Applications for Community Oncology

SABCS Review

January 26, 2023

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2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2

- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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KEY QUESTION

CDK4/6 inhibitors

Are all CDK4/6 inhibitors the same?

Which CDK4/6 inhibitor and when?

What to do after progression on CDK4/6 inhibition and ET?

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CLINICAL QUESTION

monarchE Clinical Trial

Will abemaciclib plus endocrine therapy benefit pts with HR+/HER2-, node-positive, high-risk early BC?

OS interim analysis

On October 12, 2021, the FDA approved abemaciclib (brand name Verzenio) with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score of 20% or higher, as determined by an FDA approved test. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

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KEY DATA

monarchE Clinical Trial

Study Design: international, randomized, open-label Phase 3 trial

- Women or men with high-risk, node-positive, HR+/HER2- EBC
- Prior (neo)adjuvant CT permitted
- Pre- or postmenopausal
- No distant metastasis
- ≤16 mo from surgery to randomization
- ≤12 wk of ET after last non-ET

(N = 5637)

Stratified by prior CT, menopausal status, region

Cohort 1 (91% of patients)
High risk based on clinical pathological features:
≥4 positive ALNs *or* 1-3 positive ALNs plus histologic grade 3 and/or tumor ≥5 cm

Cohort 2 (9% of patients)
High risk based on Ki-67:
1-3 positive ALNs, Ki-67 ≥20% per central testing, grade 1-2, tumor size <5 cm

Abemaciclib 150 mg BID up to 2 yr + ET per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2808)

On-study treatment period 2 years

ET per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2829)

Follow-up period: ET 3-8 years as clinically indicated

Primary endpoint: iDFS

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

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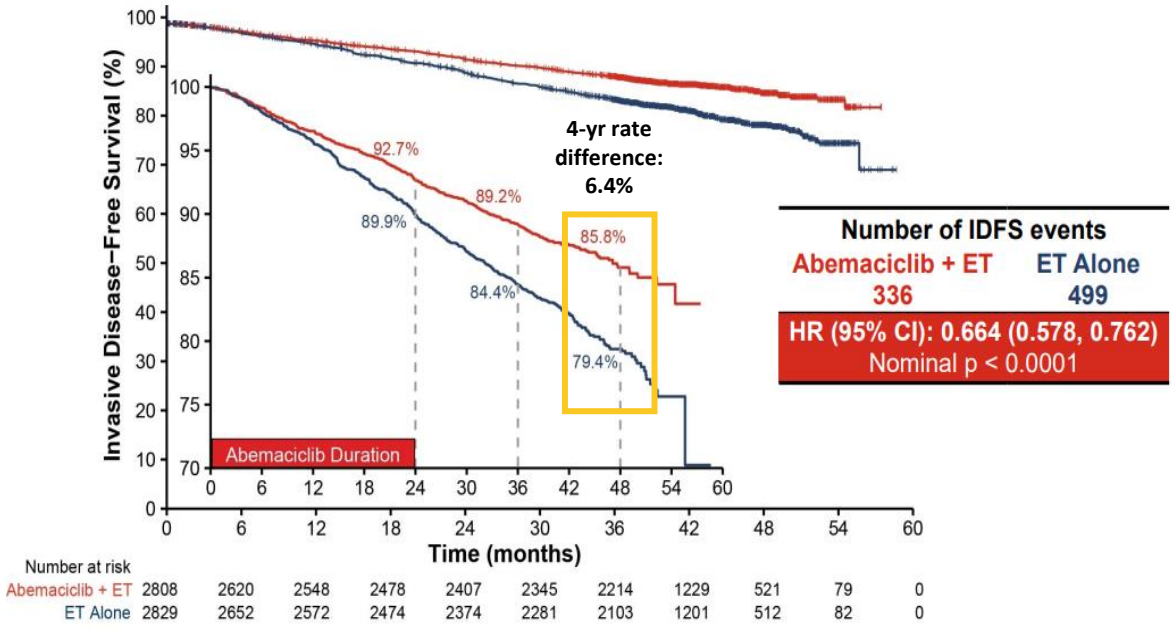
KEY DATA

