UCI Chao Family Comprehensive Cancer Center

Hormone Positive Breast Cancer Updates 2024 ASCO & ESMO Annual Meetings (MLS Irvine)

Sayeh Lavasani, MD, MSc, FRCPC

Associate Clinical Professor

Division of Hematology Oncology

Department of Medicine, UCI Health

ASCO 2024 HR+ Breast Cancer Abstracts

Destiny-Breast06

- Trastuzumab deruxtecan (T-DXd) vs. treatment of physician's choice of chemotherapy (TPC) in patients with HR+, HER2-low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: Primary results from Destiny-Breast06 (DB-06)

PostMONARCH

- Abemaciclib plus Fulvestrant vs. Fulvestrant alone for HR+, HER2- advanced breast cancer after progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of Phase 3 PostMONARCH trial

INAVO120

- First-line inavolisib/placebo+palbociclib+fulvestrant in patients with PIK3CA-mutated, HR+, HER2-

RxPONDER – SWOG 1007 – AMH and benefit from chemotherapy in premenopausal women

ESMO 2024 HR+ BC Updates

NATALEE 4-year updates

2024 ASCO ANNUAL MEETING

DESTINY BREAST06

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06

Giuseppe Curigliano
European Institute of Oncology, IRCCS, Milan, Italy;
Department of Oncology and Hematology-Oncology, University of Milan, Italy

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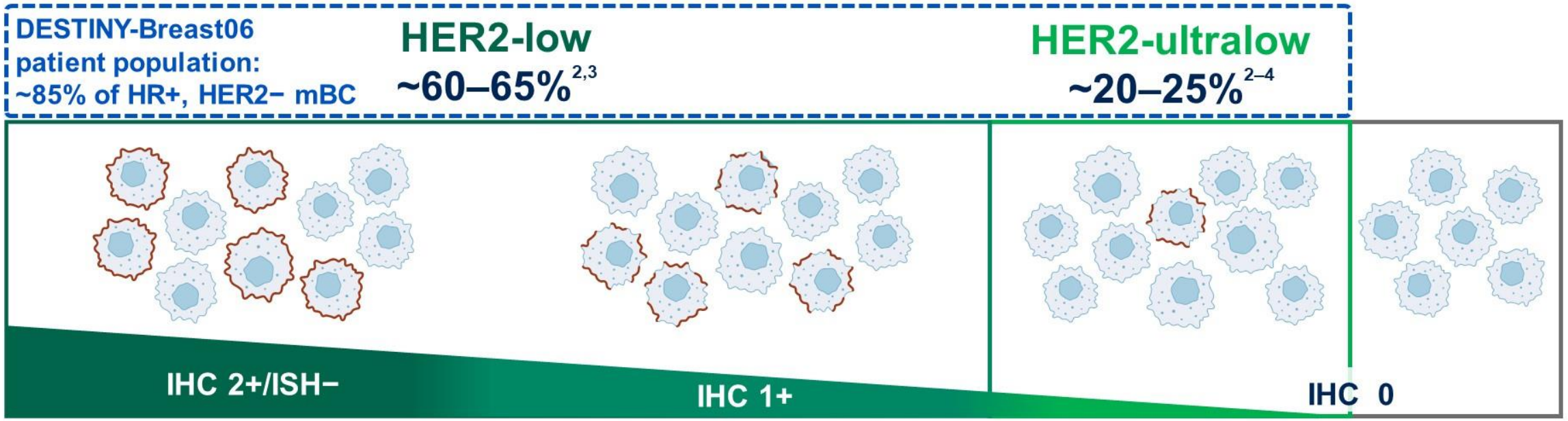
Additional authors: Xichun Hu, Rebecca Dent, Kan Yonemori, Carlos H Barrios, Joyce A O'Shaughnessy, Hans Wildiers, Qingyuan Zhang, Seock-Ah Im, Cristina Saura, Laura Biganzoli, Joohyuk Sohn, Christelle Lévy, William Jacot, Natasha Begbie, Jun Ke, Gargi Patel, Aditya Bardia

On behalf of the DESTINY-Breast06 investigators

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

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/

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

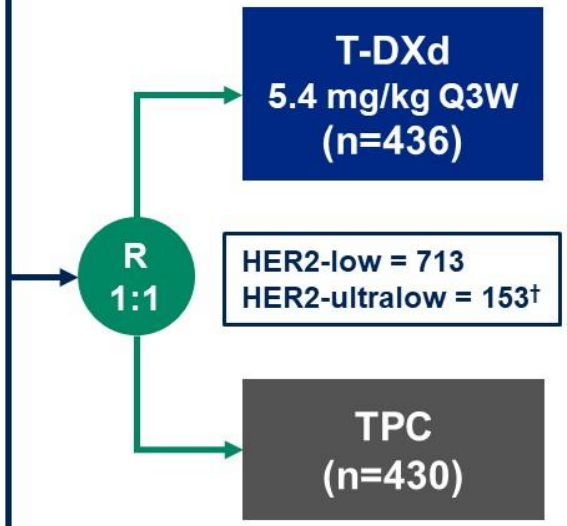
- ≥2 lines of ET ± targeted therapy for mBC

  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

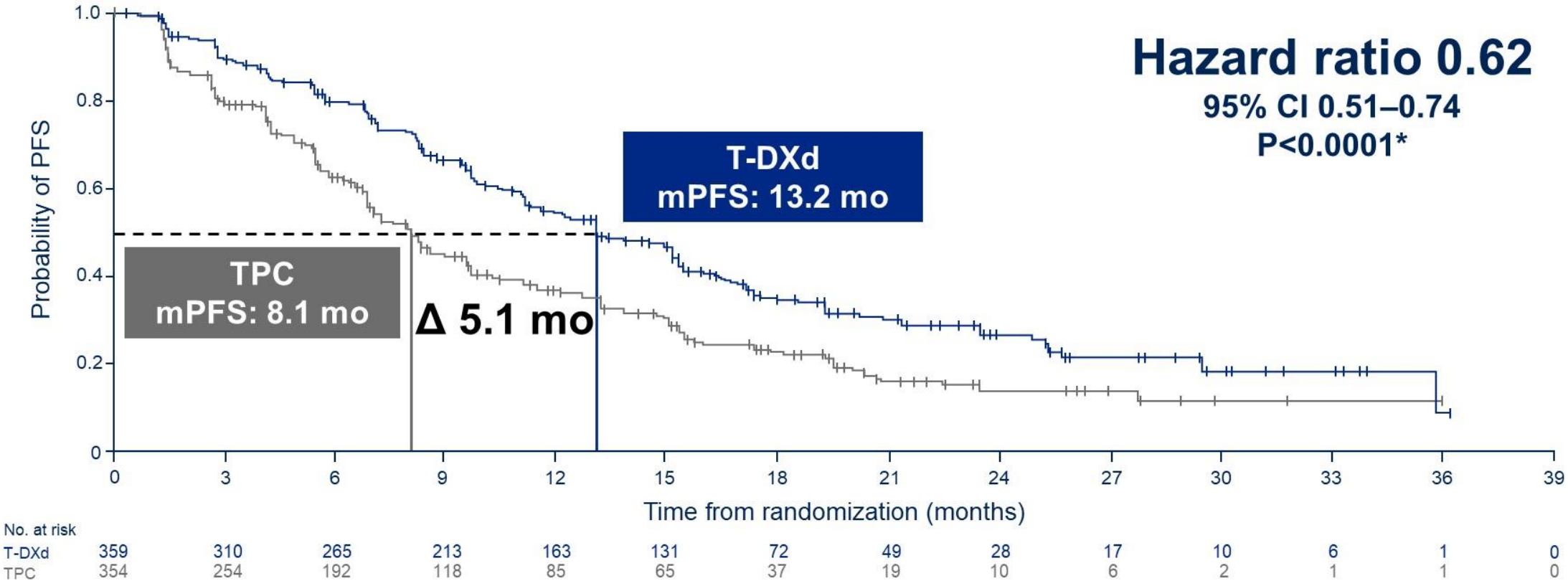
- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*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)

Baseline characteristics

- Median age: 58
- Patients on average had 2 lines of endocrine therapy
- 89% of patients had prior CDK4/6i
- 86% of patients had visceral metastatic disease
- 3% of patients had bone only mets
- 30% of patients had primary endocrine resistance

PFS (BICR) in HER2-low: primary endpoint



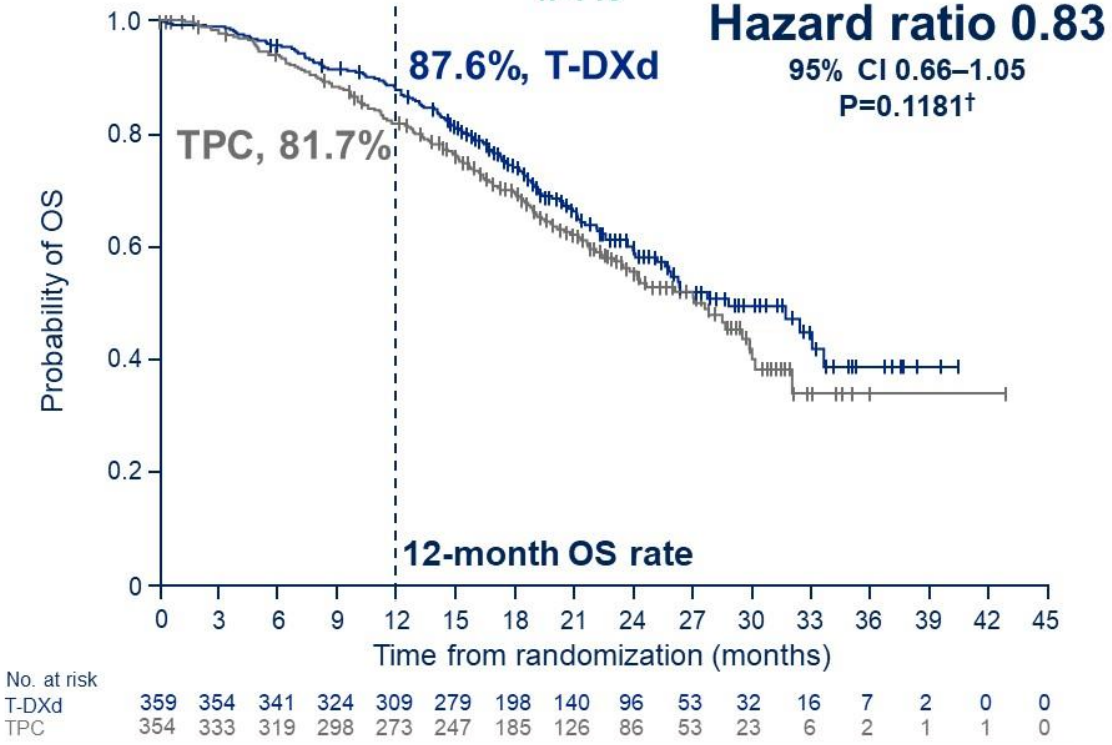
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*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

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

HER2-low*

n=713



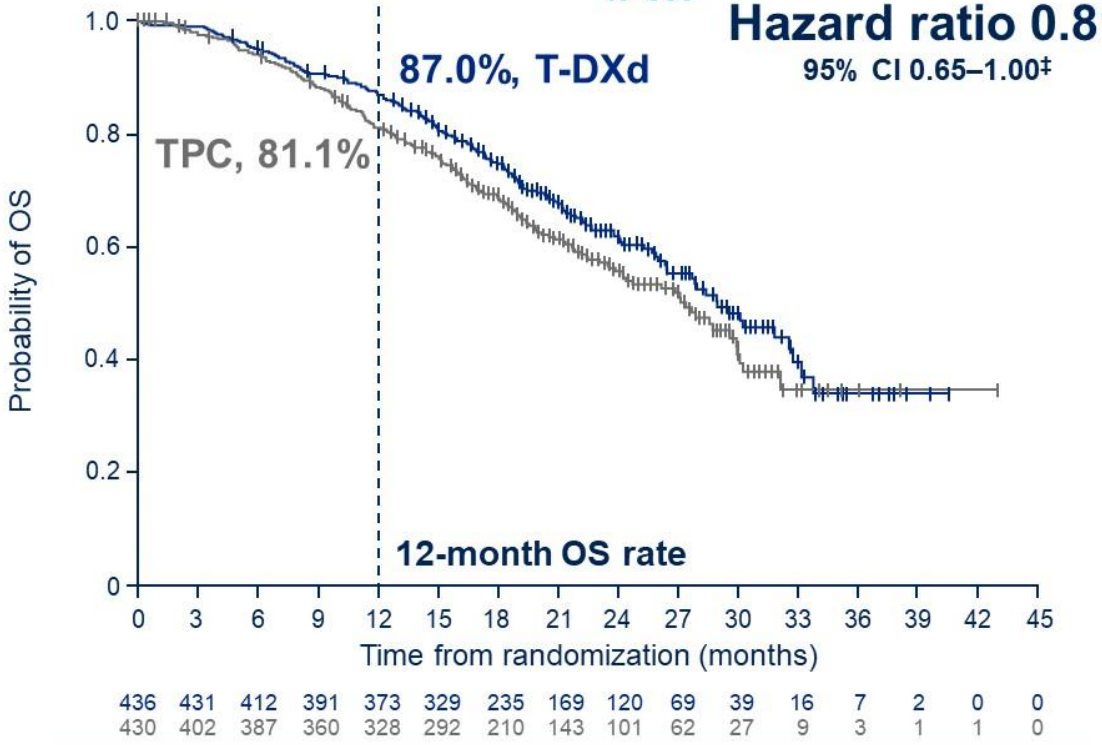
No. at risk

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)

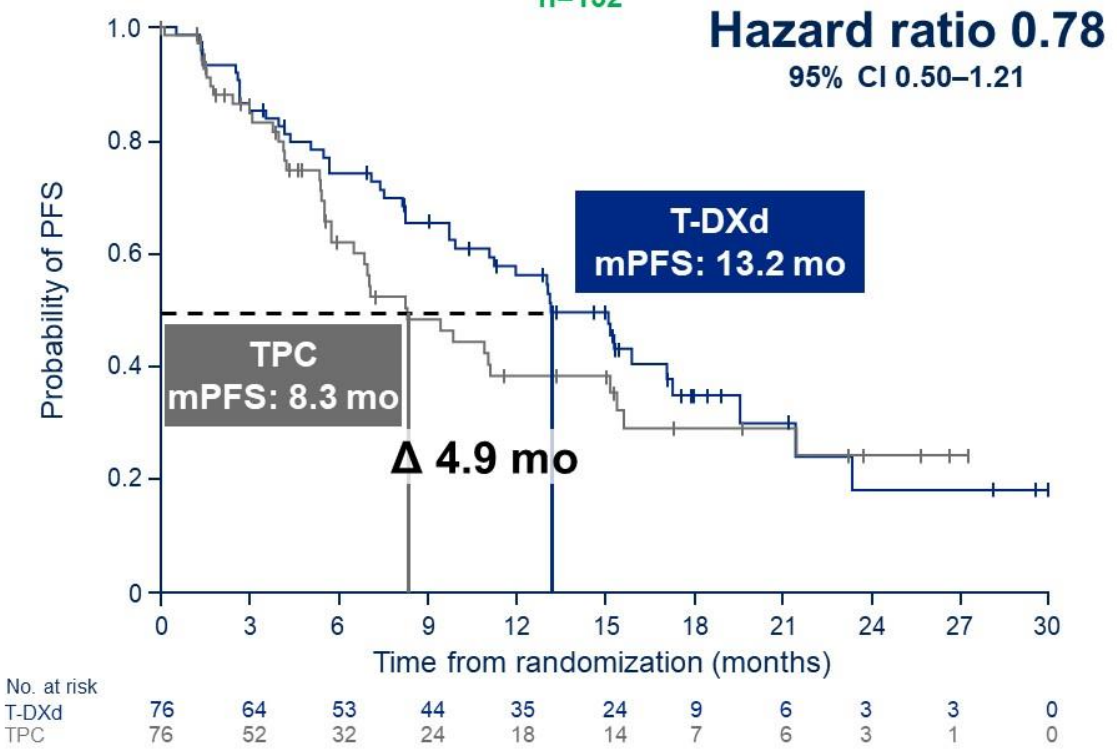
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow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

