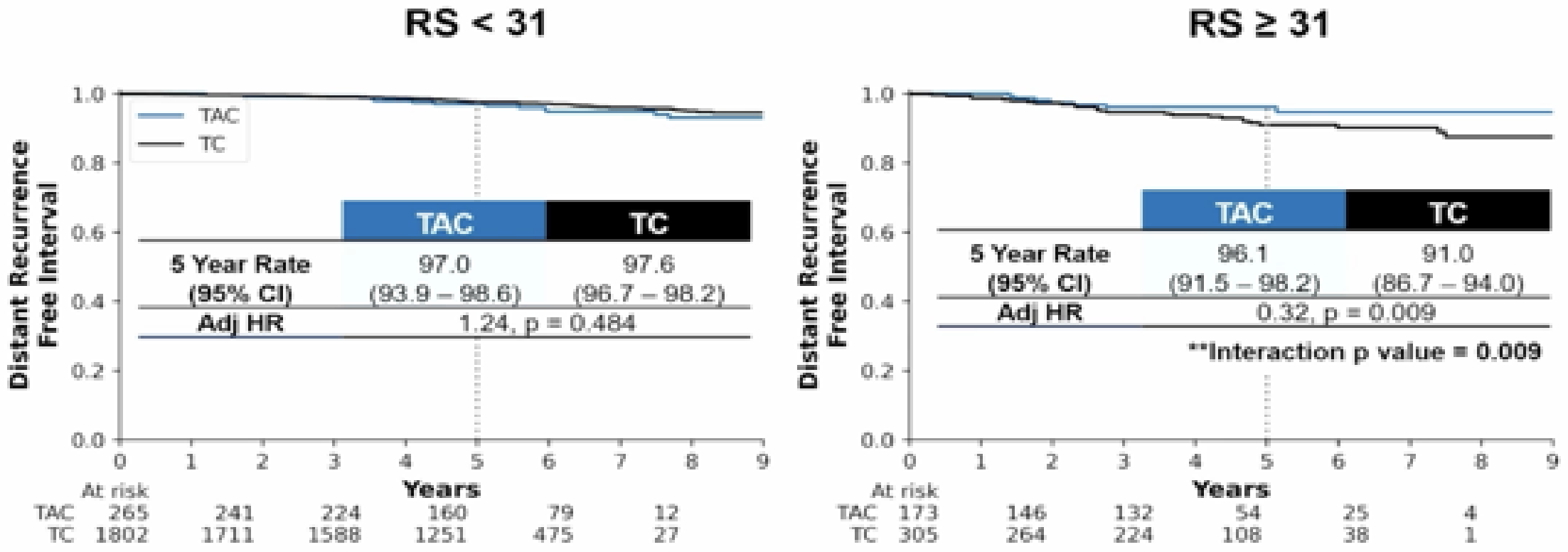
Reference: Sparano et al. NEJM 2018

Patient Characteristics

	T-AC n = 438	TC n = 2111
Age, mean (SD)	53.0 (9.3)	55.1 (9.1)
Menopausal Status, n (%)		
Postmenopausal	256 (58.4)	1359 (64.4)
Premenopausal	182 (41.6)	752 (35.6)
Tumor Size (mm), mean (SD)	19.6 (9.0)	17.7 (8.1)
Grade, n (%)		
Low	63 (14.4)	461 (21.8)
Medium	203 (46.3)	1096 (51.9)
High	159 (36.3)	504 (23.9)
PR Status		
Positive	348 (79.5)	1810 (85.7)
Negative	90 (20.5)	301 (14.3)

	T-AC n = 438	TC n = 2111
Recurrence Score, mean (SD)	29.6 (14.2)	22.3 (9.5)
Recurrence Score, n (%)		
11-25	196 (44.7)	1554 (73.6)
26-30	69 (15.8)	251 (11.9)
31-100	173 (39.5)	306 (14.5)
Chemotherapy Regimen, n (%)		
Dose dense AC-T	186 (42.5)	
Standard AC-T	110 (25.1)	
Concurrent TAC	57 (13.0)	
Other Anthracycline / Taxane	85 (19.4)	
TC		2111 (100.0)