monarchE Clinical Trial

IDFS in ITT Population

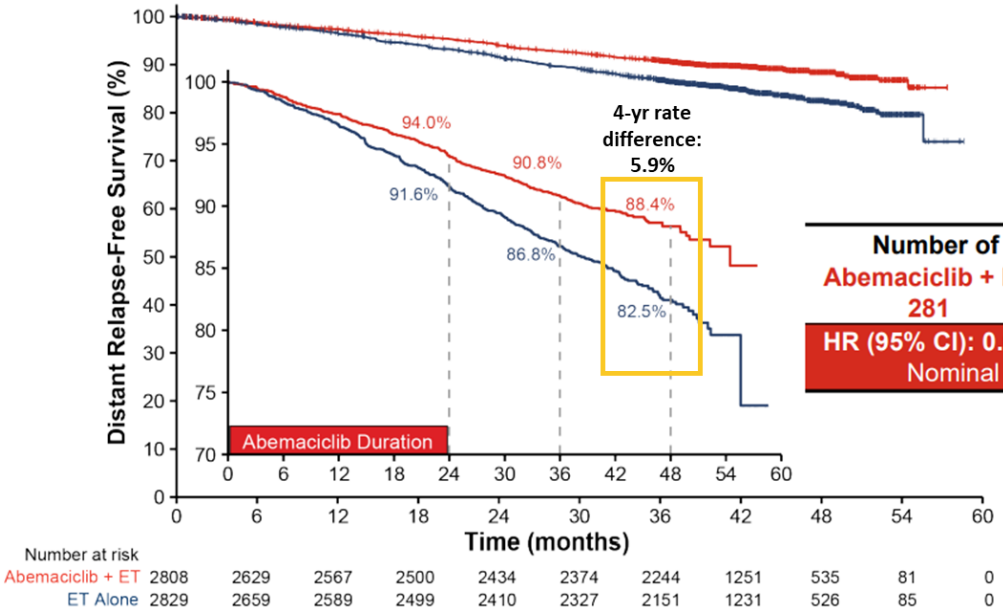


Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

DRFS in ITT Population



Number of DRFS events

Abemaciclib + ET	ET Alone
281	421

HR (95% CI): 0.659 (0.567, 0.767)
Nominal p < 0.0001

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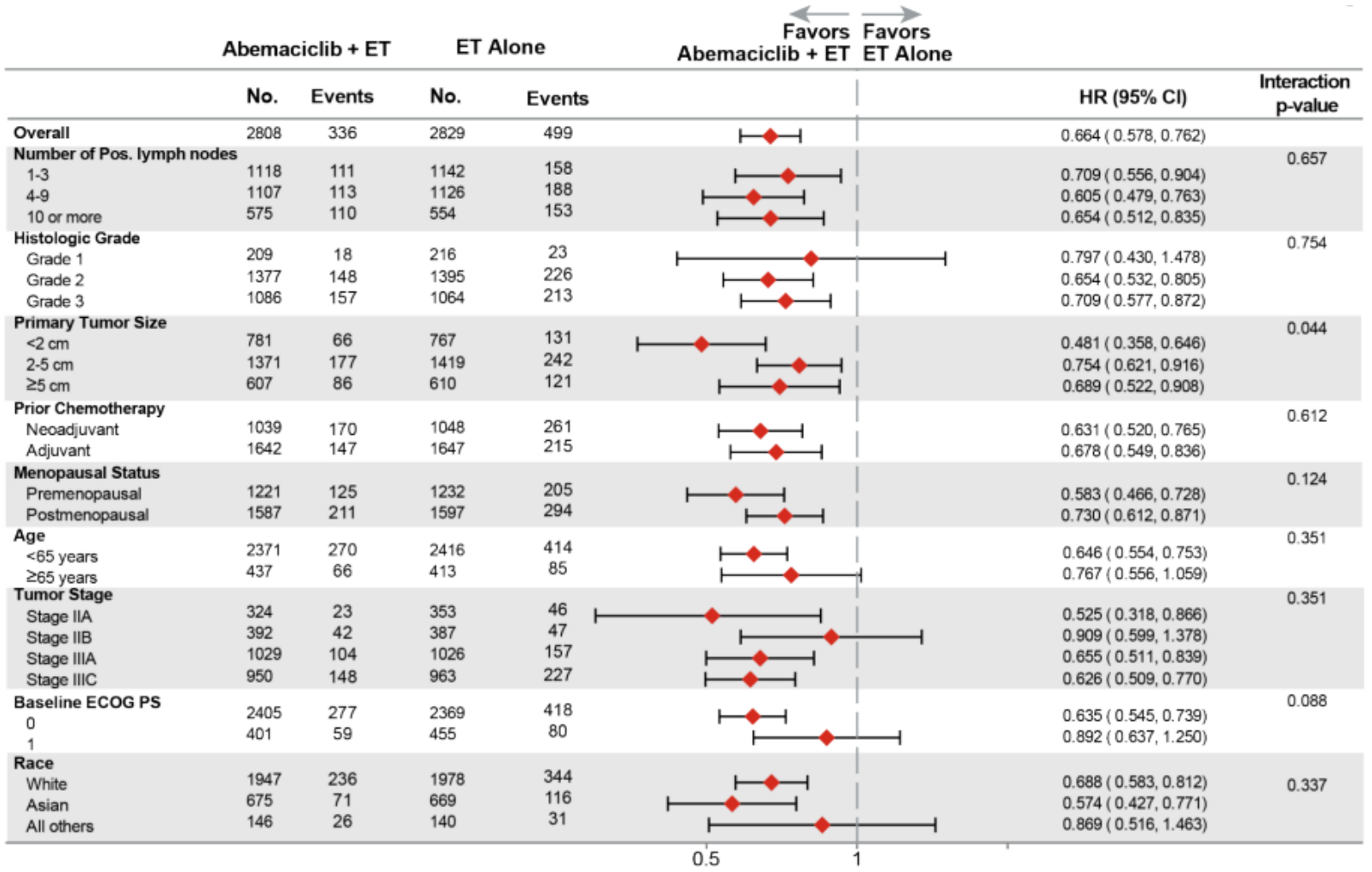
monarchE Clinical Trial

