Hormone Receptor Positive Breast Cancer

Wisconsin Review of the San Antonio Breast Cancer Symposium 2023
1/3/2024

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Disclosure

I have no actual or potential conflict of interest in relation to this program and presentation.

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Therapeutic developmental pathways in ER+ Breast Cancer

- CDK 4/6i
- SERDs
- AKT/PIK3i
- ICIs
- ADCs

Therapeutic developmental pathways in ER+ Breast Cancer

- **CDK 4/6i- MONARCH3**
  MonarchE updates
  NATALEE
- SERDs
- AKT/PIK3i
- ICIs
- ADCs

Wisconsin Association of Hematology and Oncology

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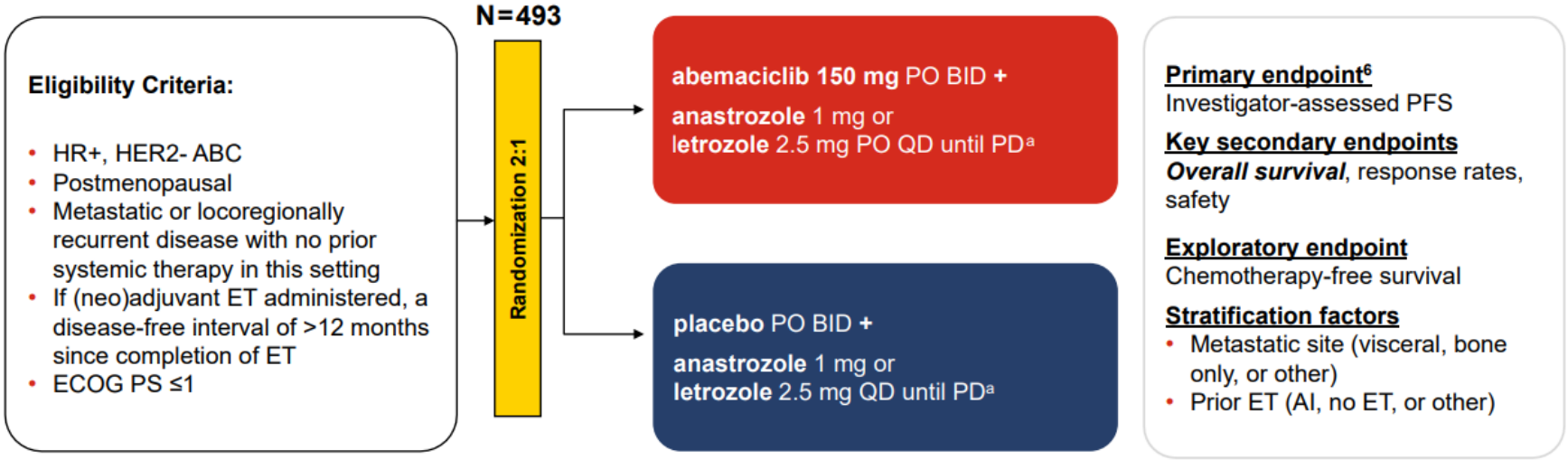
MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer

MONARCH 3 Study Design

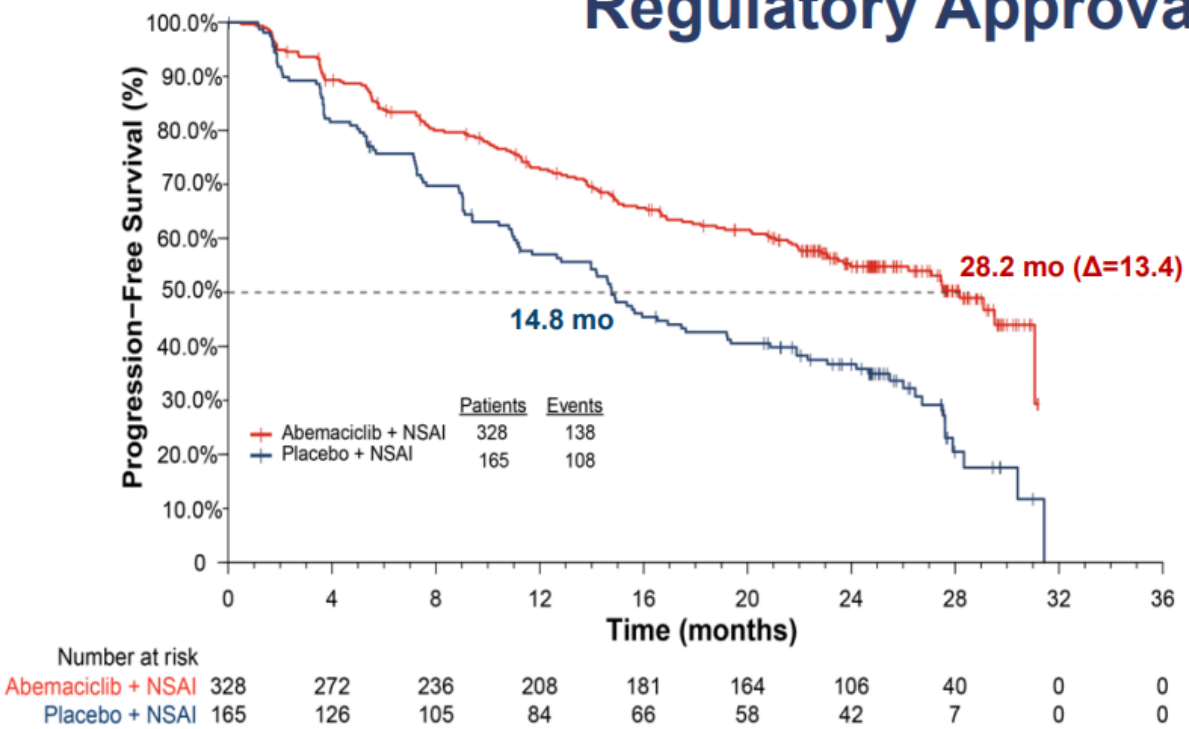


MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

[6]Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646

Robust PFS Benefit in MONARCH 3 Led to Global Regulatory Approval



	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	28.2	14.8
HR (95% CI) 2-sided *P* value	0.540 (0.418-0.698) nominal p=0.000002*	
Pre-planned Final PFS Analysis[5] Data cut: 03 Nov 2017		

*Statistical significance was reached at the interim PFS analysis[6]

At the final PFS data cut with a median follow-up of 26.7 months, PFS was prolonged by a median 13.4 months in patients receiving abemaciclib. At that time, OS was immature with 29.5% events observed across both arms.

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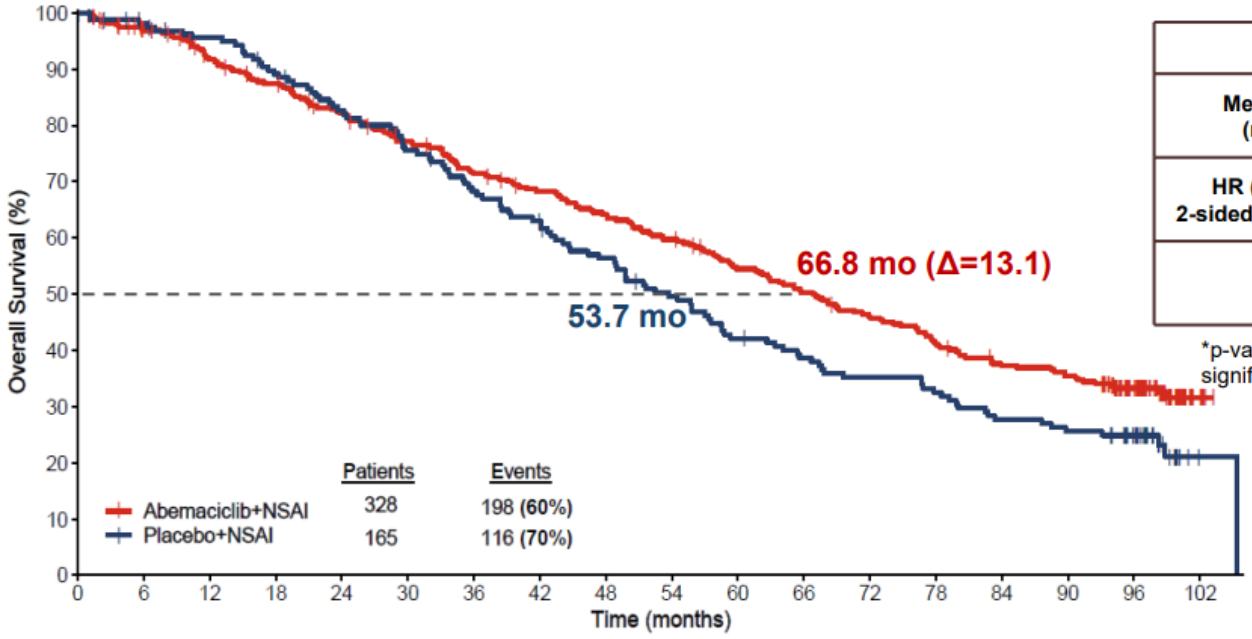
Johnston S, et al. NPJ Breast Cancer. 2019;5:5
Goetz M, et al. J Clin Oncol. 2017;35(32):3638-3646

OS in the ITT Population



Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	
Final OS Analysis Data cut: 29 Sep 2023		

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone; however, statistical significance was not reached. The observed improvement in median OS was 13.1 months.

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Johnston S, et al. NPJ Breast Cancer. 2019;5:5
Goetz M, et al. J Clin Oncol. 2017;35(32):3638-3646

Conclusions

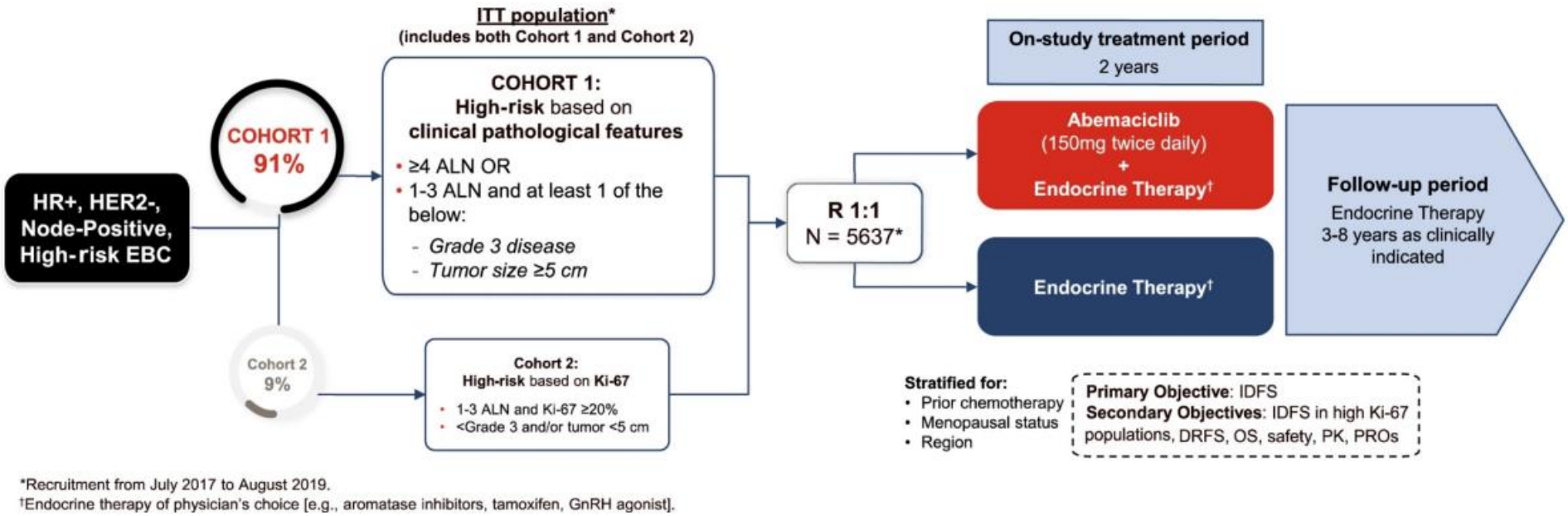
- With a median follow-up of 8.1 years, abemaciclib in combination with a NSAI resulted in numerically longer OS compared to NSAI alone; however, statistical significance was not reached
  - Clinically meaningful improvement in median OS: 13.1 months (66.8 vs 53.7 months) in the ITT and 14.9 months (63.7 vs 48.8 months) in the subgroup with visceral disease

- The previously demonstrated PFS benefit persists, with substantial differences well beyond 5 years
  - Median PFS improvement: 14.3 months
  - 6-year PFS rates: 23.3% vs 4.3% for abemaciclib vs placebo

- Abemaciclib delayed subsequent receipt of chemotherapy (median improvement of 16.1 months)

- No new safety concerns were observed with prolonged exposure to abemaciclib

Adjuvant CDK 4/6i Therapy: MonarchE Update



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

- Superior and persistent improvement in IDFS and DRFS with adjuvant abemaciclib plus ET versus ET alone

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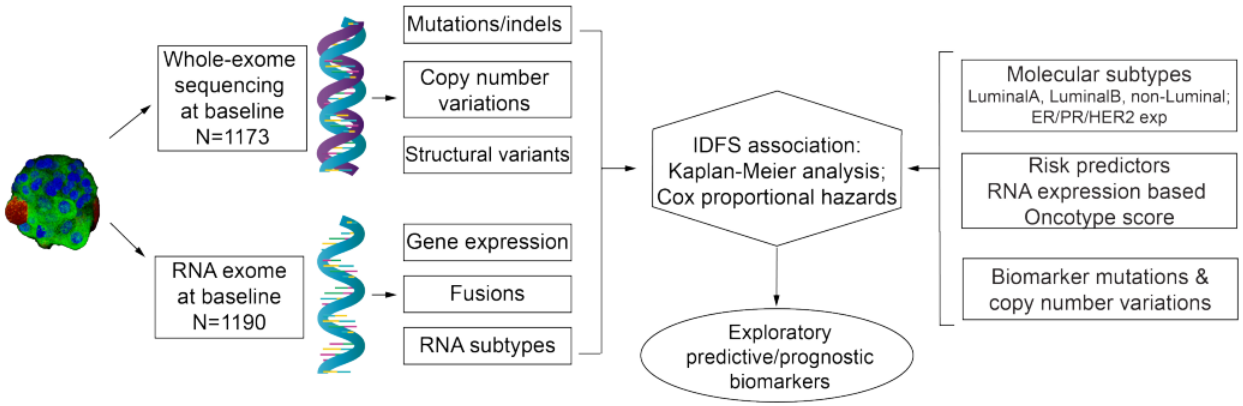
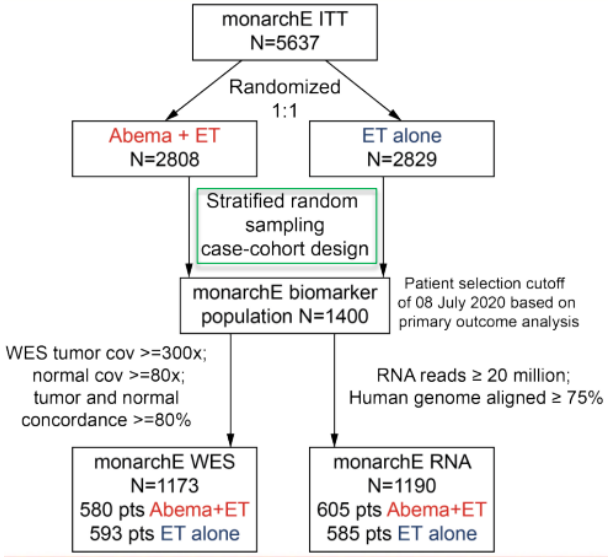
J Clin Oncol. 2020 Dec 1;38(34):3987-3998
Lancet Oncol. 2023 Jan;24(1):77-90

Genomic and transcriptomic profiling of primary tumors from patients with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial

Biomarker analysis overview

Stratified random sampling case-cohort design to select patients with an IDFS event at a pre-specified primary outcome analysis (08 July 2020)





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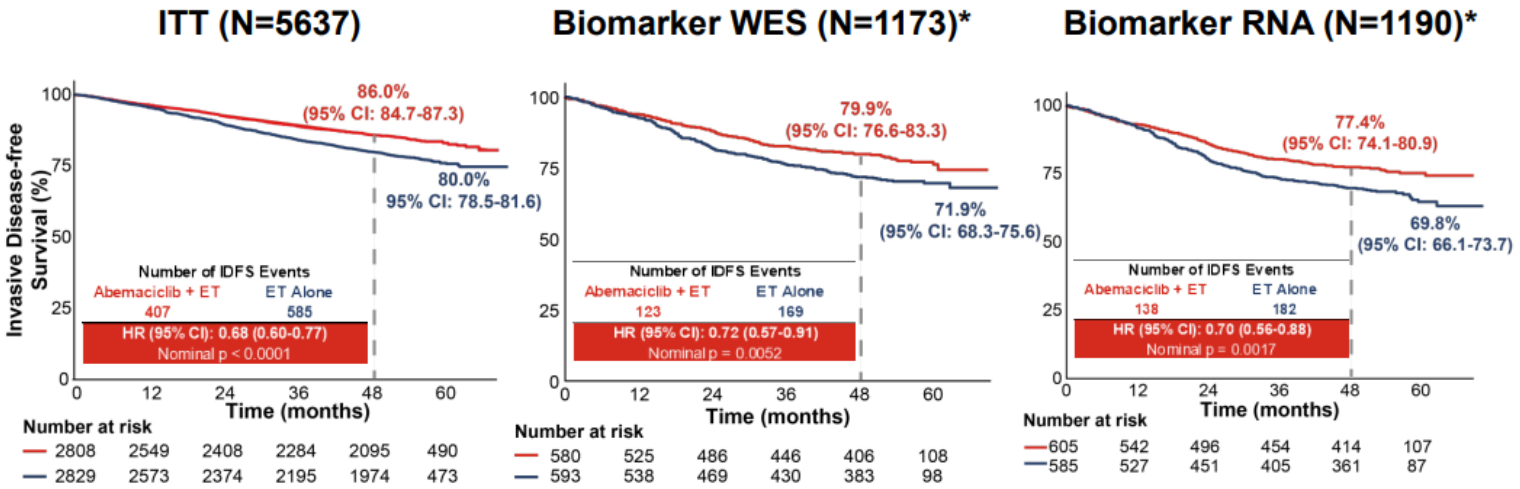
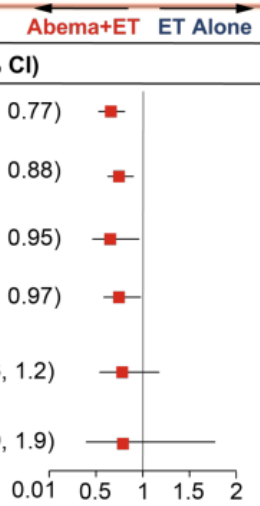
Abemaciclib benefit was consistently observed in biomarker subset of monarchE