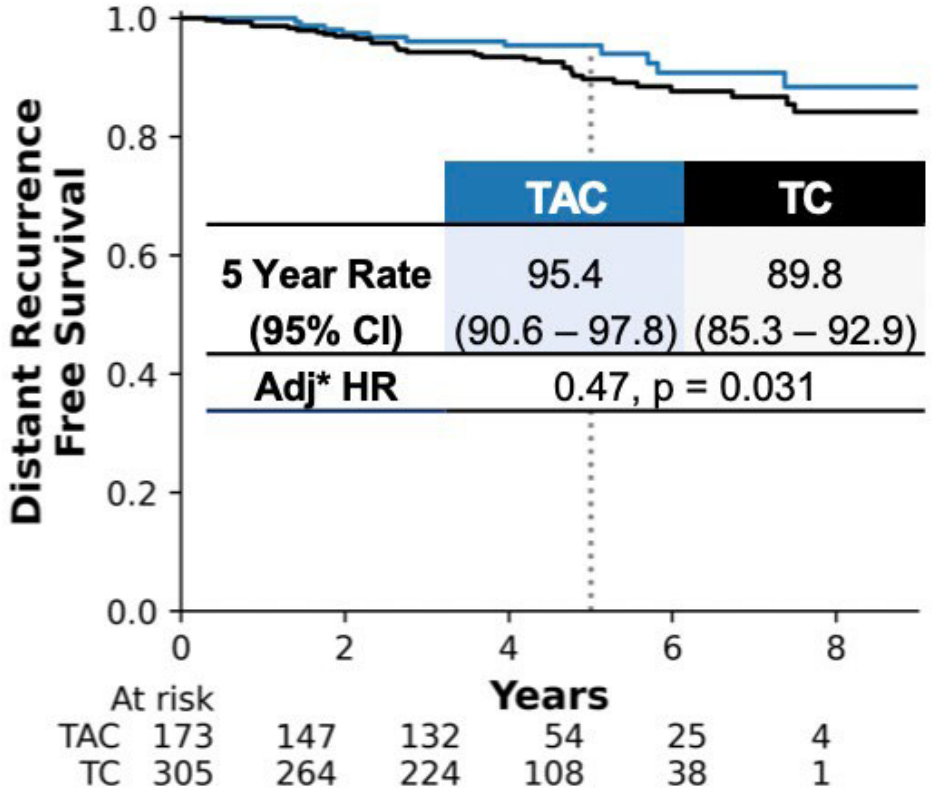
Primary Survival Outcome: Distant Recurrence-Free Interval at 5 years



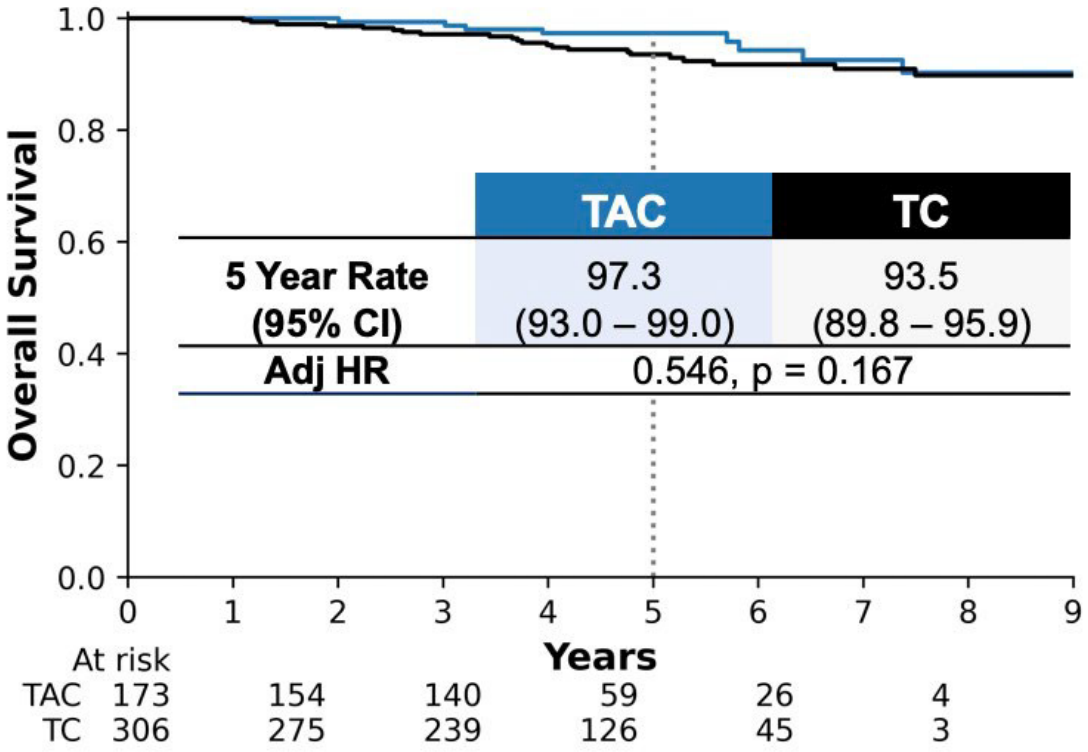
*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received, and interaction of treatment with RS