IDFS in Prespecified Subgroups



	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction p-value
	No.	Events	No.	Events		
Overall	2808	336	2829	499	0.664 (0.578, 0.762)	
Number of Pos. lymph nodes						0.657
1-3	1118	111	1142	158	0.709 (0.556, 0.904)	
4-9	1107	113	1126	188	0.605 (0.479, 0.763)	
10 or more	575	110	554	153	0.654 (0.512, 0.835)	
Histologic Grade						0.754
Grade 1	209	18	216	23	0.797 (0.430, 1.478)	
Grade 2	1377	148	1395	226	0.654 (0.532, 0.805)	
Grade 3	1086	157	1064	213	0.709 (0.577, 0.872)	
Primary Tumor Size						0.044
<2 cm	781	66	767	131	0.481 (0.358, 0.646)	
2-5 cm	1371	177	1419	242	0.754 (0.621, 0.916)	
≥5 cm	607	86	610	121	0.689 (0.522, 0.908)	
Prior Chemotherapy						0.612
Neoadjuvant	1039	170	1048	261	0.631 (0.520, 0.765)	
Adjuvant	1642	147	1647	215	0.678 (0.549, 0.836)	
Menopausal Status						0.124
Premenopausal	1221	125	1232	205	0.583 (0.466, 0.728)	
Postmenopausal	1587	211	1597	294	0.730 (0.612, 0.871)	
Age						0.351
<65 years	2371	270	2416	414	0.646 (0.554, 0.753)	
≥65 years	437	66	413	85	0.767 (0.556, 1.059)	
Tumor Stage						0.351
Stage IIA	324	23	353	46	0.525 (0.318, 0.866)	
Stage IIB	392	42	387	47	0.909 (0.599, 1.378)	
Stage IIIA	1029	104	1026	157	0.655 (0.511, 0.839)	
Stage IIIC	950	148	963	227	0.626 (0.509, 0.770)	
Baseline ECOG PS						0.088
0	2405	277	2369	418	0.635 (0.545, 0.739)	
1	401	59	455	80	0.892 (0.637, 1.250)	
Race						
White	1947	236	1978	344	0.688 (0.583, 0.812)	0.337
Asian	675	71	669	116	0.574 (0.427, 0.771)	
All others	146	26	140	31	0.869 (0.516, 1.463)	