Consistent abemaciclib treatment benefit across all intrinsic molecular subtypes

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4-yr IDFS Rate (95% CI)	Events/n (%)	4-yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7–87.3)	585/2829 (21%)	80.0 (78.5–81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)
LumA	28/230 (12%)	87.5 (83.2–92)	45/228 (20%)	81.4 (76.3–86.8)	0.59 (0.37, 0.95)
LumB	65/265 (25%)	76.3 (71.2–81.7)	88/262 (34%)	66.6 (61.1–72.7)	0.70 (0.51, 0.97)
HER2E	32/69 (46%)	52.6 (41.8–66.2)	34/59 (58%)	42.5 (31.4–57.5)	0.74 (0.46, 1.2)
Basal	9/21 (43%)	57.1 (39.5–82.8)	8/15 (53%)	46.7 (27.2–80.2)	0.75 (0.29, 1.9)

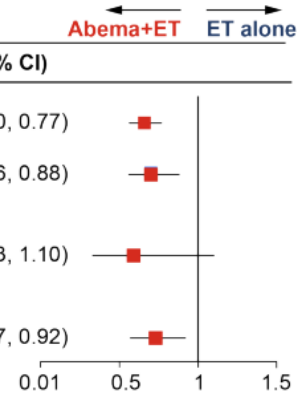


Interaction p-value (all subtypes) = 0.621

Turner et al. GS03-06, SABCS 2023

Treatment benefit observed in inferred Oncotype risk scores

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4yr IDFS Rate (95% CI)	Events/n (%)	4yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7−87.3)	585/2829 (21%)	80.0 (78.5−81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1−80.9)	182/585 (31%)	69.8 (66.1−73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8−94.9)	28/165 (17%)	84.2 (78.7−90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1−76.8)	154/420 (37%)	64.1 (59.6−69)	0.73 (0.57, 0.92)

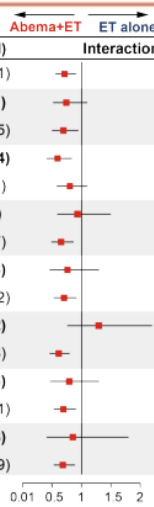


Interaction p-value (inferred Oncotype scores high and low) = 0.532

These data support the use of abemaciclib in patients with HR+, HER2- node-positive, high-risk early breast cancer regardless of intrinsic subtype, inferred Oncotype-RNA score, and most common genomic alterations

Consistent treatment benefit across most prevalent genomic alterations

		Abemaciclib + ET	ET Alone		
	Prevalence	Events/n (%)		HR (95% CI)	Interaction p-value
All patients		123/580 (22%)	169/593 (28%)	0.72(0.57,0.91)	
PIK3CA mut	**38%**	**55/217 (26%)**	**73/229 (32%)**	**0.75(0.53,1.1)**	0.758
PIK3CA wt		68/363 (18%)	96/364 (26%)	0.70(0.51,0.95)	
TP53 mut/homdel	**32%**	**55/189 (30%)**	**82/184 (44%)**	**0.60(0.42,0.84)**	0.184
TP53 wt		68/391 (18%)	87/409 (22%)	0.81(0.59,1.1)	
CCND1 amp	**20%**	**36/113 (32%)**	**42/129 (32%)**	**0.94(0.6,1.5)**	0.177
CCND1 wt		87/467 (18%)	127/464 (28%)	0.66(0.5,0.87)	
ZNF703 amp	**16%**	**28/96 (30%)**	**37/100 (36%)**	**0.77(0.47,1.3)**	0.776
ZNF703 wt		95/484 (20%)	132/493 (26%)	0.71(0.54,0.92)	
MYC amp	**16%**	**34/92 (36%)**	**25/84 (30%)**	**1.30(0.77,2.2)**	0.014
MYC wt		89/488 (18%)	144/509 (28%)	0.62(0.47,0.8)	
FGFR1 amp	**16%**	**26/88 (30%)**	**35/98 (36%)**	**0.80(0.48,1.3)**	0.641
FGFR1 wt		97/492 (20%)	134/495 (28%)	0.70(0.54,0.91)	
GATA3 mut	**14%**	**13/73 (18%)**	**17/88 (20%)**	**0.86(0.42,1.8)**	0.513
GATA3 wt		110/507 (22%)	152/505 (30%)	0.69(0.54,0.89)	



MUT = mutation

HOMDEL = homozygous deletion

AMP = amplification

MYC, GATA3, FGFR1, ZNF703: analyses limited by small sample size

Turner et al. GS03-06, SABCS 2023

Objective, Sampling Timeline, & Patient Selection

Objective: Pilot study to investigate the technical feasibility of ctDNA detection at baseline and 24 months, as well as rates of persistence and clearance in a subset of early breast cancer patients (pts) from monarchE using a Signatera™ ctDNA assay.

- **monarchE (NCT03155997) randomized 5637 pts to receive 2 years adjuvant abemaciclib in combination with ET vs. ET alone and demonstrated a significant and sustained improvement in IDFS and DRFS with the addition of abemaciclib**
- **Pilot subset was enriched for IDFS events compared to the total monarchE population, but excluded pts with IDFS events that occurred within the 2-year treatment period**
  - Eligible patients included those who received adjuvant chemotherapy and began ET prior to randomization

- **Existing whole exome sequencing (WES) data from primary tumors was used to select patient samples representing a range of tumor mutation burden for a technical feasibility pilot cohort**
- **Blood samples utilized for this pilot were obtained from monarchE patients at the timepoints indicated**
  - For this pilot of 178 patients, samples from 0 and 24 months were pre-selected and analyzed for positivity rates and dynamics using a Signatera™ assay developed for each patient
  - Up to 16 genetic variants were selected for each patient based on WES baseline data

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ctDNA Positivity at 24 Months is Highly Associated with Recurrences >24 months Post-Randomization

	N (%)	ctDNA positivity at baseline (%)	ctDNA positivity at 24 months (%)	IDFS Event (%)	Median time from ctDNA detection at baseline to recurrence in months (range)	Median time from ctDNA detection at 24 months to recurrence in months (range)
Pilot Subset*	178	10 (5.6)	42 (23.6)	70 (39.3)	NA	NA
With recurrence	70 (39.3)	7 (10.0)	42 (60.0)	70 (100.0)	NA	NA
Without recurrence	108 (60.7)	3 (2.8)	0 (0.0)	0 (0.0)	NA	NA
ctDNA+ at baseline	10 (5.6)	10 (100.0)	7 (70.0)	7 (70.0)	27 (25-43)	3 (1-19)
Remained ctDNA+	7 (3.9)	7 (100.0)	7 (100.0)	7 (100.0)	27 (25-43)	3 (1-19)
Cleared at 24 months	3 (1.7)	3 (100.0)	0 (0.0)	0 (0.0)	NA	NA
Became ctDNA+ at 24 months	35 (19.7)	0 (0.0)	35 (100.0)	35 (100.0)	NA	5 (0-25)
Persistently ctDNA- (at 0 & 24 months)	133 (74.7)	0 (0.0)	0 (0.0)	28 (21.1)	NA	NA

		Recurrence Y	Recurrence N	
ctDNA at 0 month	+	7	3	PPV = 70%
	-	63	105	NPV = 63%
ctDNA at 24 months	+	42	0	PPV = 100%
	-	28	108	NPV = 79%

*95% of patients had prior chemotherapy treatment and 60% of patients were also on adjuvant ET at the time of randomization; excludes patients who recurred before 24 months; positivity rates may change in full cohort analysis

NA = Not Applicable

- **Detection of ctDNA at baseline soon after completing (neo)adjuvant chemotherapy was infrequent (5.6%, 10/178 patients)**
  - 3 of the 10 patients cleared ctDNA at 24 months and none developed breast cancer recurrence
  - 7 of the 10 patients had persistence of ctDNA at 24 months and all experienced breast cancer recurrence
- ctDNA was detected in 24% (42/178) of patients at 24 months and was highly predictive with 100% of these patients developing disease recurrence
- Recurrences occurred in 21% (28/133) of patients who tested persistently ctDNA-, suggesting an opportunity to improve detection, with considerations for more frequent testing and timing of draws relative to active therapy

Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2− Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial

NATALEE Study Design[1-3]

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

N=5101[b]

R 1:1[c]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y

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

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

Primary End Point
– iDFS using STEEP criteria

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

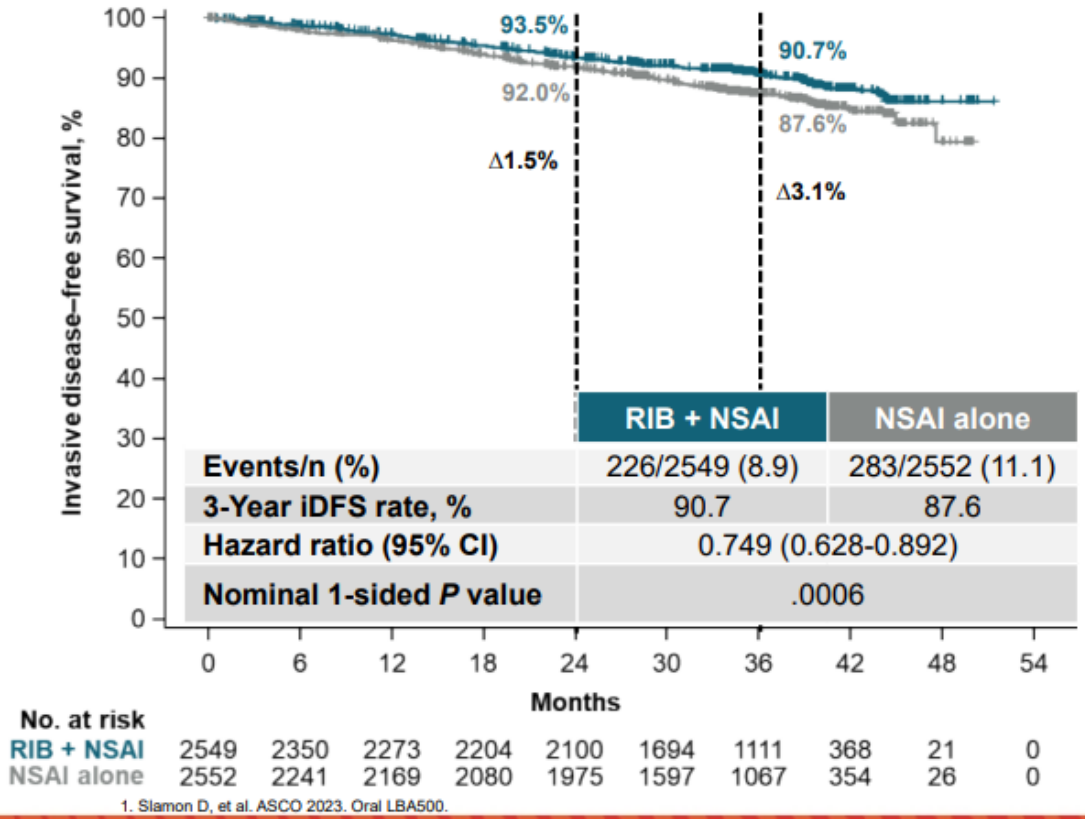
Exploratory End Points
– Locoregional recurrence–free survival
– Gene expression and alterations in tumor ctDNA/ctRNA samples

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

ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.

Invasive Disease–Free Survival



	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided *P* value	.0006	

1. Slamon D, et al. ASCO 2023. Oral LBA500.

- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis[1]
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

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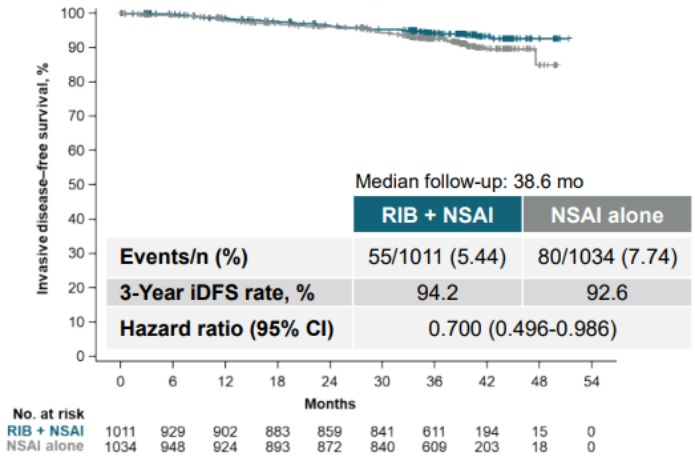
Hortobagyi et al. GS03-03, SABCS 23
Slamon D, et al. ASCO 2023. Oral LBA500

iDFS by Anatomical Stage

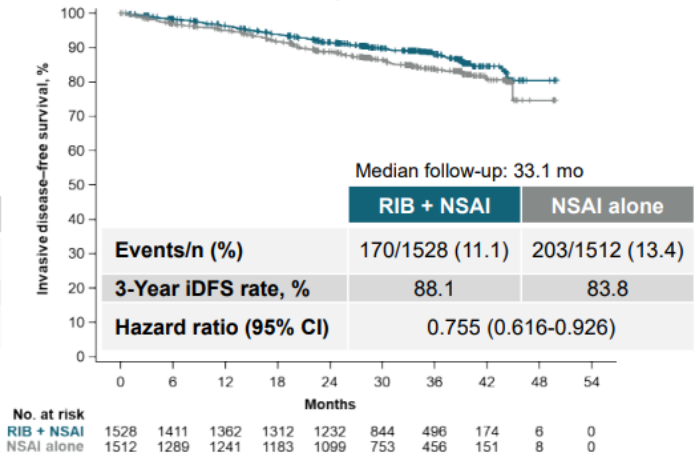
Stage II



Median follow-up: 38.6 mo

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

Stage III



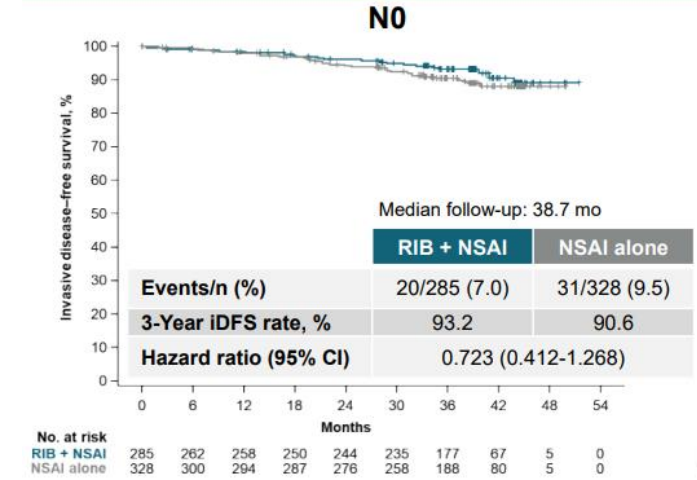
Median follow-up: 33.1 mo

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

- The risk of invasive disease was reduced by 30.0% for stage II and by 24.5% for stage III disease with ribociclib plus NSAI vs NSAI alone

iDFS by Nodal Status

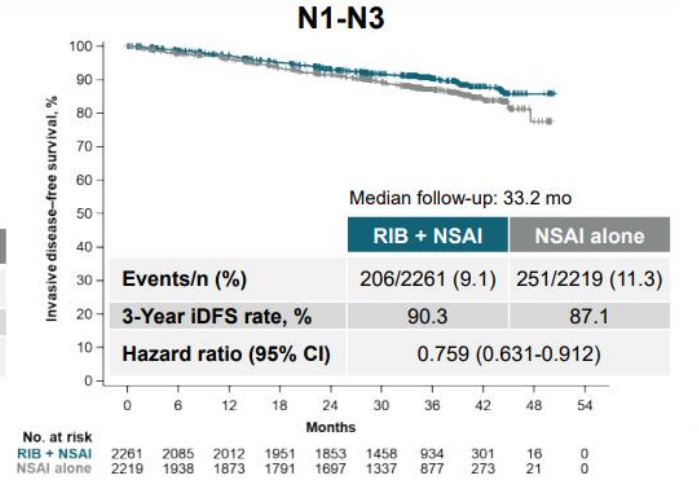
N0



Median follow-up: 38.7 mo

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

N1-N3



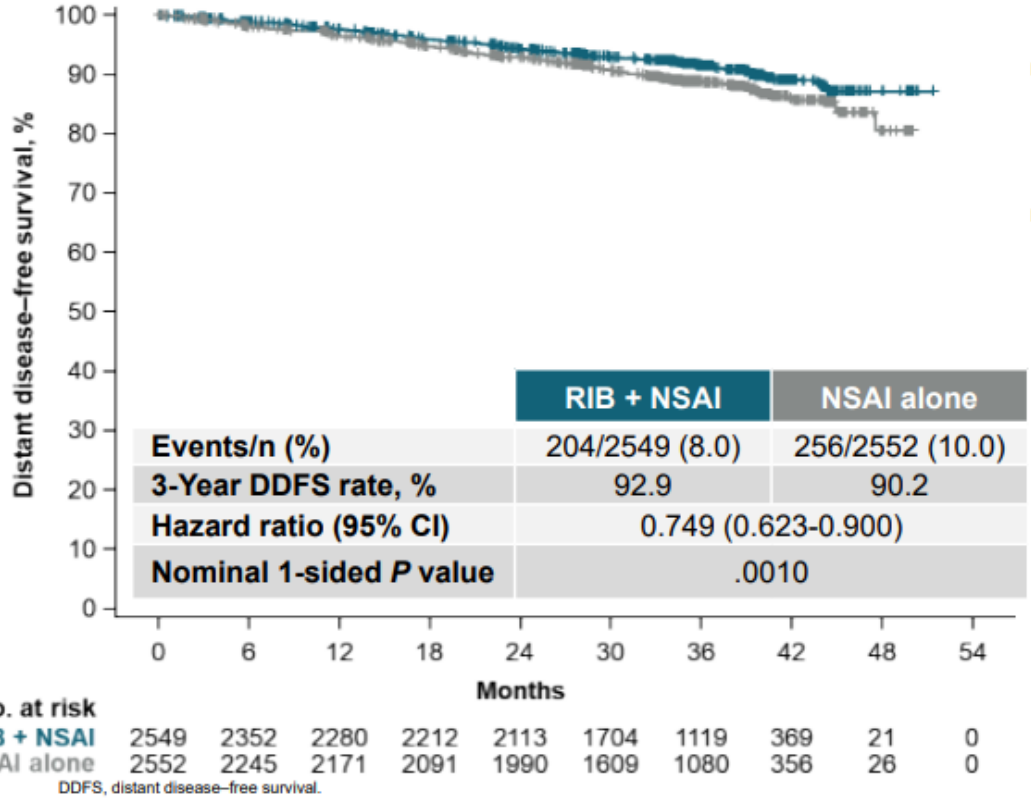
Median follow-up: 33.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