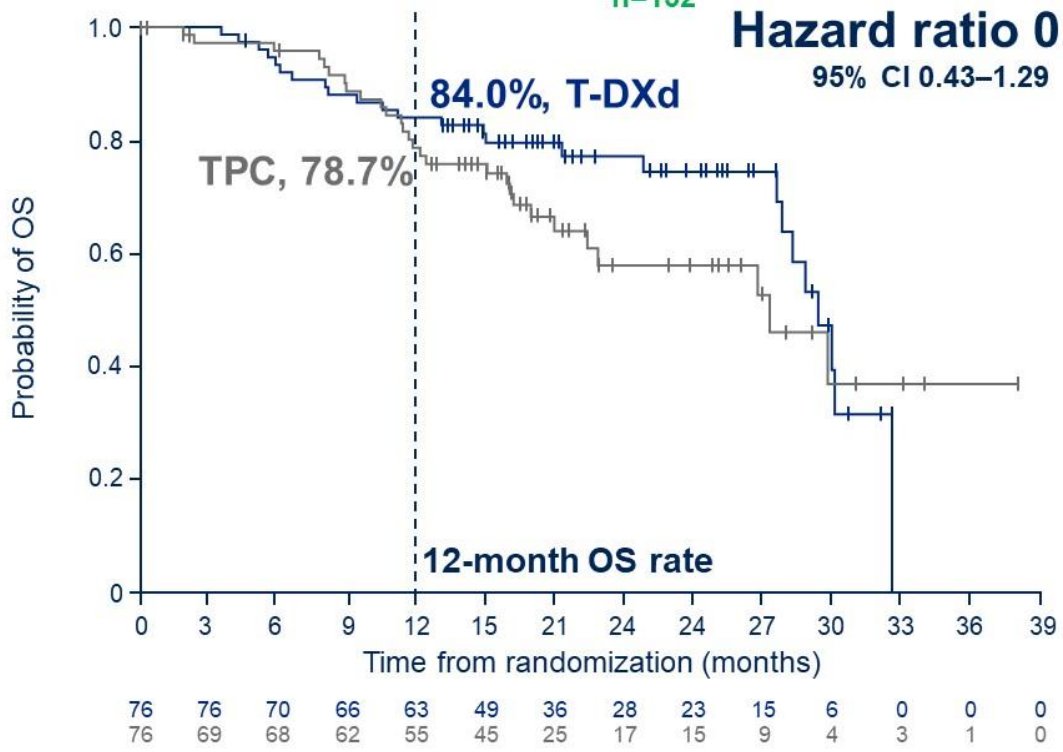


No. at risk

T-DXd	76	64	53	44	35	24	9	6	3	3	0
TPC	76	52	32	24	18	14	7	6	3	1	0

OS*

n=152



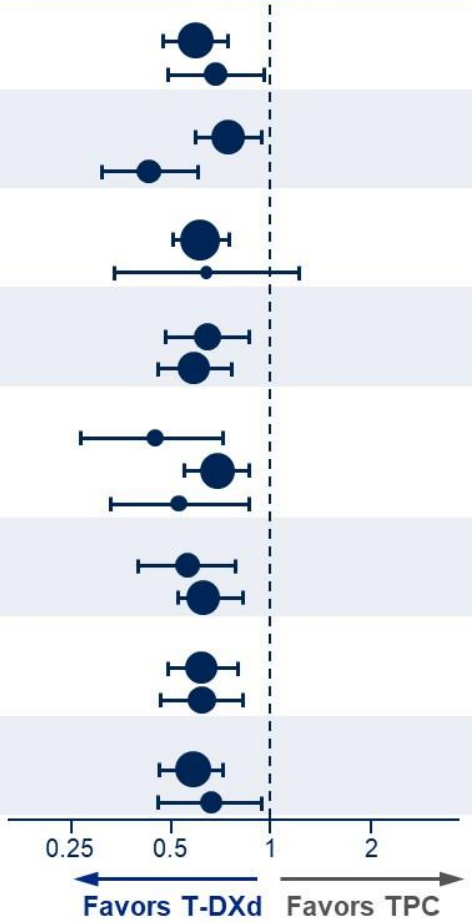
76	76	70	66	63	49	36	28	23	15	6	0	0	0
76	69	68	62	55	45	25	17	15	9	4	3	1	0

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

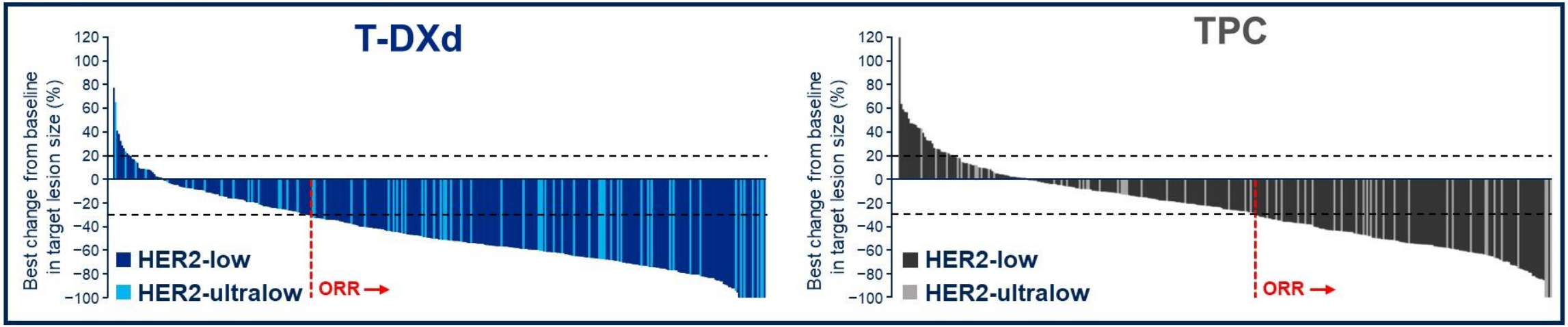
PFS (BICR) in HER2-low: subgroup analysis

	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

Antitumor activity



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

ORR based on RECIST v1.1; response required confirmation after 4 weeks
*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined by central laboratory testing data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

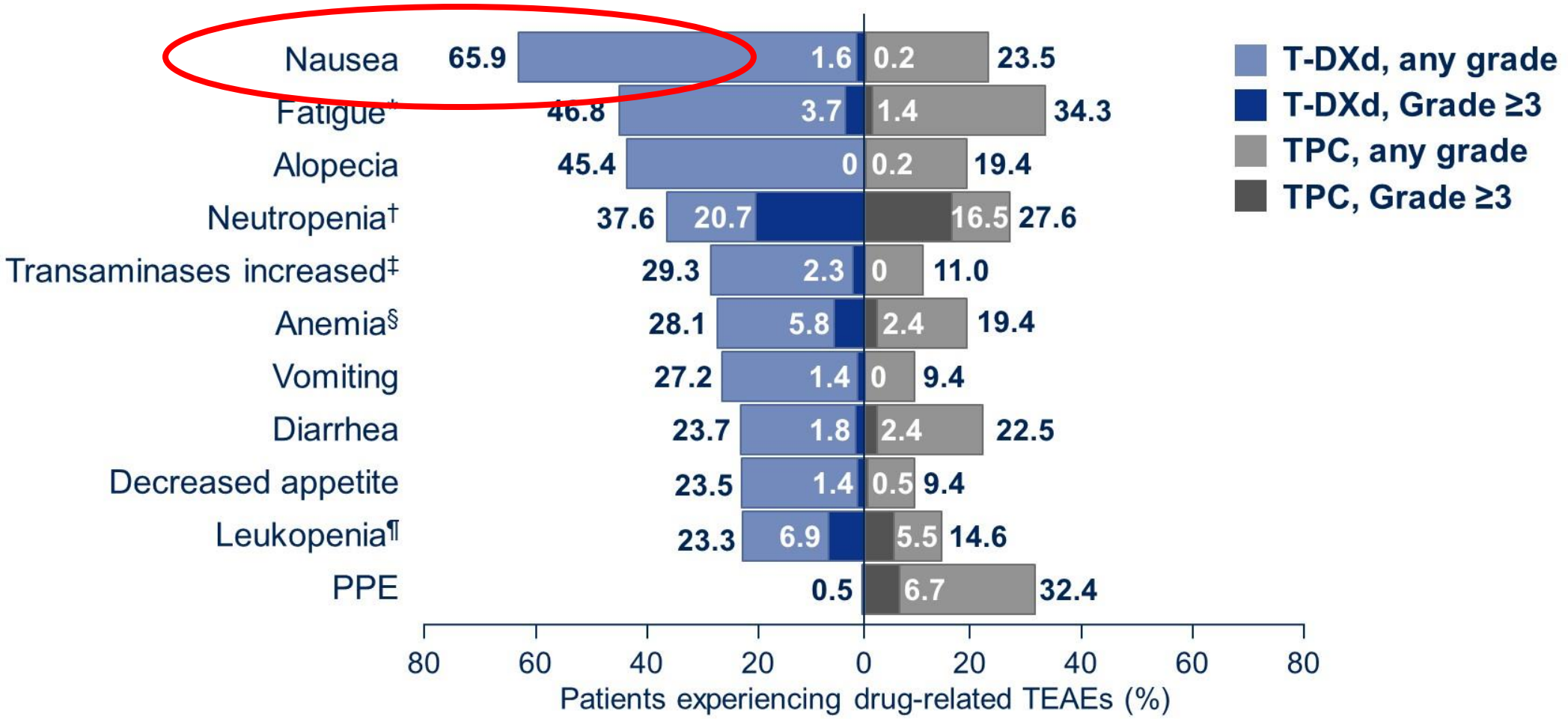
Overall safety summary

	Safety analysis set*	
	T-DXd (n=434)	TPC (n=417)
Total exposure, patient-years	438.5	263.5
Any TEAE, n (%)	429 (98.8)	397 (95.2)
Treatment-related TEAEs, n (%)	417 (96.1)	373 (89.4)
Grade ≥3	176 (40.6)	131 (31.4)
Serious TEAEs, n (%)	88 (20.3)	67 (16.1)
TEAEs associated with treatment discontinuation, n (%)	62 (14.3)	39 (9.4)
TEAEs associated with dose interruptions, n (%)	210 (48.4)	160 (38.4)
TEAEs associated with dose reductions, n (%)	107 (24.7)	161 (38.6)
TEAEs leading to death, n (%)	11 (2.5)	6 (1.4)
Treatment related (investigator assessed)‡	5 (1.2)	0

- **Median treatment duration:**
  - **T-DXd: 11.0 mo (range 0.4–39.6)**
  - **TPC: 5.6 mo (range 0.1–35.9)**
- Most common TEAE associated with treatment discontinuation:
  - T-DXd: 5.3%, pneumonitis†
  - TPC: 1.4%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction:
  - T-DXd: 4.4%, nausea
  - TPC: 16.5%, PPE

*Safety analyses included all patients who received at least one dose of study treatment; †in the T-DXd group, 3.5% of patients discontinued due to interstitial lung disease; ‡reasons were interstitial lung disease (n=2), sepsis (n=1), neutropenic sepsis (n=1) and general physical health deterioration (n=1)
mo, months; PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, chemotherapy treatment of physician's choice

Drug-related TEAEs in ≥20% of patients (either treatment group)



*Includes the preferred terms fatigue, asthenia, malaise, and lethargy; †includes the preferred terms neutrophil count decreased and neutropenia; ‡includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased; §includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased; ¶includes the preferred terms white blood cell count decreased and leukopenia

PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, chemotherapy treatment of physician's choice

Adverse events of special interest

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Left ventricular dysfunction†

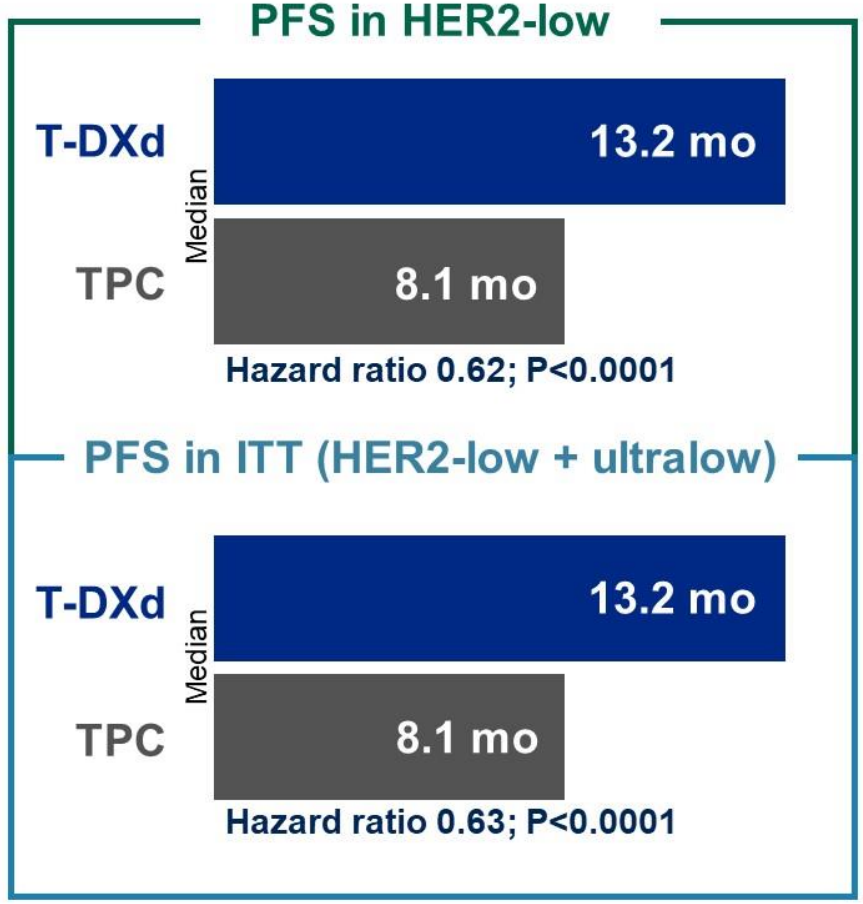
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

*Grouped term. Median time to first onset of interstitial lung disease / pneumonitis for patients with T-DXd was 141 days (range 37–835). No pending cases of drug-related interstitial lung disease / pneumonitis to be adjudicated. One interstitial lung disease–related death per investigator assessment was upheld by the adjudication committee. An additional two deaths were adjudicated as interstitial lung disease–related by the adjudication committee; †data for the most common preferred terms are shown on the slide; additionally, one patient in each treatment group had the preferred term left ventricular dysfunction (Grade 3 with T-DXd, Grade 2 with TPC)
T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Conclusions

- T-DXd demonstrated a statistically significant and clinically meaningful PFS benefit vs TPC (chemotherapy) in HR+, HER2-low mBC in an earlier line of treatment than DESTINY-Breast04
- Results in HER2-ultralow were consistent with HER2-low
- Confirmed ORR was 57.3% (T-DXd) vs 31.2% (TPC) in ITT
- No new safety signals were identified; interstitial lung disease remains an important safety risk of T-DXd

DESTINY-Breast06 establishes T-DXd as an effective new treatment option for patients with HR+, HER2-low and HER2-ultralow mBC following ≥1 endocrine-based therapy



HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-06 impact on our practice

- HER2 low and ultralow consists of 80-85% of our HR+ MBC patients
- Identifying HER2 ultralow is important, and it requires breast pathologists training in identifying and reporting the ultralow breast cancers due to low concordance among breast pathologists

2024 ASCO ANNUAL MEETING

Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the Phase 3 postMONARCH trial

Kevin Kalinsky[1], Giampaolo Bianchini[2], Erika P. Hamilton[3], Stephanie L. Graff[4], Kyong Hwa Park[5], Rinath Jeselsohn[6], Umut Demirci[7], Miguel Martin[8], Rachel M. Layman[9], Sara Hurvitz[10], Sarah Sammons[11], Peter A. Kaufman[12], Montserrat Munoz[13], Ling-Ming Tseng[14], Holly Knoderer[15], Bastien Nguyen[15], Yanhong Zhou[15], Elizabeth Ravenberg[15], Lacey M. Litchfield[15], Seth A. Wander[16]

[1]Winship Cancer Institute at Emory University, Atlanta, GA, USA, [2]IRCCS Ospedale, San Raffaele, Milan, Italy, [3]Sarah Cannon Research Institute, Nashville, TN, USA, [4]Lifespan Cancer Institute, Warren Albert School of Medicine, Brown University, Providence, RI, USA , [5]Korea University Anam Hospital, Korea University, Seoul, South Korea, [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [7]Memorial Ankara Hospital, Ankara, Turkey, [8]Hospital General Universitario Gregorio Maranon, Universidad Complutense, Madrid, Spain, [9]MD Anderson Cancer Center, University of Texas, Houston, TX, USA, [10]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA, [11]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [12]University of Vermont Medical Center, Burlington, VT, USA, [13]Hospital Clinic i Provincial, Barcelona, Spain,[14]Taipei Veterans General Hospital, Taipei, Taiwan,[15]Eli Lilly and Company, Indianapolis, IN, USA, [16]Massachusetts General Hospital, Harvard University, Boston, MA, USA