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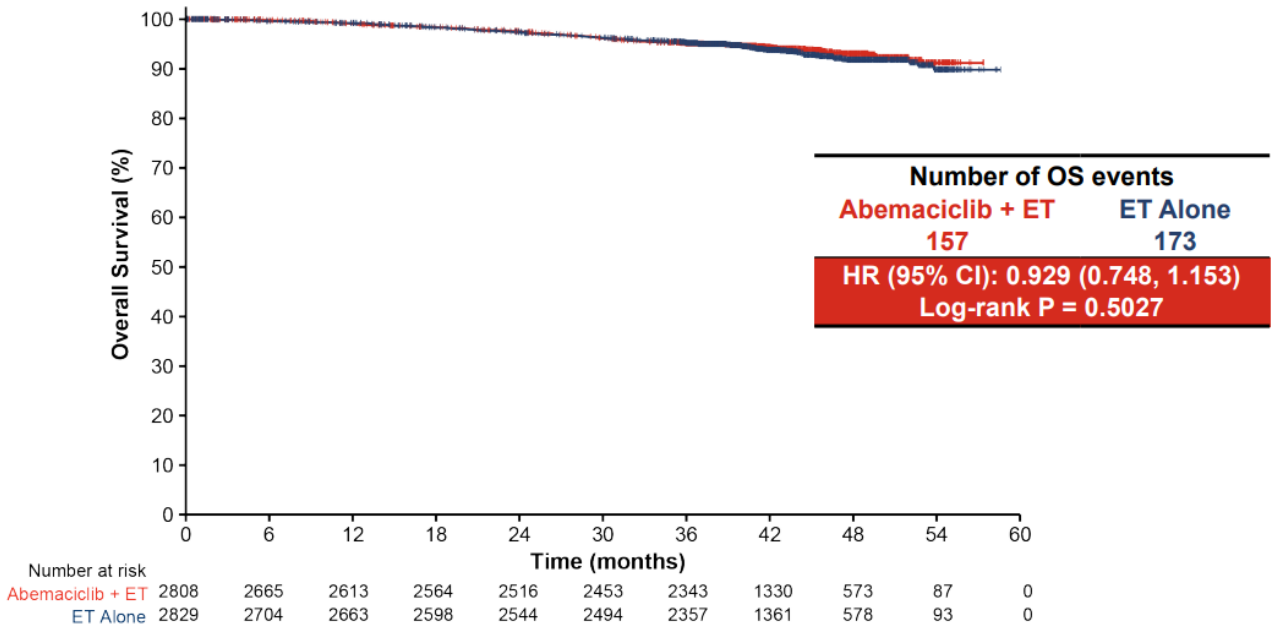
KEY DATA