- The risk of invasive disease was reduced by 27.7% for node-negative and by 24.1% for node-positive disease with ribociclib plus NSAI vs NSAI alone

Hortobagyi et al. GS03-03, SABCS 23
Slamon D, et al. ASCO 2023. Oral LBA500

Distant Disease–Free Survival



	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

No. at risk										
RIB + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI alone	2552	2245	2171	2091	1990	1609	1080	356	26	0

DDFS, distant disease–free survival.

[a]DDFS is the time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary nonbreast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

- The absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

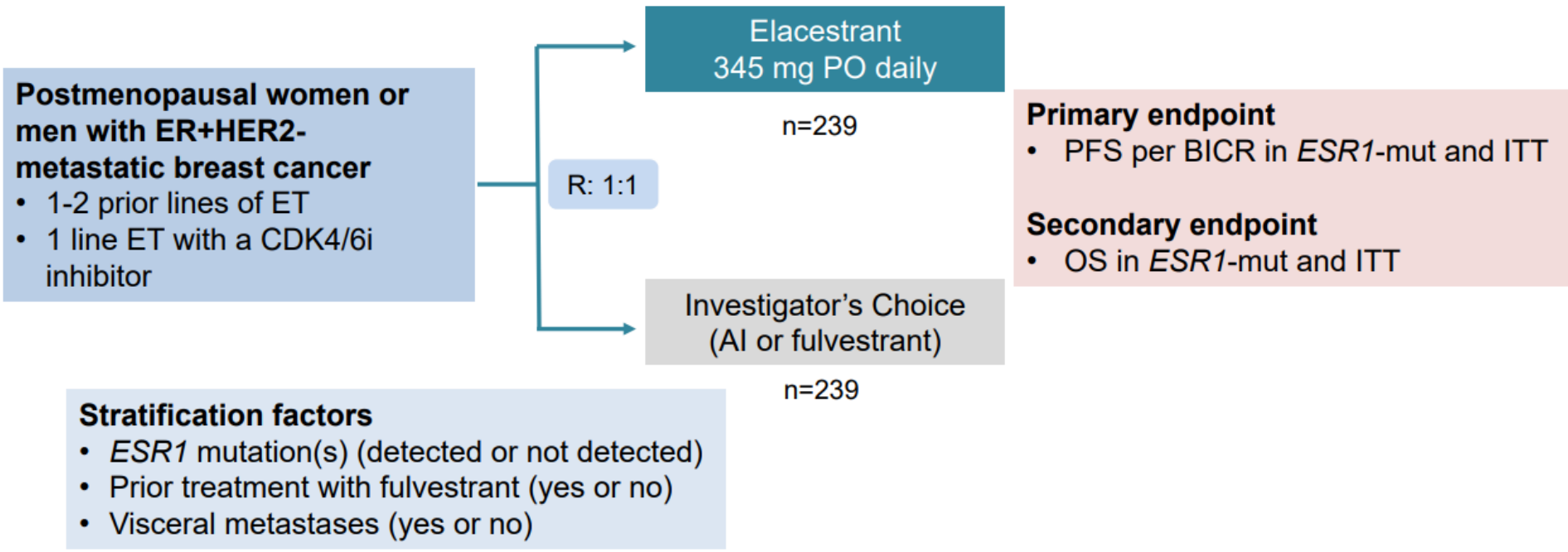
These results from NATALEE further emphasize the significant iDFS benefit of 3 years of ribociclib plus NSAI over NSAI alone in a broad population of patients with HR+/HER2− early breast cancer at risk of recurrence

Hortobagyi et al. GS03-03, SABCS 23
Slamon D, et al. ASCO 2023. Oral LBA500

Therapeutic developmental pathways in ER+ Breast Cancer

- CDK 4/6i
- **SERDs- EMERALD**
  SERENA-3
- AKT/PIK3i
- ICIs
- ADCs

EMERALD (Study RAD1901-308)



Elacestrant: Oral estrogen receptor antagonist
Approved indication: postmenopausal women and men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following ≥ 1 line of endocrine therapy

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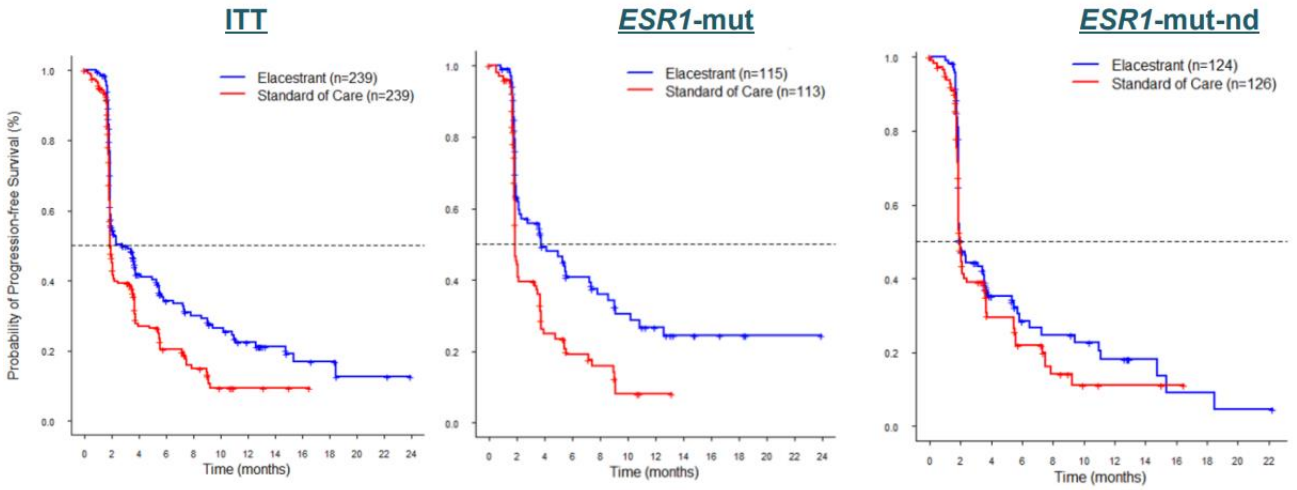
J Clin Oncol. 2022 Oct 1;40(28):3246-3256

Progression-Free Survival



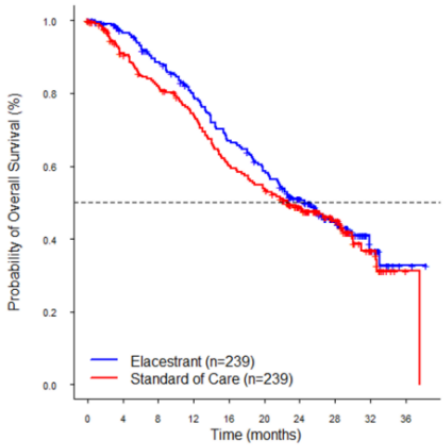
	ITT		*ESR1*-mut		*ESR1*-mut-nd*	
	Elacestrant n=239	**SOC** n=239	**Elacestrant** n=115	**SOC** n=113	**Elacestrant** n=124	**SOC** n=126
Events (%)	144 (60)	156 (65)	62 (54)	78 (69)	82 (66)	78 (62)
Median, mo. (95% CI)	**2.8** (1.9, 3.8)	**1.9** (1.9, 2.1)	**3.8** (2.2, 7.2)	**1.9** (1.9, 2.1)	**1.9** (1.9, 3.6)	**2.0** (1.9, 2.2)
HR (95% CI) p-value	**0.70** (0.55, 0.88) 0.002		**0.55** (0.39, 0.77) <0.001		**0.86** (0.63, 1.19) -	

*Not formally tested
ITT=intention to treat; ESR=estrogen receptor; mut=mutated; nd=not detected; SOC=standard of care

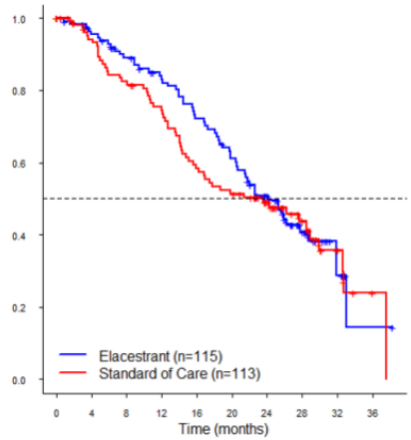
J Clin Oncol. 2022 Oct 1;40(28):3246-3256

Overall Survival

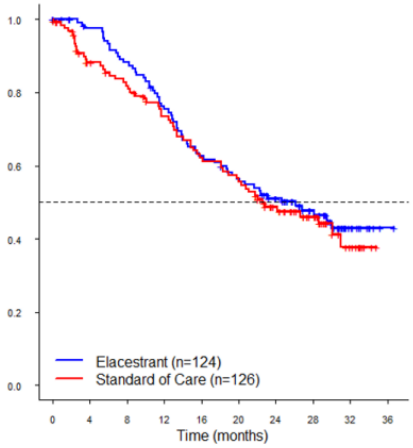
ITT



***ESR1*-mut**



***ESR1*-mut-nd**



Indication restricted to ESR1-mut subgroup due to differential benefit-risk in ESR1-mut and ESR1-mut-nd subgroups

Safety

	Elacestrant % (n=237)	SOC % (n=230)
Treatment-Emergent Adverse Events, All Grade (≥5% Higher with Elacestrant vs. SOC)		
Nausea	35	19
Vomiting	19	9
Decreased Appetite	15	10
Constipation	12	6
Dyspepsia	10	2.6
Laboratory Abnormalities, All Grade (≥5% Higher with Elacestrant vs. SOC)		
Cholesterol Increased	30	17
Triglycerides Increased	27	15
Creatinine Increased	16	6
Hemoglobin Decreased	26	20

J Clin Oncol. 2022 Oct 1;40(28):3246-3256

Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with *ESR1* mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial

In the EMERALD study that led to the approval of elacestrant, patients who had at least 12 months of prior CDK4/6i duration achieved a mPFS of 8.6 months with elacestrant vs 1.9 months mPFS with SOC indicating the endocrine sensitivity of this subpopulation, leading to a greater benefit with elacestrant.

In this endocrine-sensitive population (CDK4/6 inhibitor duration of ≥12 months) with ESR1-mut tumors, we evaluated the benefit of single-agent elacestrant in highly prevalent clinical and key biomarkers subgroups, including metastases sites (bone, liver and/or lung), common coexisting mutations (PIK3CA, TP53), and HER2-low expression, to support clinical treatment decisions.

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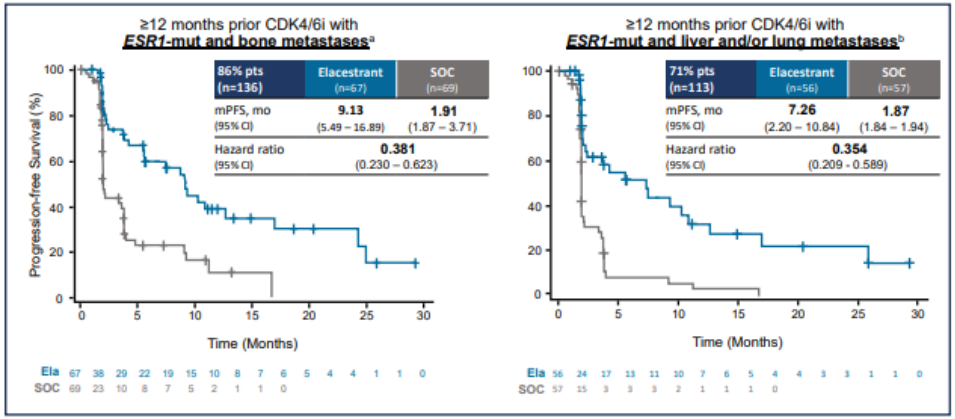
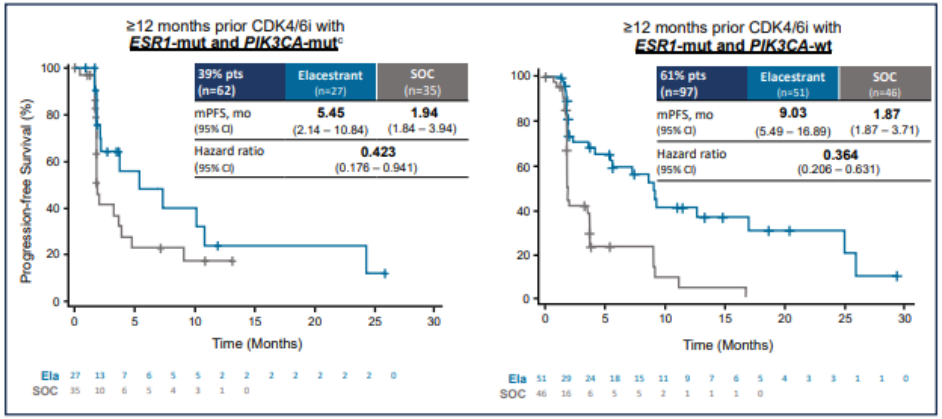
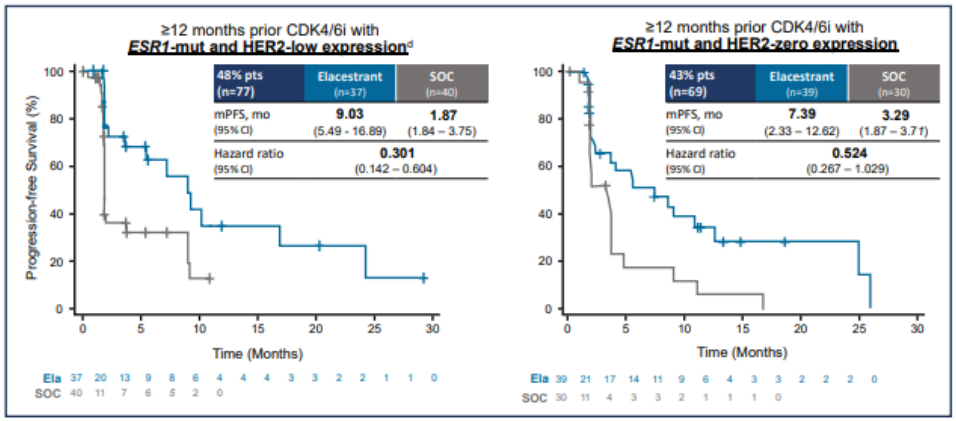
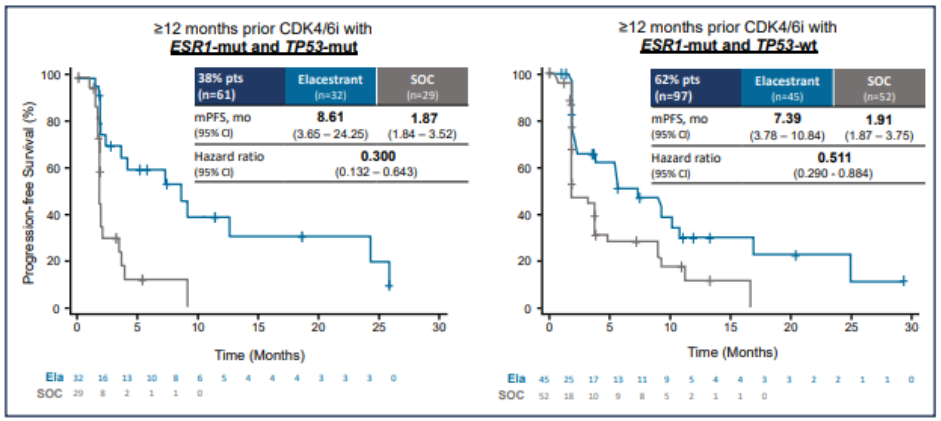
A clinically meaningful improvement in PFS favoring elacestrant vs SOC was consistent across all subgroups with *ESR1*-mut tumors who received a CDK4/6i for ≥12 months









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Conclusions

- A clinically meaningful improvement in PFS favoring elacestrant compared with SOC was consistent across all relevant subgroups with *ESR1*-mut tumors and assumed endocrine-sensitivity (prior CDK4/6 inhibitor duration ≥12 months)
- **These results indicate that when *ESR1*-mut tumors remain endocrine sensitive (eg, prior CDK4/6 inhibitor duration ≥12 months), the ER pathway could be the main driver of disease, regardless of the metastatic site or coexistence of *PIK3CA*-mut, *TP53*-mut, or HER2-low expression.**
- Adverse event data for the clinical and biomarker subgroups evaluated in this analysis revealed no substantial differences compared with the total population.
- Single-agent elacestrant enables endocrine therapy sequencing in the second line before other targeted therapies, drug combinations, and chemotherapy-based regimens, including ADCs, accompanied by a manageable safety profile.

