HR+/HER2- Breast Cancer Updates

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Outline

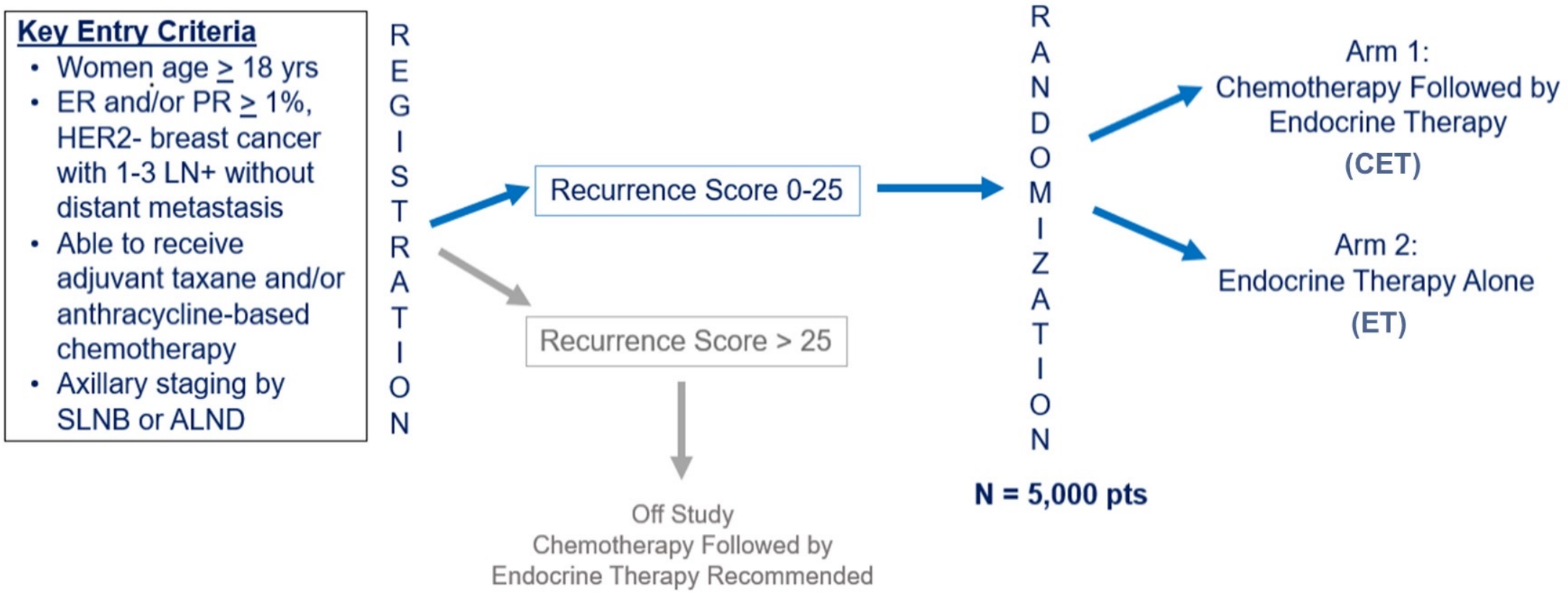
Localized breast cancer

1. Serum AMH levels in RxPONDER

Metastatic breast cancer

1. INAVO: PFS2, TTFC, PROs results
2. postMONARCH
3. DESTINY Breast-06

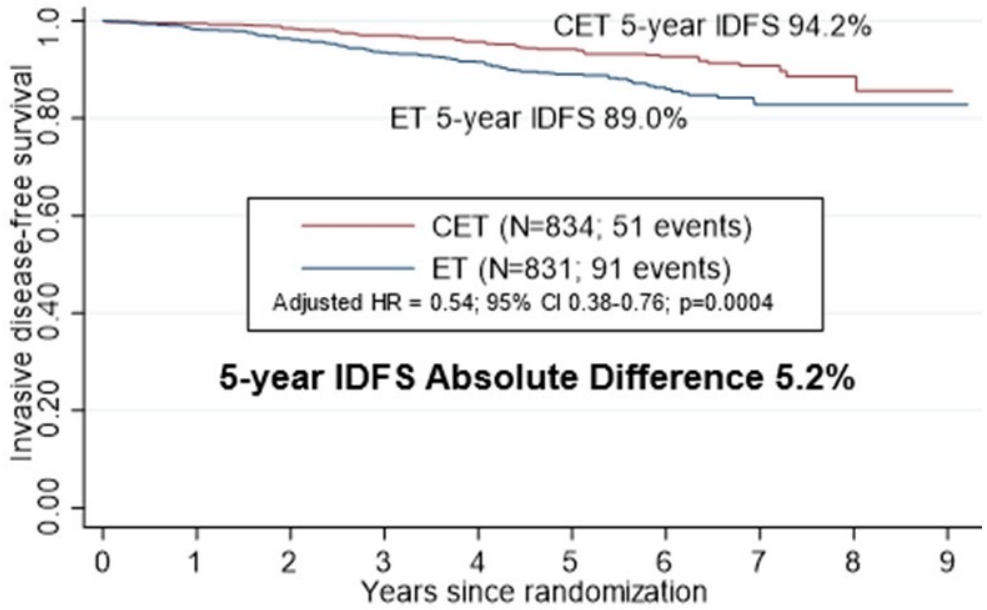
RxPONDER Trial



Kalinsky, et al. NEJM 2021

Chemotherapy benefit differed by menopausal status

"Premenopausal"

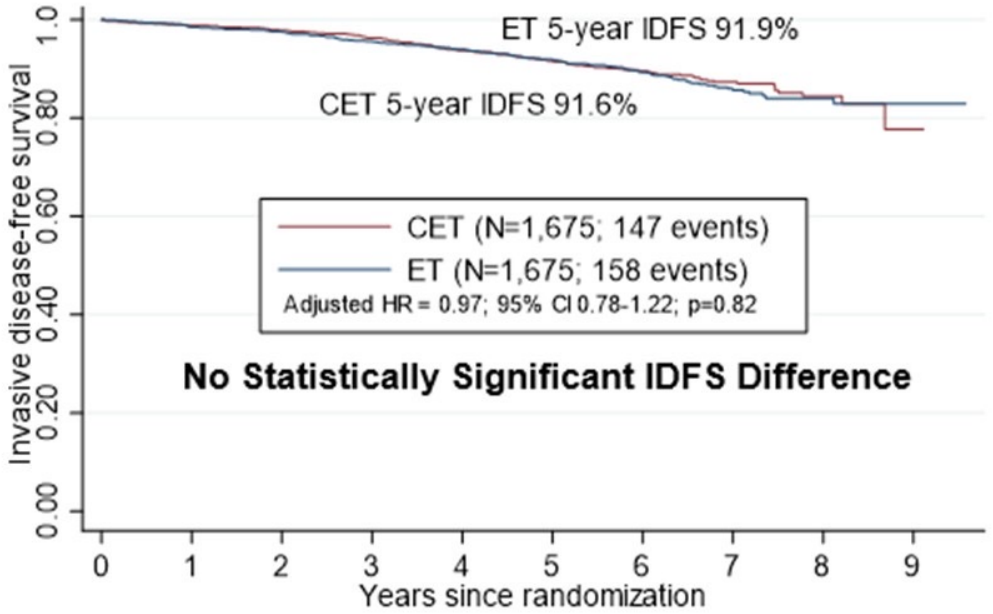


Number at risk

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

Last menstrual period < 6 mo*

"Postmenopausal"



Number at risk

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

Last menstrual period > 12 mo or BSO

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

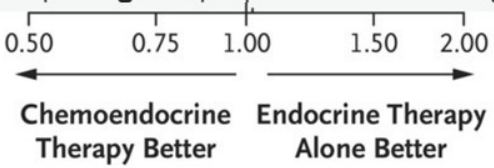
BSO = bilateral salpingo-oophorectomy

Kalinsky et al. NEJM 2021

PRESENTED BY: Kevin Kalinsky, MD, MS

Chemotherapy benefit lower in older “premenopausal” in RxPONDER

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



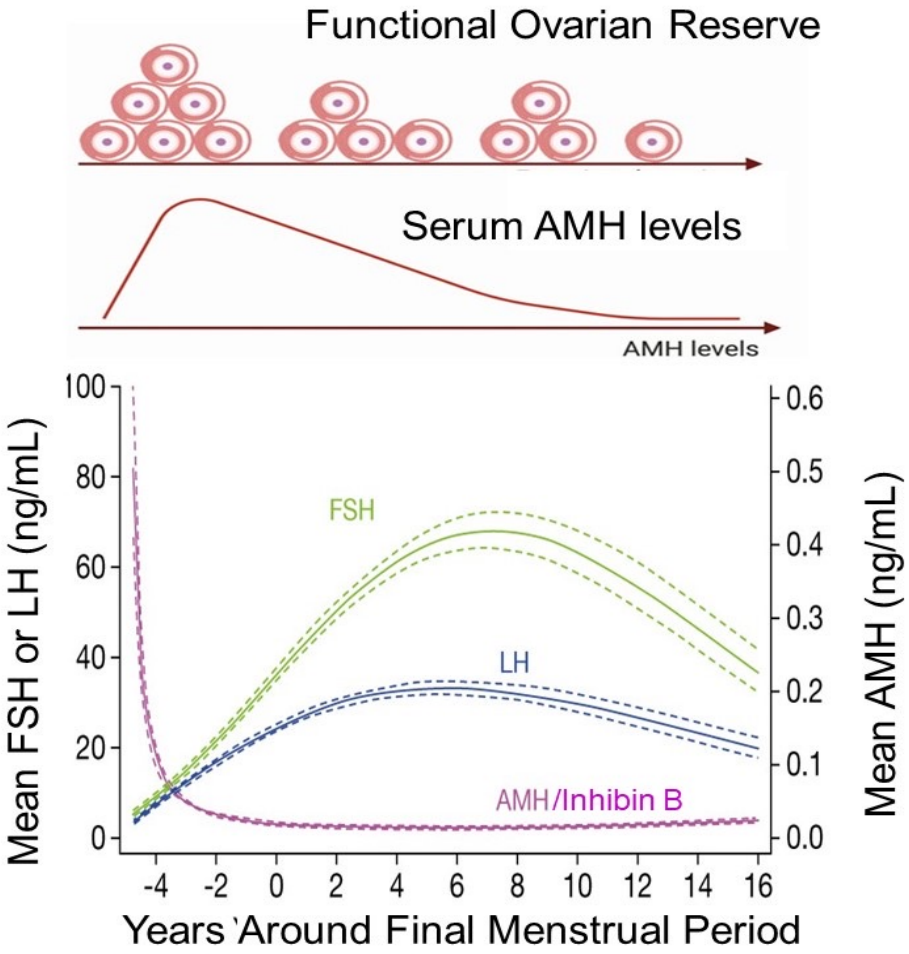
Kalinsky, et al. NEJM 2021

RxPONDER Primary Results

- ✓ Post-menopausal women with 1-3 LN+ and RS ≤ 25 derived no benefit from the addition of chemotherapy to ET
- ✓ **"Pre-menopausal"** women <55 years with 1-3 LN+ and RS ≤ 25 had an improvement in IDFS and DRFS with the addition of chemotherapy to ET
- ✓ Menopausal status is crudely estimated by clinical criteria; is there a role for serologic assays?