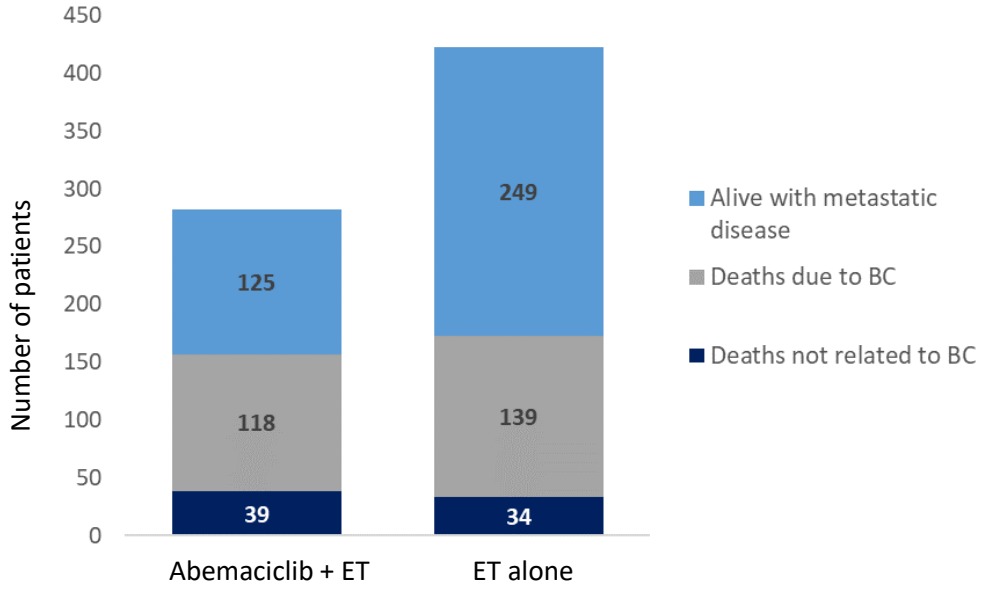
monarchE Clinical Trial

OS in ITT Population



Note: OS data immature at 42 month follow-up

Fewer Patients with Metastatic Disease in the Abemaciclib arm



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monarchE Clinical Trial

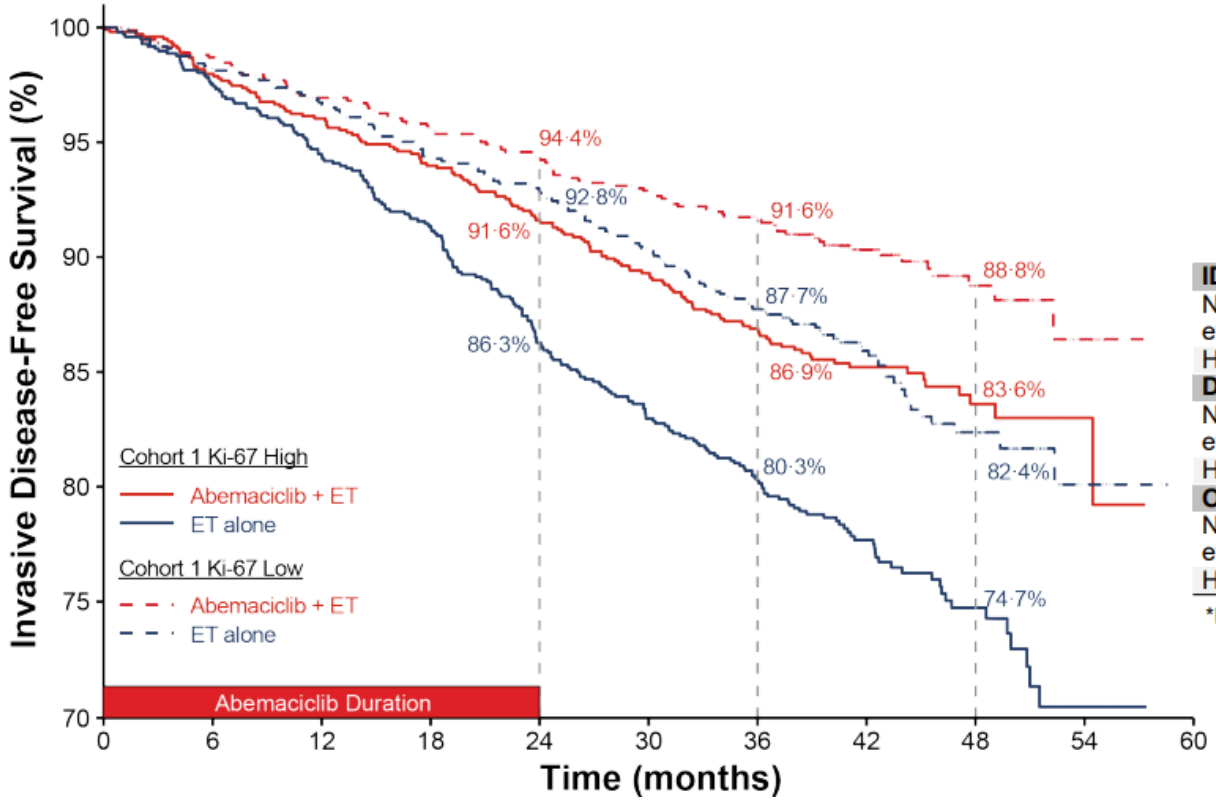
Efficacy Outcomes by Cohort

Outcome	Cohort 1 (91% of patients) High risk based on clinical pathological features		Cohort 2* (9% of patients) High risk based on Ki-67	
	Abemaciclib + ET (n = 2555)	ET alone (n = 2565)	Abemaciclib + ET (n = 253)	ET alone (n = 264)
iDFS events, n	317	474	19	25
HR (95% CI) P value	**0.653** (0.567-0.753) <0.0001		**0.773** (0.420-1.420) 0.4048	
4 yr iDFS rate, % (95% CI)	85.5 (83.8-87.0)	78.6 (76.7-80.4)	NR	NR
DRFS events, n	267	402	14	19
HR (95% CI) P value	**0.652** (0.558-0.761) <0.0001		**0.764** (0.383-1.526) 0.4448	
4 yr DRFS rate, % (95% CI)	87.9 (86.4-89.3)	81.8 (79.9-83.4)	NR	NR
OS events, n	147	168	10	5
HR (95% CI)	**0.890** (0.714-1.111)		NR	