Patient population with exposure to CDK4/6 inhibitor for ≥12 months	% (n)	Median PFS, months (95% CI)		Hazard ratio (95% CI)
		Elacestrant	SOC	
All *ESR1*-mut patients[1]	100 (159)	**8.61** (4.14 – 10.84)	**1.91** (1.87 – 3.68)	**0.410** (0.262 – 0.634)
ESR1-mut and bone metastases[a]	86 (136)	**9.13** (5.49 – 16.89)	**1.91** (1.87 – 3.71)	**0.381** (0.230 – 0.623)
ESR1-mut and liver and/or lung metastases[b]	71 (113)	**7.26** (2.20 – 10.84)	**1.87** (1.84 – 1.94)	**0.354** (0.209 – 0.589)
ESR1-mut and *PIK3CA*-mut[c]	39 (62)	**5.45** (2.14 – 10.84)	**1.94** (1.84 – 3.94)	**0.423** (0.176 – 0.941)
ESR1-mut and HER2-low expression[d]	48 (77)	**9.03** (5.49 – 16.89)	**1.87** (1.84 – 3.75)	**0.301** (0.142 – 0.604)
ESR1-mut and *TP53*-mut	38 (61)	**8.61** (3.65 – 24.25)	**1.87** (1.84 – 3.52)	**0.300** (0.132 – 0.643)

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SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer

SERENA-3: Prospective adaptive staged design

Key inclusion/exclusion criteria:

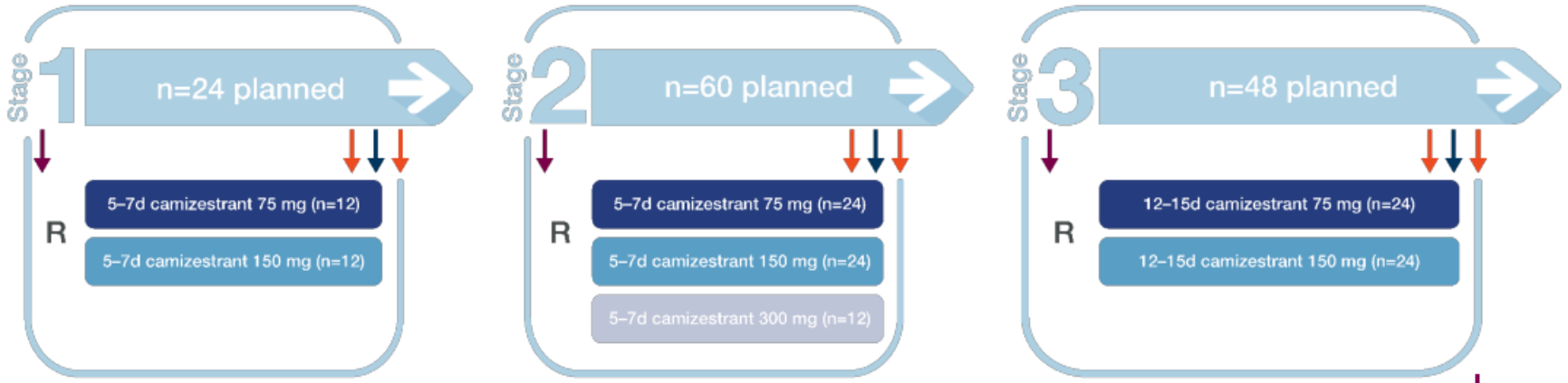
- ER+, HER2- primary breast cancer
- Histologically confirmed invasive breast cancer
- Palpable tumor of any size, or a tumor with an ultrasound assessed diameter of ≥1.0 cm

Primary endpoint:

- Change in ER IHC H-score

Secondary endpoints:

- Change in Ki67, PR; PK; safety

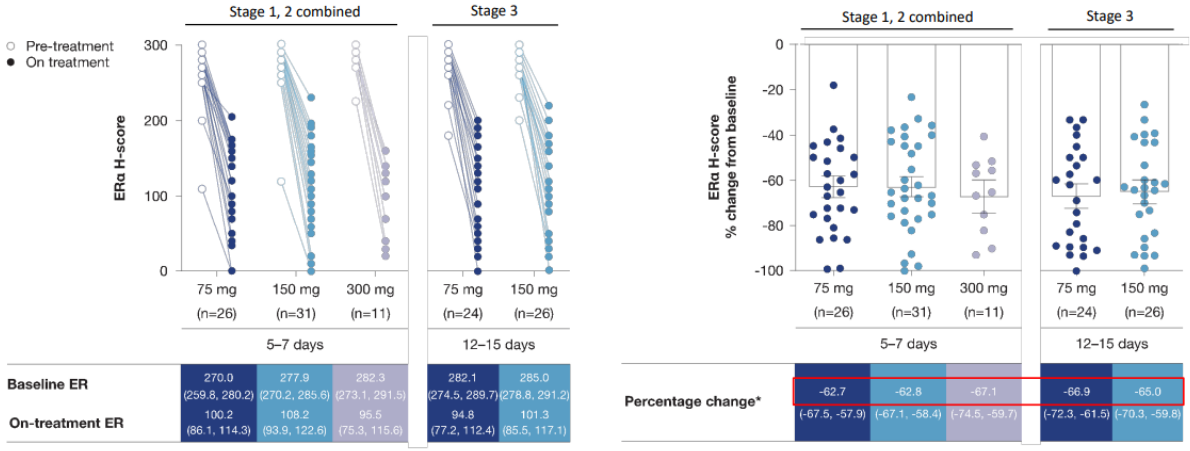


- **On-treatment core biopsy** timings: pre-biopsy PK >1h post dose; biopsy 1–12h post dose; post-biopsy PK 1–3h post biopsy
- **NB: No stipulation for baseline Ki67 score; pre-specified sensitivity analysis of patients with Ki67 baseline score ≥5%**

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; PK: pharmacokinetics; PR: progesterone receptor; R: randomized

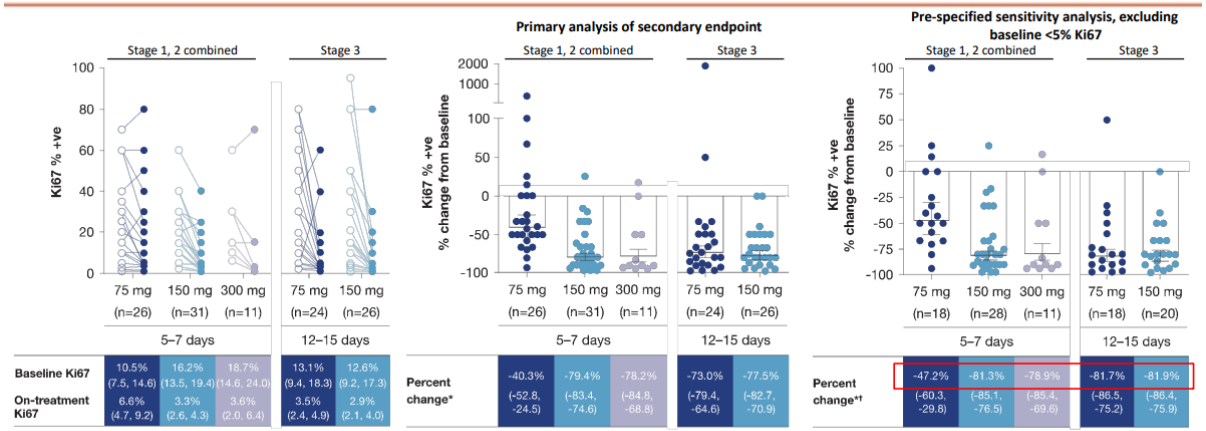
- SERENA-3 demonstrated that the 75 mg dose of camizestrant achieves maximal levels of ER degradation, antagonism and downstream Ki67 suppression
- Recruitment to Phase 3 studies in ABC continues (SERENA-4,SERENA-6)
- Recruitment to Phase 3 adjuvant studies has commenced (CAMBRIA-1, CAMBRIA-2)

Primary endpoint: Percentage change from baseline in ER expression



- ER levels at baseline, and degree of degradation on treatment, are similar across 75, 150 and 300 mg doses, and duration of exposure

Secondary endpoint: Change from baseline in Ki67 labelling index



- After 5–7d exposure, camizestrant 75 mg reduced Ki67 score to a lesser degree than 150 and 300 mg
- After 12–15d exposure, camizestrant 75 and 150 mg reduced Ki67 score to a similar substantial degree (~82%)
- PK steady state does not necessarily translate to PD steady state

Therapeutic developmental pathways in ER+ Breast Cancer

- CDK 4/6i
- SERDs
- **AKT/PIK3 - CAPItello-291**

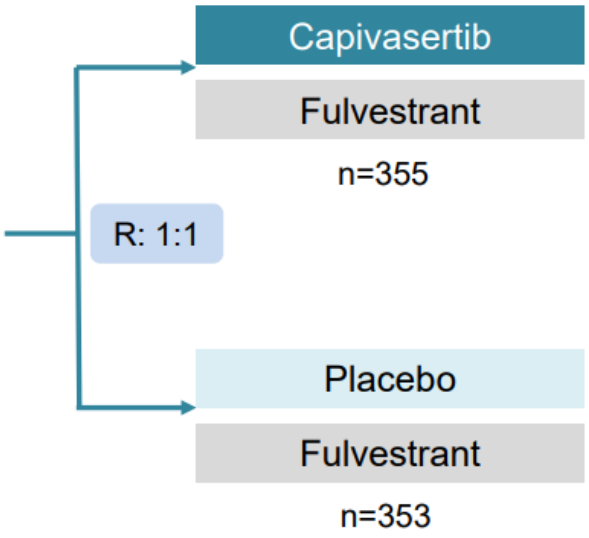
  INAVO120

  Early phase trials/drugs
- ICIs
- ADCs

CAPItello-291

Adults with HR+/HER2-unresectable or metastatic breast cancer

- Recurrence/progression while on or <12 months from the end of adjuvant AI, or progression on AI in advanced setting
- ≤ 2 lines prior endocrine therapy
- ≤ 1 line chemotherapy
- Prior CDK 4/6 inhibitor in at least 51% of patients
- HbA1c <8% and diabetes not requiring insulin
- FFPE tumor sample from the primary/recurrent cancer available for retrospective testing



Stratification:

- Liver metastases
- Prior CDK 4/6 inhibitors
- Geographic region

Co-Primary endpoints:

- PFS in overall population; AND
- PIK3CA/AKT1/PTEN-biomarker-pos population

Secondary endpoints:

- OS in overall population
- PIK3CA/AKT1/PTEN-biomarker-pos population
- ORR
- DoR

Capivasertib- potent selective inhibitor of all three AKT isoforms
Approved indication: in combination with fulvestrant for ER+ HER- MBC with ≥ PIK3CA/AKT1/PTEN-alteration and ≥1 line of endocrine therapy.

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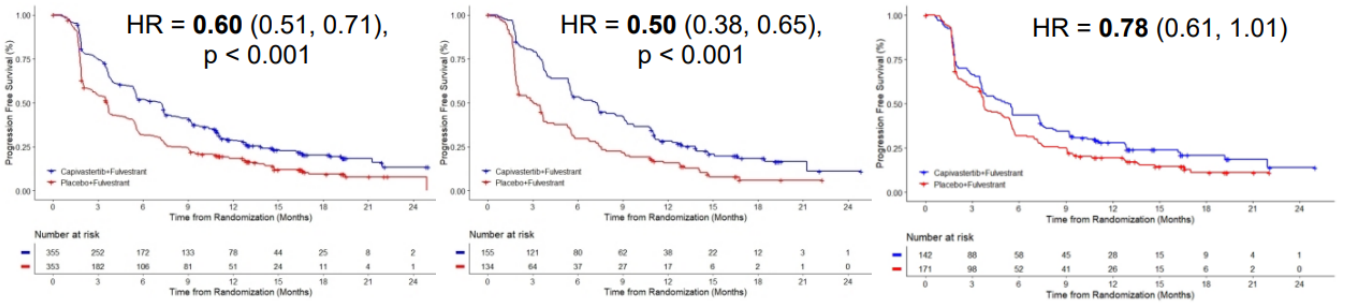
N Engl J Med. 2023 Jun 1;388(22):2058-2070

Progression-Free Survival

Overall N=708	Biomarker-Pos N=289	Biomarker-Neg N=313



Event #: 258 (73%) vs. 293 (83%) Median = 7.2 (5.5, 7.4) vs 3.6 (2.8, 3.7)	Event #: 121 (78%) vs. 115 (86%) Median = 7.3 (5.5, 9.0) vs 3.1 (2.0, 3.7)	Event #: 103 (73%) vs. 141 (82%) Median = **5.3** (3.6, 7.3) vs **3.7** (3.5, 5.1)

Adverse Events

	Hyperglycemia		Diarrhea		Cutaneous Adverse Reactions	
Overall Population	**C+F (n=355)**	**P+F (n=350)**	**C+F (n=355)**	**P+F (n=350)**	**C+F (n=355)**	**P+F (n=350)**
TEAEs (all-grade):	18	4.3	72	20	58	18
Grade ≥ 3	2.8	0.3	9	0.3	17	0.6
Leading to Reduction	0.6	0	8	0	7	0
Leading to Discontinuation	0.6	0.3	2	0	7	0

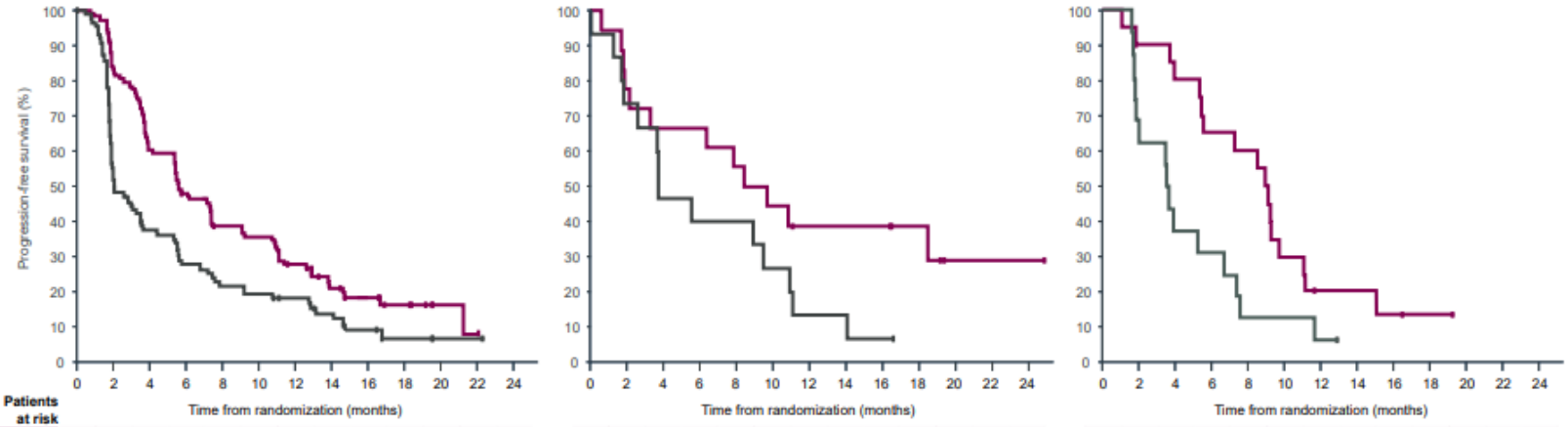
N Engl J Med. 2023 Jun 1;388(22):2058-2070

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer: exploratory analysis of PFS by *PIK3CA/AKT1/PTEN* alteration from the Phase 3 CAPItello-291 trial

PFS in patients by alteration type (Global population)

Consistent clinically meaningful benefit with capivasertib plus fulvestrant compared to placebo plus fulvestrant was observed in patients regardless of alteration detected

	***PIK3CA* alteration only**		***AKT1* alteration only**		***PTEN* alteration only**	
	Capivasertib plus fulvestrant (n=110)	Placebo plus fulvestrant (n=92)	Capivasertib plus fulvestrant (n=18)	Placebo plus fulvestrant (n=15)	Capivasertib plus fulvestrant (n=21)	Placebo plus fulvestrant (n=16)
Median (95% CI); months	**5.6** (4.2–7.4)	**2.1** (1.9–3.6)	**9.1** (2.2–NC)	**3.7** (1.7–9.5)	**9.1** (5.5–11.1)	**3.6** (1.8–6.7)
	Adjusted hazard ratio (95% CI): **0.51** (0.37–0.70)		Hazard ratio (95% CI): **0.51** (0.22–1.12)		Hazard ratio (95% CI): **0.43** (0.21–0.88)	



Patients at risk													
Capivasertib plus fulvestrant	110	90	65	51	40	37	27	17	13	7	2	1	0
Placebo plus fulvestrant	92	48	31	23	18	16	13	9	5	2	1	1	0

Capivasertib plus fulvestrant	18	14	12	12	10	8	6	6	6	4	1	1	1
Placebo plus fulvestrant	15	11	7	6	6	4	2	2	1	0	0	0	0

Capivasertib plus fulvestrant	21	18	17	13	12	6	3	3	2	1	0	0	0
Placebo plus fulvestrant	16	11	6	5	2	2	1	0	0	0	0	0	0

The hazard ratio for *PIK3CA* alteration was estimated using the Cox proportional hazard model stratified by presence of liver metastases (yes vs no) and prior use of CDK4/6 inhibitors (yes vs no).