PRESENTED BY: Kevin Kalinsky, MD, MS

postMONARCH Study Design

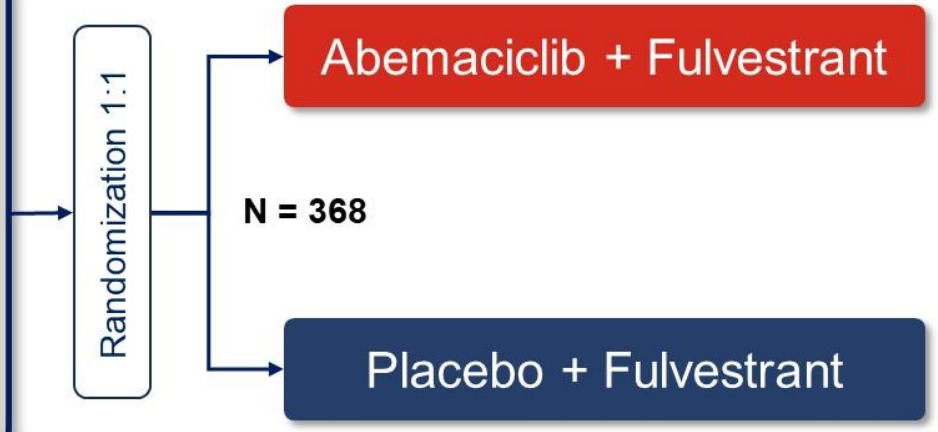
Eligibility

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



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

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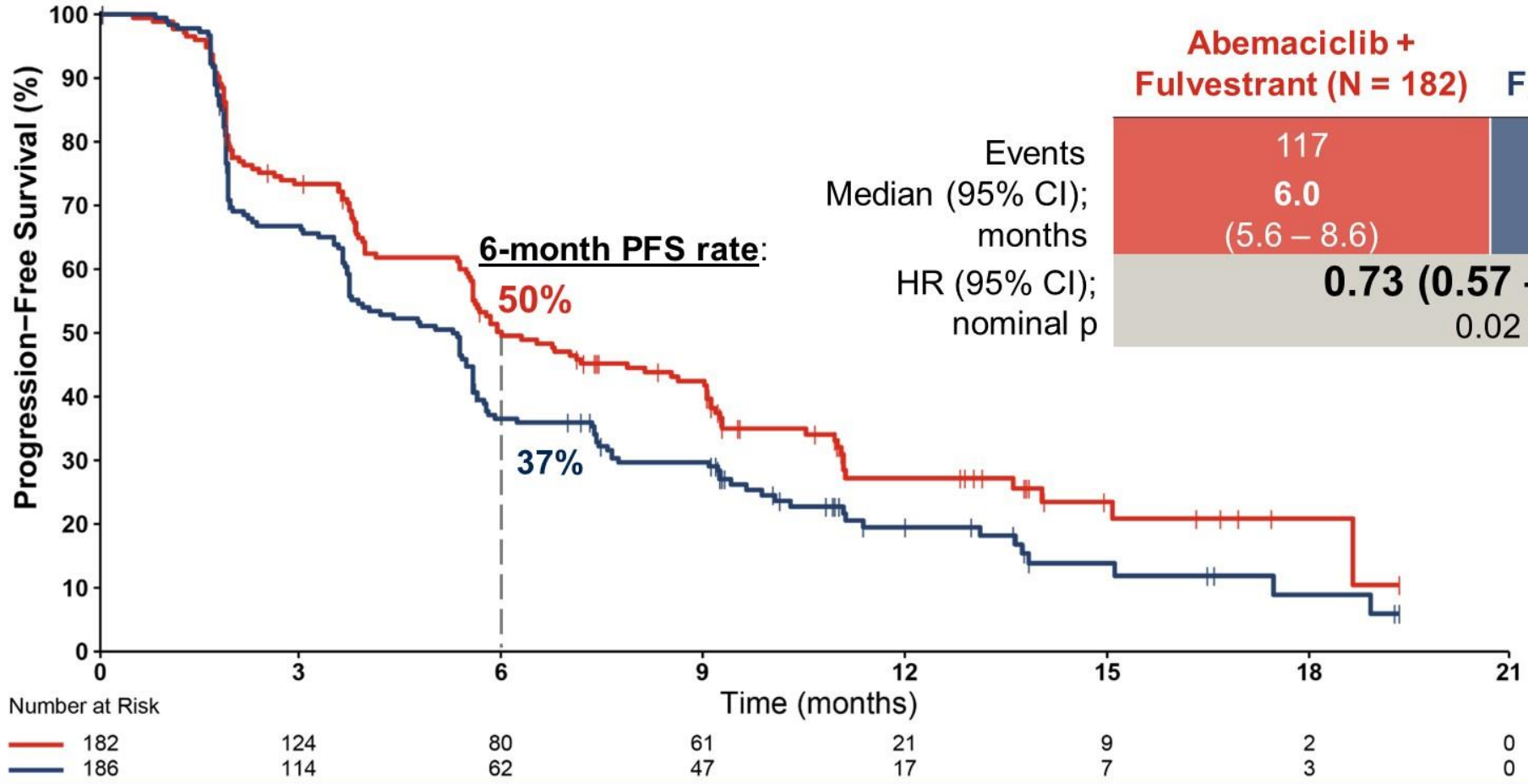
* ≥ 12 months ABC or recurrence after EBC therapy
^ < 12 months ABC or recurrence on EBC therapy
# for ABC

Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS

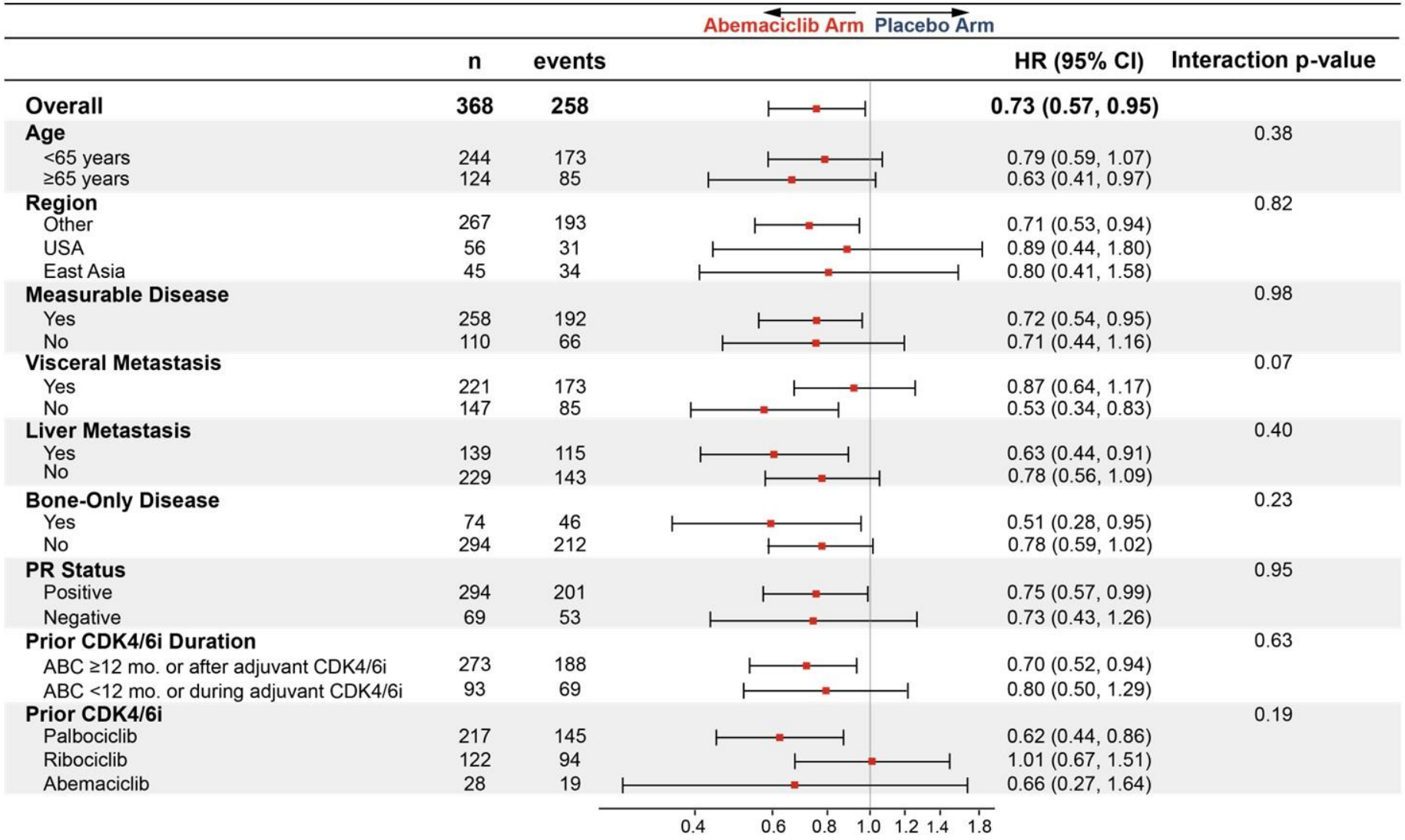


	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	**6.0** (5.6 – 8.6)	**5.3** (3.7 – 5.6)
HR (95% CI); nominal p	**0.73 (0.57 – 0.95)** 0.02	

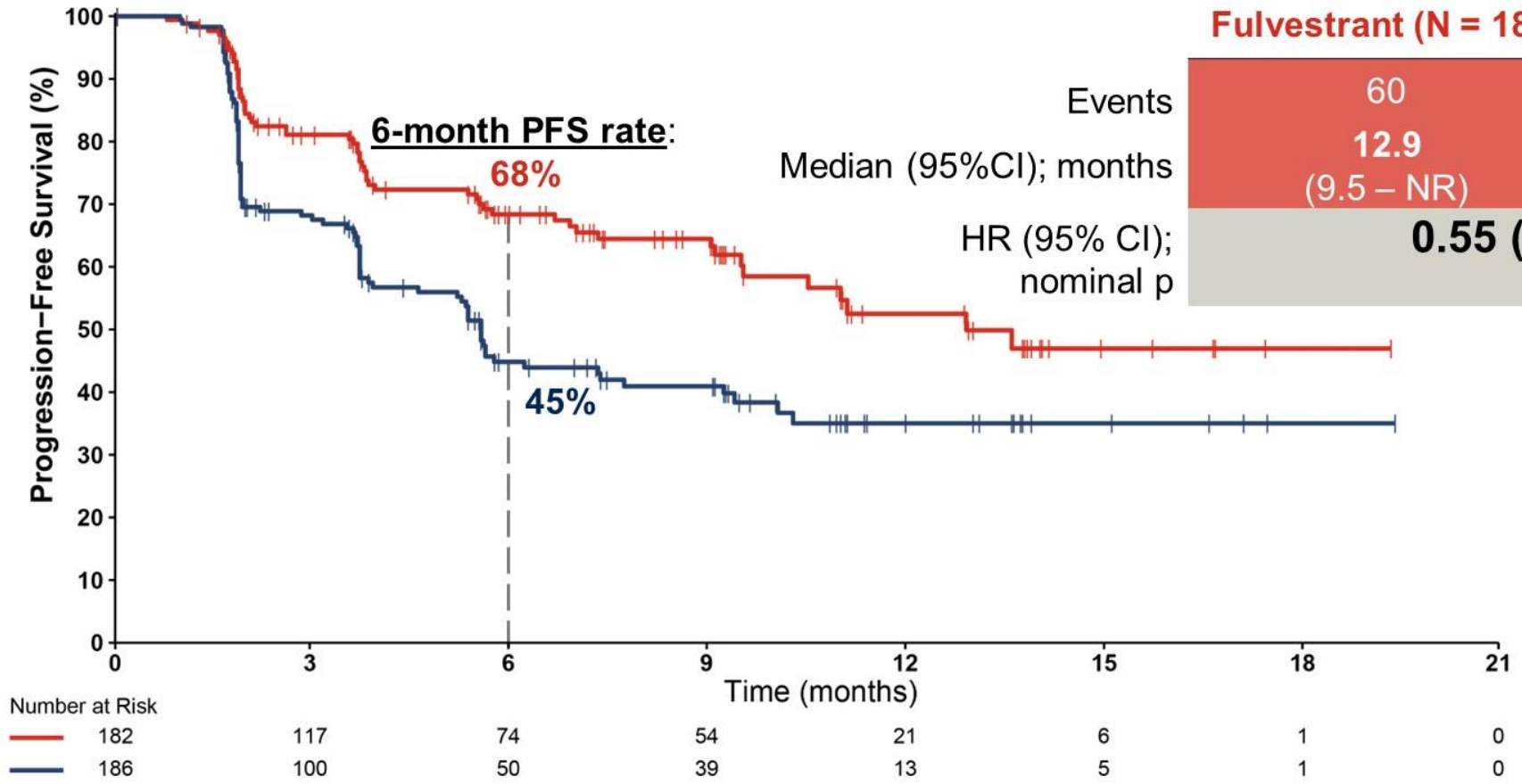
Abemaciclib led to 27% reduction in the risk of developing PFS event

PRESENTED BY: Kevin Kalinsky, MD, MS

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



Secondary Analysis: Abemaciclib Improved BICR-Assessed PFS



	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	60	92
Median (95%CI); months	**12.9** (9.5 – NR)	**5.6** (3.9 – 7.7)
HR (95% CI); nominal p	**0.55 (0.39 – 0.77)** 0.0004	

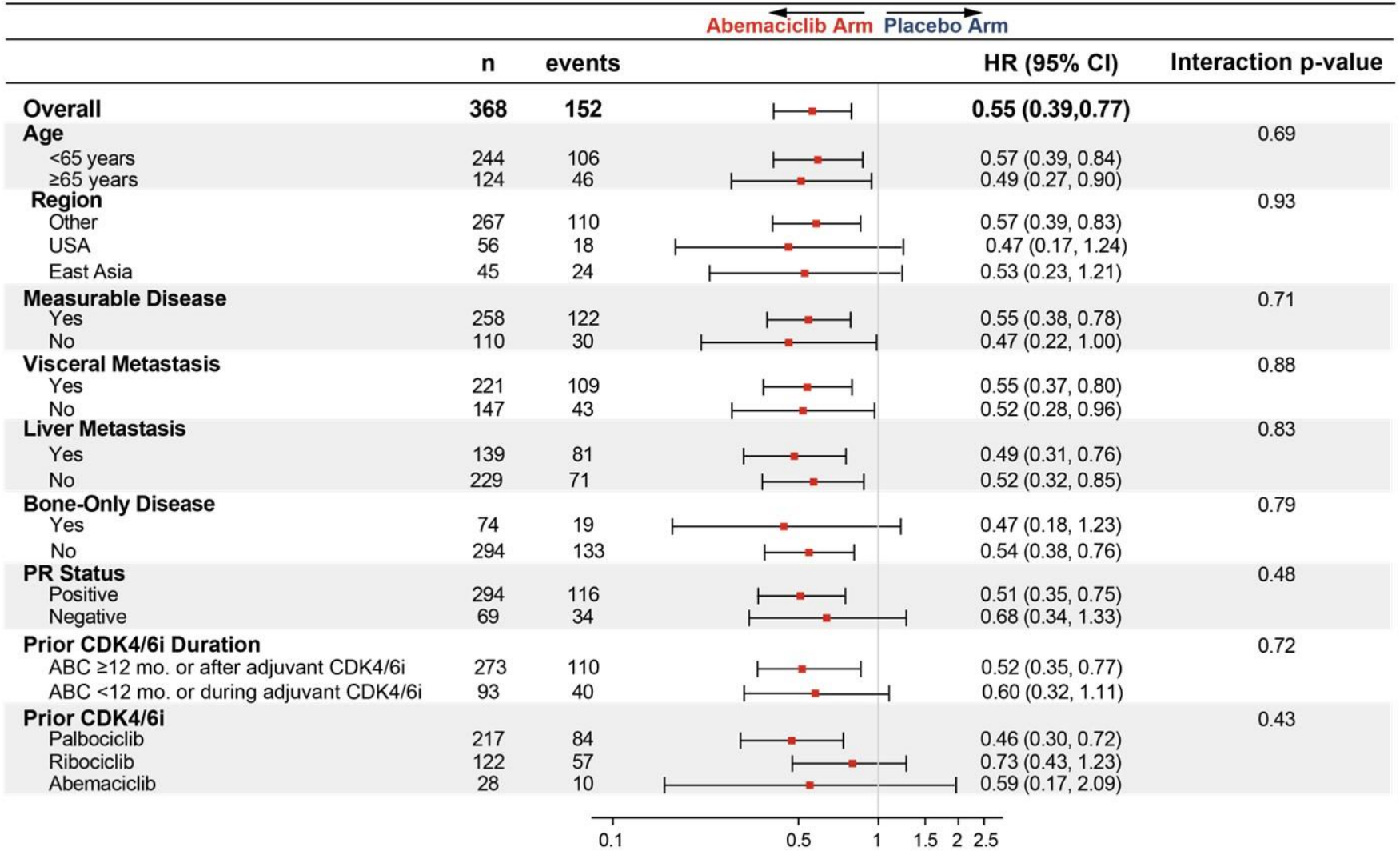
Estimates impacted by informative censoring (discordance with investigator events: **51% abemaciclib arm, 38% placebo arm**)