Selected Secondary Survival Outcomes: DRFS and OS at 5 years in RS ≥ 31

DRFS

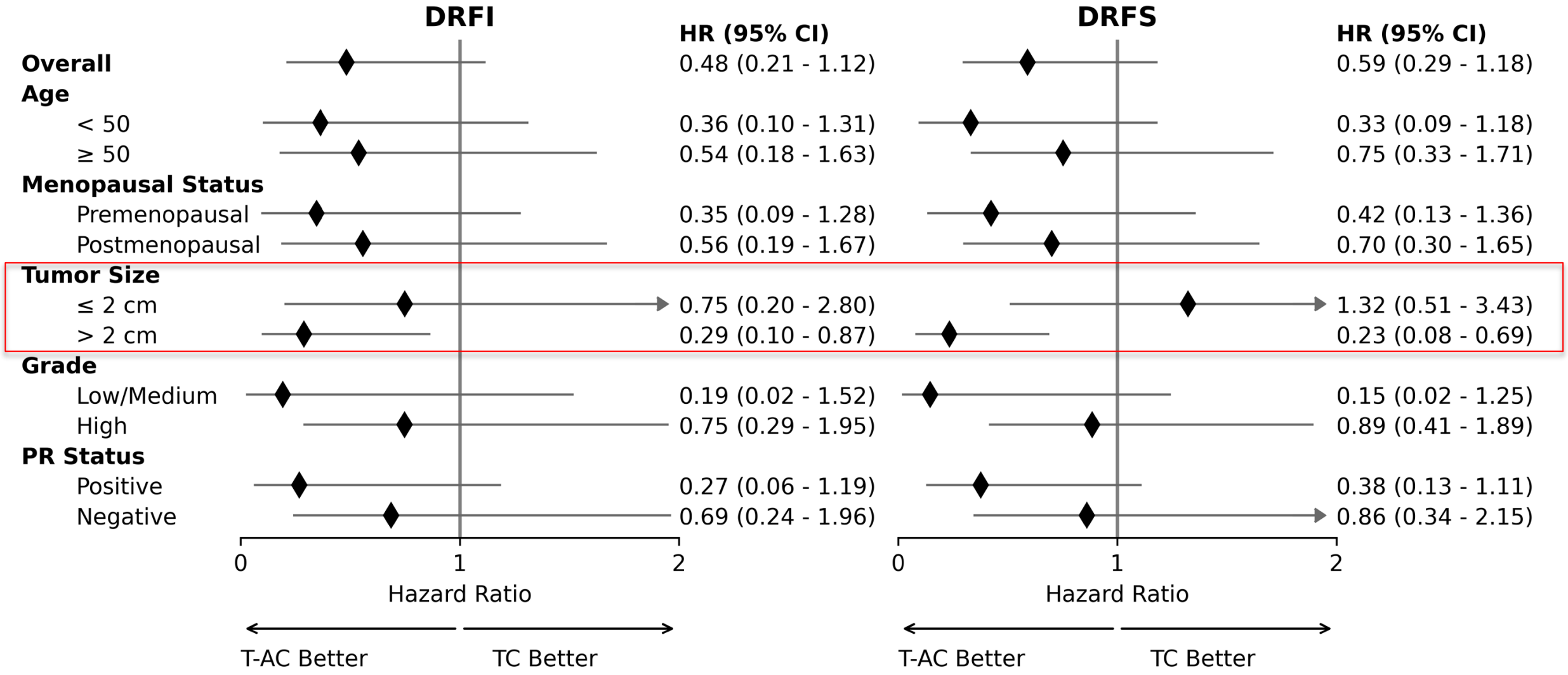