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Inavolisib

INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Enrolment period: December 2019-September 2023

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)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Inavolisib is potent PIK3αi

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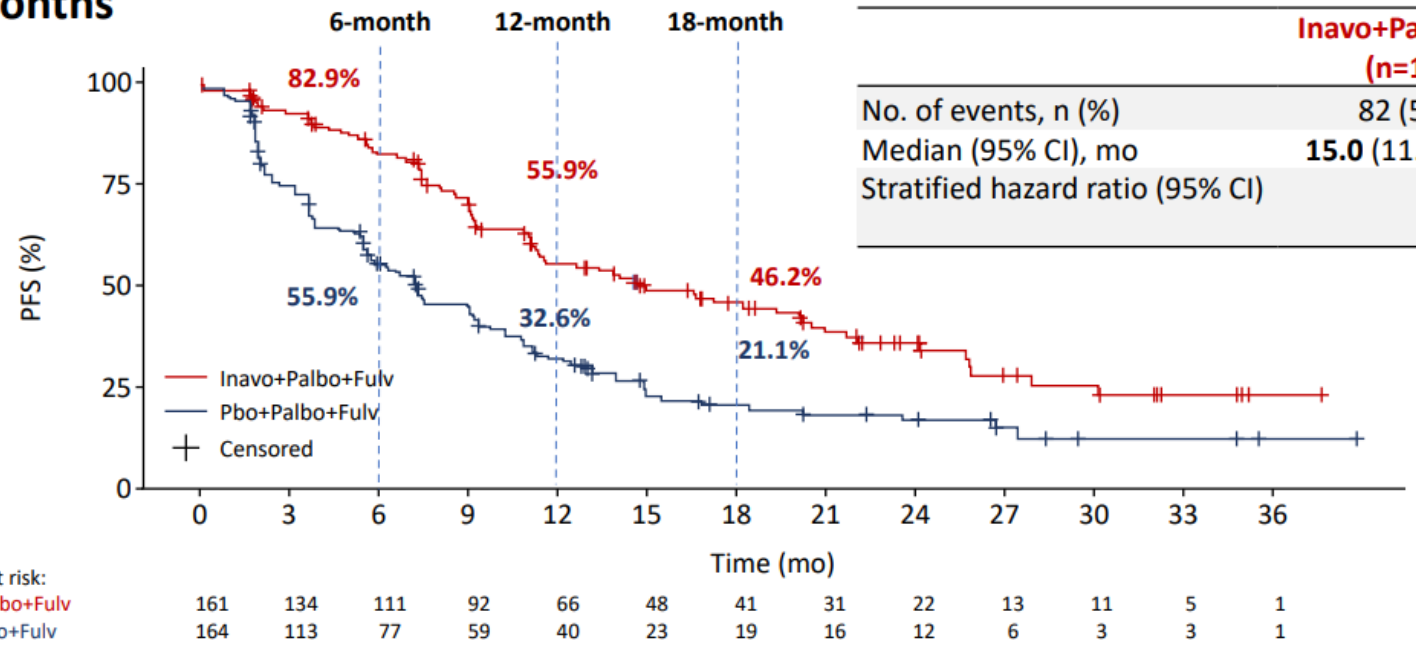
Primary endpoint: PFS (investigator assessed)

Median follow-up: **21.3 months**



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	**15.0** (11.3, 20.5)	**7.3** (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)**	
	p<0.0001	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

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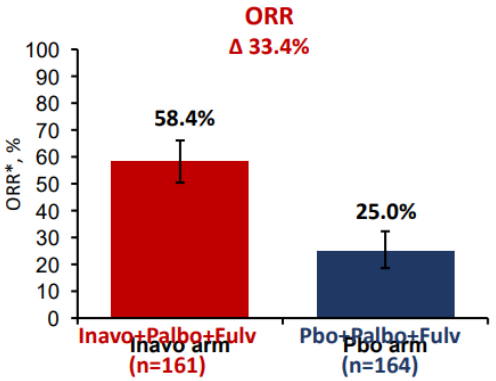
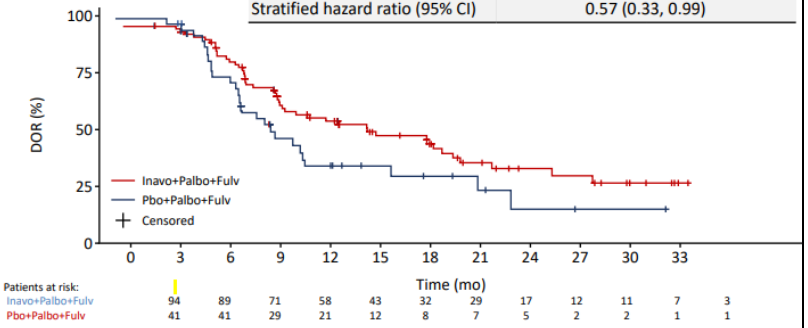
ORR and DOR



	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	**18.4 (10.4, 22.2)**	**9.6 (7.4, 16.6)**
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	



Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

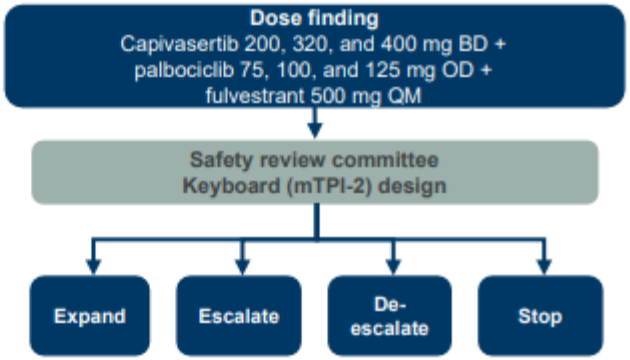
Capivasertib plus cyclin-dependent kinase 4/6 inhibitor and fulvestrant in hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: updated Phase 1b analysis from CAPItello-292

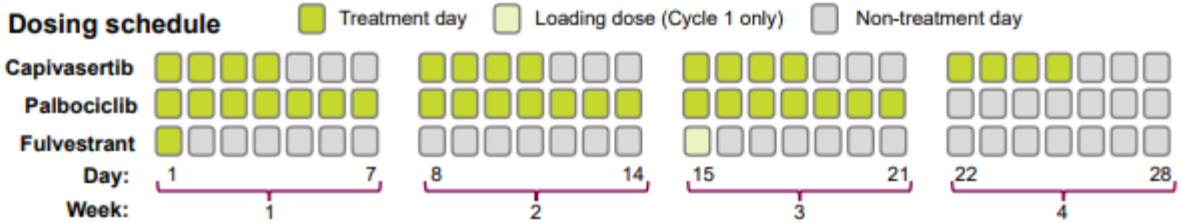
CAPItello-292 (NCT04862663) Phase 1b Study

- Simultaneously inhibiting PI3K/AKT and CDK4/6 pathways may delay CDK4/6 inhibitor resistance and/or re-sensitize tumors to ET plus CDK4/6 inhibitor, leading to improved clinical outcomes
- CAPItello-292 (NCT04862663) is a Phase 1b/3 study examining the efficacy and safety of combining capivasertib, a potent inhibitor of all three AKT isoforms,[1] with a CDK4/6 inhibitor and fulvestrant
  - Based on a preliminary analysis (data cut-off date: October 31, 2022), the RP3D of capivasertib plus palbociclib and fulvestrant was determined, and preliminary signals of clinical activity were demonstrated[2]
  - Here, we report updated safety and efficacy data from the Phase 1b (data cut-off date: July 27, 2023)

Phase 1b key inclusion criteria

- Adults ≥18 years of age with HR-positive/HER2-negative[a] locally advanced (inoperable) or metastatic breast cancer
- At least one prior ET in the advanced setting or disease recurrence within 12 months of completing (neo)adjuvant ET
- Up to two lines of prior chemotherapy in the advanced setting allowed
- Prior CDK4/6 inhibitor treatment was permitted under certain circumstances





Primary endpoints
- Safety and tolerability
- RP3D

Secondary endpoints
- Preliminary assessment of clinical activity (ORR, CBR24, DoR, PFS)

Exploratory biomarker analysis (including ctDNA)

Capivasertib, in combination with palbociclib and fulvestrant, was tolerable in heavily pre-treated patients with HR-positive/HER2-negative advanced breast cancer at all dose levels

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A phase I trial of the PI3K inhibitor (PI3Ki) copanlisib and fulvestrant in combination with continuous or intermittent abemaciclib in patients with estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer (NCI 10287)

Table 1	Dose Level	Abemaciclib (PO)	Copanlisib (IV)	#Enrolled (#DLT evaluable)	#DLT	DLT
Part A	DL 1a (start dose)	100 mg Bid continuously	45 mg D1 and D15	7 (6)	1	Grade 3 ANC, <75% abemaciclib dose received (n=1)
	DL 2a	100 mg Bid continuously	45 mg D1, D8, D15	3 (3)	2	Grade 3 rash (n=1) Grade 3 hyperbilirubinemia (n=1)
Part B	DL 1b (start dose)	100 mg Bid 5-on/2-off weekly	45 mg D1 and D15	7 (6)	1	Grade 3 rash (n=1)
	DL 2b	100 mg Bid 5-on/2-off weekly	45 mg D1, D8, D15	7 (5)	2	Grade 3, new atrial fibrillation (n=1) Grade 3 rash (n=1)

- Copanlisib/fulvestrant/intermittent abemaciclib can be safely administered with fair overall tolerability.
- Most common G3+ AEs include transient hypertension, rash, anemia, neutropenia and LFT elevation.
- Preliminary anti-tumor activity was observed. mPFS was 25.4 (95% CI: 15-40.9) wks.
- Among 21 evaluable pts, there were 5 PRs and 4 SD ≥24 weeks. CBR: 43% (95%CI: 23 ~66%).
- Clinical benefit was observed in pts with or without prior CDK4/6i, fulvestrant, or PIK3CA mut.

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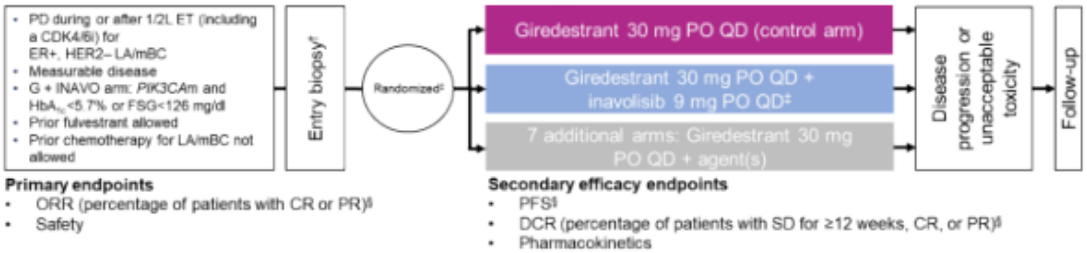
Ma et al. PS17-06, SABCS 23

Interim analysis of giredestrant + inavolisib in MORPHEUS Breast Cancer: a Phase Ib/II study of giredestrant treatment combinations in estrogen receptor-positive, HER2-negative, locally advanced/metastatic breast cancer

MORPHEUS BC, giredestrant + inavolisib 16-week IA

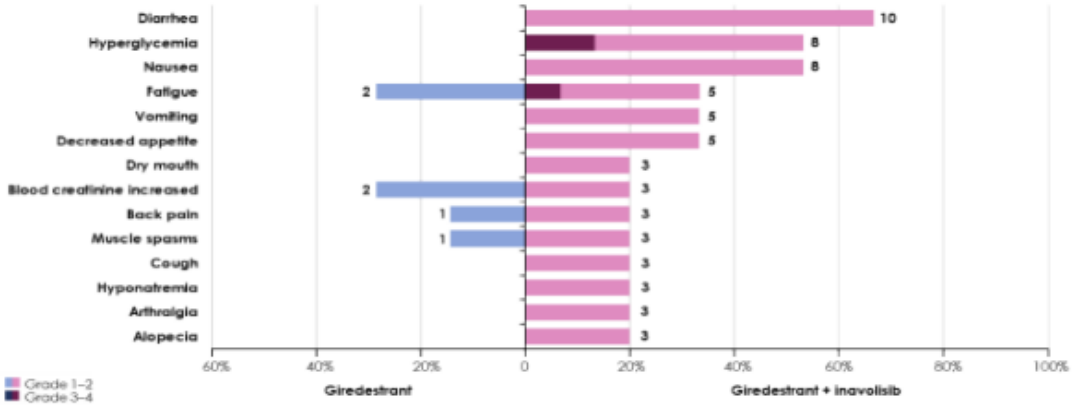
Study design



Primary endpoints
- ORR (percentage of patients with CR or PR)§
- Safety

Secondary efficacy endpoints
- PFS§
- DCR (percentage of patients with SD for ≥12 weeks, CR, or PR)§
- Pharmacokinetics

Most common AEs



Safety summary

Patient safety data n, (%)	Giredestrant n = 7	Giredestrant + inavolisib n = 15
TRAEs	3 (42.9)	15 (100)
Grade 3–4	0	5 (33.3)
AEs leading to tx discontinuation	0	1 (6.7)¶
AEs leading to dose modification/interruption	1 (14.3)	9 (60.0)
Fatal AEs	0	0
Most common TRAEs (≥20% incidence rate)	Fatigue (2; 28.6%)	Diarrhea (9; 60.0%), hyperglycemia (8; 53.3%), nausea (7; 46.7%), fatigue (5; 33.3%), decreased appetite (5; 33.3%), vomiting (4; 26.7%), alopecia (3; 20.0%)

* The study was not designed to make explicit power and type I error considerations for a hypothesis test; † If a biopsy was not deemed feasible by the investigator, archival tumor tissue could be submitted; ‡ Patients with *PIK3CA* mutation were randomized 1:6 to control (giredestrant) vs. giredestrant + inavolisib (only patients with eligible *PIK3CA* mutations were enrolled in the giredestrant + inavolisib arm); § Investigator assessed by RECIST v1.1; ¶ Discontinued treatment due to intermittent vomiting.
1/2L, first/second line; AE, adverse event; BC breast cancer; CR, complete response; DCR, disease control rate; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2–, HER2-negative; IA, interim analysis; LA, locally advanced; m, mutated; mBC, metastatic breast cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response; QD, once daily; TRAE, treatment-related adverse event; tx, treatment.

Rugo et al. PS17-07, SABCS 23

- Encouraging efficacy signal was observed with giredestrant and inavolisib.
- No new safety signals.
- Enrollment to this arm continues.

Confirmed overall response and mPFS

	Giredestrant (n = 7)	Giredestrant + inavolisib (n = 15)
Responders (OR), n (%) 95% CI	0 (0.00, 40.96)	7 (46.7) (21.27, 73.41)
Complete response, n (%) 95% CI	0 (0.00, 40.96)	1 (6.7) (0.17, 31.95)
Partial response, n (%) 95% CI	0 (0.00, 40.96)	6 (40.0) (16.34, 67.71)
Stable disease, n (%) 95% CI	3 (42.9) (9.90, 81.59)	7 (46.7) (21.27, 73.41)
Progressive disease, n (%) 95% CI	3 (42.9) (9.90, 81.59)	1 (6.7) (0.17, 31.95)
Disease control rate, n (%)* 95% CI	2 (28.6) (3.67, 70.96)	12 (80.0) (51.91, 95.67)
Clinical benefit rate, n (%)† 95% CI	1 (14.3) (0.36, 57.87)	9 (60.0) (32.29, 83.66)
Median progression-free survival, months 95% CI	1.71 (1.54, 5.62)	10.32 (6.51, NE)

42.9% of patients in the giredestrant arm and 53.3% in the giredestrant + inavolisib arm received prior fulvestrant for mBC

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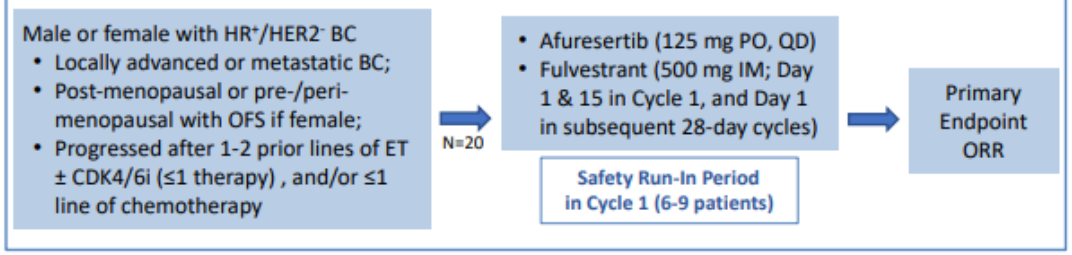
Rugo et al. PS17-07, SABCS 23

A Phase Ib Study to Evaluate the Efficacy and Safety of Afuresertib Plus Fulvestrant in Patients with Locally Advanced or Metastatic HR$^+$/HER2$^-$ Breast Cancer Who Failed Standard of Care Therapies

- The PI3K/AKT/mTOR signaling pathway is the most frequently altered pathway in HR+ breast cancer.
- Fulvestrant is the recommended second-line treatment for patients with HR$^+$/HER2$^-$ and ESR1-wild-type BC who progressed on first-line therapy with AI and CDK4/6i.
- Afuresertib (LAE002, GSK2110183, ASB183) is an oral ATP-competitive pan-AKT inhibitor.
- Phase Ib trial of the LAE205INT3101 study (NCT04851613) is a single arm, open-label study to evaluate the efficacy and safety of the combination therapy of afuresertib plus fulvestrant in HR$^+$/HER2$^-$ BC patients who were resistant 1-2L of SOC.