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

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



FSH = Follicular Stimulating Hormone

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

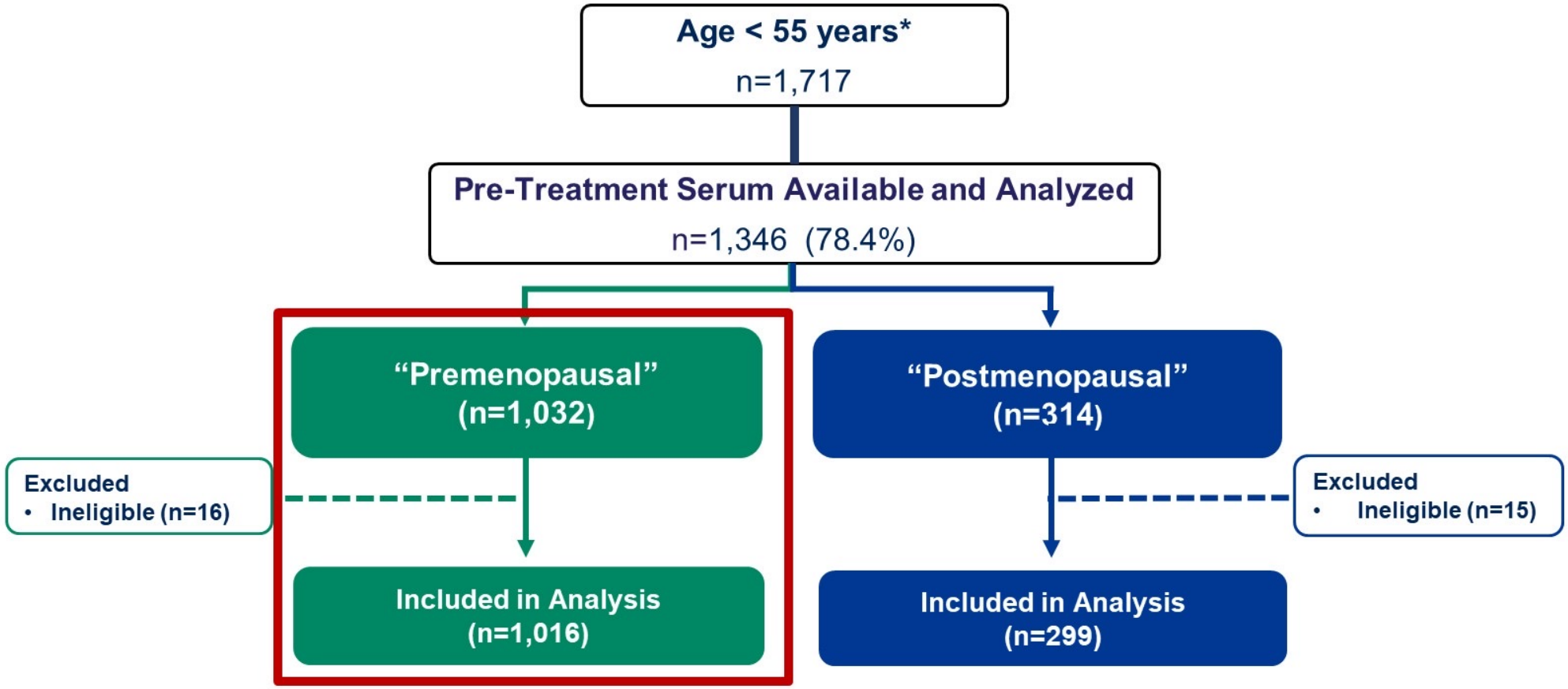
RxPONDER Subgroup analysis

Objective

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

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

Population in this analysis

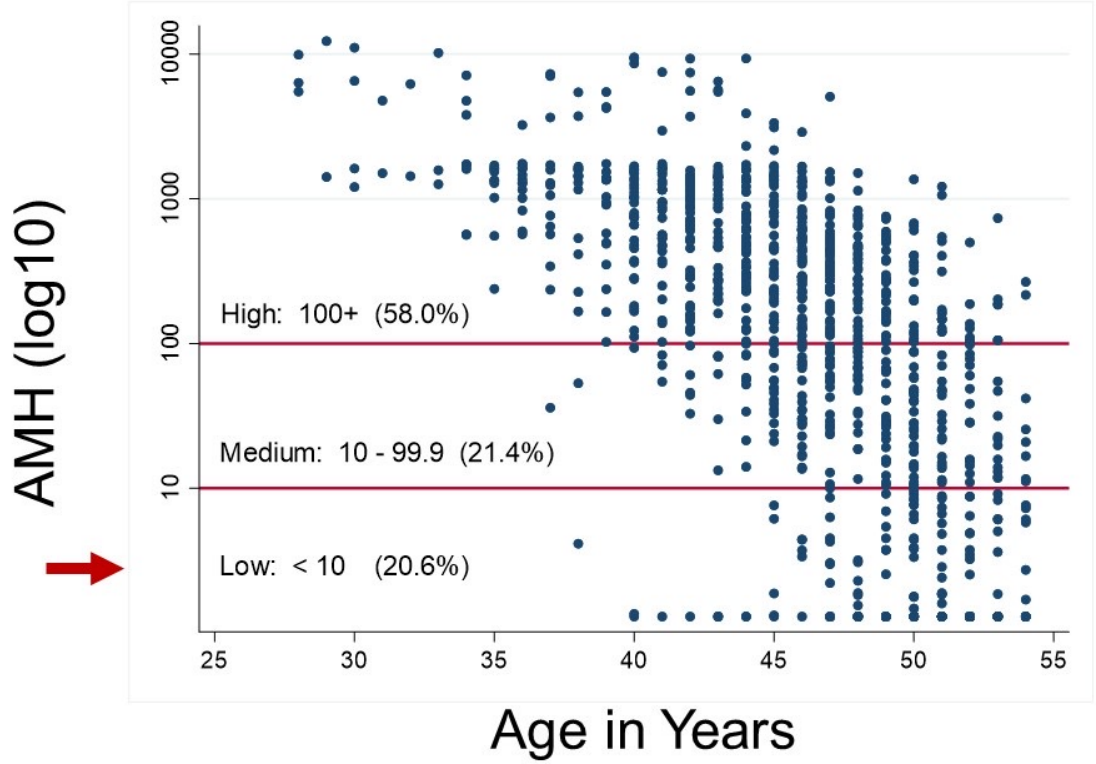


*Does not include 235 pts < 55 years from UNICANCER who will serve as validation cohort

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

21% of “premenopausal” women < 55 years had serum AMH in postmenopausal range

Anti-Mullerian hormone



Postmenopausal: < 10 pg/mL (20.6%)

Category (AMH)	Menstrual Category (Final Menstrual Period)	picoAMH (pg/mL)
Low	At FMP or Later	< 10
Medium	< 5 years from FMP	10-99.9
High	> 5 years from FMP	≥ 100

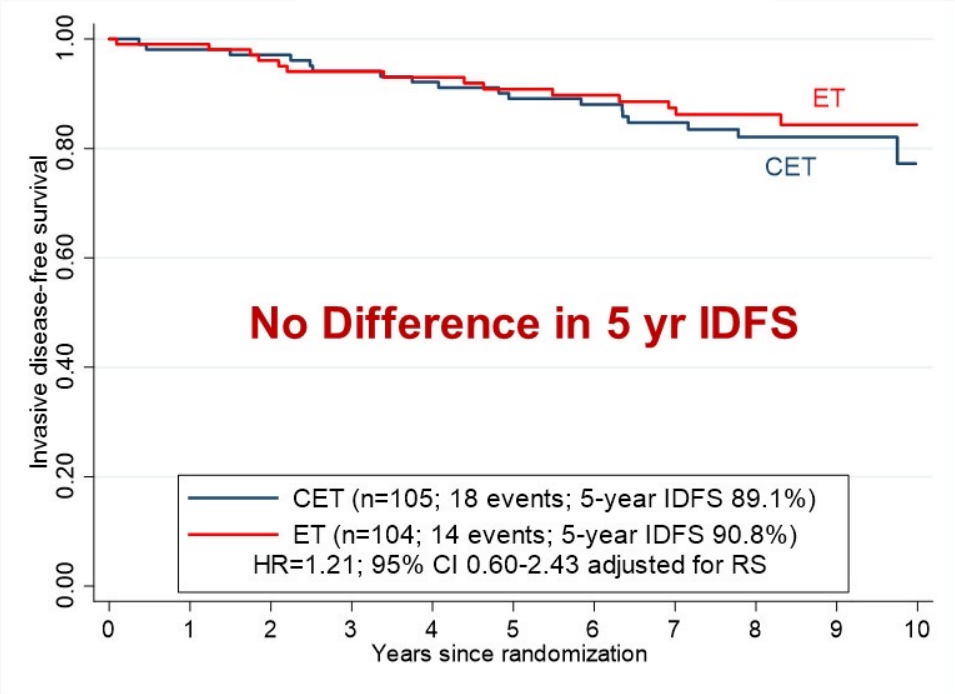
Category	Age < 45	Age 45-49	Age 50-54
Low AMH	10/348 (2.9%)	58/397 (14.6%)	141/270 (52.2%)

10 pg/ML = 0.01 ng/ML

picoAMH package insert (ELISA) 2023

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

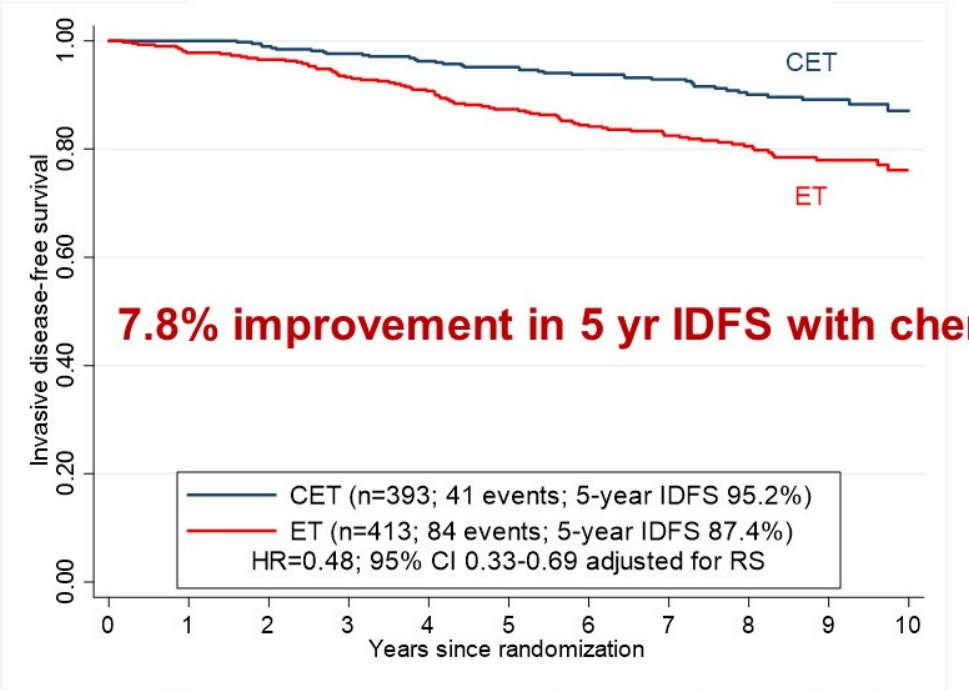
Low AMH (n=209)



No Difference in 5 yr IDFS

Postmenopausal: < 10 pg/mL

Medium/High AMH (n=806)



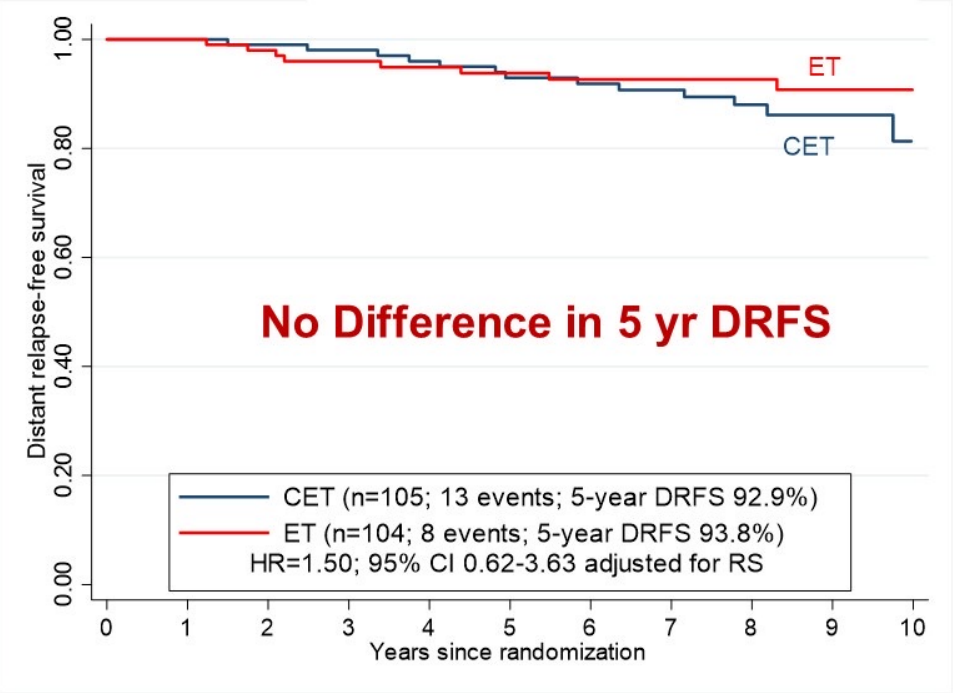
7.8% improvement in 5 yr IDFS with chemo

Premenopausal: ≥ 10 pg/mL

Significant interaction p=0.019, adjusting for RS

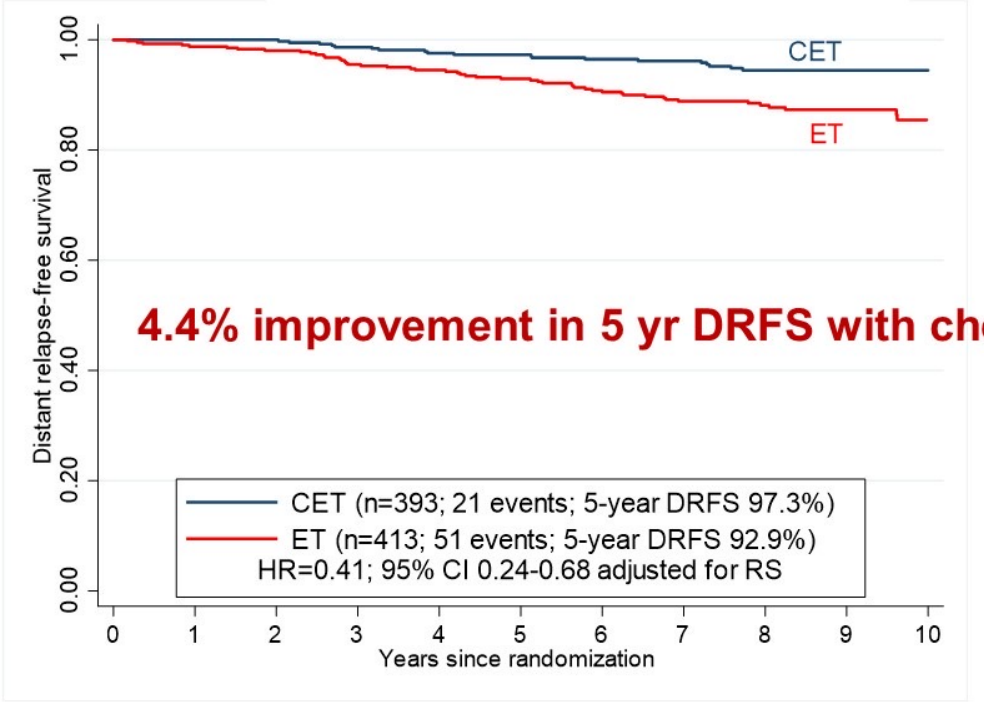
"Premenopausal" < 55 years with low AMH have no DRFS benefit with chemotherapy

Low AMH (n=209)



No Difference in 5 yr DRFS

Medium/High AMH (n=806)



4.4% improvement in 5 yr DRFS with chemo

Postmenopausal: < 10 pg/mL

Premenopausal: ≥ 10 pg/mL

Significant interaction p=0.012, adjusting for RS

Only AMH predicted chemotherapy benefit

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

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

RxPONDER (SWOG S1007)

- ✓ “Pre-menopausal” women <55 years with 1-3 LN+ and RS ≤ 25 with low AMH levels (< 10pg/ML) did not derive any benefit from the addition of chemotherapy to ET
- ✓ 52.2% of women 50-54 years had low pre-treatment serum AMH
- ✓ AMH was a better predictor of adjuvant chemotherapy benefit than menopause status, age, or other serum hormone levels
- ✓ Low serum AMH could classify who can safely forego adjuvant chemotherapy in women whose menopausal status is unclear