Abemaciclib led to 45% reduction in the risk of developing PFS event per BICR

PRESENTED BY: Kevin Kalinsky, MD, MS

BICR: Blinded Independent Central Review

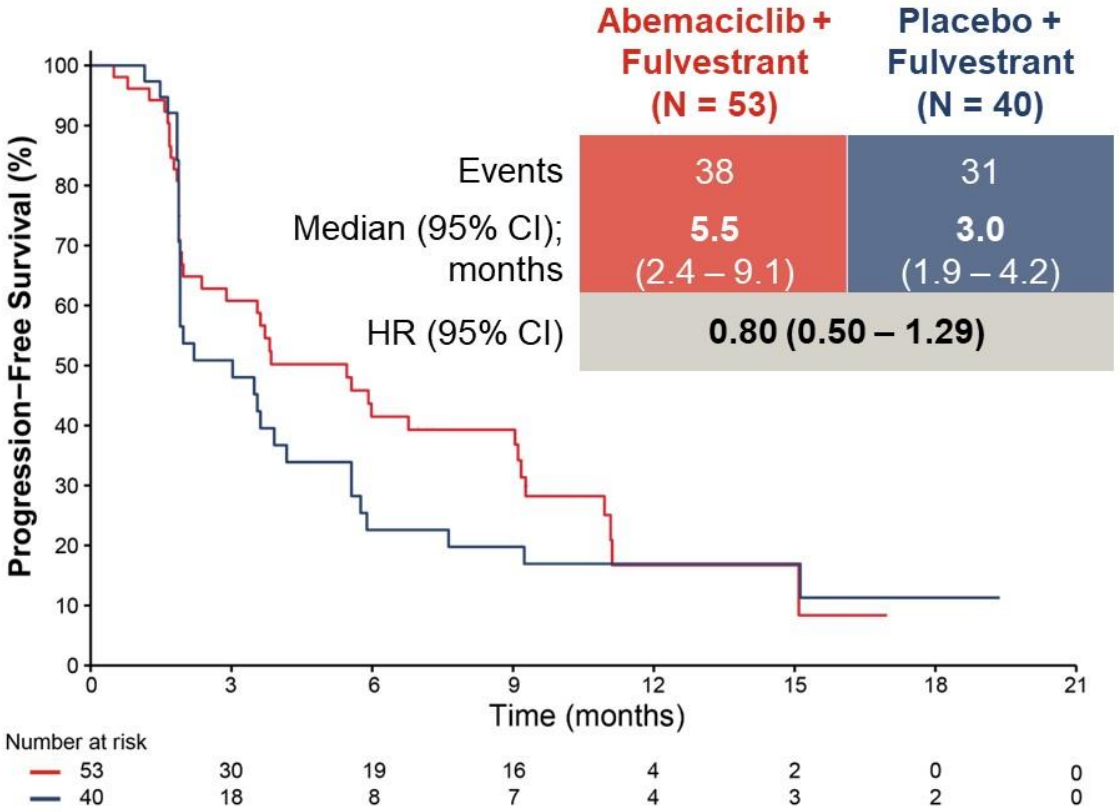
BICR-Assessed PFS by Subgroup: Consistent Abemaciclib Effect Across Subgroups



Estimates impacted by informative censoring (discordance with investigator events: **51% abemaciclib arm, 38% placebo arm**)

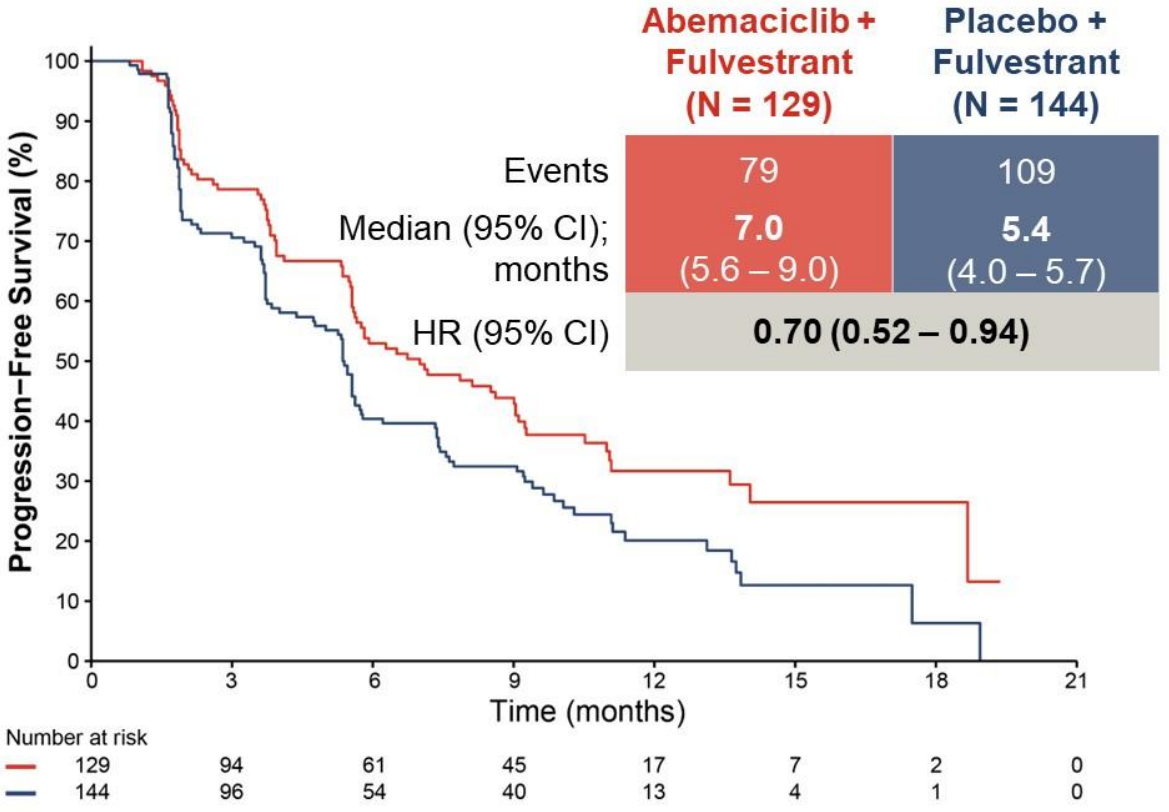
Subgroup Analysis: Investigator-Assessed PFS by Prior CDK4/6i Duration

< 12 months^



^ < 12 months ABC or recurrence on EBC therapy

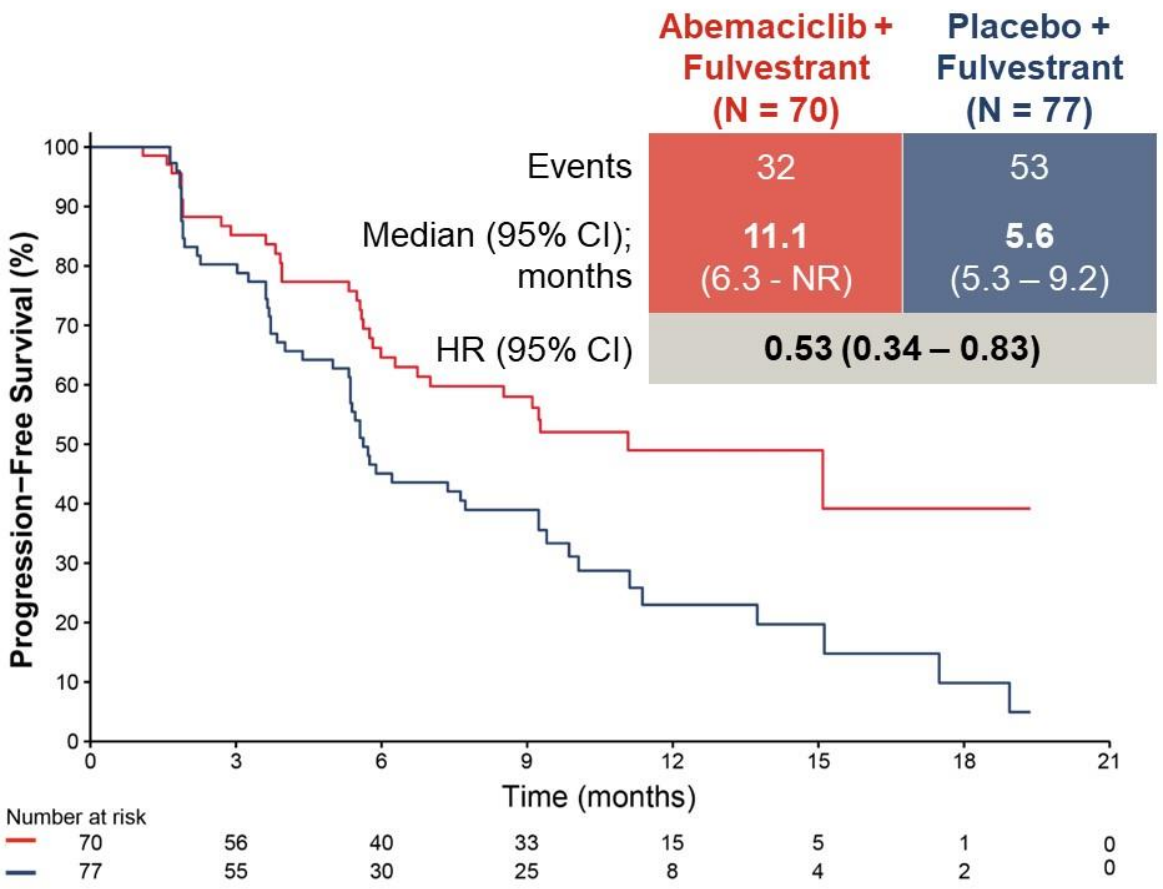
≥ 12 months*



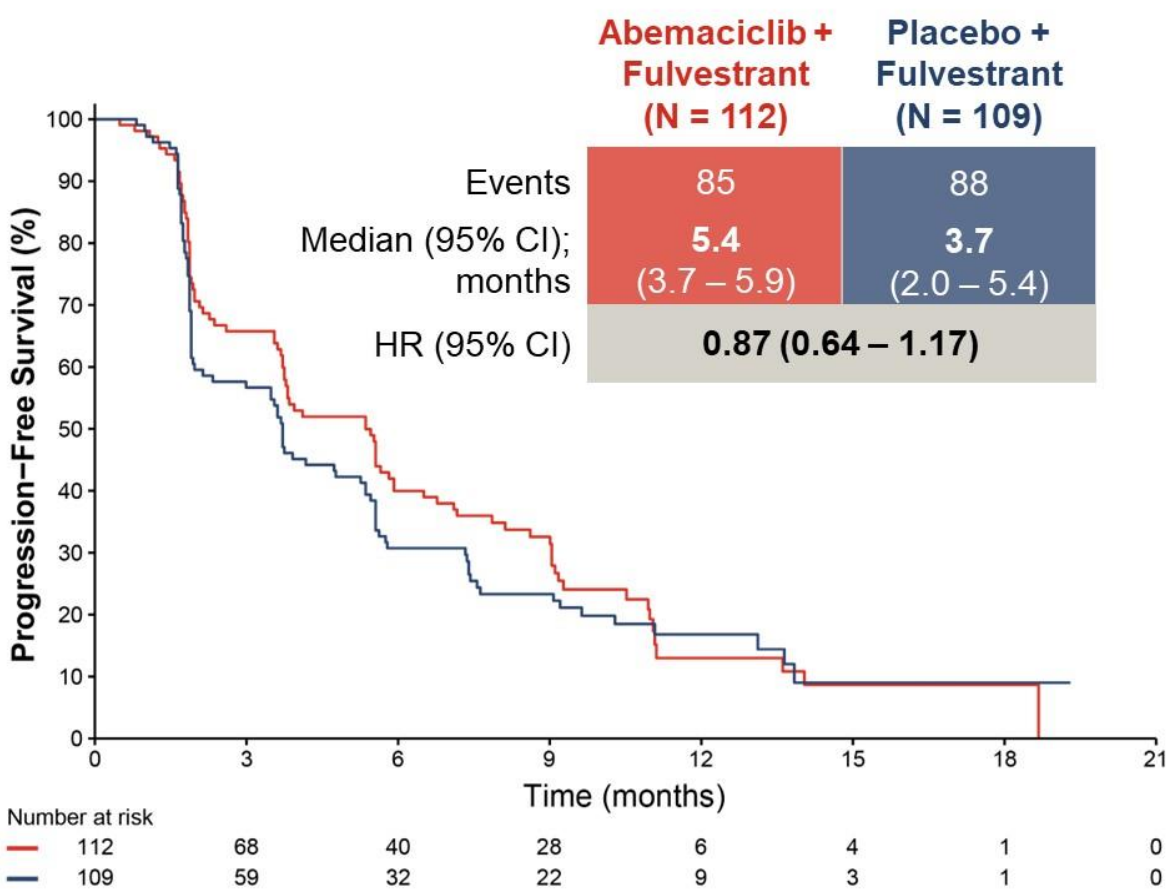
* ≥ 12 months ABC or recurrence after EBC therapy

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%

Subgroup	n	events	HR (95% CI)	Interaction p-value
ctDNA Evaluable Population	**320**	**230**	**0.77 (0.59 to 1.00)**	
ESR1				0.98
Detected	145	110	0.79 (0.54 to 1.15)	
Not detected	175	120	0.79 (0.55 to 1.13)	
PIK3CA* or *AKT1* or *PTEN				0.55
Detected	156	118	0.86 (0.60 to 1.23)	
Not detected	164	112	0.73 (0.51 to 1.06)	

Biomarker ctDNA by GuardantINFINITY assay

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

[+]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

PRESENTED BY: Kevin Kalinsky, MD, MS

Conclusions

- postMONARCH is the first randomized, placebo-controlled Phase 3 study to demonstrate benefit of continued CDK4/6 inhibition beyond progression on a CDK4/6i

- Abemaciclib improved PFS in pts with HR+, HER2- ABC with disease progression on prior CDK4/6i + ET, despite the control arm performing better than expected
  - 27% risk reduction for developing a PFS event (HR: 0.73 [0.57- 0.95])
  - Consistent benefit across multiple prespecified and clinically relevant subgroups, including key biomarker subgroups
  - Consistent improvement across key secondary efficacy endpoints, including PFS by BICR and ORR
- Safety was consistent with the known abemaciclib profile and discontinuation rate was low

Abemaciclib + fulvestrant offers a targeted therapy option after disease progression on a CDK4/6i for patients with HR+, HER2- ABC, not selected for biomarker status

PRESENTED BY: Kevin Kalinsky, MD, MS

Should we continue with CDK4/6i post progression on CDK4/6i?

POSTMONARCH

- Phase 3
- Fulvestrant + Abemaciclib
- Investigator assessed PFS: 6 vs. 5.3 months (HR, 0.73)and PFS by BICR: 12.9 vs 5.6 m (HR, 0.55)
- To be considered in:
- Patients with bone only disease benefited more
- Patients who received prior palbociclib
- **Patients w actionable mutations, PIK3CA and ESR1should be offered PI3Ki and SERD.**

MAINTAIN

- Randomized phase 2
- Switched to Fulvestrant or exemestane + Ribociclib
- PFS: 5.2 vs. 2.7 months (HR, 0.57)
- Small sample size

2024 ASCO® ANNUAL MEETING

First-line inavolisib/placebo + palbociclib + fulvestrant (Inavo/Pbo+Palbo+Fulv) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer who relapsed during/within 12 months (mo) of adjuvant endocrine therapy completion: INAVO120 Phase III randomized trial additional analyses.