OS

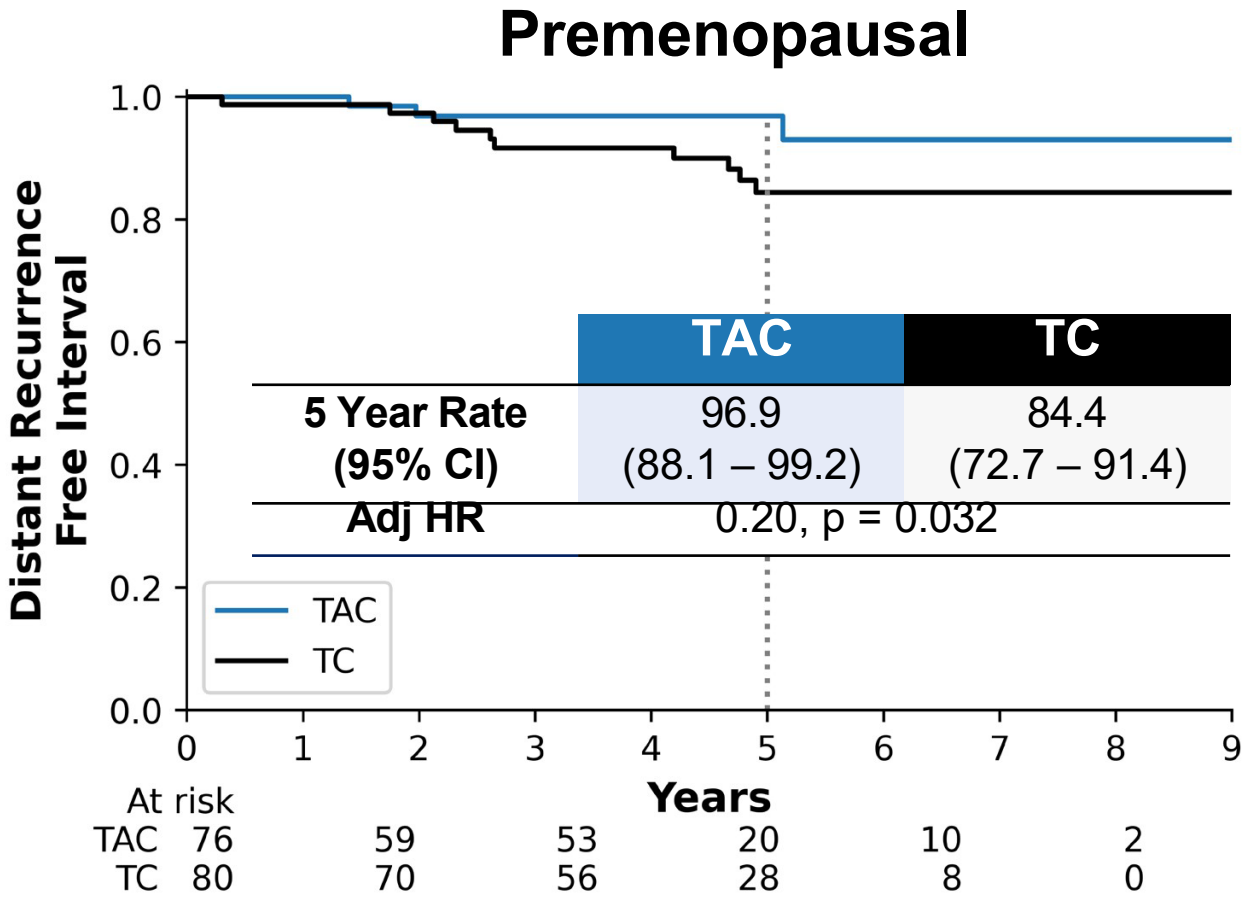


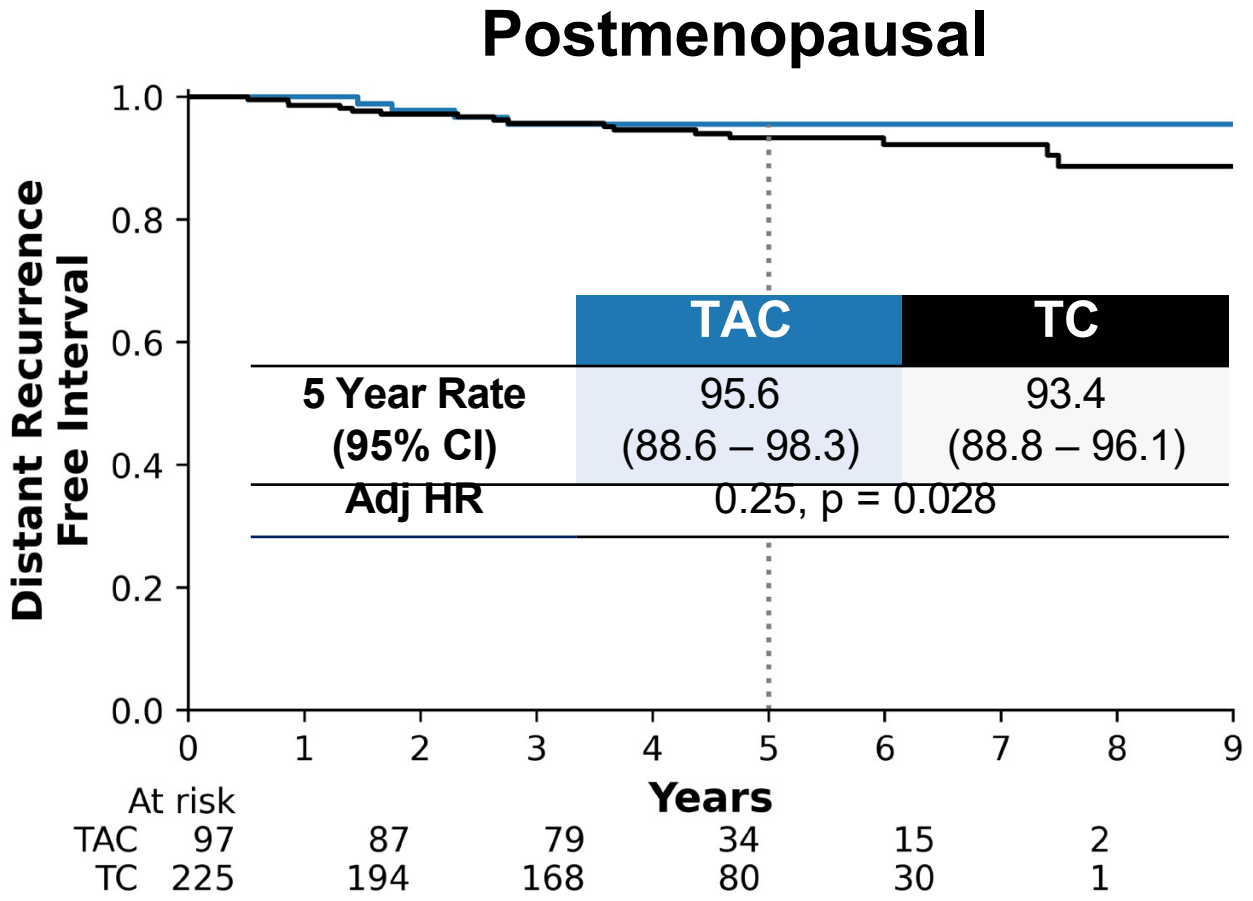
*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received, and interaction of treatment with RS