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HR+/HER2- mBC (PFS benefit)

1L	ET + CDK4/6i	*no prior CDK4/6i*	24.8 - 28.2 mo[1-3]
2L+	ET + targeted therapies	*prior CDK4/6i*	5.5 mo[4,5]
3L+	Single-agent CT	*CT naive*	6.2– 7.1 mo[6-8]
	T-DxD (HER2-low)	*prior ET and CT*	10.1 mo[9]

*Based on data from Phase 3 registrational studies only

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; 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; T-DXd, trastuzumab deruxtecan

1. Finn RS, et al. *N Engl J Med.* 2016;375:1925–1936; 2. Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541–1547; 3. Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5; 4. Turner NC, et al. *N Engl J Med.* 2023;388:2058–2070 (Supplementary Appendix); 5. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256; 6. O'Shaughnessy J, et al. *JAMA Netw Open.* 2021;4:e214103; 7. O'Shaughnessy J, et al. *Cancer Res.* 2021;81(Suppl. 4):Abstract GS4-01; 8. Robert NJ, et al. *J Clin Oncol.* 2011;29:1252–1260; 9. Modi S, et al. *N Engl J Med.* 2022;387:9–20

INAVO120 study design[1]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c <6.0% (< 42 mmol/mol)**

N = 325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)

Statistical methods

- For efficacy endpoints and TTCD, hazard ratios were estimated using a Cox proportional hazard model with 95% CI and Kaplan–Meier methodology was used to estimate the medians with the Brookmeyer–Crowley method used for the 95% CI

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- **Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)**
- **Time from randomization to first subsequent chemotherapy after treatment discontinuation**

Safety endpoints

Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†

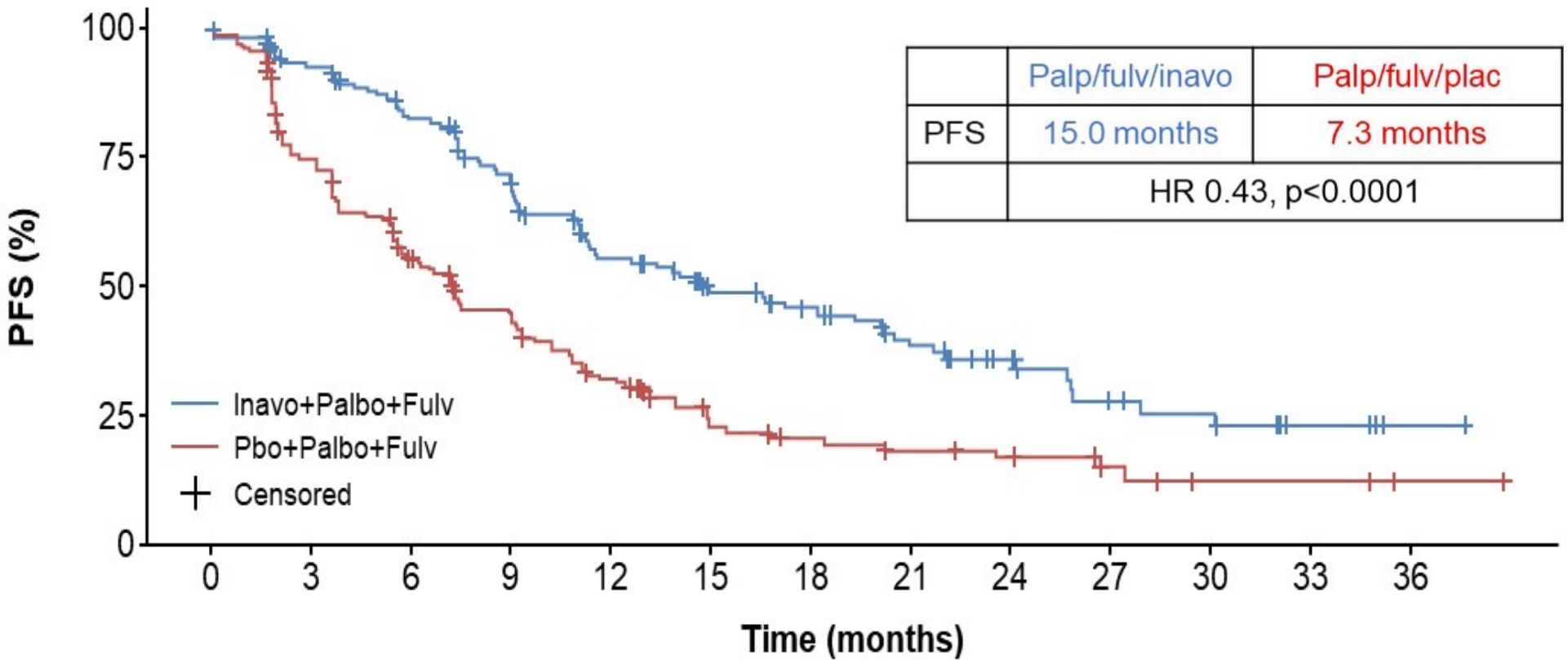
- **BPI-SF: TTCD in worse pain‡§**
- **EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖**
- **PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities**
- **An overall bother item: overall bother experienced due to side effects of treatment**

* Assessed using grouped terms; severity reported per National Cancer Institute CTCAE version 5.0. † Assessed at D1 of C1–3 then D1 of every other C thereafter (5, 7, 9, etc.), at treatment discontinuation, and every 3 months during survival follow-up; baseline completion rates in both arms were >90% for all assessments; post-baseline rates in both arms remain >80% through C15; <50% intent-to-treat sample remaining at C9 in the inavolisib arm versus C5 in the placebo arm. ‡ Type I error-controlled; hierarchically tested according to a prespecified fixed order of endpoints. § Defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item held for at least two consecutive Cs, or an initial increase followed by death or treatment discontinuation within 3 weeks from the last assessment. ‖ A ≥10-point change was defined as a clinically meaningful difference.

AE, adverse event; (LA/m)BC, (locally advanced/metastatic) breast cancer; BOR, best overall response; BPI-SF, brief pain inventory-short form; C, Cycle; CBR, clinical benefit rate; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; D, Day; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ET, endocrine therapy; HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to next progression after discontinuing study treatment for PD, or death from any cause; PO, orally; PRO, patient-reported outcomes; Q4W, every 4 weeks; QD, once daily; R, randomized; TTCD, time to confirmed clinical meaningful deterioration.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

INAVO prolongs PFS in 1st line PIK3CA$_{mut}$ HR+ mBC

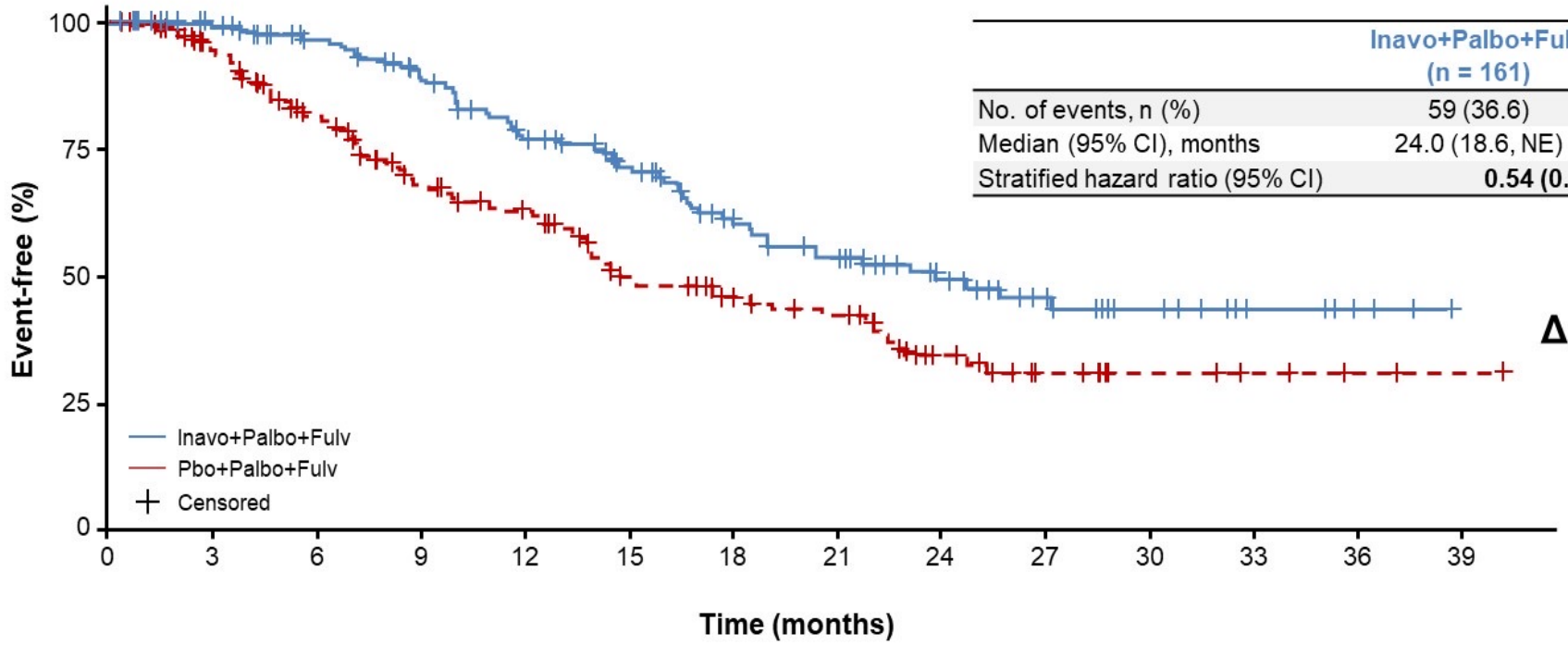


	Palp/fulv/inavo	Palp/fulv/plac
PFS	15.0 months	7.3 months
	HR 0.43, p<0.0001	

CCOD, clinical cutoff date; CI, confidence interval; Fulv, fulvestrant; HER2–, HER2-negative; HR+, hormone receptor-positive; Inavo, inavolisib; LA/mBC, locally advanced/metastatic breast cancer; OS, overall survival; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

INAVO120 (PFS2)



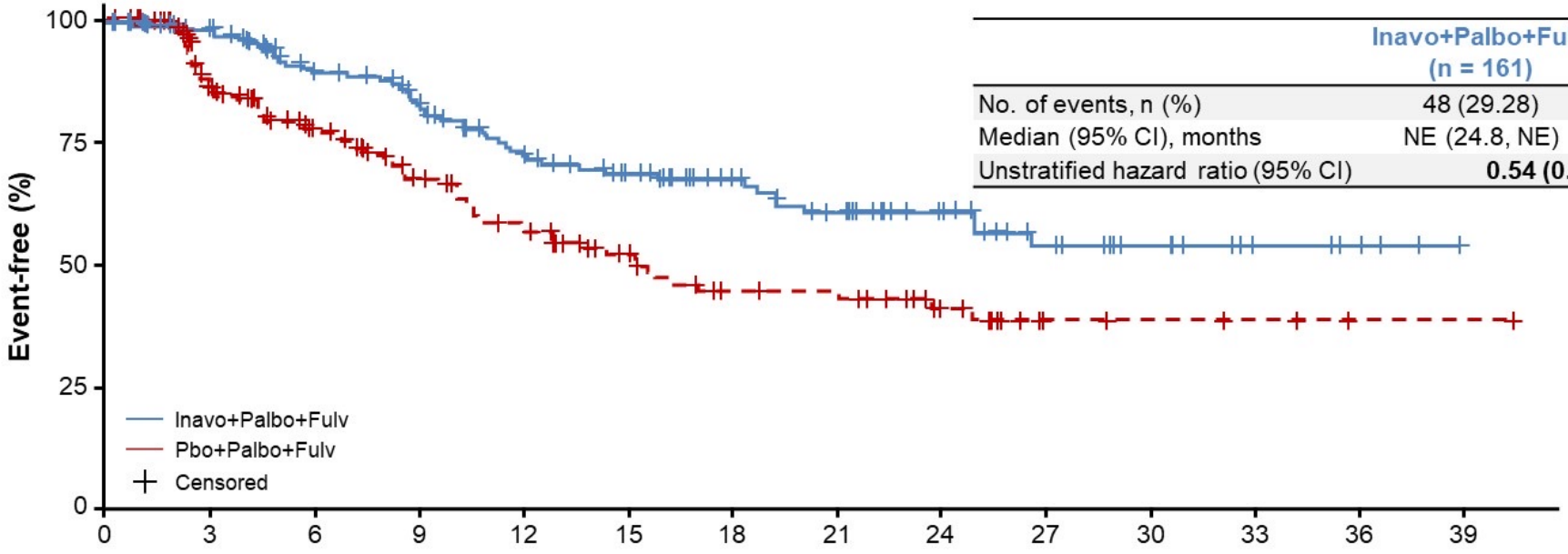
	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	59 (36.6)	80 (48.4)
Median (95% CI), months	24.0 (18.6, NE)	15.1 (13.5, 22.3)
Stratified hazard ratio (95% CI)	**0.54 (0.38, 0.77)**	

Patients at risk:

Pbo+Palbo+Fulv	164	140	110	84	74	52	43	37	22	12	6	4	2	1
Inavo+Palbo+Fulv	161	143	126	111	92	77	58	48	33	22	14	6	3	0

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo; PFS2, time from randomization to next progression after discontinuing study treatment for disease progression, or death from any cause.