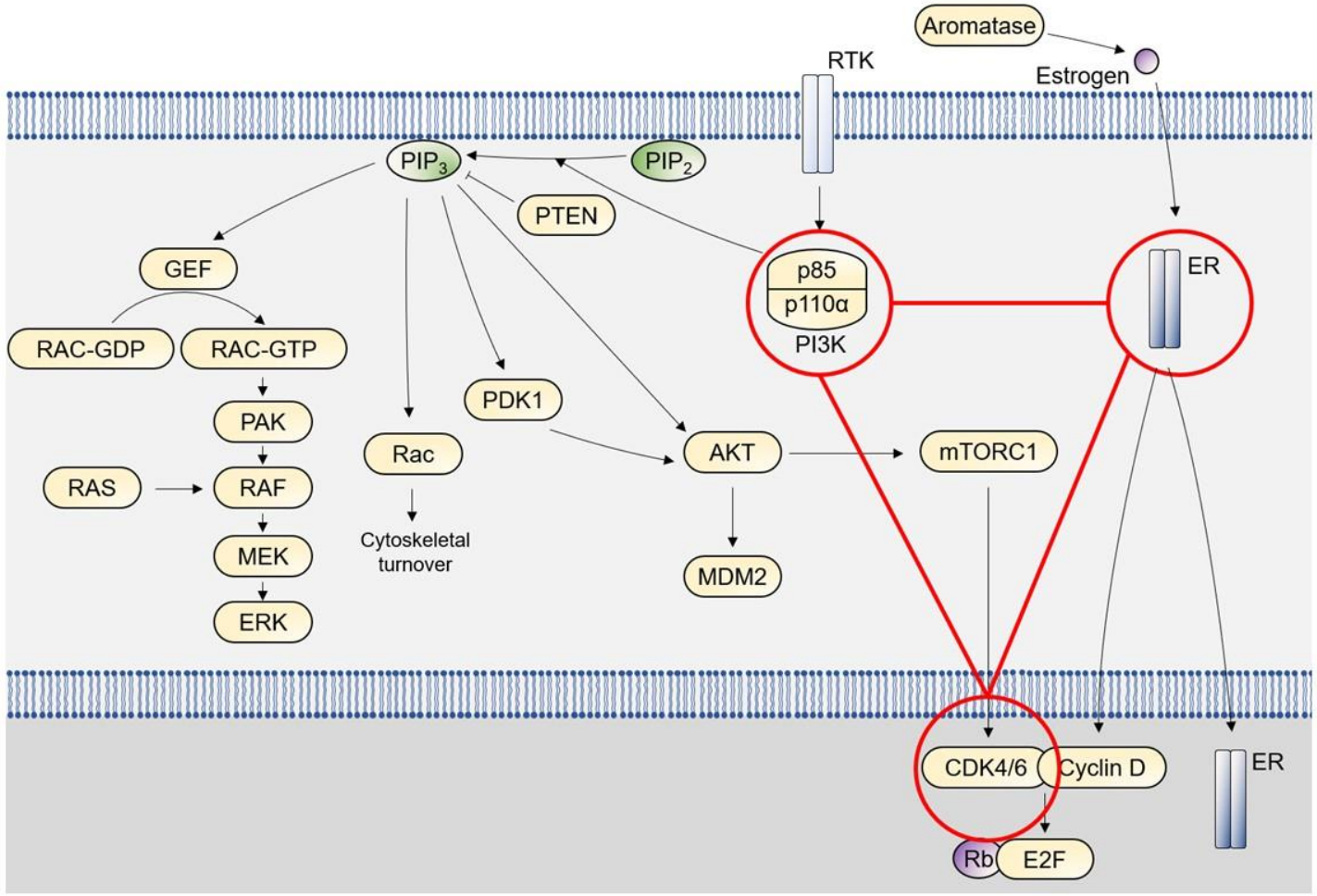
Dejan Juric, Kevin Kalinsky, Nicholas Turner, Komal L Jhaveri, Peter Schmid, Sherene Loi, Cristina Saura, Seock-Ah Im, Patrapim Sunpaweravong, Huiping Li, Antonino Musolino, Qingyuan Zhang, Zbigniew Nowecki, Roland Leung, Eirini Thanopoulou, Noopur Shankar, Guiyuan Lei, Jacob Devine, Thomas J Stout, Sibylle Loibl

Presenting author: Dejan Juric, MD

Mass General Cancer Center, Department of Medicine, Harvard Medical School, Boston, MA

Background

- More effective and tolerable treatments for patients with *PIK3CA*-mutated, HR+, HER2– advanced BC are needed[1–3]
- Preclinical data demonstrated substantial synergy upon simultaneous inhibition of the PI3K, CDK4/6, and estrogen receptor pathways in *PIK3CA*-mutated xenograft models by deepening responses and blocking routes to resistance[4–7]
- Inavolisib is a highly potent and selective inhibitor of the catalytic alpha isoform subunit (p110α encoded by *PIK3CA*) of the PI3K complex that also promotes the degradation of mutated p110α[7–9]



BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; HER2–, HER2-negative; HR+, hormone receptor-positive.

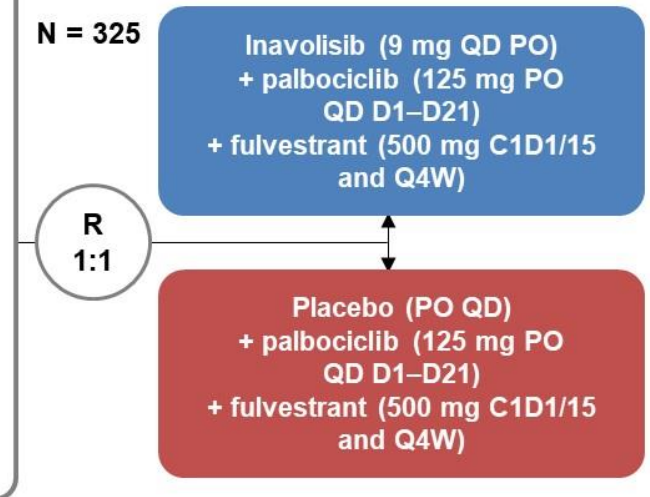
1. Cardoso F, *et al. Ann Oncol* 2020;**31:**1623–1649; 2. André F, *et al. N Eng J Med* 2019;**380:**1929–1940; 3. Dent S, *et al. Ann Oncol* 2021;**32:**197–207;
4. Hong R, *et al. Cancer Res* 2018;**78(4 Suppl):** Abstract PD4-14; 5. Herrera-Abreu MT, *et al. Cancer Res* 2016;**76:**2301–2313; 6. Vora SR, *et al. Cancer Cell* 2014;**26:**136–149.
7. Song KW, *et al. Cancer Discov* 2022;**12:**204–219; 8. Edgar K, *et al. Cancer Res* 2020;**80(4 Suppl):** Abstract P3-11-23; 9. Hanan EJ, *et al. J Med Chem* 2022;**65:**16589–16621.

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)**



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**

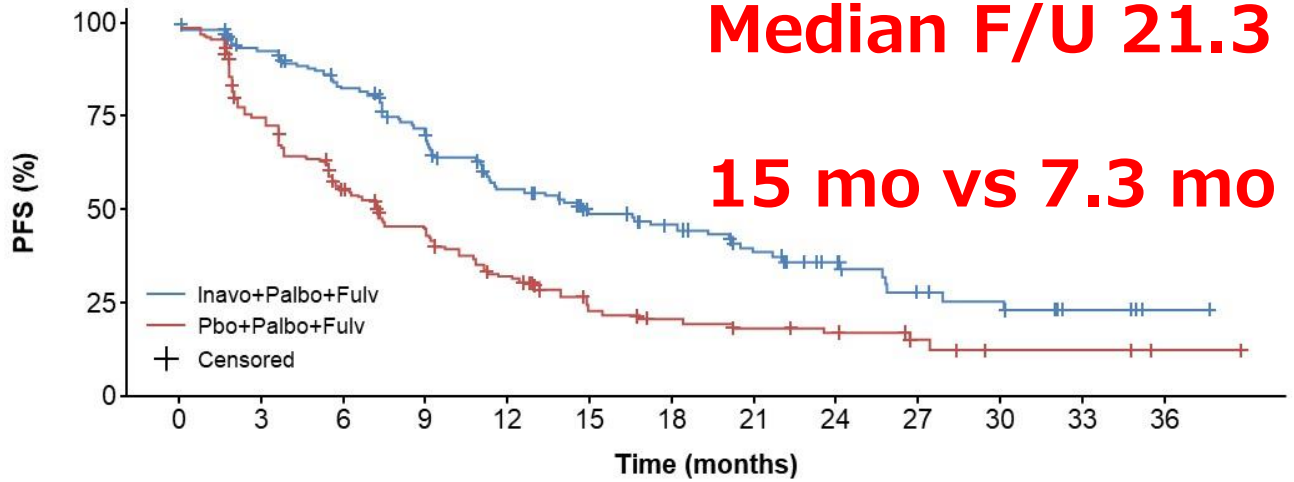
* Assessed using grouped terms; severity reported per National Cancer Institute CTCAE version 5.0. † Assessed at D1 of C1–3 then D1 of every other C thereafter (5, 7, 9, etc.), at treatment discontinuation, and every 3 months during survival follow-up; baseline completion rates in both arms were >90% 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).

INAVO120 primary analysis results - PFS

- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC who recurred on or within 12 months of adjuvant endocrine therapy
- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]



Median F/U 21.3 mo

15 mo vs 7.3 mo (HR, 0.43)

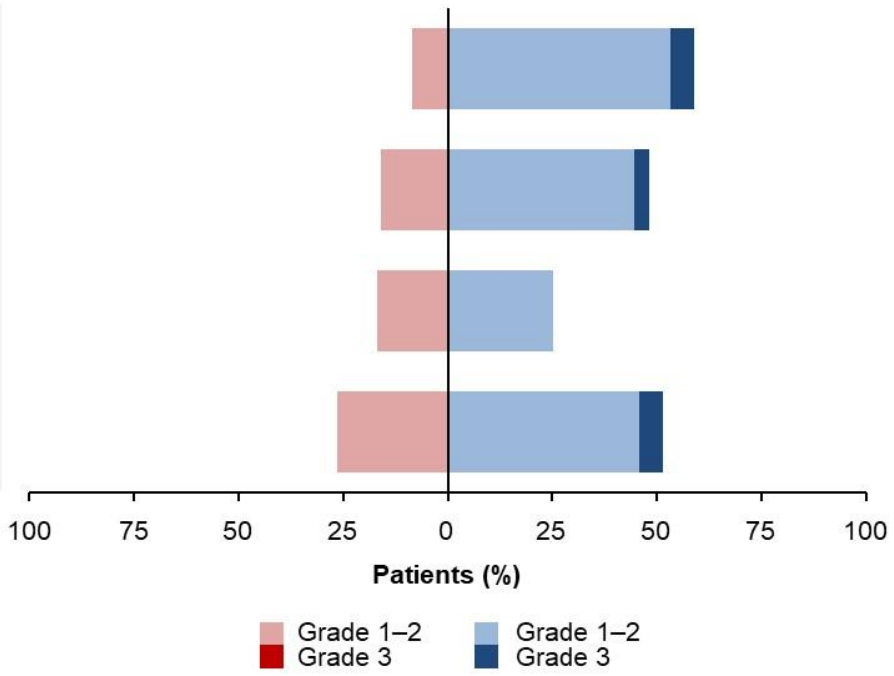
- Here we report additional efficacy, safety, and patient-reported outcomes data from the primary analysis (CCOD: September 29, 2023; median follow-up: 21.3 months)
  - As the prespecified boundary of significance for OS was not met, these analyses are descriptive

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.

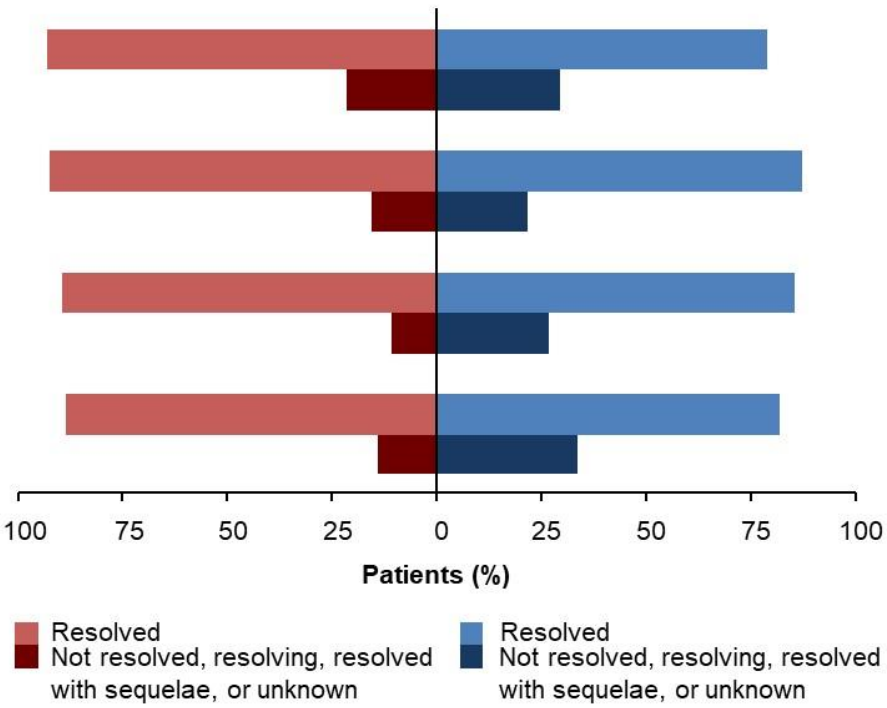
1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Safety

Key selected AEs



Resolution of key selected AEs*†



*** 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.

Conclusions

- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]
- Inavolisib with palbociclib and fulvestrant was associated with sustained benefit beyond disease progression, demonstrating a delayed need for subsequent therapy (Δ 8.9 months), including chemotherapy (NE versus 15.0 months), and supporting the clinical benefit of the inavolisib-based therapy
- Inavolisib discontinuations for hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation were low, confirming the manageable safety and tolerability profile of inavolisib
- Patient-reported outcomes data suggest patients receiving inavolisib in addition to fulvestrant and palbociclib experienced a longer median time to deterioration in pain severity (Δ 12.8 months), and maintained day-to-day functioning and HRQoL while on treatment with little increased treatment burden
- **Inavolisib with palbociclib and fulvestrant is a promising new treatment option for patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC**

HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; LA/mBC, locally advanced/metastatic breast cancer; NE, not evaluable; PFS, progression-free survival.

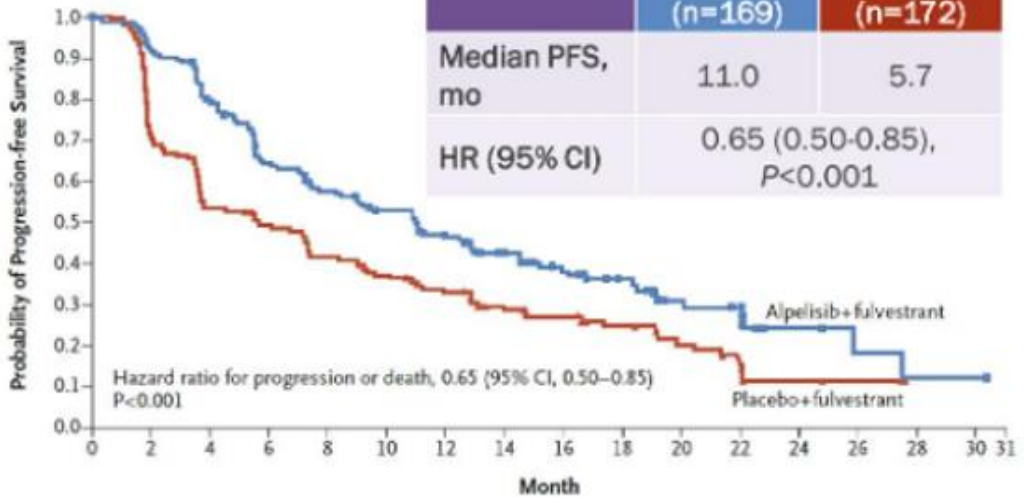
1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

The role of PI3Ki in MBC with PIK3CA mutation

SOLAR-1: Alpelisib + Fulvestrant (2nd line)

PIK3CA-Mutated Cohort

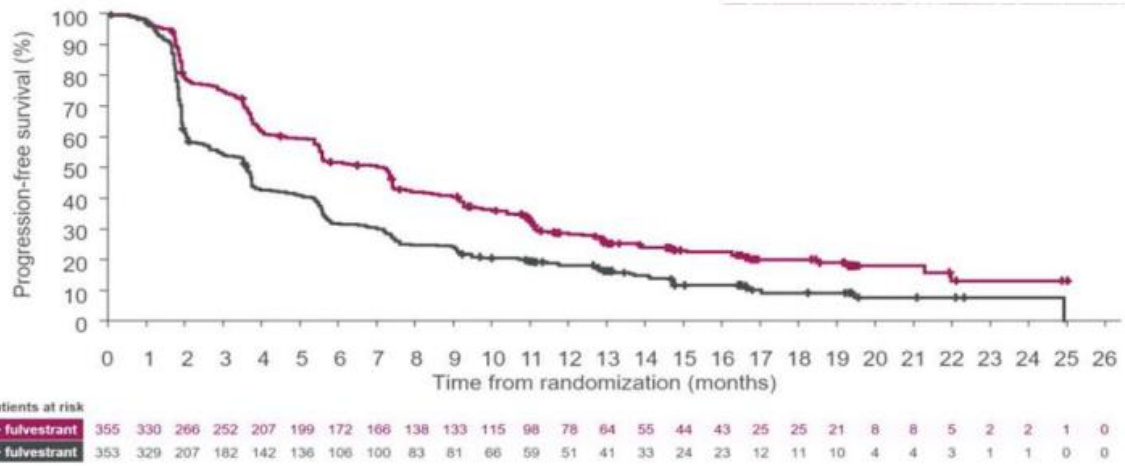
PFS Analysis	Alpelisib + Fulvestrant (n=169)	PBO + Fulvestrant (n=172)
Median PFS, mo	11.0	5.7
HR (95% CI)	0.65 (0.50-0.85), *P*<0.001	