Schema of Phase Ib Study Design



Radiographic Assessment per RECIST 1.1 (n=20)	
Confirmed ORR (95% CI)	**6 (30%) (11.9, 54.3)**
PR	6 (30%)
SD	10 (50%)
PD	4 (20%)
NE	0
Median PFS (months) (95% CI)	**7.3 (3.7, NE)**

Summary of Overall TEAEs (n = 20)	
Any TEAE	20 (100%)
Grade 3 TEAE	7 (35%)
Related Grade 3 TEAE	6 (30%)
Grade 4-5 TEAE	0
SAE	0
TEAE leading to discontinuation/dose reduction of study drug	0
TEAE leading to interruption of study drug	10 (50%)
Related TEAE leading to interruption of study drug	6 (30%)
TEAE leading to death	0

Conclusions

- The preliminary data has shown promising efficacy of the fulvestrant-afuresertib combination therapy with a well-tolerated safety profile in patients with HR$^+$/HER2$^-$ LA/mBC who had disease progression after 1-2 prior lines of standard of care therapies.
- Further evaluation of this combination therapy will be conducted in the phase III part of the study.

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Phadke et al. PS17-08, SABCS 23

Therapeutic developmental pathways in ER+ Breast Cancer

- CDK 4/6i
- SERDs
- AKT/PIK3i
- **ICIs- KEYNOTE 756**
  CheckMate 7L
  Early phase MORPHEUS

Wisconsin Association of Hematology and Oncology

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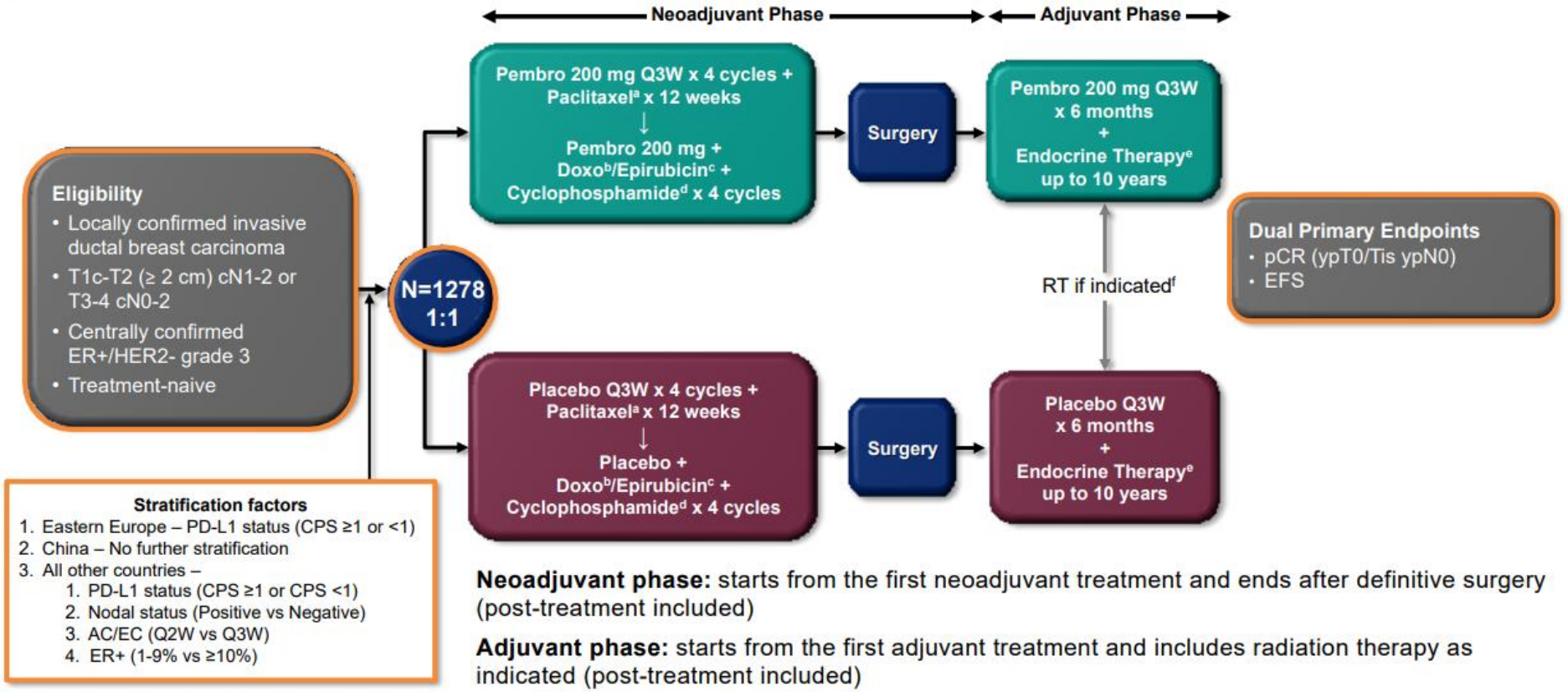
Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo Plus Chemotherapy, Followed by Adjuvant Pembrolizumab or Placebo Plus Endocrine Therapy for Early-Stage High-Risk ER+/HER2− Breast Cancer:

KEYNOTE-756 Study Design (NCT03725059)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

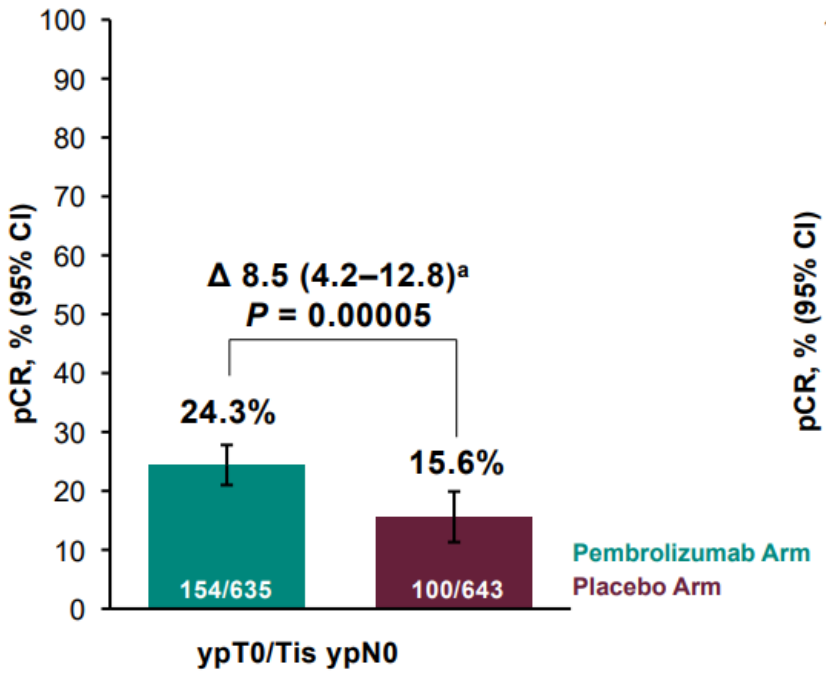
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m² QW. [b]Doxorubicin dose was 60 mg/m² Q3W. [c]Epirubicin dose was 100 mg/m² Q3W. [d]Cyclophosphamide dose was 600 mg/m² Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

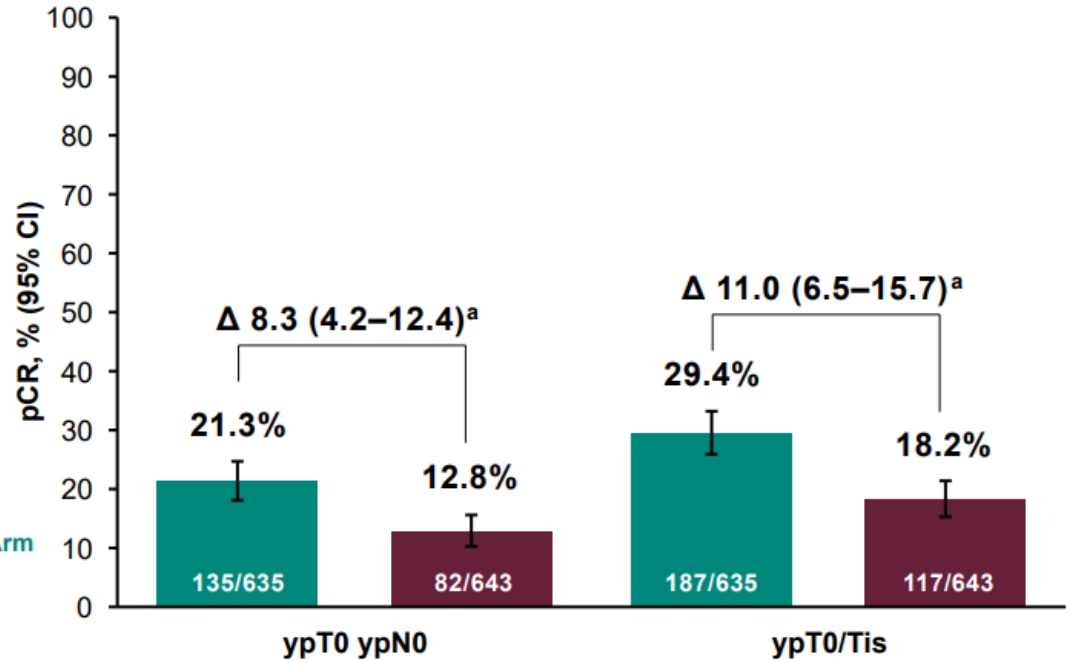
Cardoso et al. GS01-02, SABCS 23
Cardoso F, et al. Ann Oncol. 2023;34(suppl 2):S1260-S1261

Pathological Complete Response at IA1

Primary Endpoint



Secondary Endpoints: Other pCR Definitions



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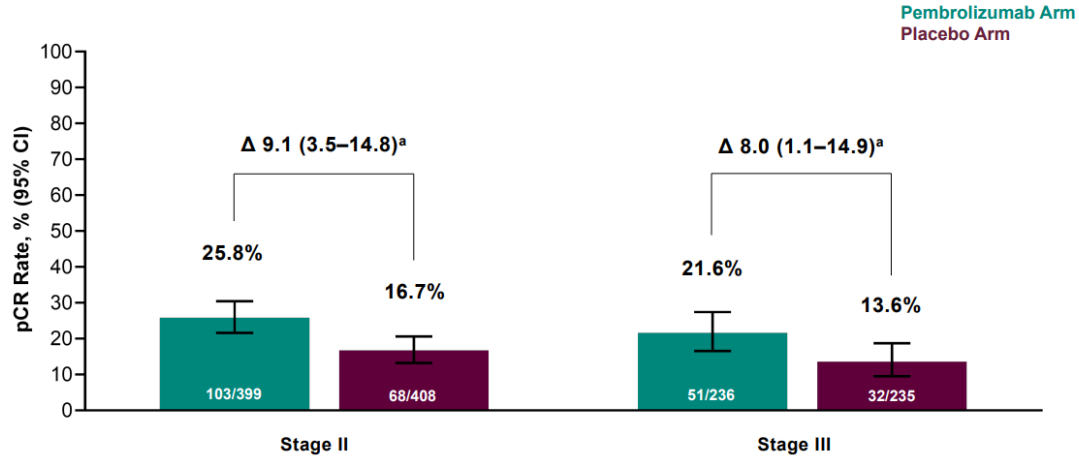
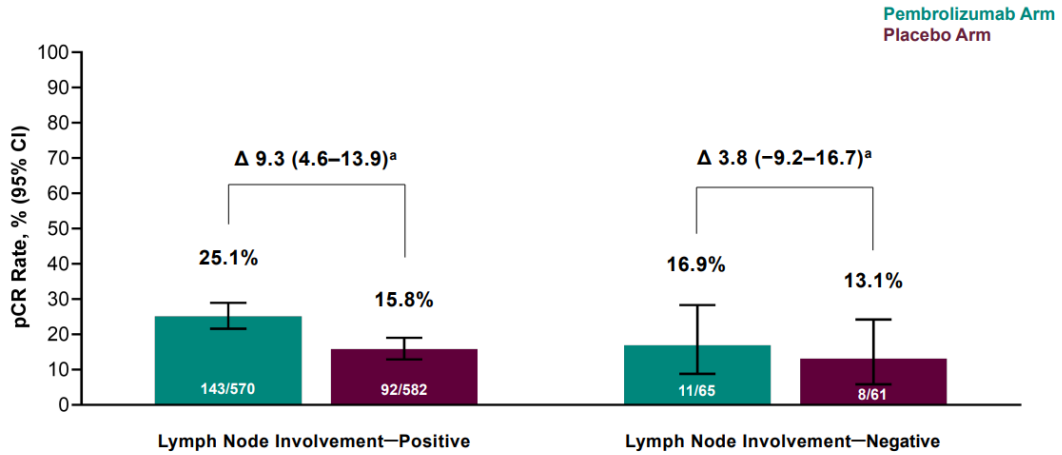
Cardoso et al. GS01-02, SABCS 23
Cardoso F, et al. Ann Oncol. 2023;34(suppl 2):S1260-S1261

Pathological Complete Response at IA1 by Disease Stage

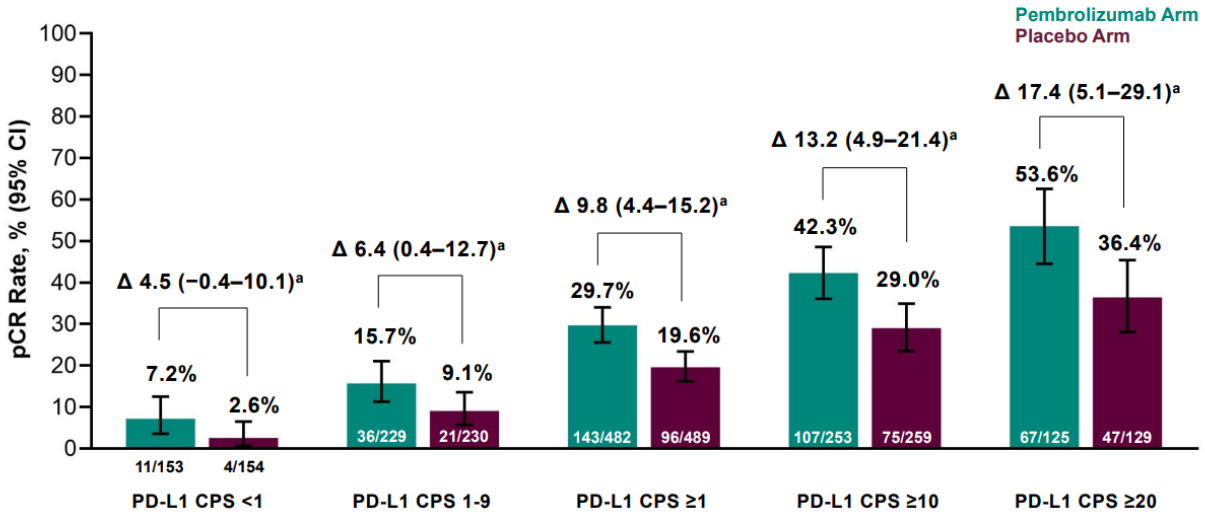


Pathological Complete Response at IA1 by Baseline Clinical Lymph Node Involvement

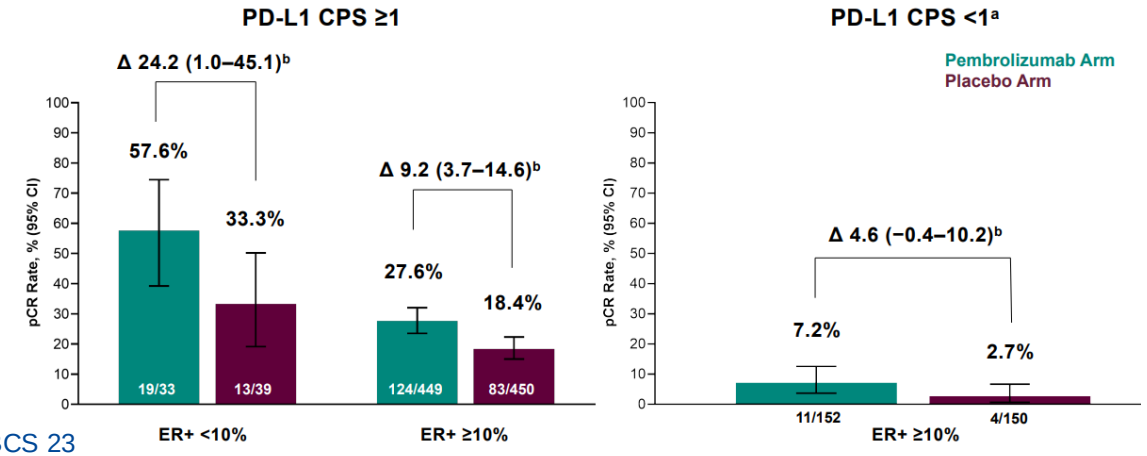


Cardoso et al. GS01-02, SABCS 23
Cardoso F, et al. Ann Oncol. 2023;34(suppl 2):S1260-S1261