INAVO120 (TTFC)



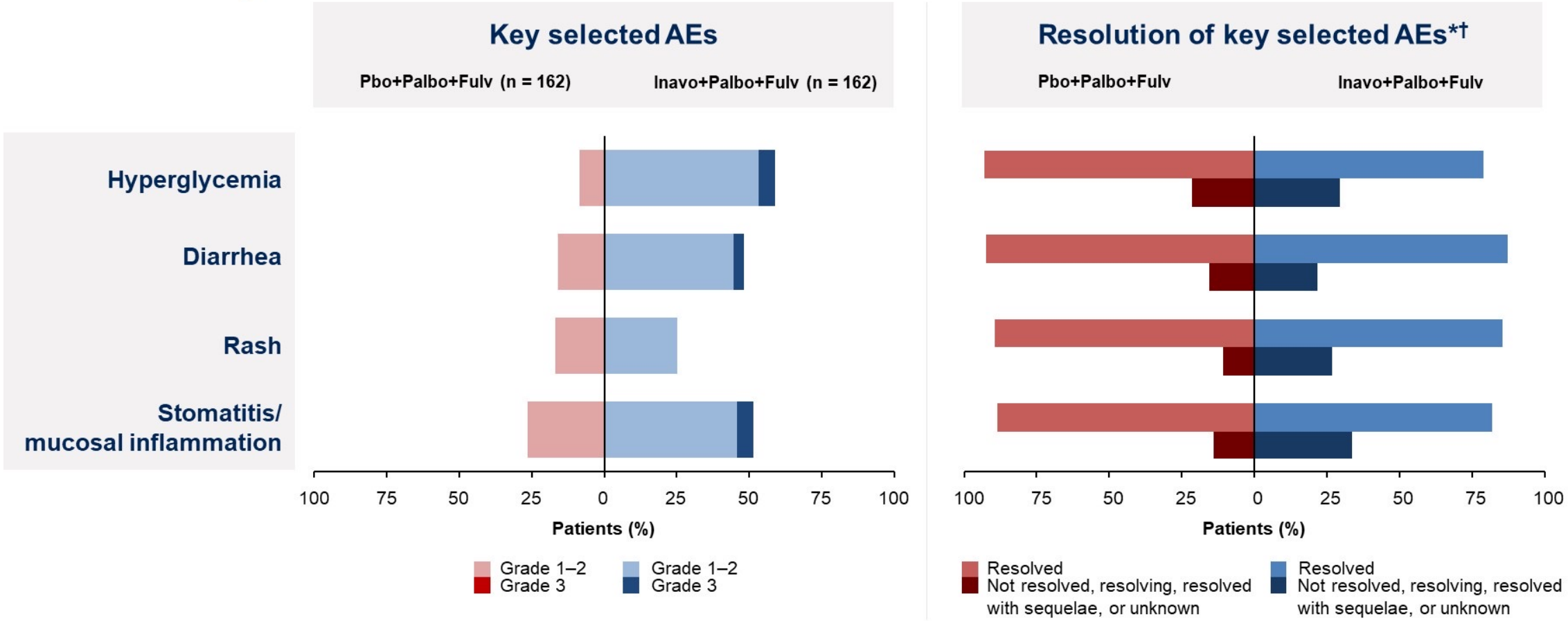
	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	48 (29.28)	68 (41.5)
Median (95% CI), months	NE (24.8, NE)	15.0 (10.6, 24.8)
Unstratified hazard ratio (95% CI)	**0.54 (0.37, 0.78)**	

Patients at risk:

Pbo+Palbo+Fulv	164	121	94	71	56	41	29	27	18	7	5	4	2	1
Inavo+Palbo+Fulv	161	141	115	98	78	66	51	42	30	20	13	6	3	0

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo.

Safety



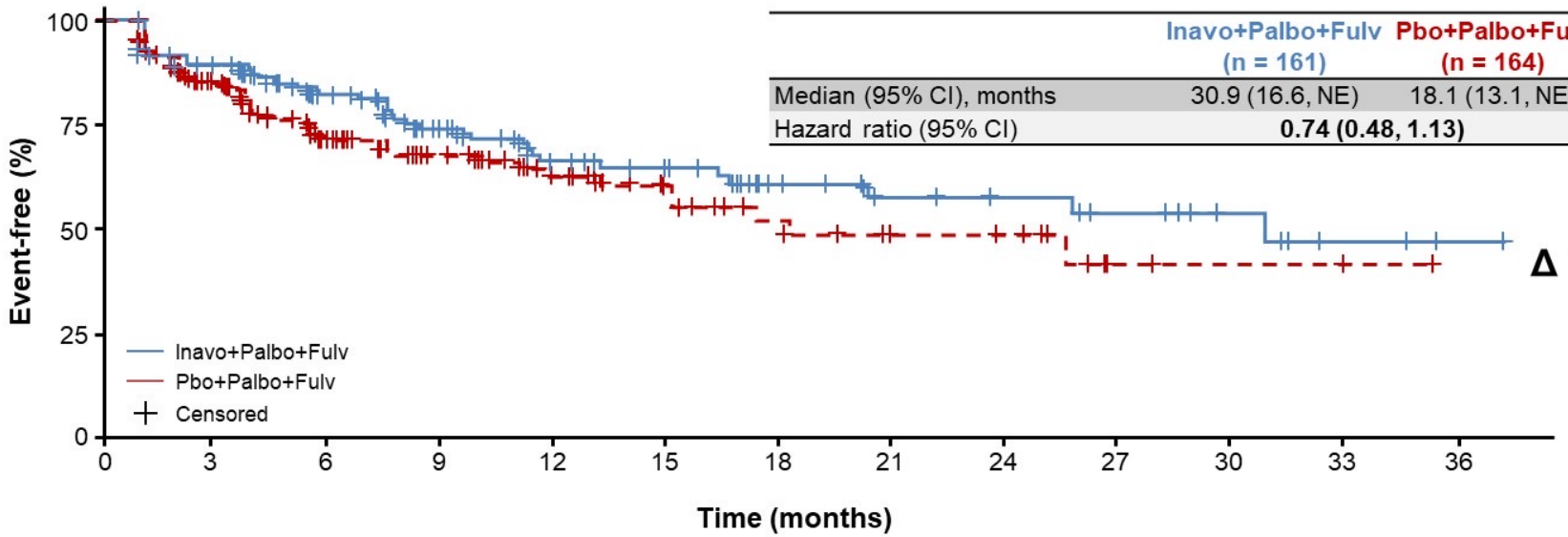
*** Majority of key selected AEs had resolved ('resolution' was per investigator decision) by the CCOD; some patients were enrolled close to the CCOD and AE follow-up is ongoing for these patients.**

† Denominators are patients with at least one AE (hyperglycemia, Inavo+Palbo+Fulv: n = 95, Pbo+Palbo+Fulv: n = 14; diarrhea, Inavo+Palbo+Fulv: n = 78, Pbo+Palbo+Fulv: n = 26; rash, Inavo+Palbo+Fulv: n = 41, Pbo+Palbo+Fulv: n = 28; and stomatitis/mucosal inflammation, Inavo+Palbo+Fulv: n = 83, Pbo+Palbo+Fulv: n = 43).

AE, adverse event; CCOD, clinical cutoff date; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Time to confirmed clinical meaningful deterioration in worst pain severity (BPI-SF)

Patients in the inavolisib arm experienced a longer duration of time without confirmed, clinically meaningful worsening pain severity than patients in the placebo arm



	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
Median (95% CI), months	30.9 (16.6, NE)	18.1 (13.1, NE)
Hazard ratio (95% CI)	**0.74 (0.48, 1.13)**	

Δ 12.8 months

Patients at risk:													
Pbo+Palbo+Fulv	164	100	66	48	33	23	16	11	10	3	2	2	0
Inavo+Palbo+Fulv	161	120	92	65	46	37	23	18	15	12	8	3	1

BPI-SF, brief pain inventory-short form; CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo.

INAVO120

- ✓ Inavolisib + palbociclib + fulvestrant is a promising option in **high risk** *PIK3CA*-mutated, HR+/HER2- mBC who relapsed during/within 12 months of adjuvant ET completion
  - improvement in PFS1 and PFS2
  - delay time to chemotherapy
  - improvement in worst bone pain
- ✓ Inavolisib discontinuation rate was low with manageable safety profile
- ✓ Received breakthrough therapy designation on May 20th, 2024
- ✓ Caveat: Unclear efficacy/toxicity with other CDK4/6i combinations

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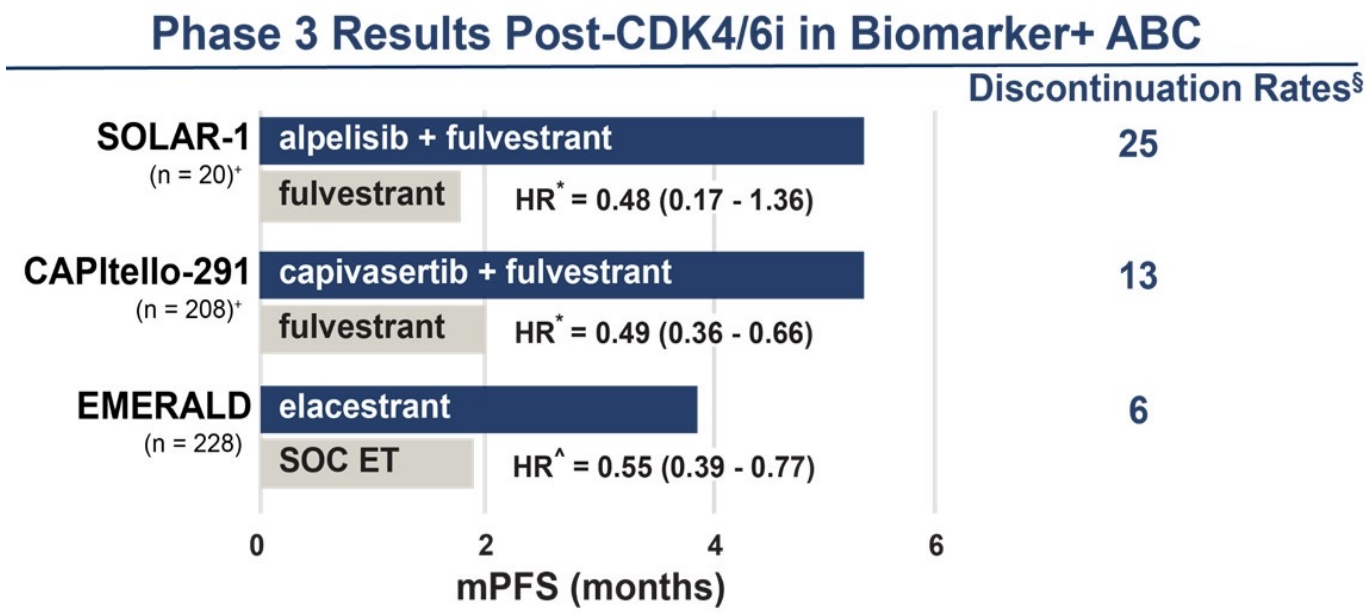
Treatment options after 1L CDK4/6i

- Biomarker driven approach
- Everolimus + ET
  (if no targetable mutation)
- mPFS with these agents is <6months and toxicities vary



Juric D. et al 2019 Proceedings of SABCS 79(4) Abstract nr GS3-08
Oliveira M. et al 2023 Annals of Oncology 8(1)
Turner N. et al 2023 N Engl J Med 388(22) 2058-2070
Bidard F. et al 2022 J Clin Oncology 40(28) 3246-32568

postMONARCH Study Design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:

- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

Placebo + Fulvestrant

Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:

- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY assay

Balanced Baseline Patient & Disease Characteristics

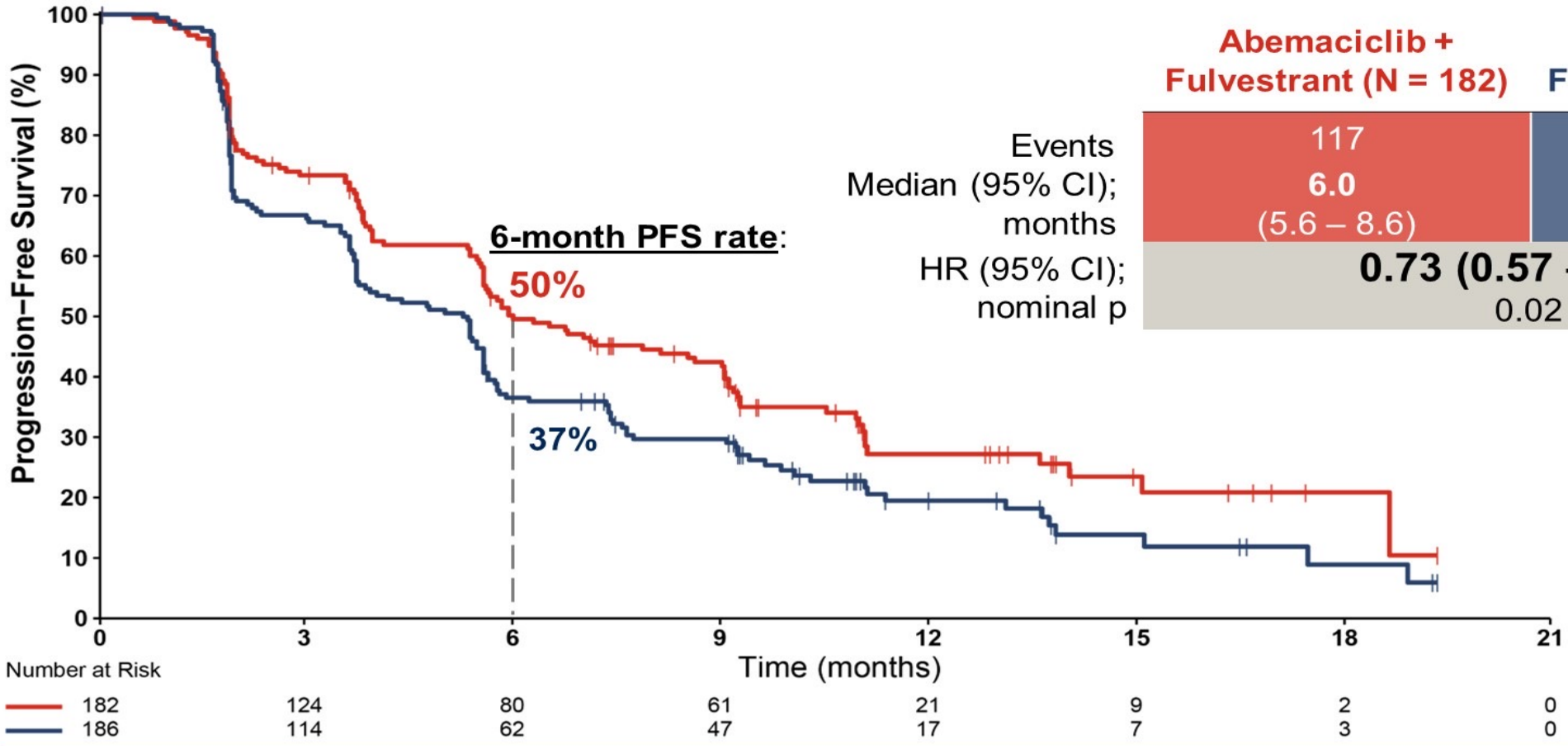
		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Age	Median (range)	58 (27, 86)	61 (28, 85)
	< 65 years	69	63
	≥ 65 years	31	37
Gender	Female	99	100
ECOG	0	57	58
	1	43	43
Region	Other (includes EU)	73	72
	Asia	12	13
	USA	15	15
Race	White	82	82
	Asian	12	15
	Black/African American	4	2
Ethnicity	Not Hispanic/Latino	74	77
	Hispanic/Latino	15	15
HR Status	ER+	100	99
	PR+	79	81