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

monarchE Clinical Trial

Outcomes by Ki-67 Status



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

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

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

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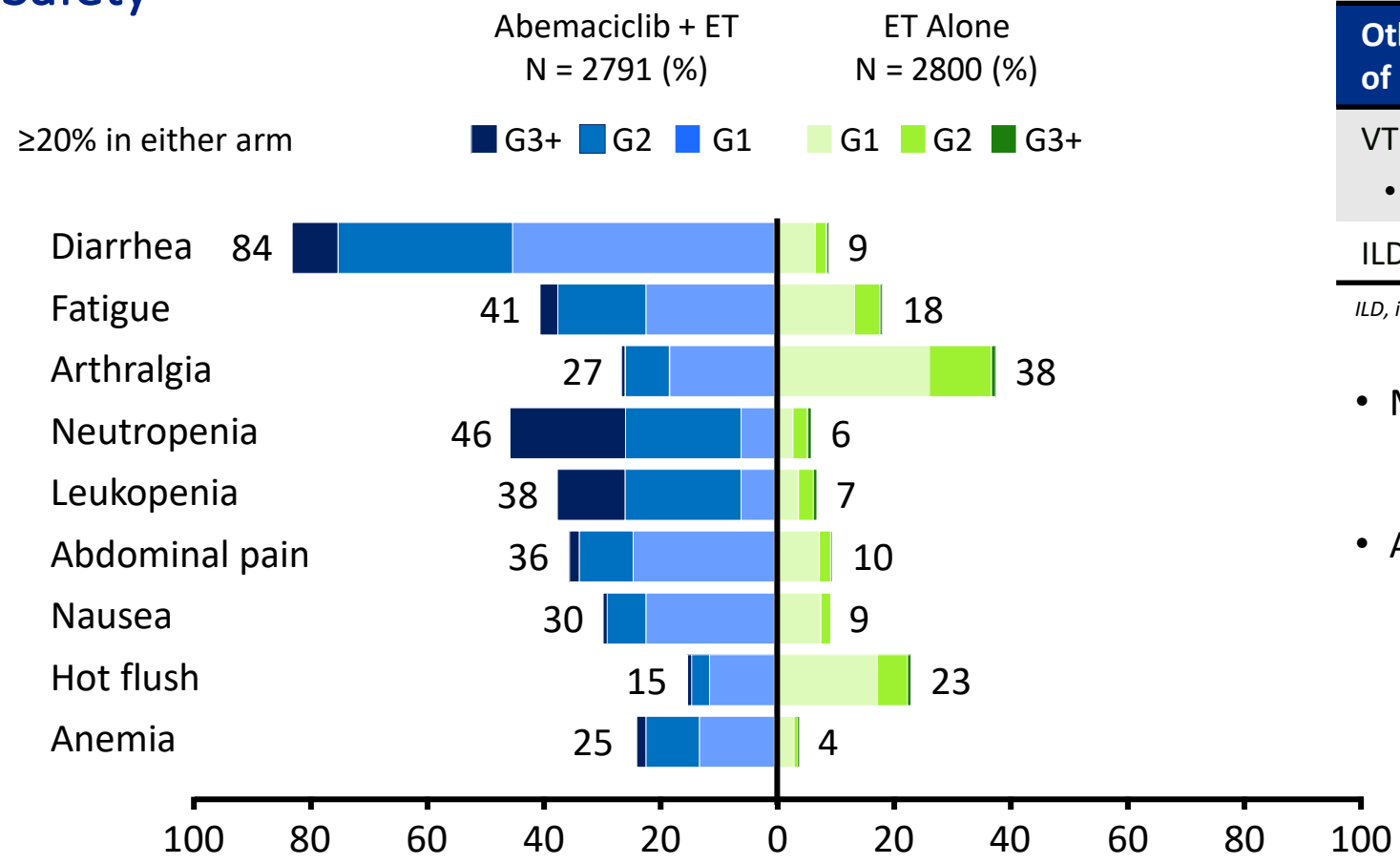
monarchE Clinical Trial