Andre F, et al. NEJM 2019;380(20):1929-1940

CAPItello-291: Capivasertib + Fulvestrant (2nd line)

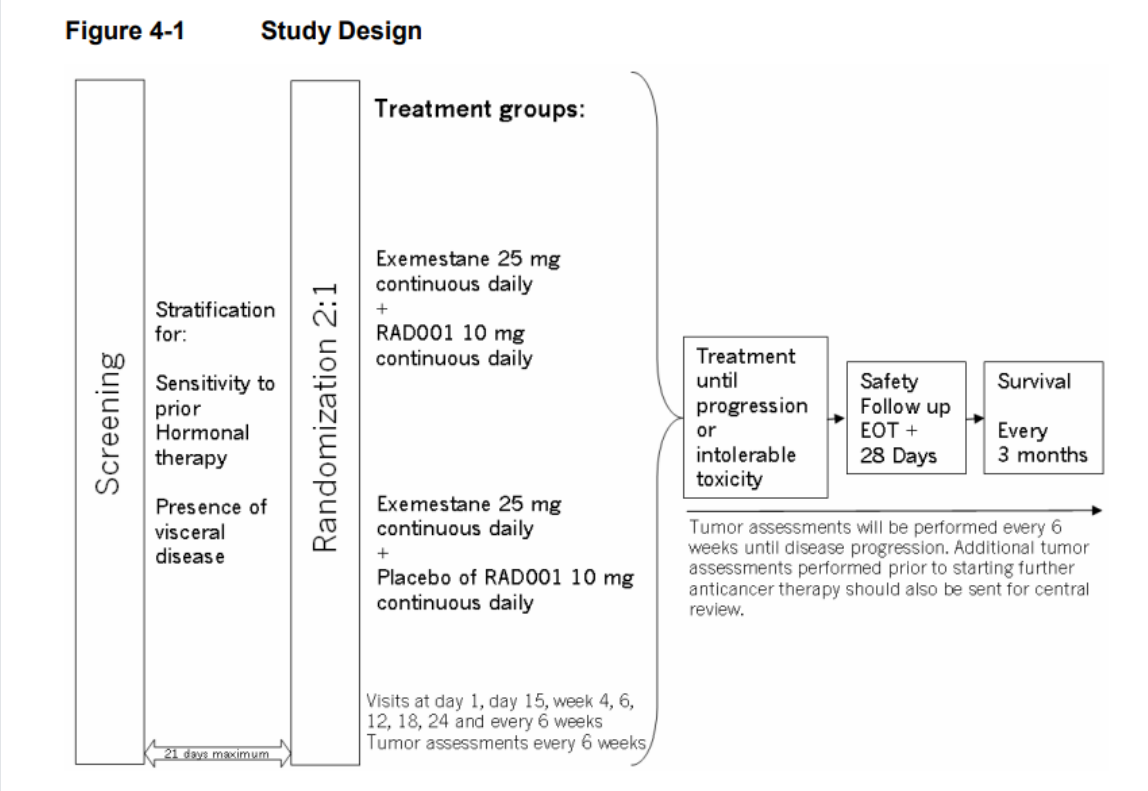
PFS by Investigator in Overall Population

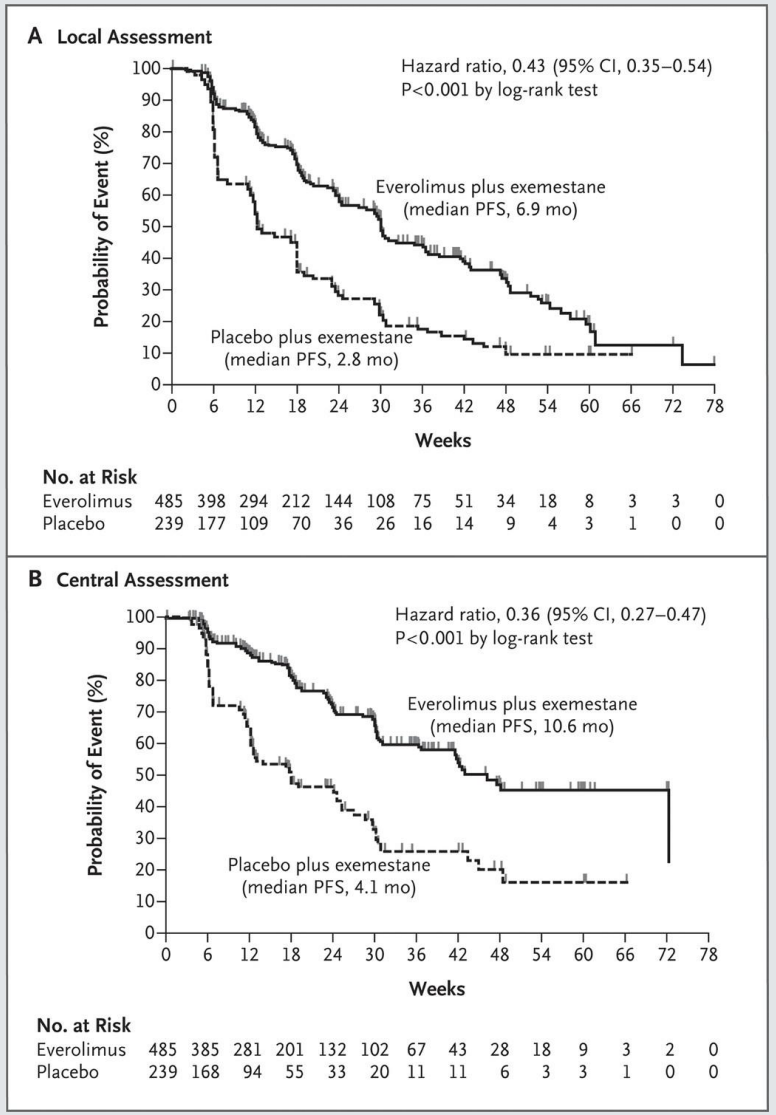


Overall Population	C+F (n=355)	P+F (n=353)
PFS events	258	293
Median PFS, mo (95% CI)	7.2 (5.5-7.4)	3.6 (2.8-3.7)
Adjusted HR (95% CI)	0.60 (0.51-0.71)	
Two-sided *P* value	<0.001	

Turner NC, et al. NEJM 2023;388(22): 2058-2070

Bolero-2: Exemestane + Everolimus (mtori): 1st line MBC





Baselga et al., N Engl J Med 2012;366:520-529

Comparing SOLAR-1, CAPItelo-291, Bolero-2 & INAVO120

	ALPELISIB (≥G3)	CAPIVASERTIB (≥G3)	Everolimus (≥G3)	Inavolisib (≥G3)
Scheduling:	every day	4 days on, 3 days off	every day	Every day
Hyperglycemia:	64% (37%)	19% (1.9%)	13% (4%)	58.6% (5.6%)
Diarrhea:	7%	77% (12%)	30% (≥G3 2%)	48.1 (3.7%)
Rash:	10%	56% (15%)	36% (1%)	25.3% (0)
Discontinuation: (Due to AE)	25%	10%	19%	6.8%

2024 ASCO ANNUAL MEETING

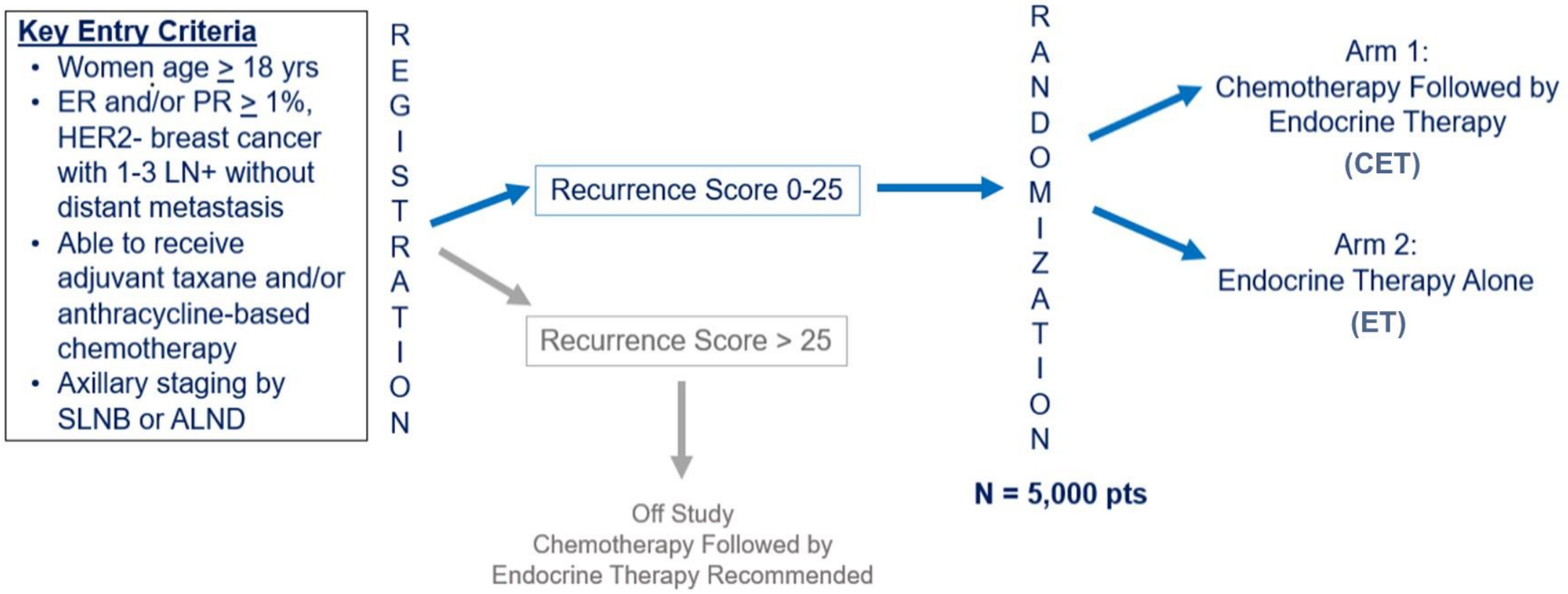
SWOG
Leading cancer research. Together.

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

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

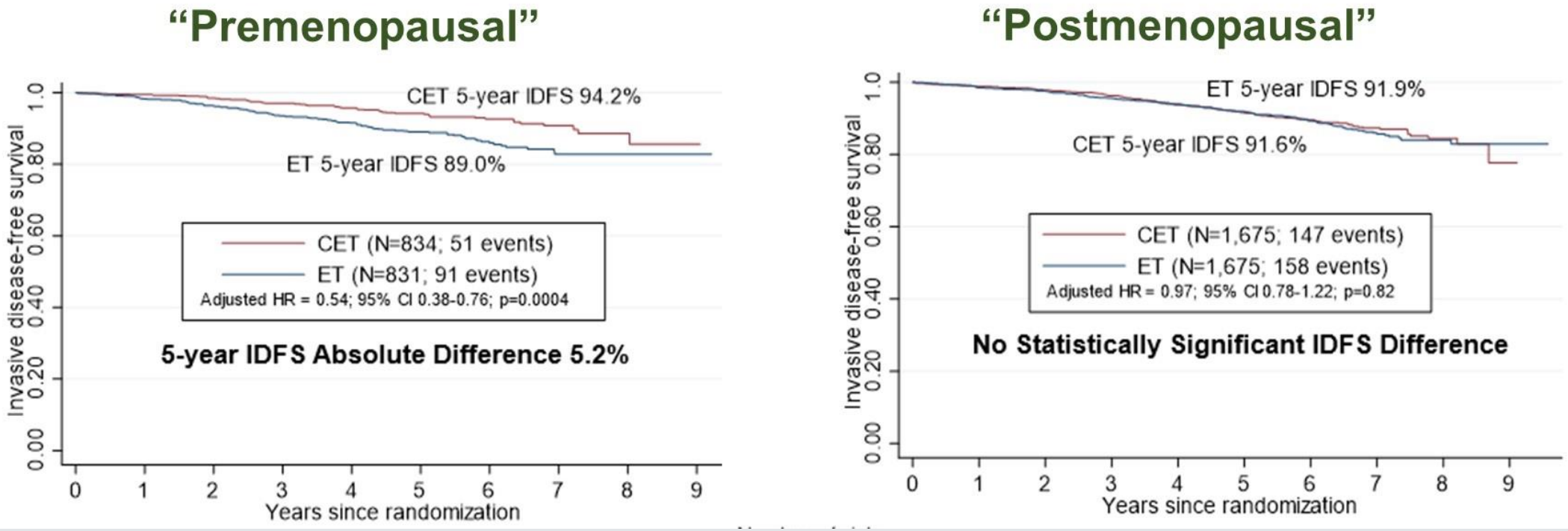
PRESENTED BY: Kevin Kalinsky, MD, MS

RxPONDER Trial



Kalinsky, et al. NEJM 2021

Chemotherapy benefit differed by menopausal status

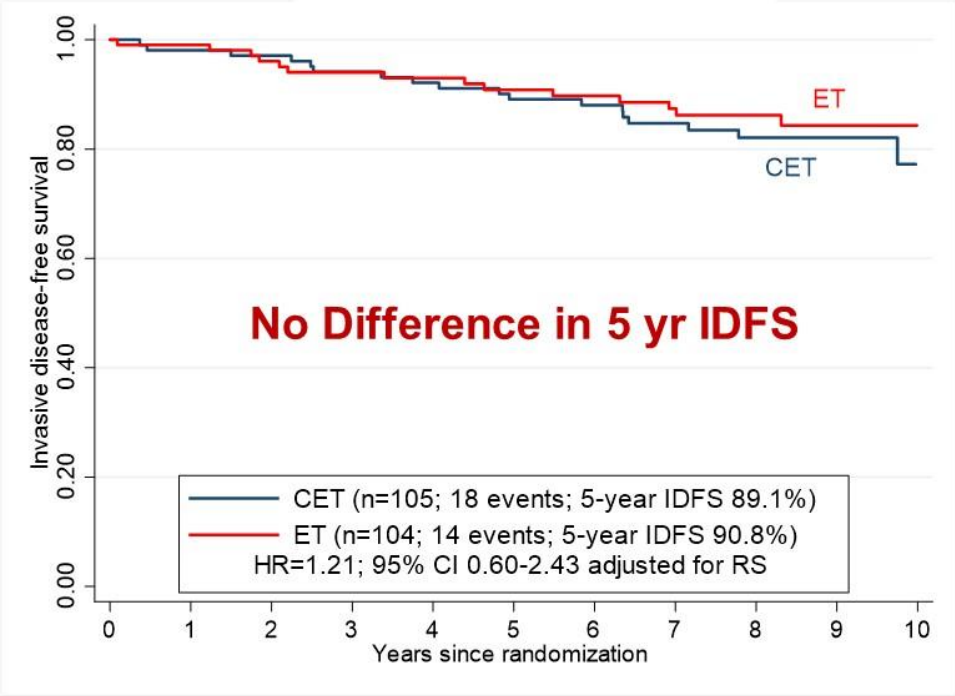


Kalinsky et al. NEJM 2021

- RxPONDER:
- no evidence of predictive value of Oncotype Dx RS 0-25 for chemotherapy benefit in HR+ Node+ BC.
- Premenopausal women uniformly benefited from chemo
- Menopausal status was estimated clinically.
- Is there a role for serologic assays to identify premenopausal patients who would