Subgroup Analyses of T-AC vs TC with OncotypeDX RS ≥ 31



DRFI by Menopausal Status in RS ≥ 31

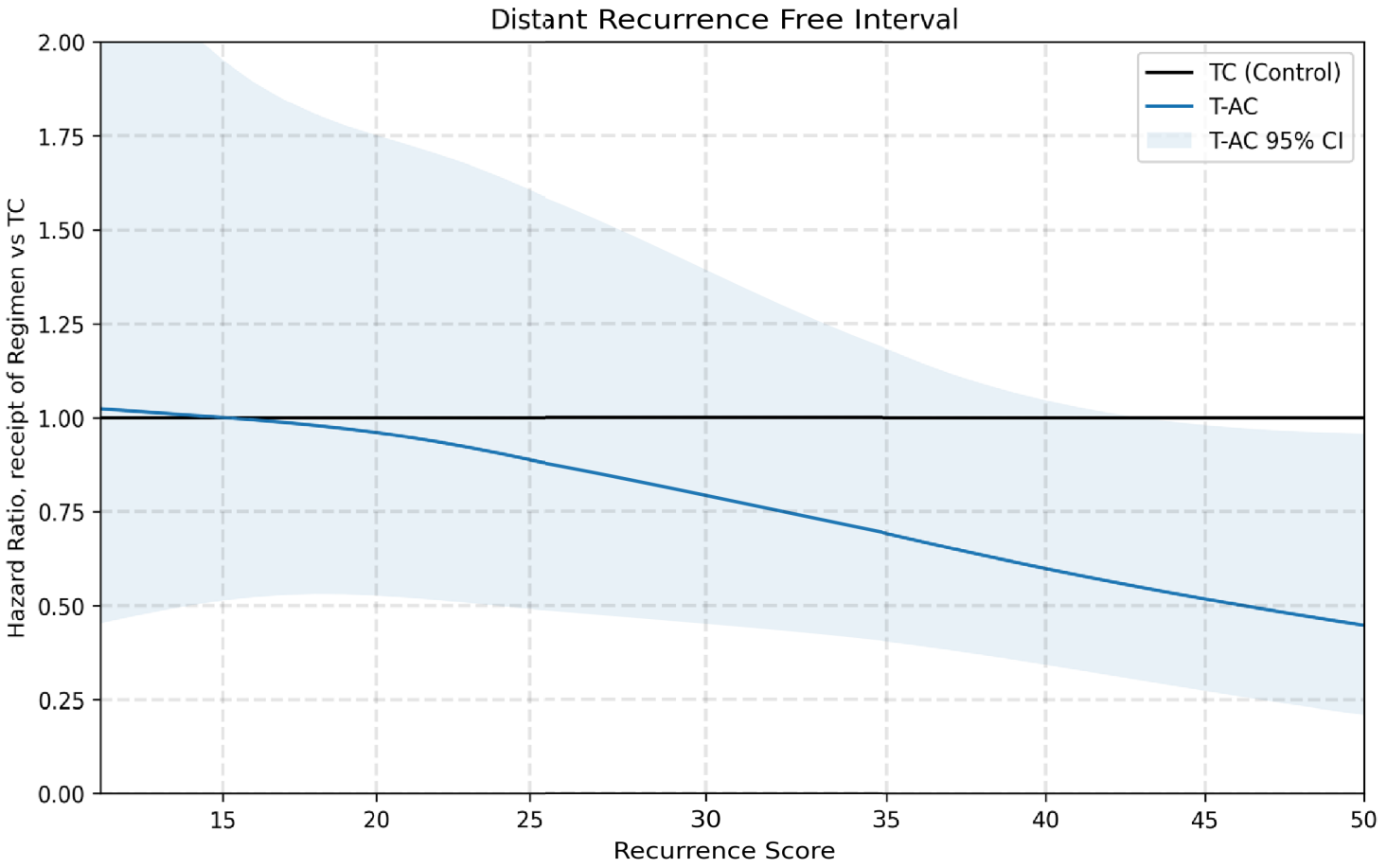




*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received in high RS population

Increasing Benefit of Anthracyclines with Increasing RS

RS	Adj HR, DRFI
15	1.00 (0.51 - 1.95)
20	0.96 (0.53 - 1.75)
25	0.89 (0.49 - 1.61)
30	0.79 (0.45 - 1.39)
35	0.69 (0.40 - 1.18)
40	0.60 (0.34 - 1.05)
45	0.52 (0.27 - 0.98)
50	0.45 (0.21 - 0.96)



Limitations

- Post-hoc analysis not designed to evaluate endpoint
- Chemotherapy choice not randomized
- Late effects of anthracycline usage

Despite the bias of higher risk patients receiving anthracyclines, this analysis still noted a benefit in high genomic risk patients.

Conclusions

In patients with HR+/HER2-, LN- breast cancer with a RS ≥ 31:

- Significant benefit in 5-year estimates of DRFI (96.1% vs 91.0%, aHR 0.32, p=0.009) and DRFS in patients receiving T-AC compared to TC
- Trend towards benefit in OS in patients receiving T-AC compared to TC
- Benefit most clearly demonstrated in patients with tumors > 2cm
- Increasing RS greater than 31 corresponded to increasing benefit of addition of anthracycline

<u>Anthracyclines should be considered in patients with high genomic risk HR+/HER2-, LN- disease</u>

Thank you and Happy Valentines Day!