Pathological Complete Response at IA1 by PD-L1 Expression Level



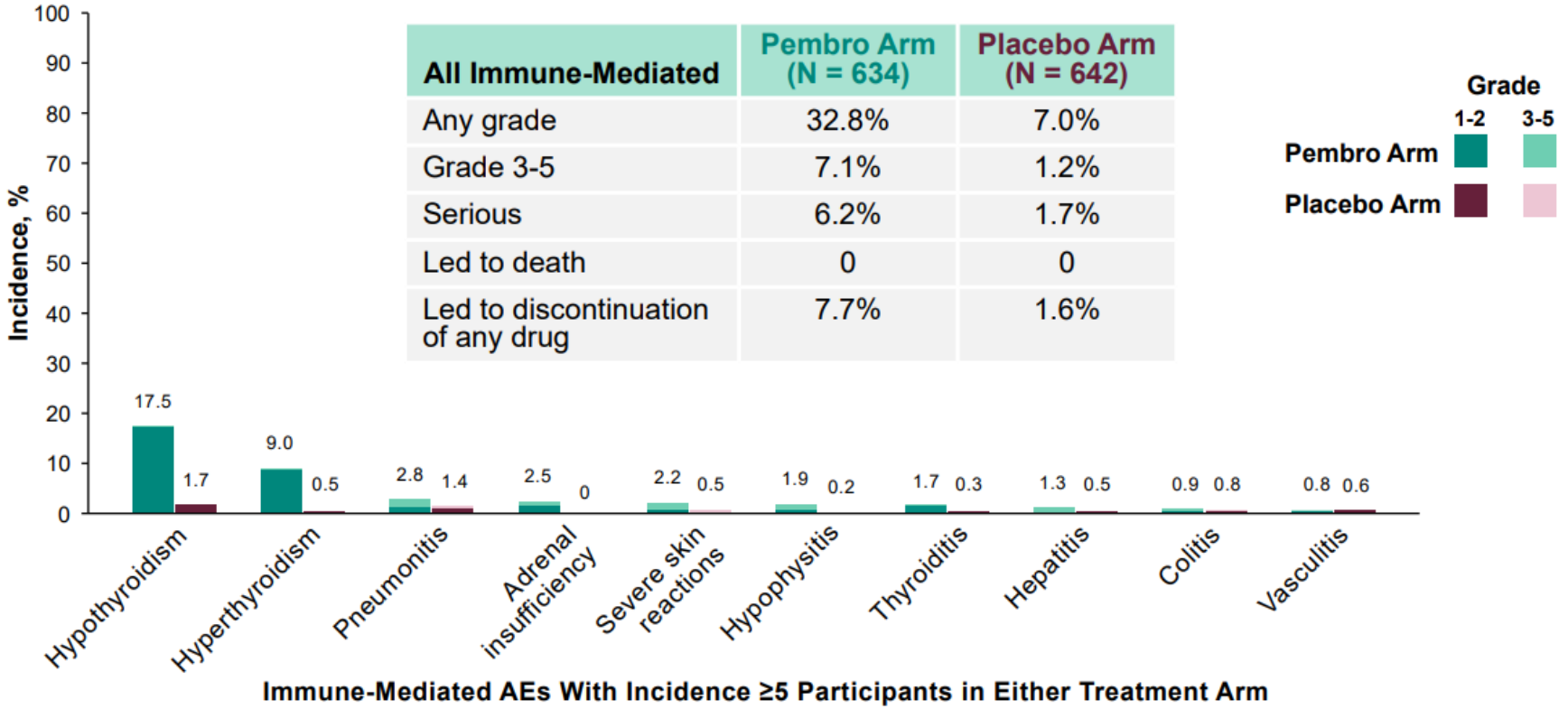
Pathologic Complete Response at IA1 by ER Status and PD-L1 Expression



Cardoso et al. GS01-02, SABCS 23
Cardoso F, et al. Ann Oncol. 2023;34(suppl 2):S1260-S1261

Immune-Mediated AEs in Neoadjuvant Phase

All Immune-Mediated	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	32.8%	7.0%
Grade 3-5	7.1%	1.2%
Serious	6.2%	1.7%
Led to death	0	0
Led to discontinuation of any drug	7.7%	1.6%



Immune-Mediated AEs With Incidence ≥5 Participants in Either Treatment Arm

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Cardoso et al. GS01-02, SABCS 23
Cardoso F, et al. Ann Oncol. 2023;34(suppl 2):S1260-S1261

Conclusions

- Addition of pembrolizumab to neoadjuvant chemotherapy led to a statistically significant increase in pCR in the ITT population regardless of stage, nodal status and levels of PD-L1 expression.
- A larger magnitude of pCR benefit was observed in patients with node-positive disease, higher PD-L1 CPS thresholds, and ER-low tumors (<10%)
- Patients who received less than the planned chemotherapy doses had lower pCR rates, although pCR rates were improved with pembrolizumab regardless of chemotherapy exposure
- Immune-mediated AE rates were consistent with the known toxicity profile of pembrolizumab
- EFS results are immature and continue to be evaluated.

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Neoadjuvant chemotherapy ± Nivolumab: CheckMate 7FL

CA209-7FL study design

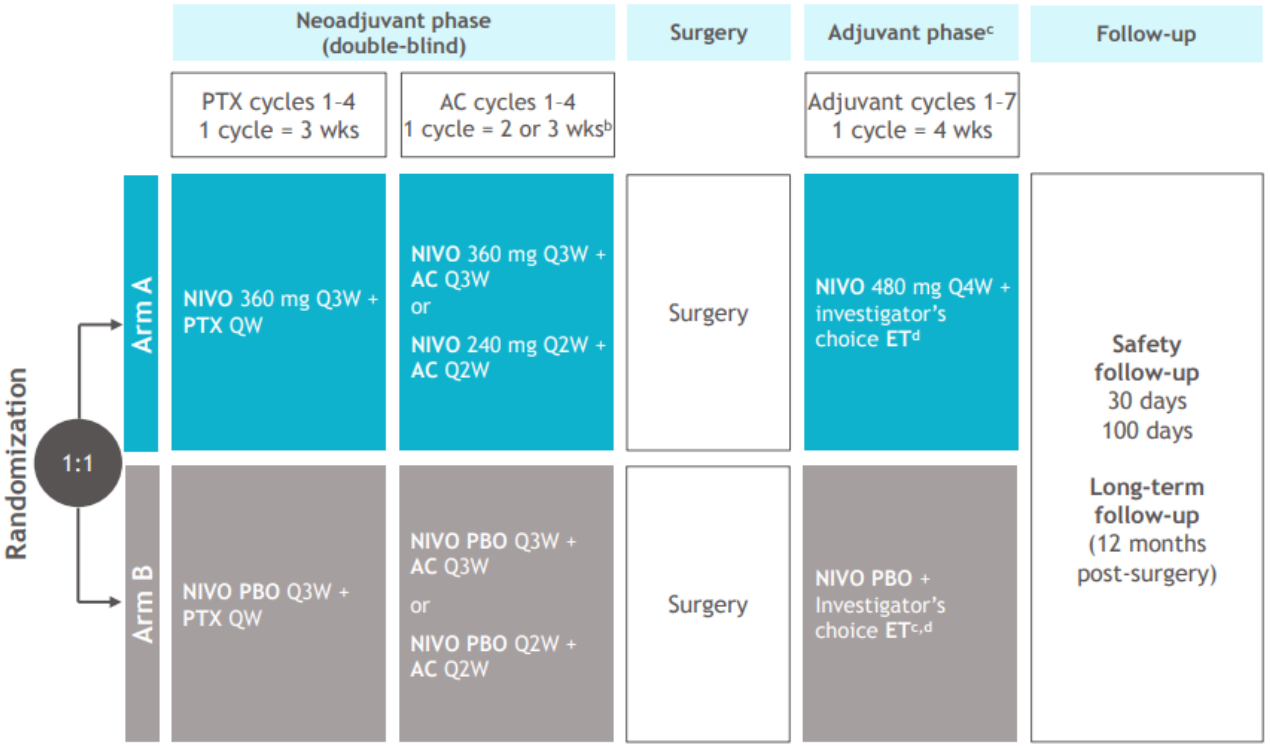
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors

- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



[a]Grade was determined locally by investigator. [b]Investigator's choice: anthracycline dosing frequency of Q2W or Q3W for AC cycles determined by the investigator. [c]After protocol amendment 3, the study was unblinded in the adjuvant phase; participants in arm B did not receive NIVO PBO. [d]Available ET agents included tamoxifen, letrozole, anastrozole, and exemestane.
AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel;

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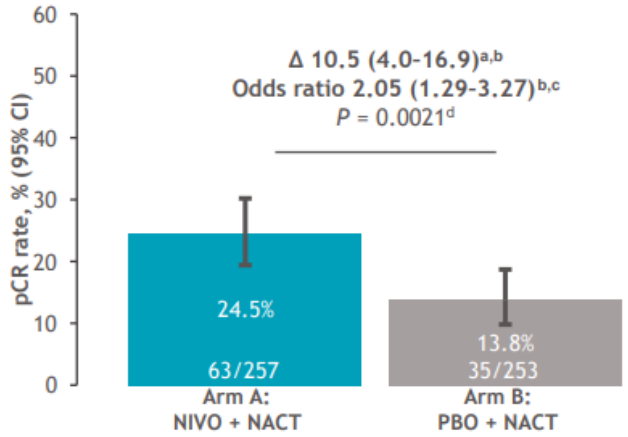
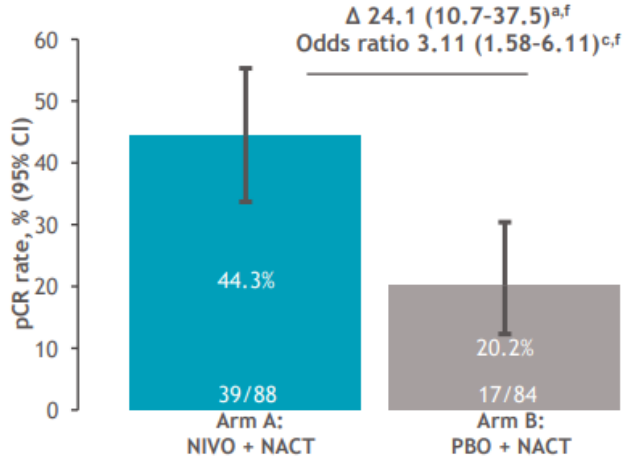
Loi S, et al. Oral presentation at ESMO; October 20–24, 2023; Madrid, Spain. Abstract LBA20.

- The addition of NIVO to NACT resulted in a statistically significant improvement in pCR (the primary endpoint) in the overall population (mITT: n = 510); RCB 0–1 rate was also meaningfully improved[1]
- Benefit of NIVO was greater in the PD-L1+ population (SP142 > 1%)

mITT population (primary endpoint)



PD-L1 IC ≥ 1%e (secondary endpoint)



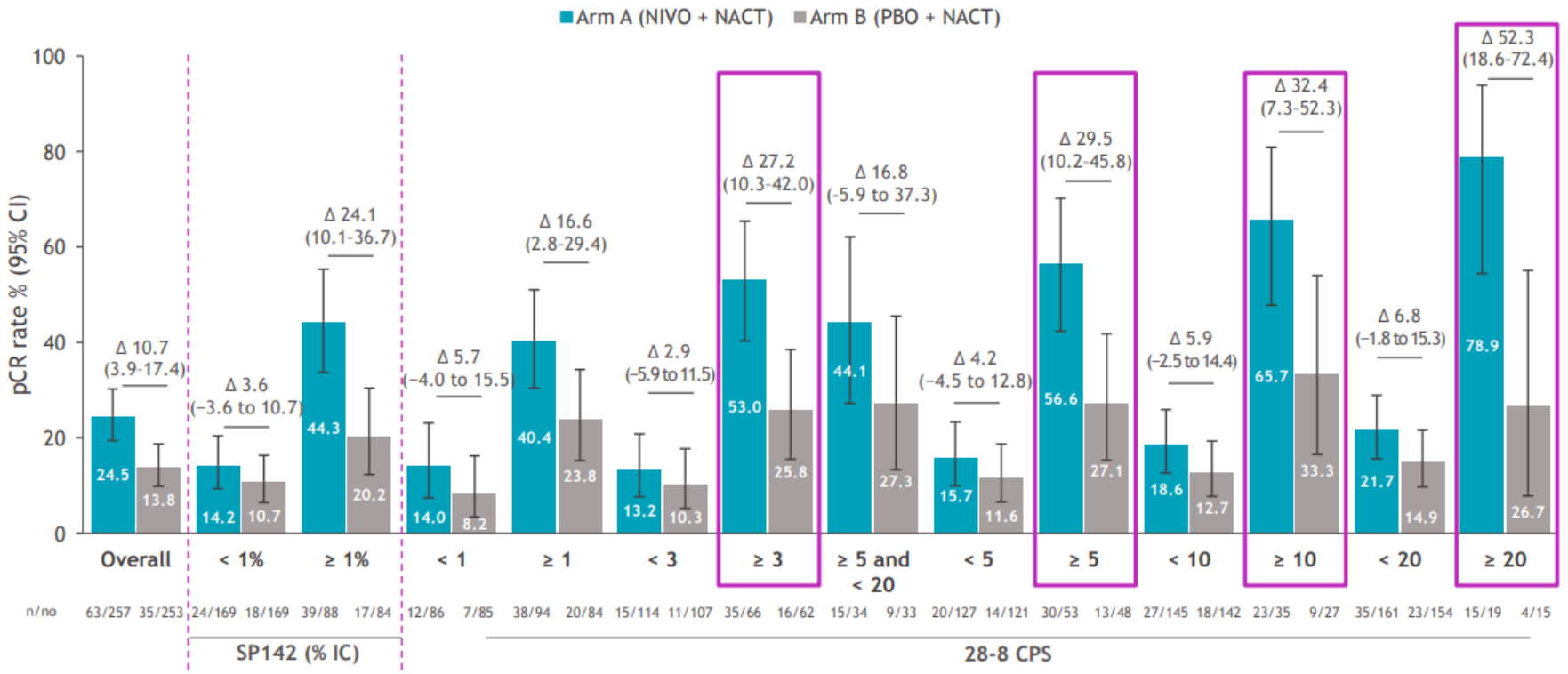
Froedtert & Medical College of Wisconsin

1. Loi S, et al. Oral presentation at ESMO; October 20–24, 2023; Madrid, Spain. Abstract LBA20

Biomarker study: Exploratory analysis of CheckMate 7FL

pCR by PD-L1 status determined by SP142 (IC%) and 28-8 CPS (cutoffs 1-20)

CheckMate 7FL
San Antonio Breast Cancer Symposium®, December 5-9, 2023



- PD-L1 CPS ≥ 3 was determined as the optimal cut-off for the prediction of NIVO benefit based on the ROC and lift plot analyses
- The benefit of NIVO was increased in patients with PD-L1+ tumors defined by both SP142 IC (≥ 1%) and 28-8 CPS (≥ 1); the benefit was greater with the increased CPS score

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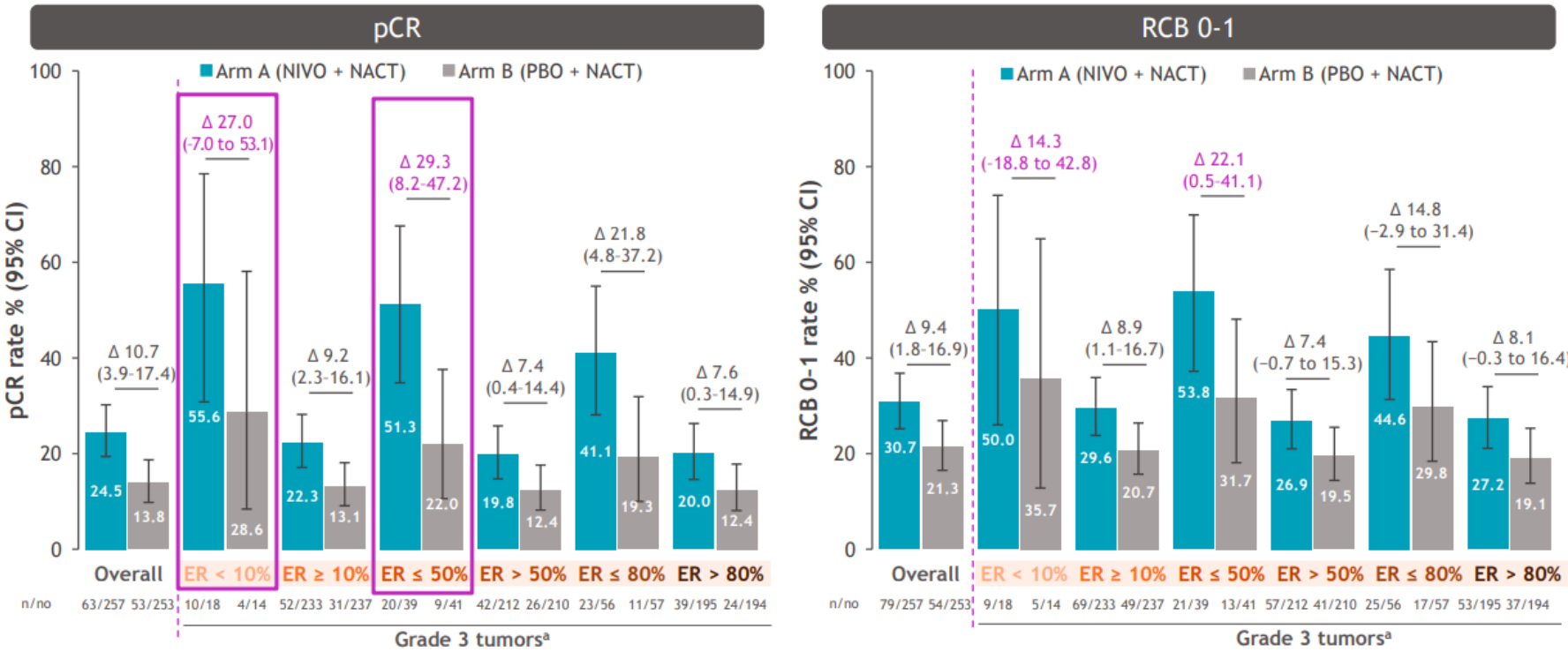
Loi et al. GS01-01, SABCS 23

pCR and RCB 0-1 by tumor ER expression



- ER > 50%, ER > 80% and PR ≥ 10% were exploratory cutoffs
- NIVO benefit on pCR and RCB 0-1 rates was the highest in patients with tumors with low ER (≤ 50%)