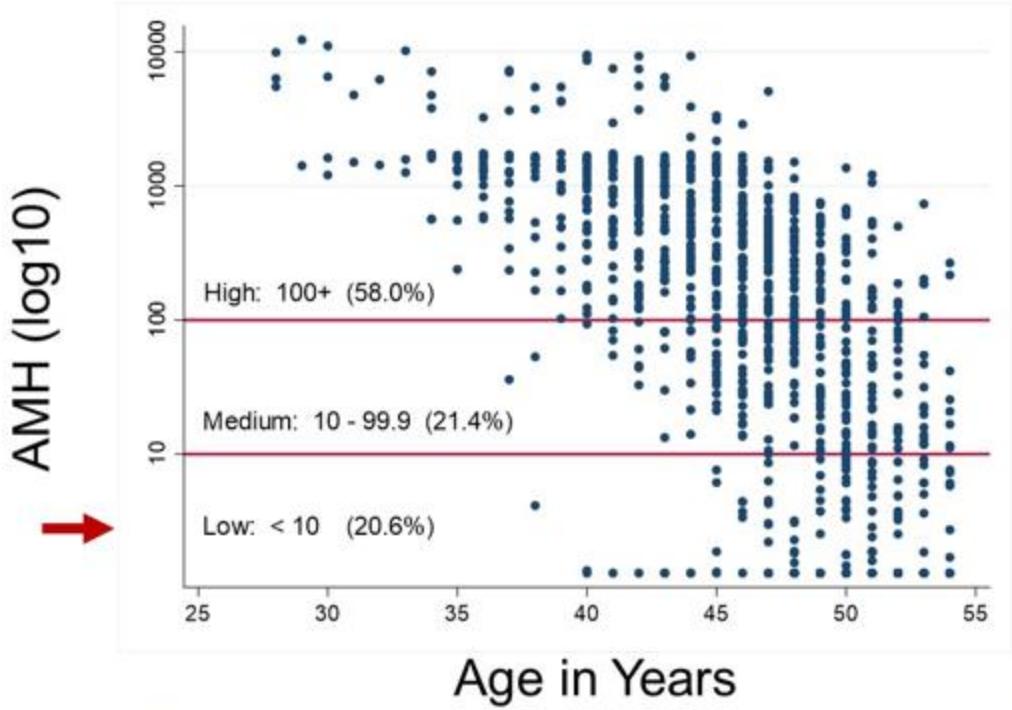
"Premenopausal" < 55 years with low AMH have no IDFS benefit with chemotherapy

Low AMH (n=209)



Postmenopausal: < 10 pg/mL

Anti-Mullerian hormone



Postmenopausal: < 10 pg/mL (20.6%)

Significant interaction p=0

PRESENTED BY: Kevin Kalinsky, MD, MS

Conclusion

- In RxPONDER, “premenopausal” women < 55 years with 1-3 LN+ and RS ≤ 25, 20.6% have low pre-treatment serum AMH levels < 10 pg/ML by traditional ELISA assay and did not benefit from adding chemotherapy to ET
- 52.2% of women 50-54 years had low pre-treatment serum AMH
- AMH was a better indicator of adjuvant chemotherapy benefit than reported menopause status, age, or other serum hormone levels
- Ongoing analyses include assessing serum hormones in ~300 UNICANCER pts < 55 years
- Low serum AMH could classify who can safely forego adjuvant chemotherapy in women whose menopausal status is unclear

Impact on practice – Can we utilize AMH to recommend or forgo chemotherapy in women ≤ 50 with 1-3 LN+ and Oncotype ≤25?

- AMH serologic ovarian function assay may help when menopausal status is uncertain, but it is not recommended by American College of Ob/Gyn to predict menopause.
- This was an unplanned post hoc subset analysis.
- Lack of chemotherapy benefit in low AMH group support the hypothesis that a part of chemo benefit in premenopausal women is ovarian suppression.
- This question will be answered in **NRG BR009 (OFSET) study - Phase III adjuvant trial evaluating the addition of adjuvant chemotherapy to ovarian suppression and endocrine therapy in premenopausal women with pN0-1, ER+/HER2- and Oncotype RS ≤ 25**

ESMO 2024 updates (HR+ BC)

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: 4-year landmark analysis of NATALEE trial

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 months
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

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

NSAI
Letrozole or anastrozole[d] for ≥5 years
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥5 years
+ goserelin in men and premenopausal women

Primary end point[e]
- iDFS using STEEP criteria

Secondary end points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

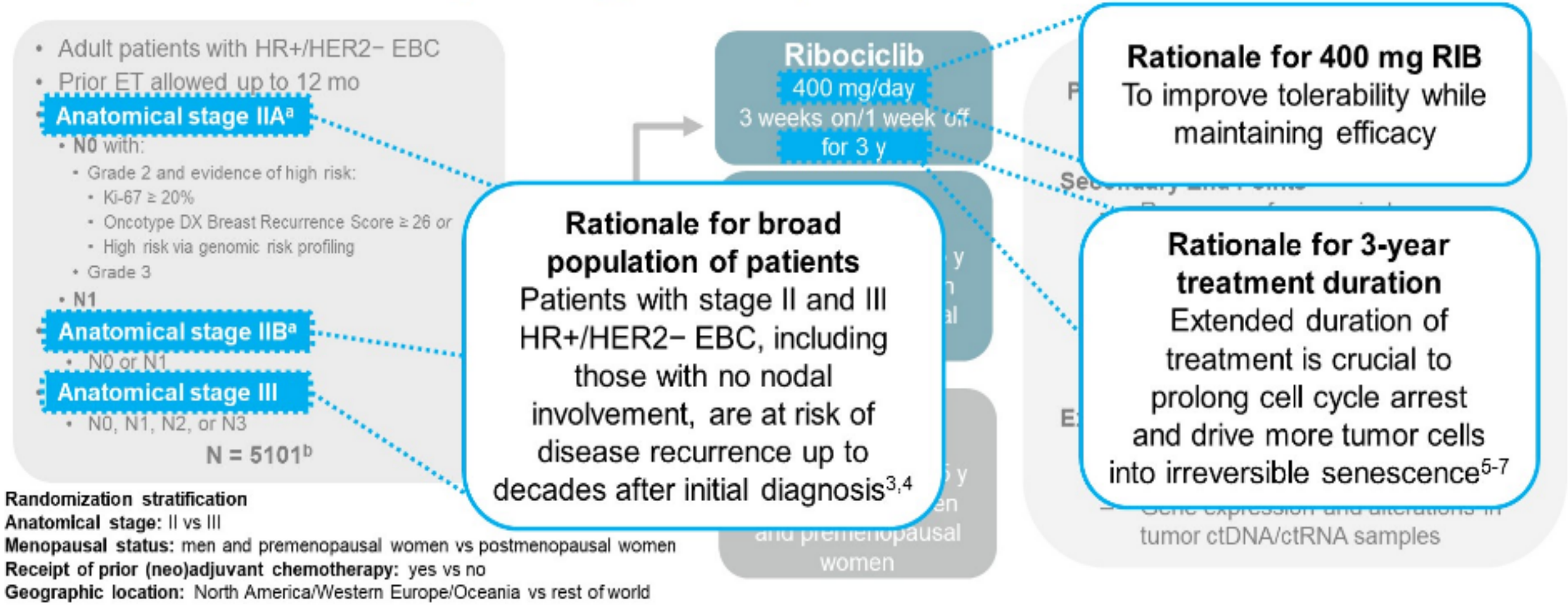
Exploratory end points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
- Anatomical stage: II vs III
- Menopausal status: men and premenopausal women vs postmenopausal women
- Receipt of prior (neo)adjuvant chemotherapy: yes vs no
- Geographic location: North America/Western Europe/Oceania vs rest of world

They reported results from an exploratory 4-year landmark analysis of NATALEE, with an additional 10.9 months of follow-up since the final iDFS analysis, assessing efficacy and safety beyond the planned 3-year treatment duration with all patients off ribociclib[1]

1. Fasching PA et al. ESMO 2024

NATALEE study design: unique features[1,2]



Slamon D, ASCO 2023

NATALEE and monarchE Population Criteria

Nodal involvement[1]	NATALEE[2,3]	monarchE[4]
N0 (*no nodal involvement*)	**T2 with restrictions, ≥1 of the following:** – **Grade 2 and high genomic risk[a] or Ki-67 ≥20%** – **Grade 3**	**Not allowed**
	All T3-T4 allowed	
N1 (*1-3 axillary lymph nodes*)	**All N1 allowed (except micrometastatic N1)**	**With restrictions, ≥1 of the following:** – **Tumor size ≥5 cm** – **Grade 3** – **Ki-67 ≥20%**
N2-N3 (*N2: 4-9 axillary lymph nodes; N3: ≥10 axillary lymph nodes or collarbone lymph nodes*)	**All allowed**	

NATALEE allowed:
- Any **N1, N2,** or **N3**
- **N0: T2** (*G2 + high genomic risk or Ki-67 ≥20% or G3*), **T3**, or **T4**

monarchE allowed:
- Any **N2** or **N3**
- **N1** only if G3 or tumor size ≥5 cm or Ki-67 ≥20%

N0 not allowed in monarchE

G, grade; N, node; T, tumor.

[a] High risk as determined by Oncotype DX/Prosigna/MammaPrint/EndoPredict.

References: 1. Amin MB et al. AJCC Cancer Staging Manual. 8th ed. Springer; 2017:587-636. **2**. Slamon DJ et al. Poster presented at: ASCO 2019; May 31-June 4, 2019; Chicago, IL. Poster TPS597. **3**. Data on file. NATALEE CLEE011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020. **4**. Harbeck N et al. *Ann Oncol*. 2021;32(12):1571-1581.

Table created by NG based on cited references.

Primary | Final Protocol-Specified | 4-Year Landmark

NATALEE Patient Disposition

Second interim efficacy analysis[1]

Data cutoff: January 11, 2023
iDFS events: n = 426

Ribociclib + NSAI, n = 2549

- NSAI ongoing: 1984 (77.8%)
  - **RIB ongoing: 1147 (45.0%)**
- Stopped RIB: 1377 (54.0%)
  - **Completed 3 years: 515 (20.2%)**
  - **Early discontinuation: 862 (33.8%)**
    - Discontinued due to AEs: 477 (18.7%)

NSAI alone, n = 2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

Final protocol-specified iDFS analysis[2]

Data cutoff: July 21, 2023
iDFS events: n = 509

Ribociclib + NSAI, n = 2549

- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)[a]**
    - Discontinued due to AEs: 498 (19.5%)[b]

NSAI alone, n = 2552

- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

4-year landmark exploratory efficacy analysis[4]

Data cutoff: April 29, 2024
iDFS events: n = 603

Ribociclib + NSAI, n = 2549

- NSAI ongoing: 1794 (70.4%)
  - **RIB ongoing: 0**
- Stopped RIB: 2524 (100%)[c]
  - **Completed 3 years: 1601 (62.8%)**
  - **Early discontinuation: 923 (36.2%)**
    - Discontinued due to AEs: 509 (20.0%)

NSAI alone, n = 2552

- NSAI ongoing: 1628 (63.8%)
- Discontinued NSAI: 813 (31.9%)[d]

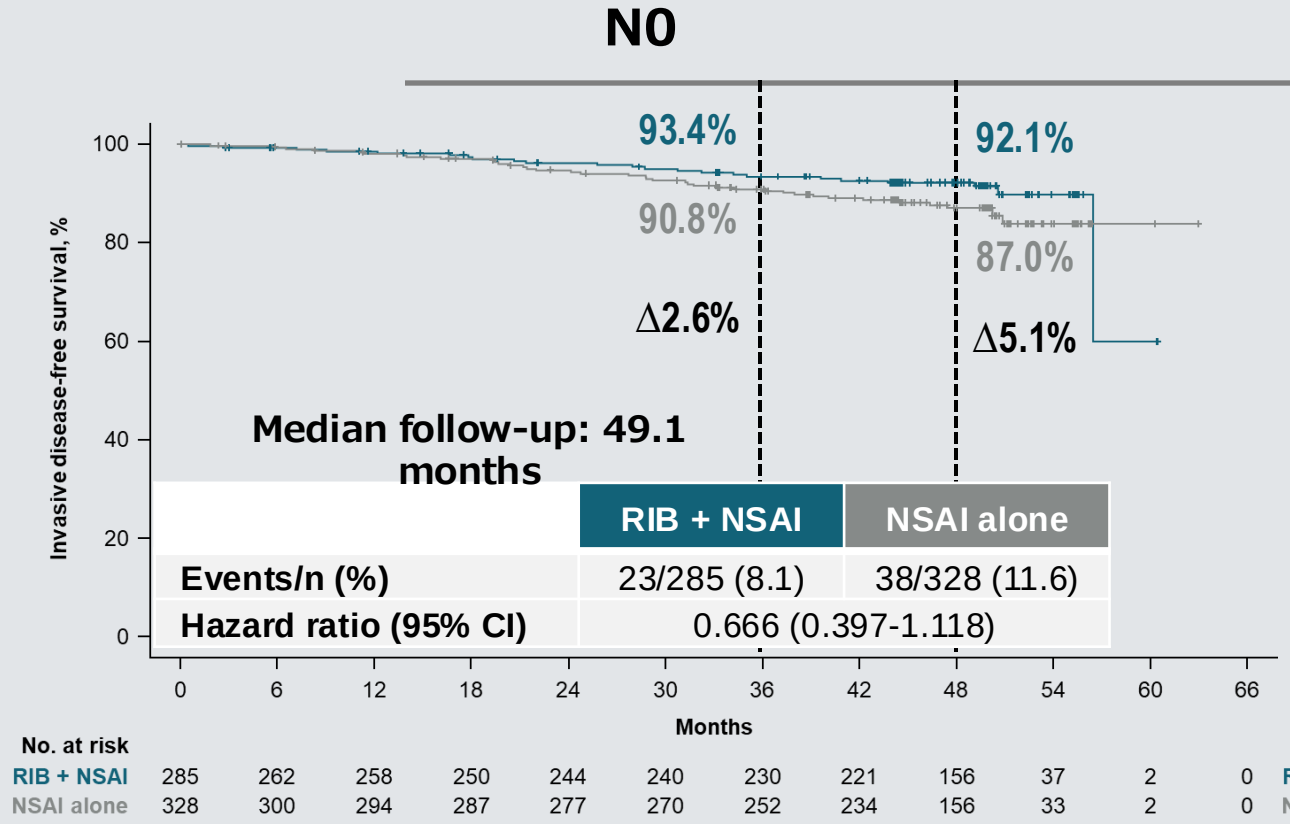
- Most discontinuations of RIB due to an AE occurred early in treatment, with the median time being 4 months[1]
- The most frequent all-grade AEs that led to discontinuation were liver-related AEs[e] (8.9%) and arthralgia (1.3%)[1]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ET, endocrine therapy; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] The primary reasons for discontinuation besides AE include patient decision to discontinue treatment (5.3%), disease relapse (4.8%), withdrawal by patient (3.2%), physician decision (0.9%), other (0.9%), loss to follow-up (0.3%), protocol deviation (0.2%), death (0.2%), and ET discontinuation (0.1%).[3] [b] Patients discontinued RIB most commonly for ALT increased (7.1%), AST increased (2.8%), and arthralgia (1.5%). All other AEs leading to discontinuation were <1%.[3] [c] Of the 2549 patients randomized to the ribociclib + NSAI arm, 2524 were treated with ribociclib. [d] Includes 9 patients (0.4%) who completed NSAI treatment. [e] Grouped term that includes all preferred terms identified by standardized Medical Dictionary for Regulatory Activities queries for drug-related hepatic disorders.