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22
Median Prior CDK4/6i Duration (mo; range)#	All	19 (2, 110)	21 (3, 87)
	Palbociclib	19	23
	Ribociclib	15	18
	Abemaciclib	26	21

PRESENTED BY: Kevin Kalinsky, MD, MS

* ≥ 12 months ABC or recurrence after EBC therapy
^ < 12 months ABC or recurrence on EBC therapy
# for ABC

Abemaciclib + Fulvestrant prolongs PFS post CDK4/6i + AI

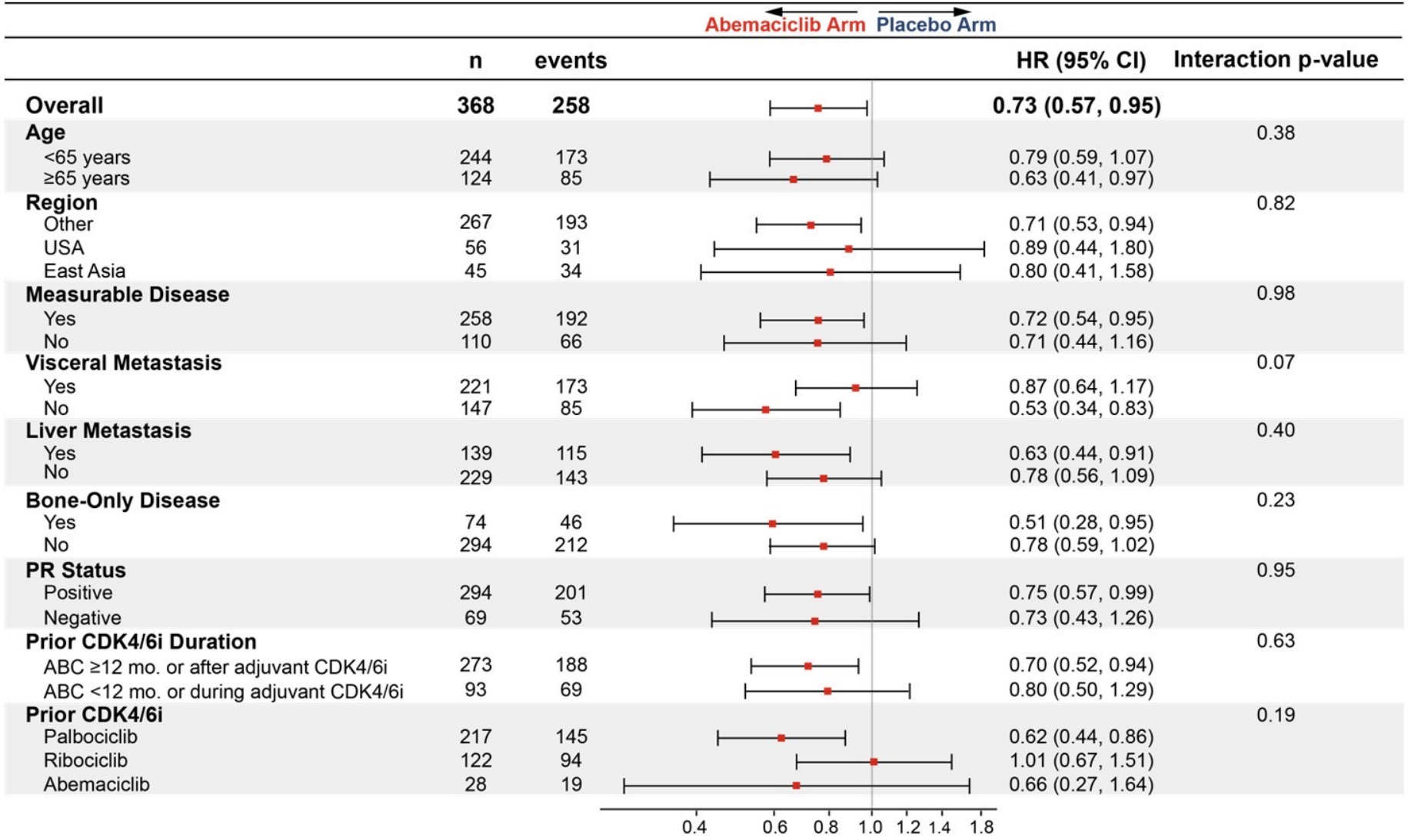


	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	**6.0** (5.6 – 8.6)	**5.3** (3.7 – 5.6)
HR (95% CI); nominal p	**0.73 (0.57 – 0.95)** 0.02	

Abemaciclib led to 27% reduction in the risk of developing PFS event

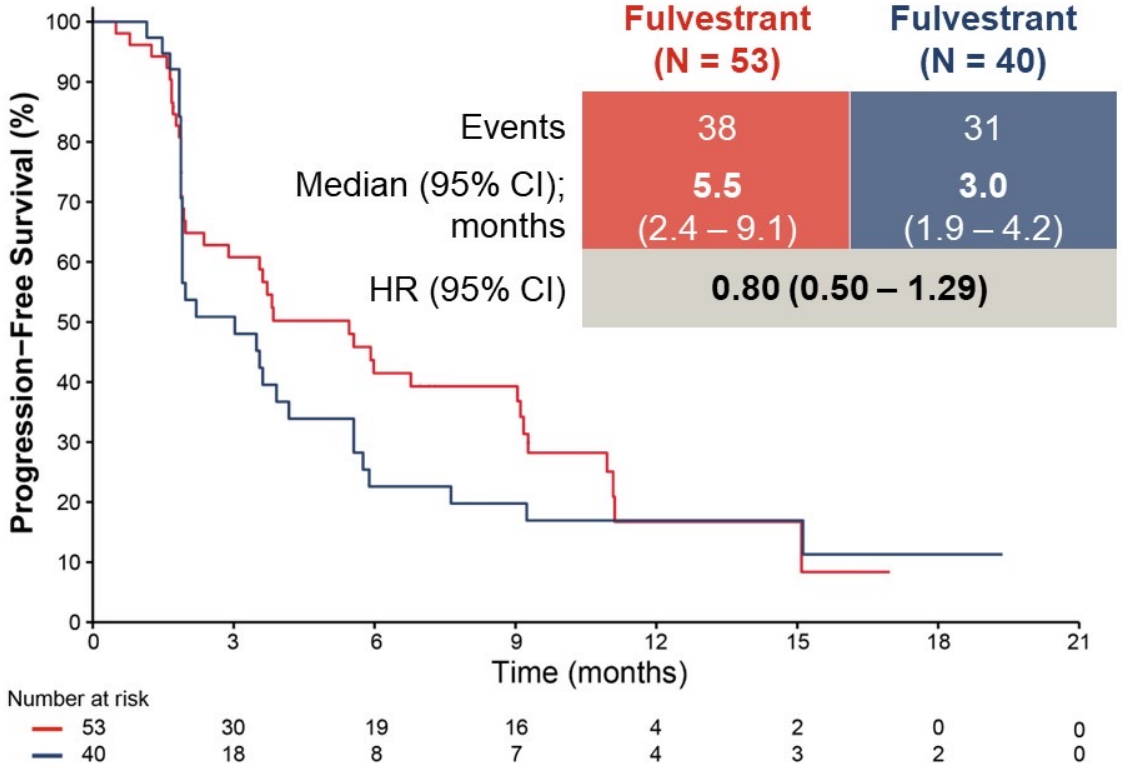
PRESENTED BY: Kevin Kalinsky, MD, MS

Investigator-Assessed PFS by Subgroup: Consistent Abemaciclib Effect Across Subgroups



Subgroup Analysis: Investigator-Assessed PFS by Prior CDK4/6i Duration

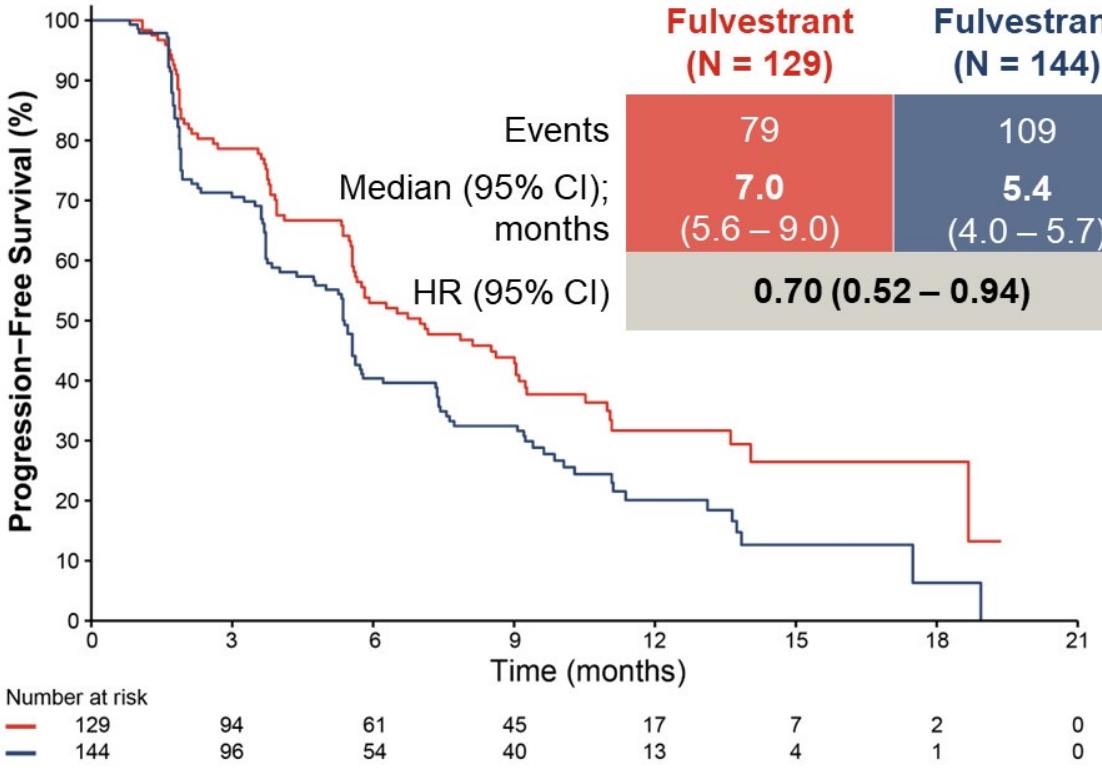
< 12 months^



	Abemaciclib + Fulvestrant (N = 53)	Placebo + Fulvestrant (N = 40)
Events	38	31
Median (95% CI); months	**5.5** (2.4 – 9.1)	**3.0** (1.9 – 4.2)
HR (95% CI)	**0.80 (0.50 – 1.29)**	

^ < 12 months ABC or recurrence on EBC therapy

≥ 12 months*



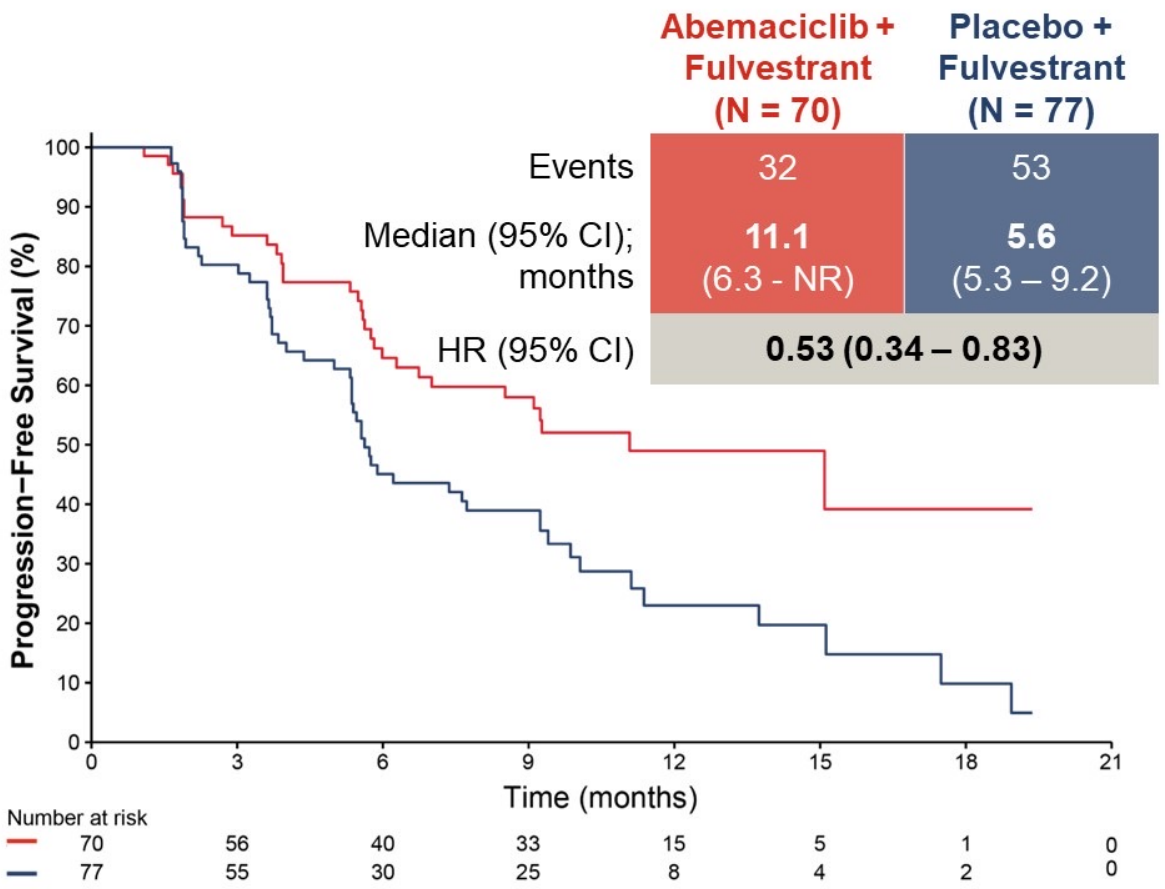
	Abemaciclib + Fulvestrant (N = 129)	Placebo + Fulvestrant (N = 144)
Events	79	109
Median (95% CI); months	**7.0** (5.6 – 9.0)	**5.4** (4.0 – 5.7)
HR (95% CI)	**0.70 (0.52 – 0.94)**	