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Loi et al. GS01-01, SABCS 23

Conclusions

- CheckMate 7FL met its primary endpoint showing a statistically significant improvement in pCR with NIVO added to NACT in the ITT population.
- Higher magnitude of benefit was observed in patients with PD-L1+ tumors defined by SP142 IC (≥ 1%)
- NIVO benefit on pCR and RCB 0–1 rates was the highest in patients with tumors with higher CPS, sTIL ≥ 5%, low ER (≤ 50%) and/or PR expression (≤ 10% in ER ≥ 10%)
    - Increased pCR was seen with any sTIL (>1%)
    - High pCR rates were observed in patients with CPS ≥10, 20
- No association between NIVO benefit and Ki67 was observed
- Moderate (~70-80%) overlap between the SP142 IC (≥ 1%), 28-8 CPS assays and sTIL was observed
- Additional exploratory and correlative analyses are ongoing to further refine the patient subpopulation with primary ER+/HER2− breast cancer who could benefit from the addition of NIVO to NACT

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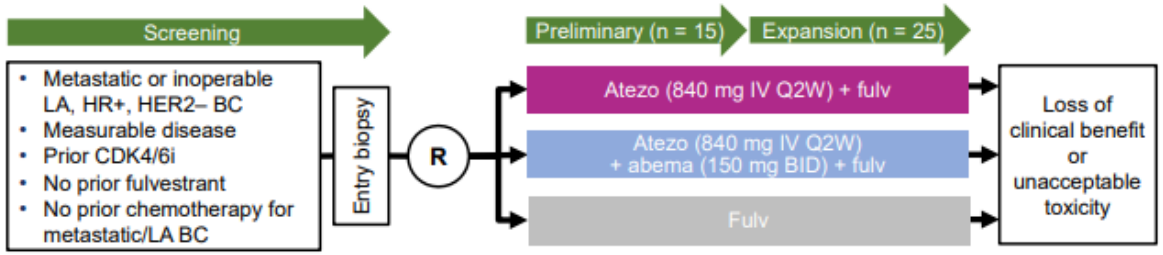
MORPHEUS hormone receptor-positive breast cancer: interim analysis of a Phase Ib/II study of fulvestrant ± atezolizumab and abemaciclib triplet treatment in patients with metastatic disease

MORPHEUS HR+ BC: atezolizumab (atezo) + fulvestrant (fulv) ± abemaciclib (abema) vs. fulv: 24-week interim analyses



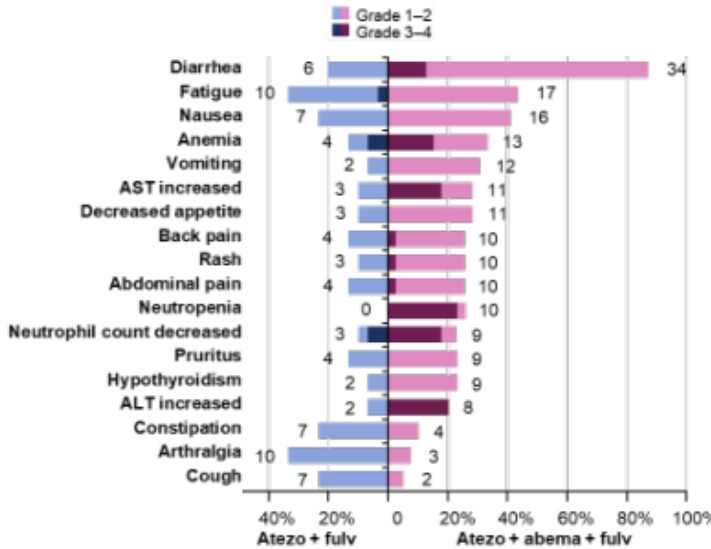
Primary endpoints
- ORR (RECIST v1.1), safety

Secondary efficacy endpoints
- PFS, CBR, OS, DOR

Safety summary*,†

Patients, n (%)	Fulv (n = 20)	Atezo + fulv (n = 30)	Atezo + abema + fulv (n = 39)
Any-grade TRAEs	7 (35.0)	23 (76.7)	38 (97.4)
Grade 3–4 AEs	3 (15.0)	8 (26.7)	32 (82.1)
AEs leading to treatment discontinuation	0	2 (6.7) atezo: 2 (6.7), fulv: 2 (6.7)	8 (20.5) atezo: 7 (17.9), abema: 2 (5.1), fulv: 2 (5.1)
AEs leading to dose modification/interruption	1 (5.0)	5 (16.7)	35 (89.7)
Most common TRAEs with ≥20% incidence rate	0	Fatigue, 8 (26.7), arthralgia, 6 (20.0)	Diarrhea, 34 (87.2), fatigue, 17 (43.6), nausea, 13 (33.3), anemia, 11 (28.2), vomiting, 10 (25.6), neutropenia, 10 (25.6), hypothyroidism, 9 (23.1), AST increased, 8 (20.5), neutrophil count decreased, 8 (20.5), rash, 8 (20.5)

AEs by highest grade in the atezo + fulv and atezo + abema + fulv arms‡



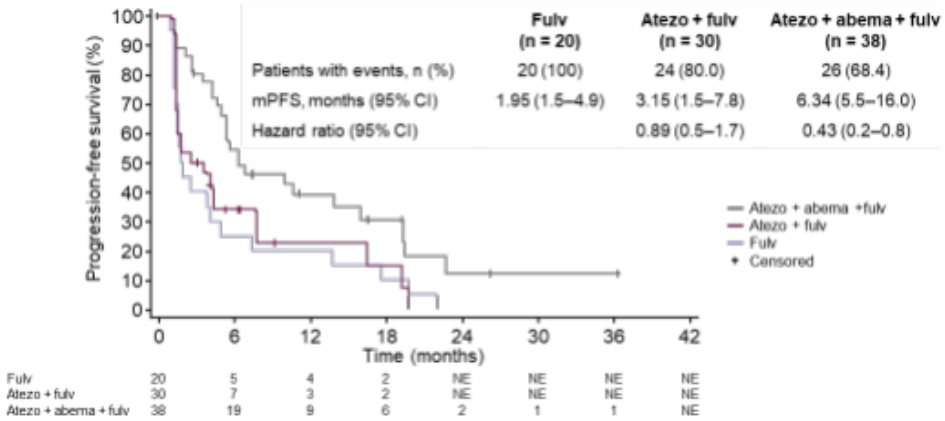
Atezo + abema + fulv arm key safety results:
- Mild/moderate (grade 1–2) ILD/pneumonitis: 7.7%
- No unexpected safety signals identified

- The triplet therapy of atezo + abema + fulv showed improved ORR and mPFS compared with fulv monotherapy in the post-CDK4/6i, post-ET second- or third-line metastatic setting.
- No unexpected safety signals, including no high-grade ILD/pneumonitis.

Best overall response per RECIST v1.1

Patients	Fulv (n = 20)	Atezo + fulv (n = 30)	Atezo + abema + fulv (n = 38)
Responders (OR), n (%) (95% CI)	**2 (10.0)** (1.2–31.7)	**3 (10.0)** (2.1–26.5)	**10 (26.3)** (13.4–43.1)
CBR, n (%) (95% CI)	**3 (15.0)** 3.2–37.9	**7 (23.3)** 9.9–42.3	**16 (42.1)** 26.3–59.2

Progression-free survival



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Therapeutic developmental pathways in ER+ Breast Cancer

- CDK 4/6i
- SERDs
- AKT/PIK3i
- ICIs
- **ADCs- TropionBreast-01**

  DESTINY-Breast08

TROPION-Breast01 Study Design

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

Randomization stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

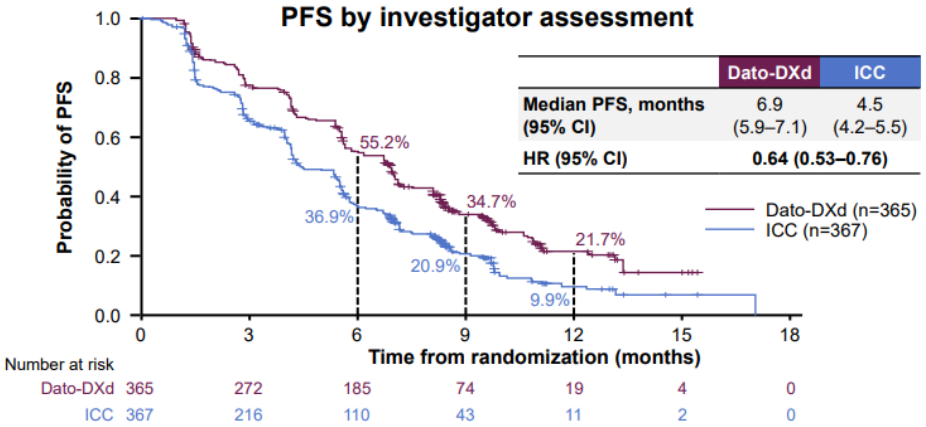
- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Dato-DXd is a TROP2-directed ADC, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells.

Froedtert & Medical College of Wisconsin

Bardia A, et al. Future Oncol 2023; doi: 10.2217/fon-2023-0188
Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

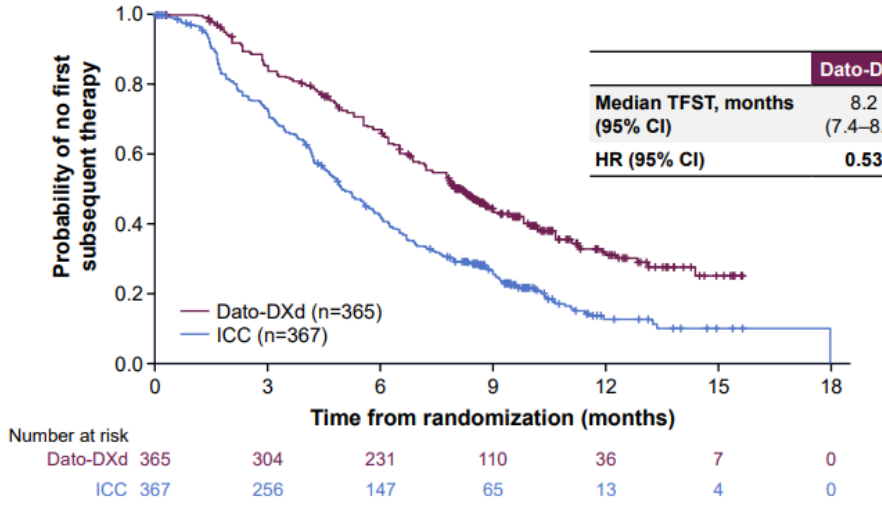
Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Time to First Subsequent Therapy



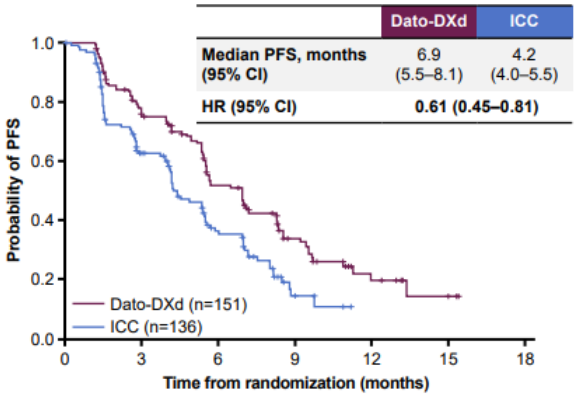
	Dato-DXd	ICC
Median TFST, months (95% CI)	8.2 (7.4–8.9)	5.0 (4.6–5.7)
HR (95% CI)	0.53 (0.45–0.64)	

Bardia A, et al. Future Oncol 2023; doi: 10.2217/fon-2023-0188
Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11

PFS by BICR in Subgroups

Prior CDK4/6 Inhibitor

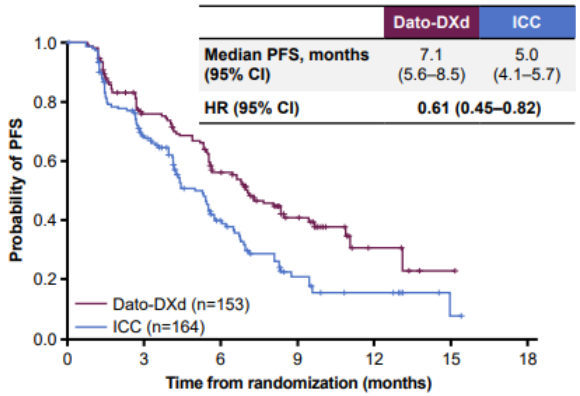
Prior duration of CDK4/6 inhibitor: ≤12 months



No. at risk

Dato-DXd	151	106	63	26	8	2	0
ICC	136	74	35	7	0	0	0

Prior duration of CDK4/6 inhibitor: >12 months



No. at risk

Dato-DXd	153	102	70	28	6	1	0
ICC	164	90	40	13	7	1	0

Overall Safety Summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

- Most common TRAEs leading to dose interruption:
  - Dato-DXd: fatigue*, infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia† (17%), leukopenia‡ (3%)
- No TRAEs led to discontinuation in ≥1% of patients in either arm
- One treatment-related death in the ICC arm due to febrile neutropenia

Bardia A, et al. Future Oncol 2023; doi: 10.2217/fon-2023-0188
Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Conclusions

- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with ICC.
- Median PFS improvement observed regardless of prior duration of CDK4/6 inhibitor or brain metastases.
- Time to first subsequent therapy was longer with Dato-DXd compared with ICC.
- Overall, Dato-DXd demonstrated a favorable safety profile compared with ICC.

Overall, results support Dato-DXd as a potential new therapeutic option for patients with endocrine-resistant metastatic HR+/HER2– breast cancer

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DESTINY-Breast08

Investigating T-DXd in combination with endocrine therapies in patients with HER2-low HR+ advanced/mBC

DESTINY-Breast08: A Phase 1b, multicenter, open-label, two-part, modular study (NCT04556773)

Population for T-DXd-ET combination arms

- Locally assessed HER2-low (IHC 1+, IHC 2+/ISH−) HR+ advanced/mBC
- ≤1 prior treatment line of ET ± a targeted therapy (such as CDK4/6, mTOR, or PI3K inhibitors) for mBC allowed
- No prior chemotherapy in the metastatic setting allowed
- At least one measurable lesion per RECIST 1.1
- ECOG PS 0–1

Allocation

HR+/HR−
T-DXd + capecitabine, n=20

HR−
T-DXd + capivasertib, n=40

HR+
T-DXd + ANA, n=21
(T-DXd 5.4 mg/kg IV Q3W + anastrozole 1 mg daily*)

HR+
T-DXd + FUL, n=20
(T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg IM Q4W, with a 500 mg loading dose on Cycle 1, Day 15*)

Endpoints for the dose-expansion phase

- **Primary:** Safety and tolerability, including AEs, AESIs, and SAEs
- **Secondary:** ORR, PFS, DOR (all evaluated by investigator per RECIST 1.1), and OS

Part 1 dose-finding and Part 2 dose-expansion; results reported here are from the dose-expansion phase

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- Safety profiles for T-DXd + ET combinations were generally consistent or comparable to the known safety profile of both agents.
- T-DXd in combination with anastrozole or fulvestrant was active in chemotherapy-naïve patients with HER2-low HR+ mBC, demonstrating encouraging antitumor activity.
- Small datasets limit the interpretation of the efficacy results; further research to evaluate T-DXd in combination with endocrine therapies is warranted.

Efficacy overview

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	**71.4 (47.8, 88.7)**	**40.0 (19.1, 64.0)**
Unconfirmed ORR, % (95% CI)	**76.2 (52.8, 91.8)**	**50.0 (27.2, 72.8)**
Median DOR, months (95% CI)*	**9.8 (6.7, NE)**	**NE (4.1, NE)**
Total PFS events, n (%)	**14 (66.7)**	**7 (35.0)**
Median PFS, months (95% CI)*	**13.4 (8.5, 19.4)**	**NE (5.6, NE)**
PFS rate at 6 months, % (95% CI)	80.7 (56.3, 92.3)	75.3 (46.4, 90.0)
PFS rate at 12 months, % (95% CI)	50.4 (27.5, 69.5)	52.7 (25.0, 74.4)

- **Efficacy results need to be interpreted with caution owing to the small datasets**
  - **Of note, 15% of patients in the T-DXd + FUL arm withdrew consent and discontinued study treatment before disease progression**

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Jhaveri et al. RF02-03, SABCS 23

Big picture goals!

- Treatment landscape for ER+ BC has drastically changed in the last decade with significant improvement in patient outcomes.
- Clinical trials , pathway identification and drug discovery is crucial to this growth.
- Clinical trial accruals and being actively involved in clinical and translational research is the future of breast academia.
- Thank you to the patients for participating!

Thank you

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