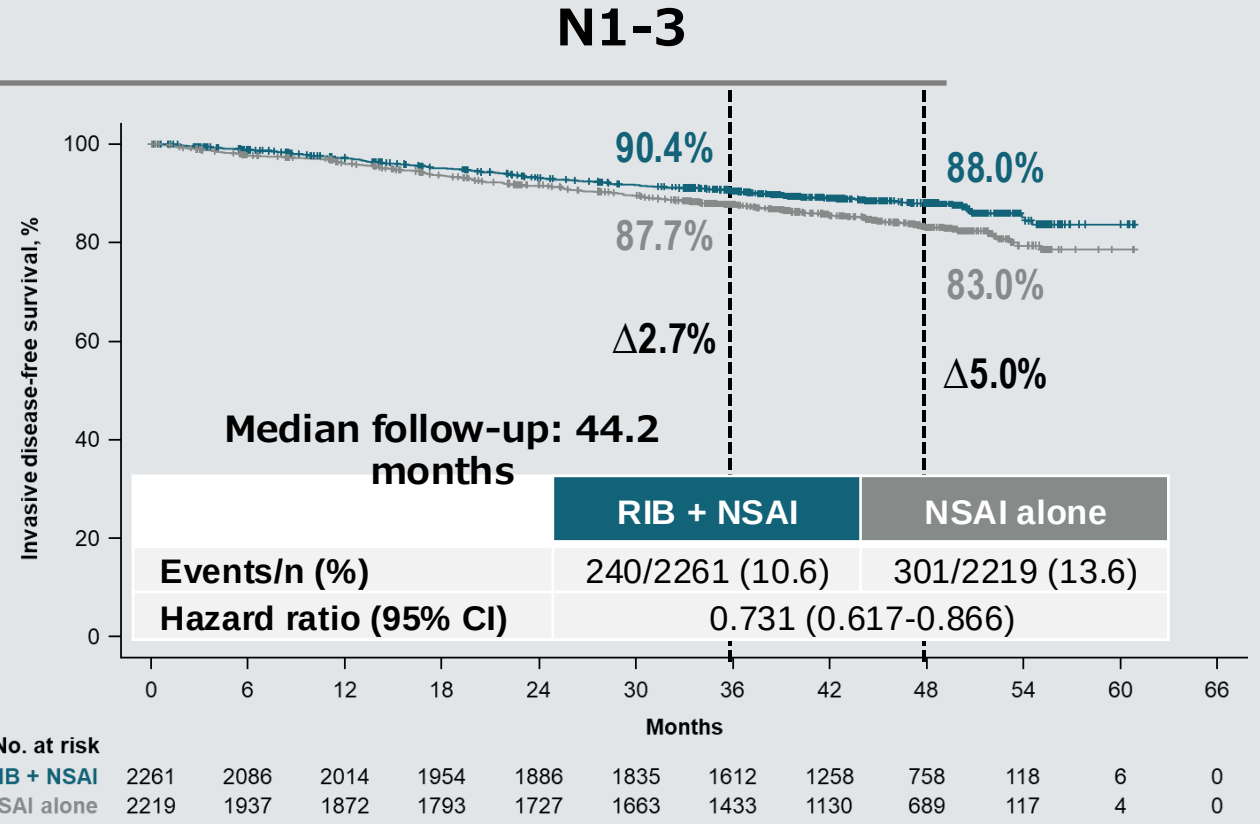
References: 1. Slamon D et al. *N Engl J Med*. 2024;390(12):1080-1091. **2**. Hortobagyi G et al. Oral presented at: SABCS 2023; December 5-9, 2023; San Antonio, TX. Oral GS03-03. **3.** Data on file. NATALEE CLEE011O12301C. Novartis Pharmaceuticals Corp; December 7, 2023. **4.** Fasching PA et al. Oral presented at: ESMO 2024; September 13-17, 2024; Barcelona, Spain. Oral LBA13.

iDFS by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease



	RIB + NSAI	NSAI alone
Events/n (%)	23/285 (8.1)	38/328 (11.6)
Hazard ratio (95% CI)	0.666 (0.397-1.118)	



	RIB + NSAI	NSAI alone
Events/n (%)	240/2261 (10.6)	301/2219 (13.6)
Hazard ratio (95% CI)	0.731 (0.617-0.866)	

iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

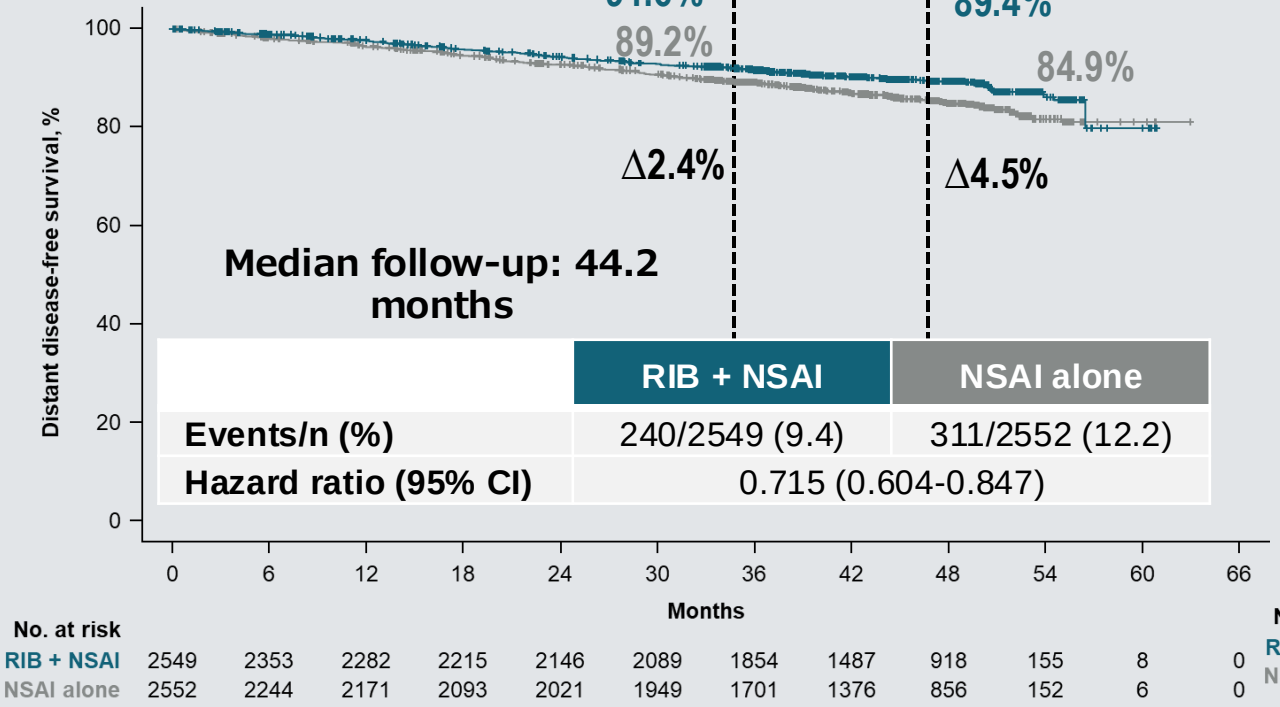
Reference: Fasching PA et al. Oral presented at: ESMO 2024; Sept 13-17, 2024; Barcelona, Spain. Oral LBA13.

Figures adapted from Fasching PA et al. with permission.

Distant Disease–Free Survival and Overall Survival

- RIB + NSAI continued to improve DDFS and showed a positive trend for OS

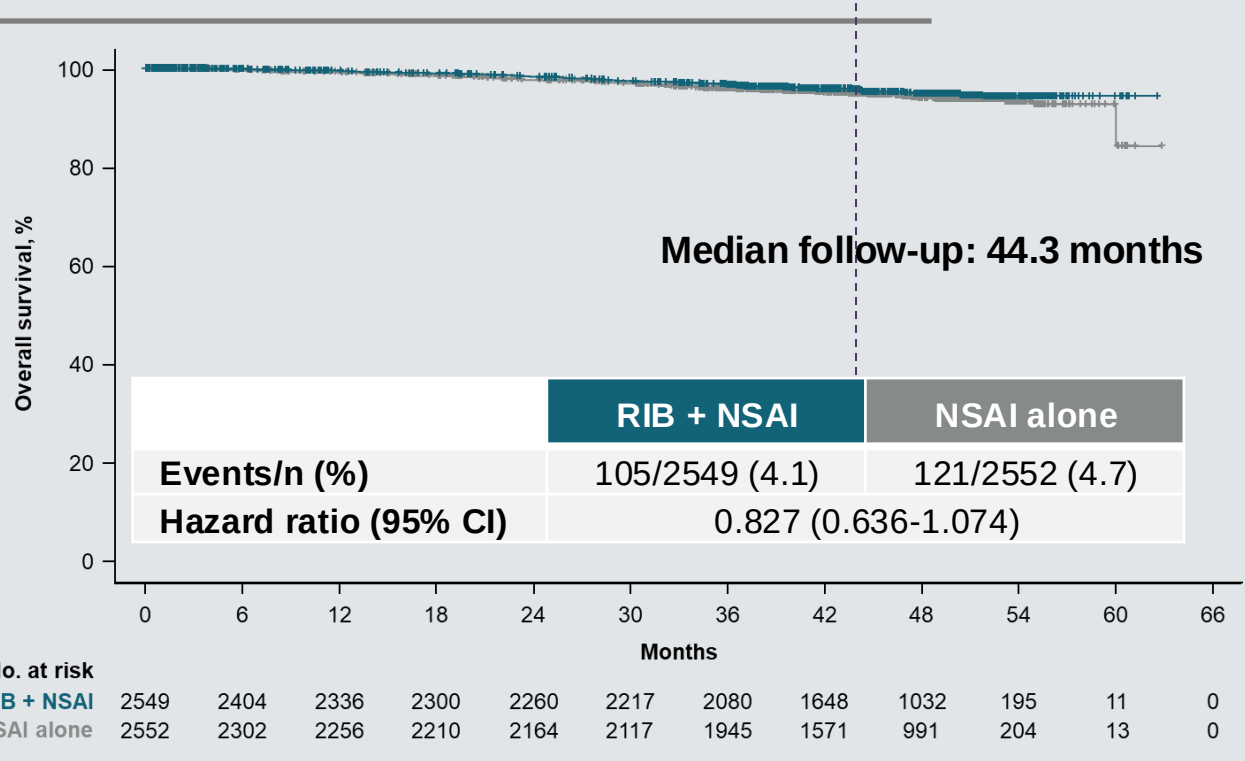
DDFS[1,2]



	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS[1]



	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

DDFS, distant disease–free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

References: 1. Fasching PA et al. Oral presented at: ESMO 2024; Sept 13-17, 2024; Barcelona, Spain. Oral LBA13. **2**. Data on file. LEE011O1 End of RIB analysis (cut-off date: 29-April-2024). Novartis Pharmaceuticals Corp; September 16, 2024.

Figures adapted from Fasching PA et al. with permission.

Adverse Events of Special Interest[1]

AESIs, %	RIB + NSAI n = 2525		NSAI alone n = 2442	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia[a]	**62.8**	44.4	4.5	0.9
Febrile neutropenia	**0.3**	0.3	0	0
Liver-related AEs[b]	**26.7**	8.6	11.4	1.7
QT interval prolongation[c]	5.4	1.0	1.6	0.7
ECG QT prolonged	4.4	0.2	0.8	<0.1
Interstitial lung disease/pneumonitis[d]	**1.6**	0	0.9	0.1
Other clinically relevant AEs, %				
Arthralgia	38.8	1.0	44.4	1.3
Nausea	23.5	0.2	7.9	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.8	0.8	13.5	0.2
Diarrhea	14.6	0.6	5.5	0.1
VTE[e]	1.1	0.6	0.5	0.3

- Incidence of AEs remained stable from prior analyses
- Rates of discontinuation due to AEs (20.0%) remained stable through all of the data cuts, with a <1.0% increase from the previous cutoff[2,3]
- Liver-related AEs were predominately ALT/AST elevations without concomitant bilirubin increase

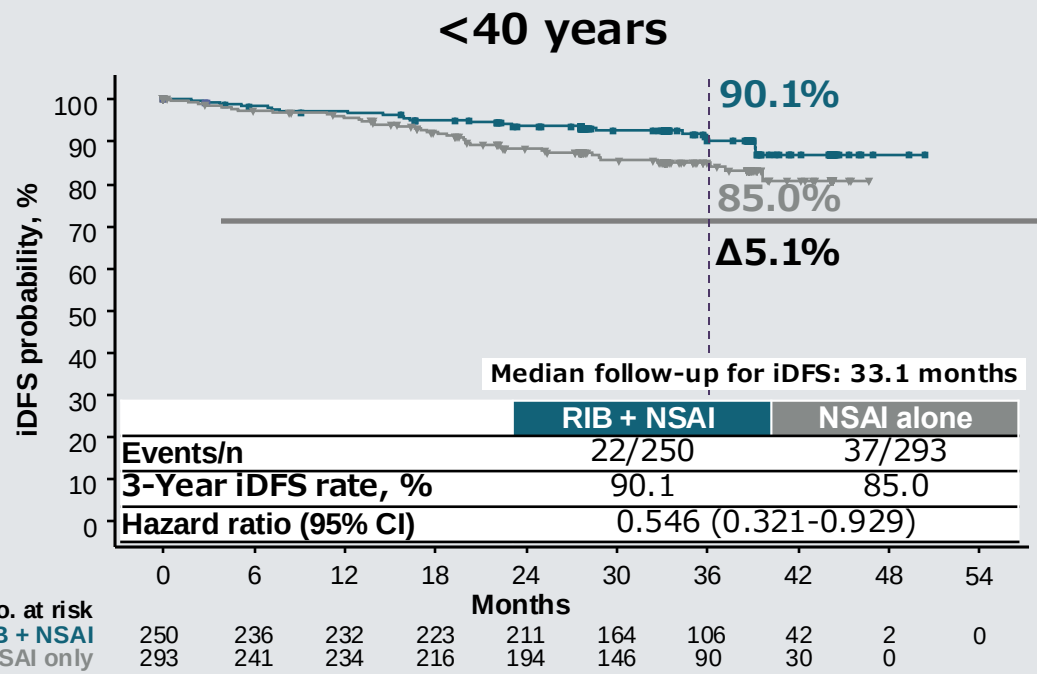
AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase ECG, electrocardiogram; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolism.

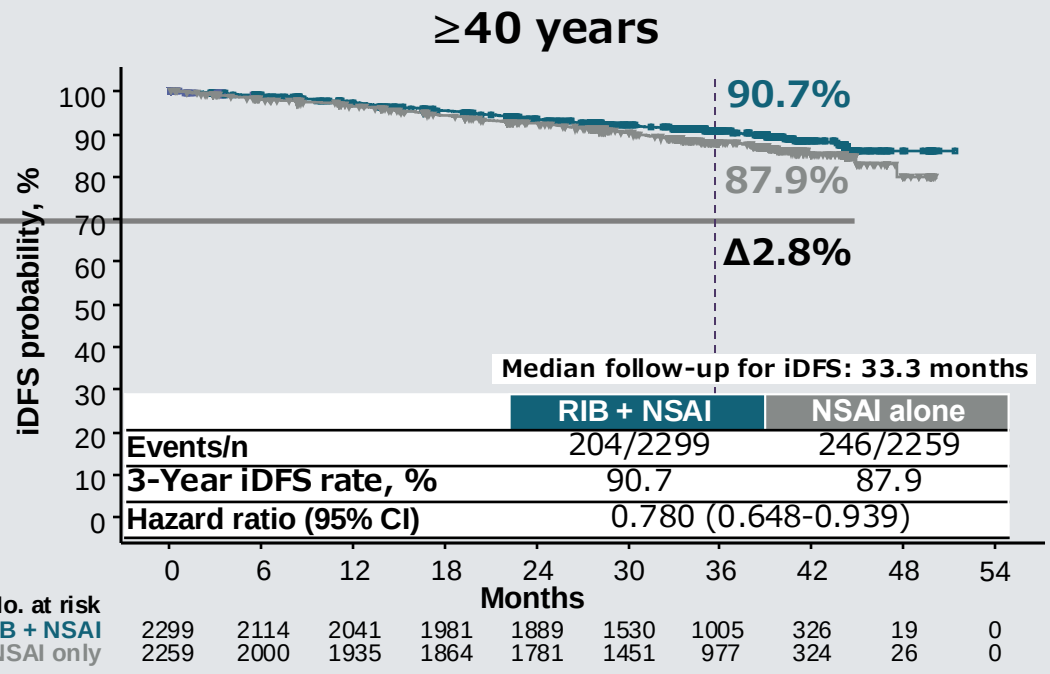
[a] Grouped term that combines neutropenia and neutrophil count decreased. [b] Grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] Grouped term. [d] Grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. [e] Grouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.

References: 1. Fasching PA et al. Oral presented at: ESMO 2024; Sept 13-17, 2024; Barcelona, Spain. Oral LBA13. **2**. Slamon D et al. *N Eng J Med*. 2024;390(12):1080-1091. **3.** Hortobagyi G et al. Oral presentation at: SABCS 2023. Oral GS03-03.

Table adapted from Fasching PA et al. with permission.

iDFS in Patients Aged <40 Years and ≥40 Years





- iDFS benefit of RIB + NSAI was observed regardless of menopausal status[a]
- The absolute differences in 3-year iDFS rates between arms, when adjusted for menopausal status and prior neoadjuvant CT, were similar to those without adjustment (Δ4.0% for patients aged <40 years and Δ2.9% for patients aged ≥40 years)
- Consistent benefits were observed for RFS, DRFS, and DDFS

CT, chemotherapy; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; RFS, recurrence-free survival HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; TTFD, time to first deterioration

[a] Premenopausal women were required to receive goserelin in addition to RIB + NSAI or NSAI alone.

Reference: Loi S et al. Oral presented at: ESMO 2024; Sept 13-17, 2024; Barcelona, Spain, Mini Oral 235MO.

Figures adapted from Loi S et al. with permission.

Adjuvant Ribociclib

- **4-year landmark exploratory efficacy analysis showed i**ncreasing efficacy benefit with RIB + NSAI across subgroups and secondary endpoints
- **In combination with an AI for the adjuvant treatment of adults with HR+, HER2-**
  Relative risk reduction of invasive disease by 28.5%
- Absolute iDFS benefit of 4.9% at 4 years
- Incidence of AEs remained stable from prior analyses
- **Recently approved by FDA**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