* ≥ 12 months ABC or recurrence after EBC therapy

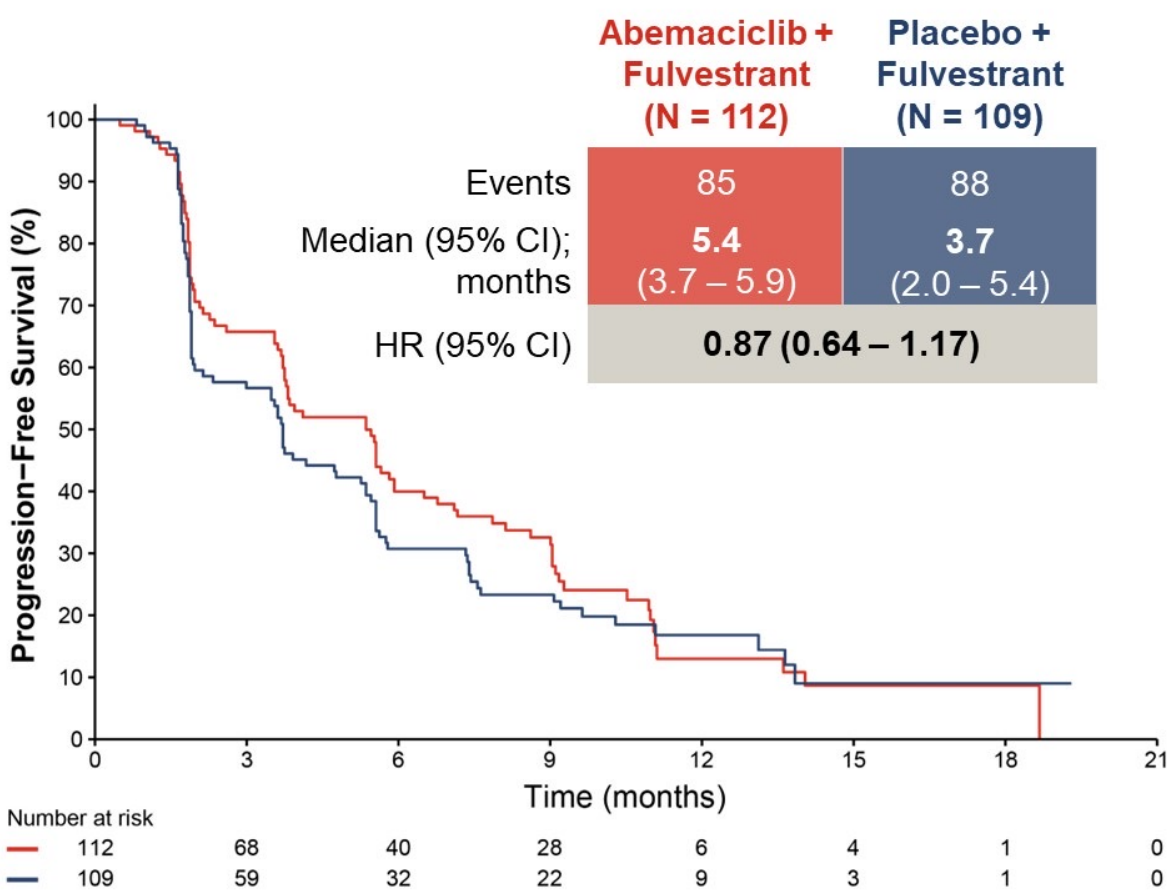
PRESENTED BY: Kevin Kalinsky, MD, MS

Subgroup Analysis: Investigator-Assessed PFS by Visceral Metastasis

No visceral metastasis



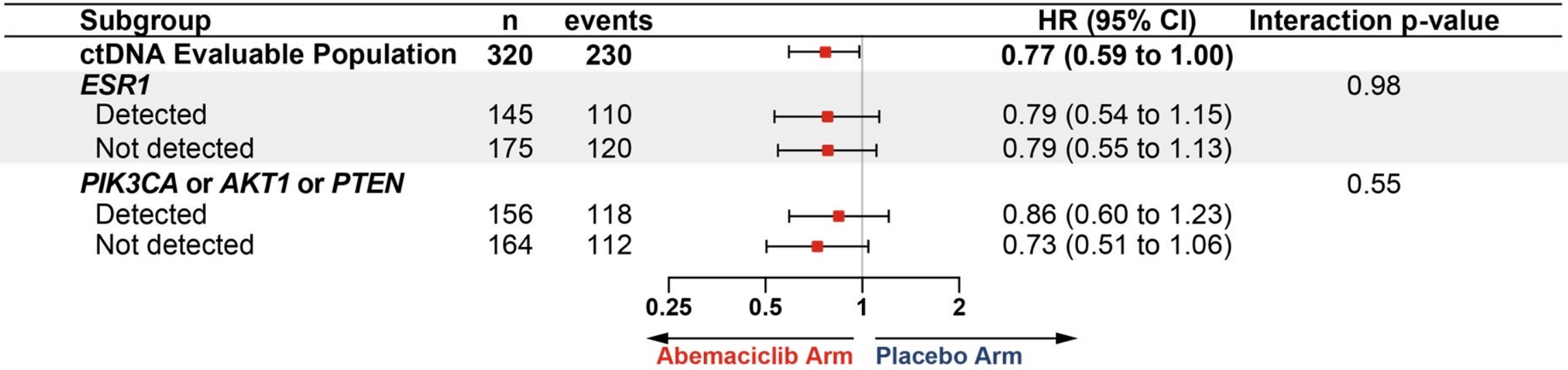
Visceral metastasis



PRESENTED BY: Kevin Kalinsky, MD, MS

Exploratory: Consistent Effect Across Biomarker Subgroups

		Abemaciclib + Fulvestrant N=182	Placebo + Fulvestrant N=186
ctDNA Evaluable Population		161 (88%)	159 (85%)
Biomarker Status	*ESR1* mutation	40%	51%
	PIK3CA or *PTEN* or *AKT1* alteration	46%	52%



Biomarker ctDNA by GuardantINFINITY assay

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Safety Consistent with Known Abemaciclib Profile

	Abemaciclib + Fulvestrant N = 181	Placebo + Fulvestrant N = 185
Grade 5 TRAE+, n (%)	1 (0.6)	0
Dose reductions due to AE, n (%)	55 (30)	6 (3)
Discontinuations due to AE, n (%)	11 (6)	0

	Abemaciclib + Fulvestrant, N=181, %		Placebo + Fulvestrant, N=185, %	
TEAEs	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	**97**	**55**	**82**	**20**
Diarrhea	75	4	17	2
Neutropenia*	41	25^	3	0
Anemia*	35	11	15	4
Fatigue*	33	3	23	1
Nausea	33	3	18	0
Abdominal Pain*	24	2	16	0
Vomiting	20	2	6	0
Thrombocytopenia*	18	4	6	2
Decreased Appetite	18	1	7	0
Leukopenia*	18	8	3	0
AST Increased	15	6	11	2
ALT Increased	13	4	10	2
Arthralgia	12	1	12	1
Creatinine Increased	11	0	2	0
Cough	11	0	7	0
VTE*	5	2#	3	1
ILD*	3	1§	1	0

PRESENTED BY: Kevin Kalinsky, MD, MS

+1 Grade 5 treatment-related AE (TRAE) of pneumonia
*Consolidated term
Includes: ^2 Febrile Neutropenia (1 Grade 3; 1 Grade 4), #1 Grade 5 Pulmonary Embolism, §1 Grade 3, 1 Grade 4 ILD

postMONARCH

- ✓ 1st Phase III RCT to show benefit of continued CDK4/6i with abemaciclib + fulvestrant following progression on a CDK4/6i
- ✓ Greatest benefit seen in patients who received prolonged benefit with 1st line CDK4/6i + ET and w/o visceral metastasis
- ✓ Safety was consistent with known abemaciclib profile and discontinuation rate was low

Outline

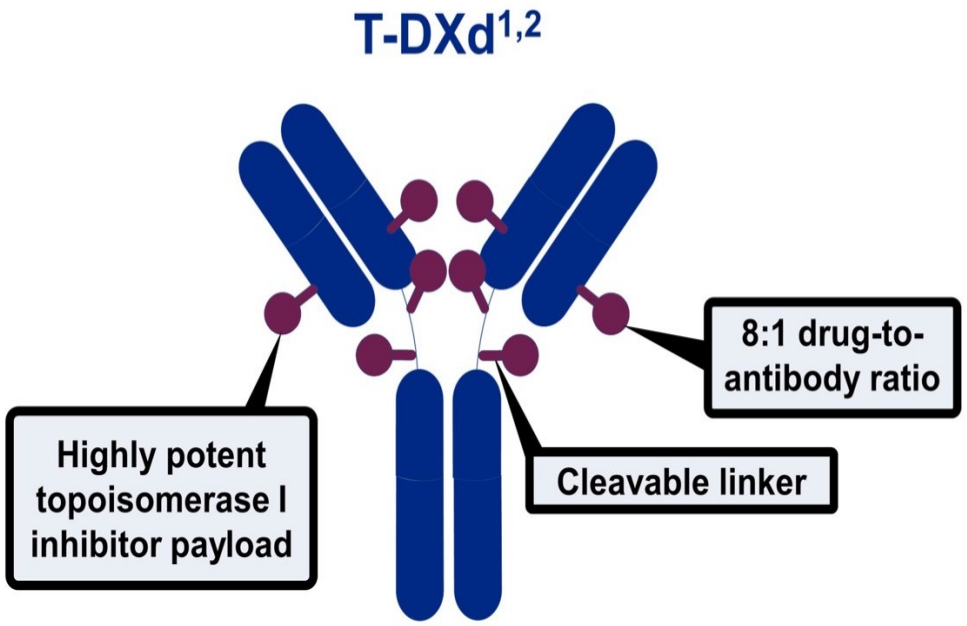
Localized breast cancer

1. Serum AMH levels in RxPONDER

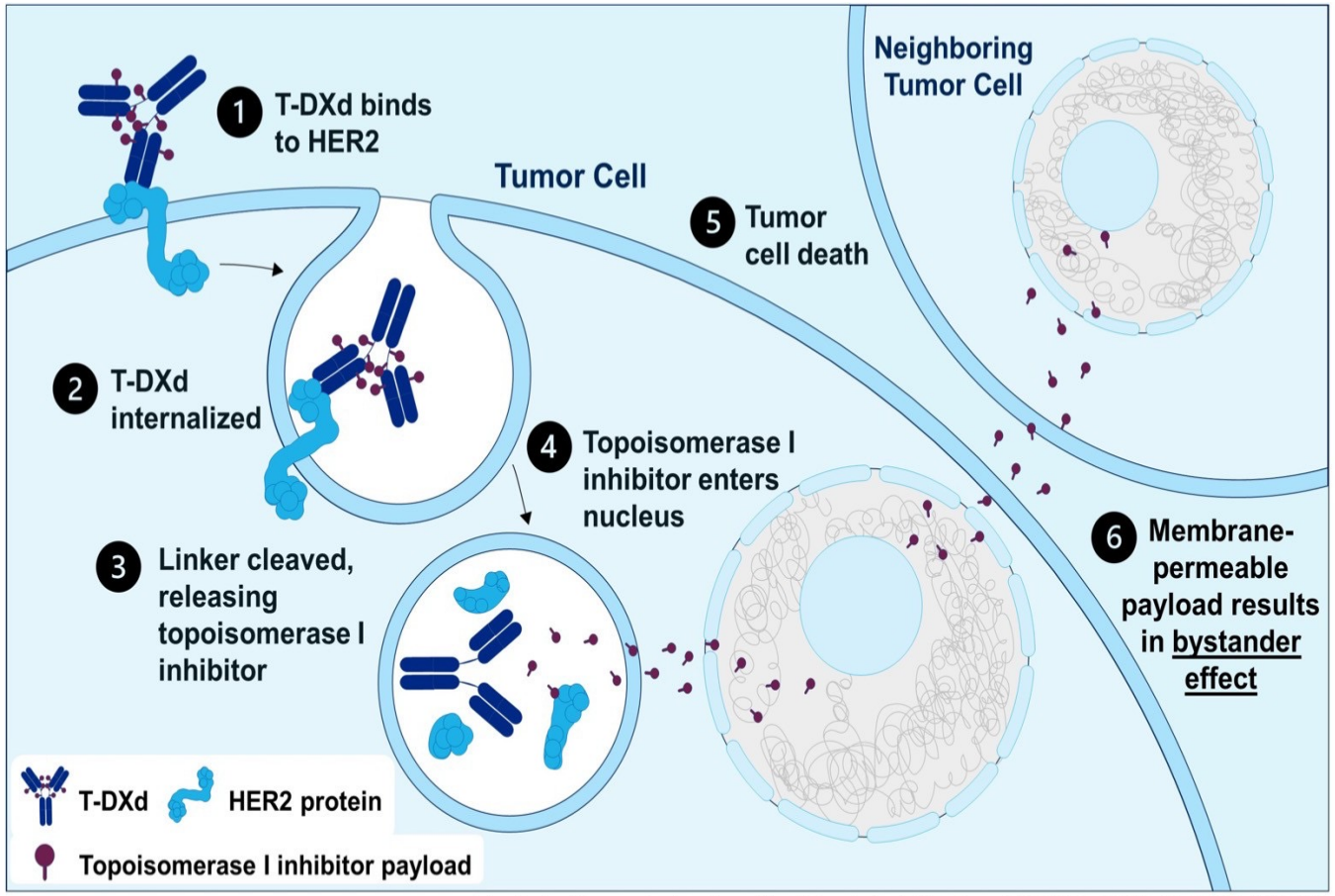
Metastatic breast cancer

1. INAVO: PFS2, TTFC, PROs results
2. postMONARCH
3. DESTINY Breast-06

Trastuzumab Deruxtecan is approved for HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



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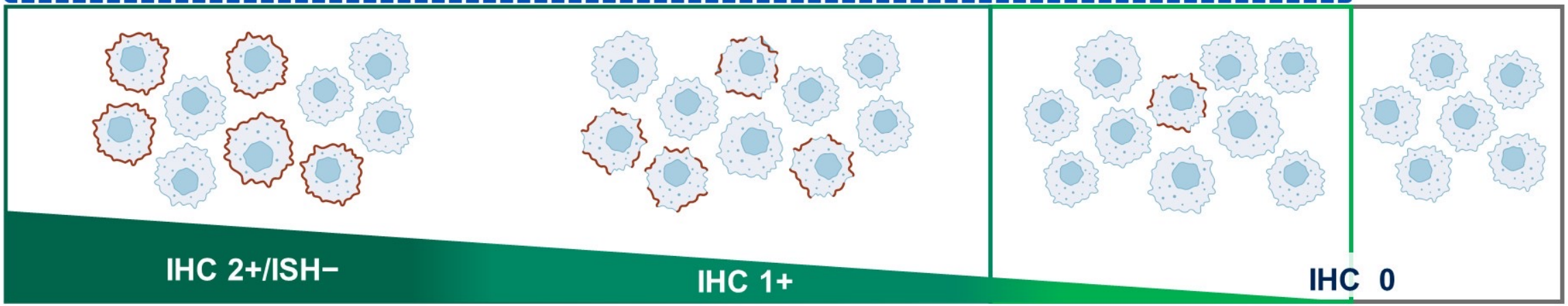
Targeting 'low' and 'ultralow' HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC



ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

Study design

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

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

Prior lines of therapy

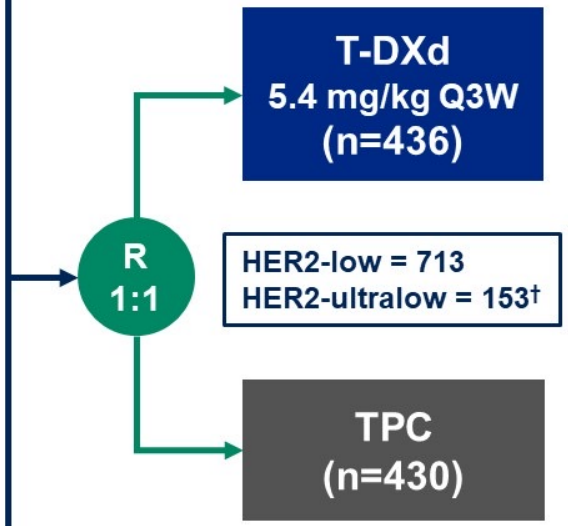
- ≥2 lines of ET ± targeted therapy for mBC

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

    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)



ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

PRESENTED BY: Giuseppe Curigliano, MD, PhD

Patient demographics and key baseline characteristics

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Age, median (range), years	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female, n (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
ECOG PS at screening, n (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)‡						
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
ER/PR status, n (%)§						
ER+/PR+	206 (57.4)	193 (54.5)	253 (58.0)	237 (55.1)	46 (60.5)	44 (57.9)
ER+/PR−	141 (39.3)	152 (42.9)	167 (38.3)	181 (42.1)	26 (34.2)	29 (38.2)
ER−/PR+	3 (0.8)	2 (0.6)	3 (0.7)	2 (0.5)	–	–
Primary endocrine resistance¶	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
De-novo disease at diagnosis, n (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline, n (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease at baseline, n (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver metastases at baseline, n (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)

*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data. With mis-stratification, the combined sample size of these two populations may not match the ITT total; †n=14 patients had missing ECOG PS status at baseline; ‡n=2 patients in the ITT (1 per treatment group) were found to have HER2 IHC 0 with absent membrane staining per central laboratory testing; §patients with ER−/PR− status were excluded from the study; however, n=1 patient with ER−/PR− status was randomized in error; ¶defined as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Prior therapies

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
≤6 months on first-line ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies, n (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with other targeted therapy†	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Adjuvant/neoadjuvant setting‡						
Prior therapies, n (%)						
ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

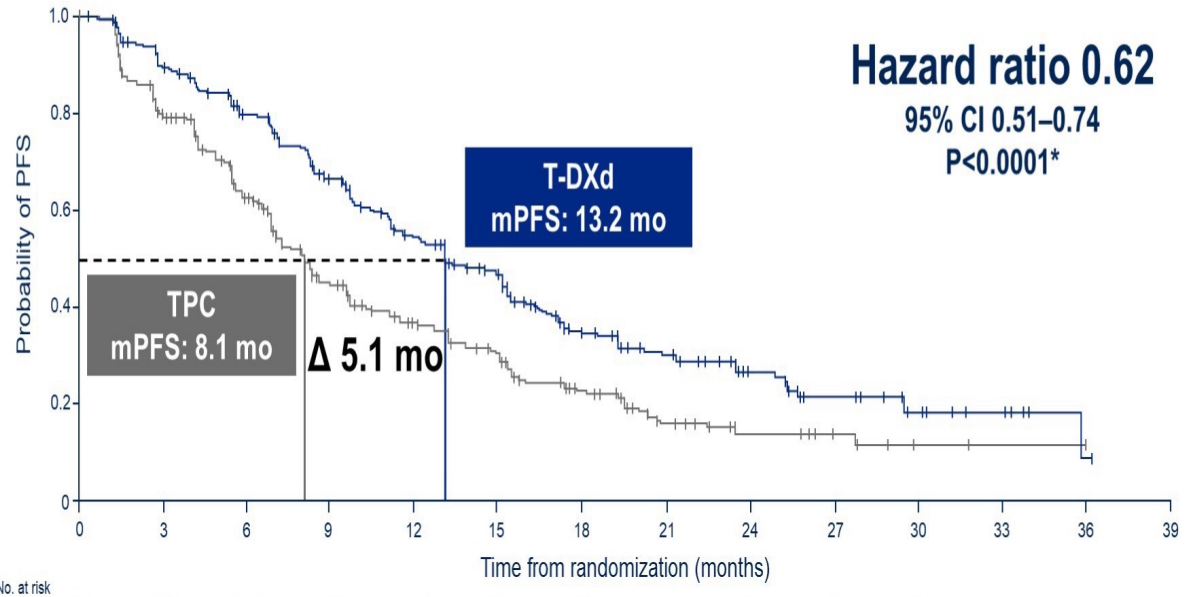
*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data; †other targeted therapies were mTORi (23.8%), PI3Ki (4.2%), or PARPi (0.9%) in the ITT; ‡approximately 30% of the patient population had de-novo metastatic disease and were not included in this category

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mTORi, mammalian target of rapamycin inhibitor; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; PI3Ki, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha inhibitor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

T-DxD improves PFS in HER2-low and HER2-ultralow mBC

DESTINY-Breast06

PFS (BICR) in HER2-low: primary endpoint



No. at risk

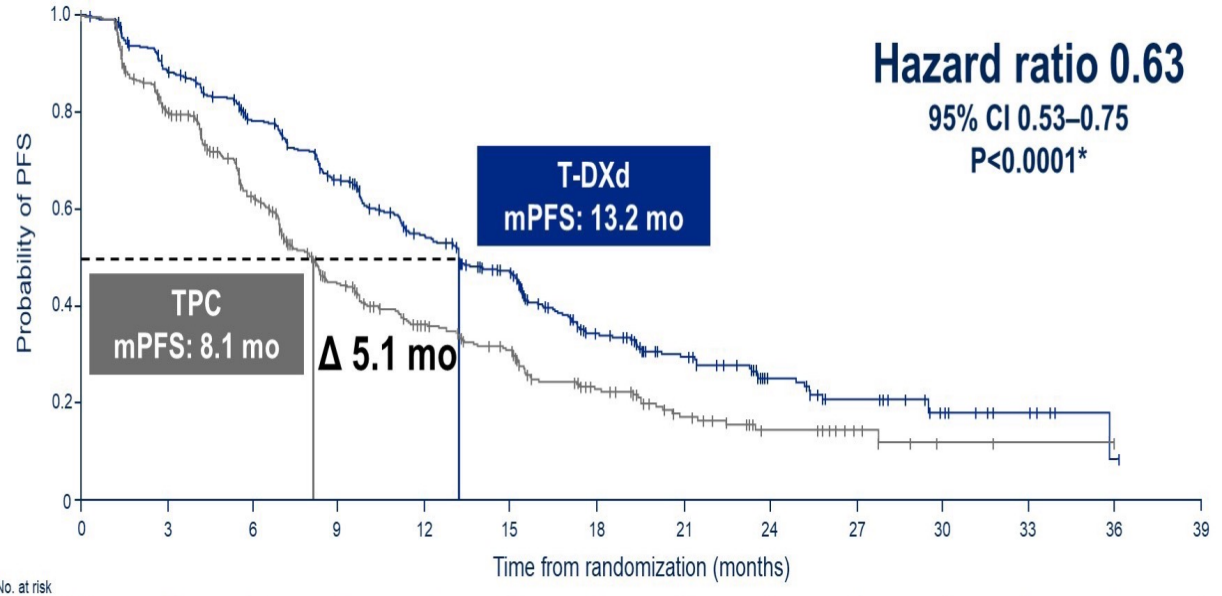
T-DXd	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0

T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast06

PFS (BICR) in ITT: key secondary endpoint



No. at risk

T-DXd	436	375	319	258	199	156	82	56	32	21	11	6	1	0
TPC	430	306	224	142	103	79	44	25	13	7	2	1	1	0

T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

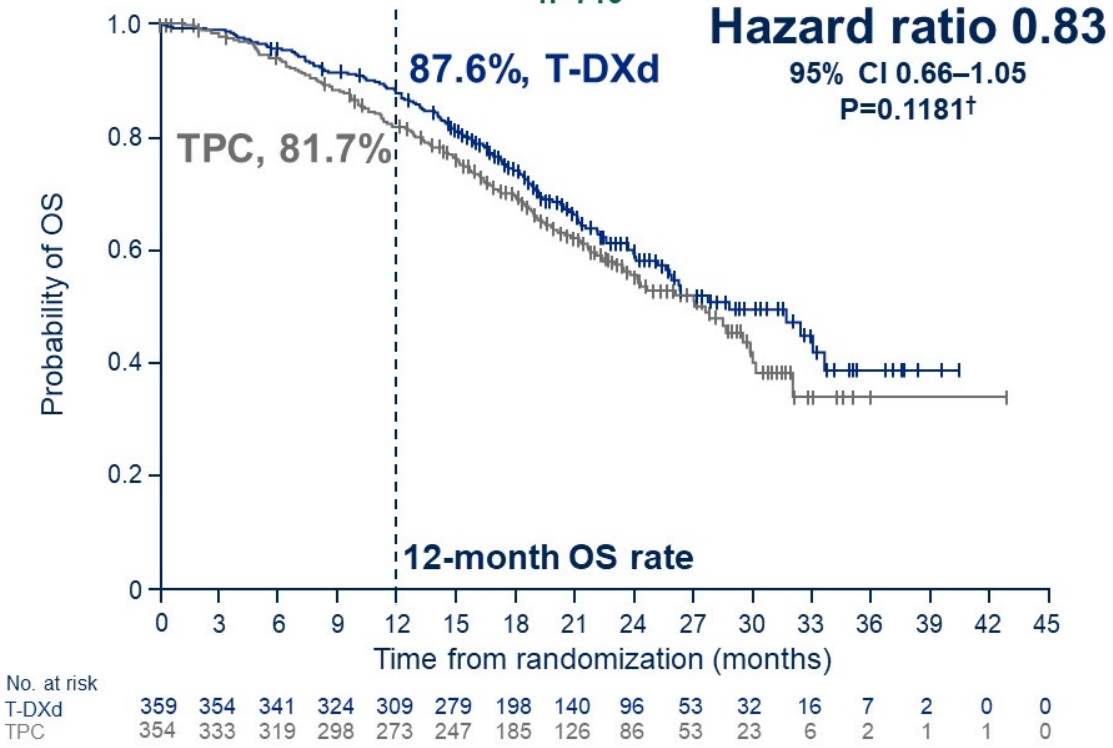
*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Giuseppe Curigliano, MD, PhD

OS in HER2-low and ITT: key secondary endpoints (~40% maturity)

HER2-low*

n=713



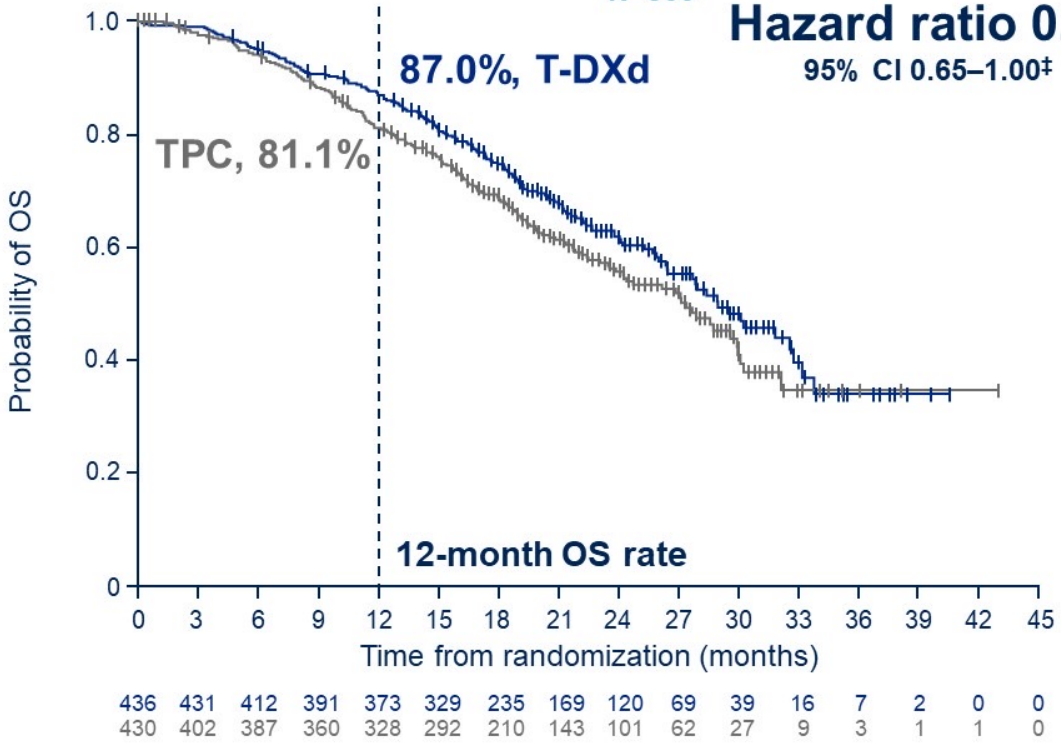
No. at risk

T-DXd	359	354	341	324	309	279	198	140	96	53	32	16	7	2	0	0
TPC	354	333	319	298	273	247	185	126	86	53	23	6	2	1	1	0

20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

ITT (HER2-low + HER2-ultralow)

N=866



T-DXd	436	431	412	391	373	329	235	169	120	69	39	16	7	2	0	0
TPC	430	402	387	360	328	292	210	143	101	62	27	9	3	1	1	0

17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

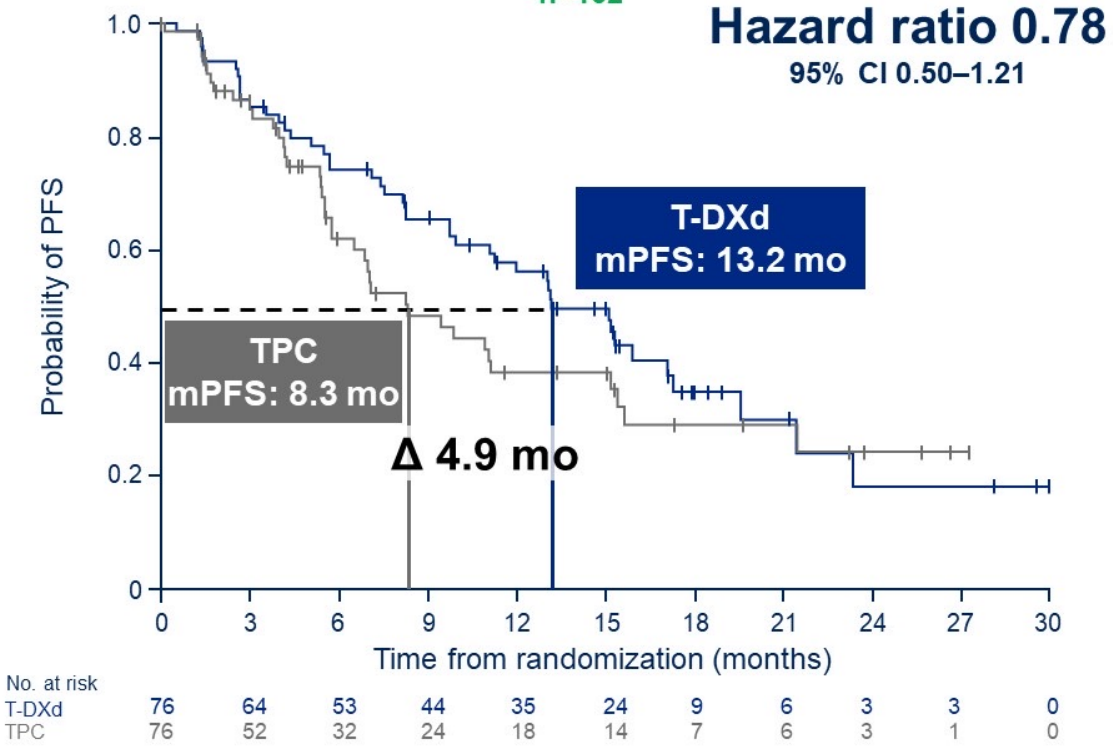
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)

CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS and OS in HER2-ultralow: prespecified exploratory analyses

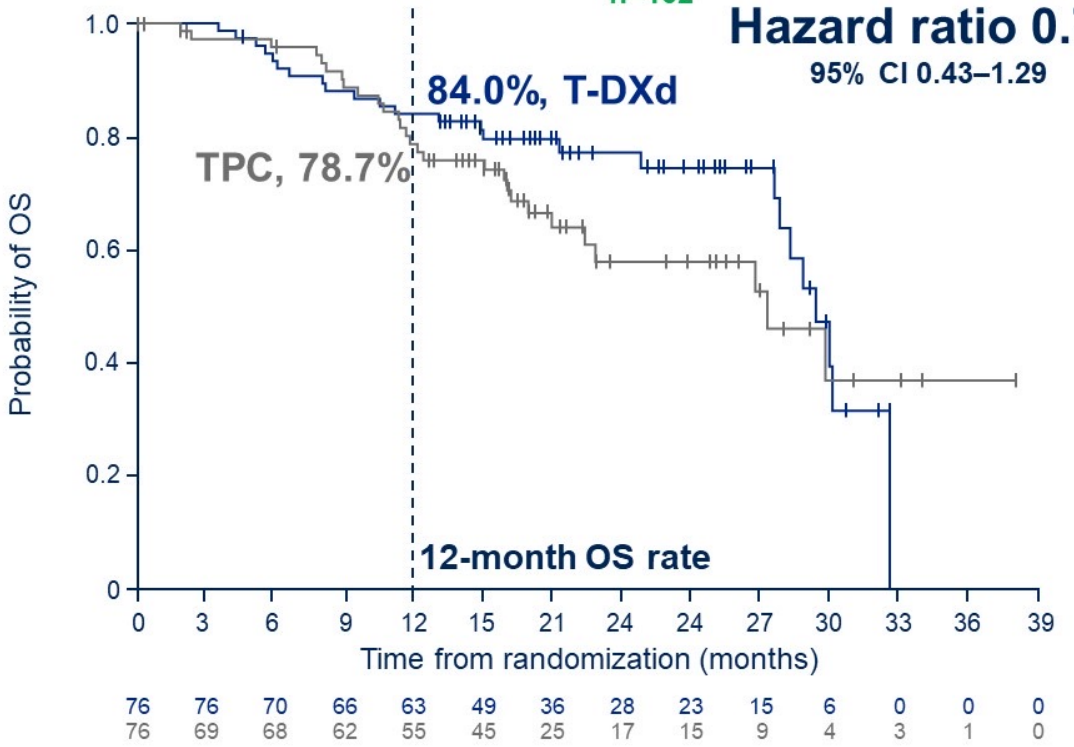
PFS (BICR)

n=152



OS*

n=152



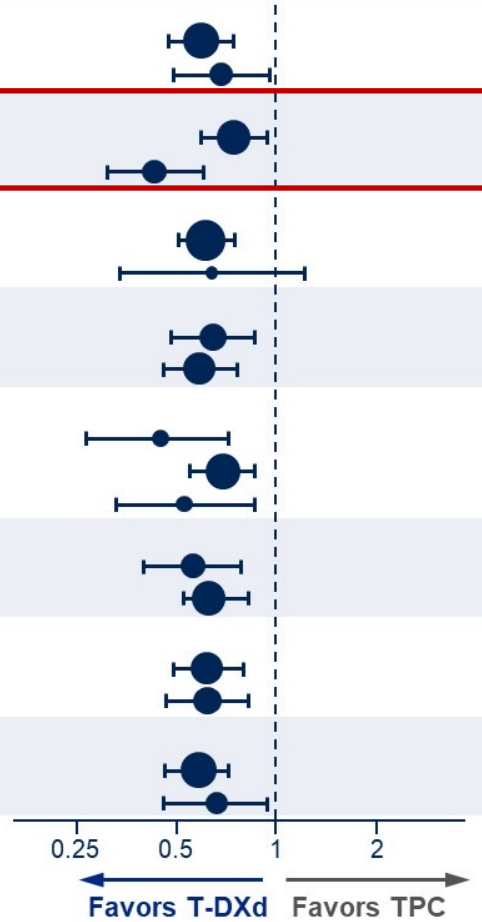
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PRESENTED BY: Giuseppe Curigliano, MD, PhD

PFS (BICR) in HER2-low: subgroup analysis

	No. of events / no. of patients		mPFS (95% CI), months		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Age					
<65 years	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 years	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 status*					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+/ISH−	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Prior CDK4/6i					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Prior taxane use (adjuvant/neoadjuvant setting)					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
Number of prior lines of ET (metastatic setting)					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Choice of chemotherapy†					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes (Nab-paclitaxel + paclitaxel)	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)



Size of circle is proportional to the number of events
*Based on central laboratory data (ie the HER2 result from the most recent evaluable sample prior to randomization); †specified by the investigator prior to randomization
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy;
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; (m)PFS, (median) progression-free survival;
NE, not evaluable; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY Breast-06

- ✓ T-DxD demonstrated a statistically significant and clinically meaningful PFS benefit vs. chemotherapy in HR+, HER2-low mBC **after ≥ 1L ET**

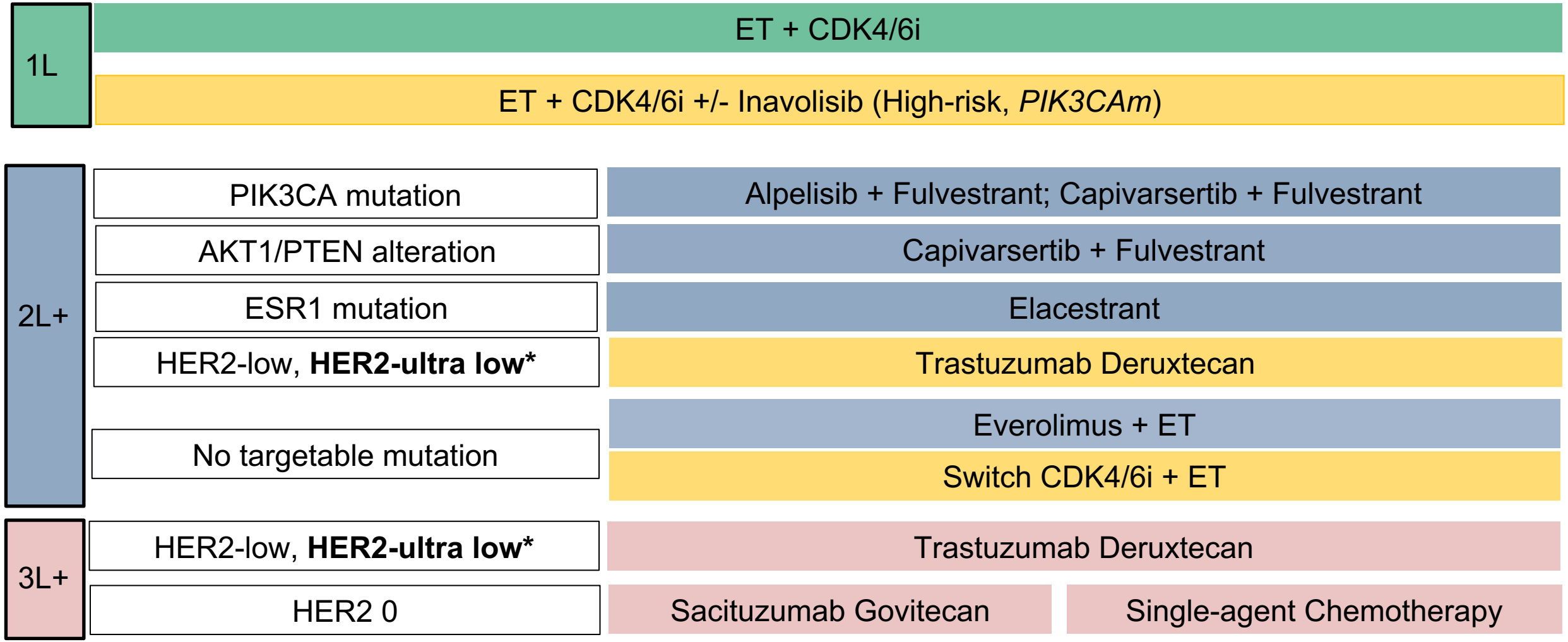
- ✓ Consistent results also observed in HR+, HER2-ultralow mBC

- ✓ ~85% of patients with HR+/HER2- mBC eligible for T-DxD
  - HER2-low (60-65%) and HER2-ultralow (20-25%)

Key Take Aways (ASCO 2024)

- ✓ In RxPONDER, AMH was a better predictor of adjuvant chemotherapy benefit than menopause status, age, or other serum hormone levels
- ✓ Inavolisib + palbociclib + fulvestrant is a promising option in high risk *PIK3CA*-mutated, HR+/HER2- mBC who relapsed during/within 12 months of adjuvant ET completion
- ✓ The addition of abemaciclib to fulvestrant significantly improved PFS in patients who previously received a CDK4/6i in the 1L setting
- ✓ T-DxD demonstrated a statistically significant and clinically meaningful PFS benefit vs. chemotherapy in HR+, HER2-low mBC after ≥ 1L ET
  - consistent results in the HER2-ultralow cohort

Treatment landscape in HR+/HER2- mBC (2024)



g*BRCA*: PARP inhibitor (2L+)