Safety



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

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

ILD, interstitial lung disease; PE, pleural effusion; VTE, venous thromboembolism

- Median duration of abemaciclib: 23.7 mo
- Abemaciclib dose adjustments due to AE:
  - Dose holds: 61.7%
  - Dose reductions: 43.6%
  - Discontinuations: 18.5% (8.9% after dose reduction)

SUMMARY

monarchE Clinical Trial

- Adjuvant abemaciclib plus ET provides persistent greater benefit over time after completion of treatment
  - Increase in absolute IDFS and DRFS greater at 4 years compared to 2- and 3- years
  - Benefit maintained across all prespecified subgroups for IDFS and DRFS
- OS data remain immature, but fewer deaths were observed with abemaciclib plus ET group compared to ET alone
- Ki-67 remains prognostic but not predictive; similar abemaciclib benefit observed *regardless* of Ki-67 index
- No new safety signals at 4 years

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monarchE Clinical Trial

Abemaciclib plus endocrine therapy in the adjuvant setting continues to provide benefit beyond completion of treatment for patients with high-risk, node-positive HR+/HER2- early breast cancer and should be considered standard of care

The National Comprehensive Cancer Network and American Society of Clinical Oncology guideline recommendations are independent of Ki-67 score compared to the FDA approval

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CLINICAL QUESTION

RIGHT Choice Clinical Trial

Will ribociclib plus endocrine therapy benefit pts with HR+/HER2- aggressive advanced BC?

Ribociclib (RIB) + endocrine therapy (ET) demonstrated statistically significant PFS and OS benefits over ET alone in 3 Phase III clinical trials (MONALEESA-2, -3, and -7) in patients with HR+/HER2− ABC, including patients with visceral metastases and a high tumor burden

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KEY DATA

RIGHT Choice Clinical Trial

Study Design: Multi-national, randomized, open-label Phase 2 trial

- Pre/perimenopausal women
- HR+/HER2- advanced breast cancer (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease*
- ECOG PS ≤2
- Total bilirubin ≤1.5 ULN

(N = 222)**

*Aggressive disease includes symptomatic visceral metastases, rapid disease progression or impending visceral compromise, or markedly symptomatic nonvisceral disease.

**Patients were enrolled from Feb 2019 to Nov 2021

Stratified by prior CT, menopausal status, region

Ribociclib
600 mg QD PO, 3 wk on/1 wk off
+ ET (letrozole *or* anastrozole + goserelin)

Investigators' Choice of Combination CT
Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W

Primary endpoint: PFS (locally assessed per RECIST 1.1)

Key secondary endpoints: TTF, 3-mo TFR, ORR, CBR, TTR, OS, safety, QoL

Exploratory endpoints: Biomarker analyses, healthcare resource utilization

OS data were immature at data cutoff (12 April 2022)

RIGHT Choice Clinical Trial

Baseline Characteristics

	Ribociclib +ET n=112	Combo CT n=110
Median age, yr (range)	44	43
≥40 years	80 (71.4)	72 (65.5)
Race*		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

*One patient (0.9%) in the RIB arm was African American

	Ribociclib +ET n=112	Combo CT n=110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites**		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid Progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis***	61 (54.5)	55 (50.0)

**The same patient may have multiple visceral metastatic sites.

***Based on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

KEY DATA

RIGHT Choice Clinical Trial

Treatment Status

	Ribociclib +ET n=112	Combo CT n=110*	All Patients N=222
Patients treated			
Treatment ongoing**	51 (45.5)	26 (23.6)	77 (34.7)
Reason for end of treatment* **			
Progressive disease	50 (44.6)	58 (52.7)	108 (48.6)
Adverse event	8 (7.1)	2 (2.7)	11 (5.0)
Death	1 (0.9)	0	1 (0.5)
Physician decision	1(0.9)	5 (4.5)	6 (2.7)
Patient decision	1 (0.9)	8 (7.3)	9 (4.1)

* Ten patients in CT arm did not receive any treatment

** Patients continued study treatment at the time of the cutoff (12 April 2022)

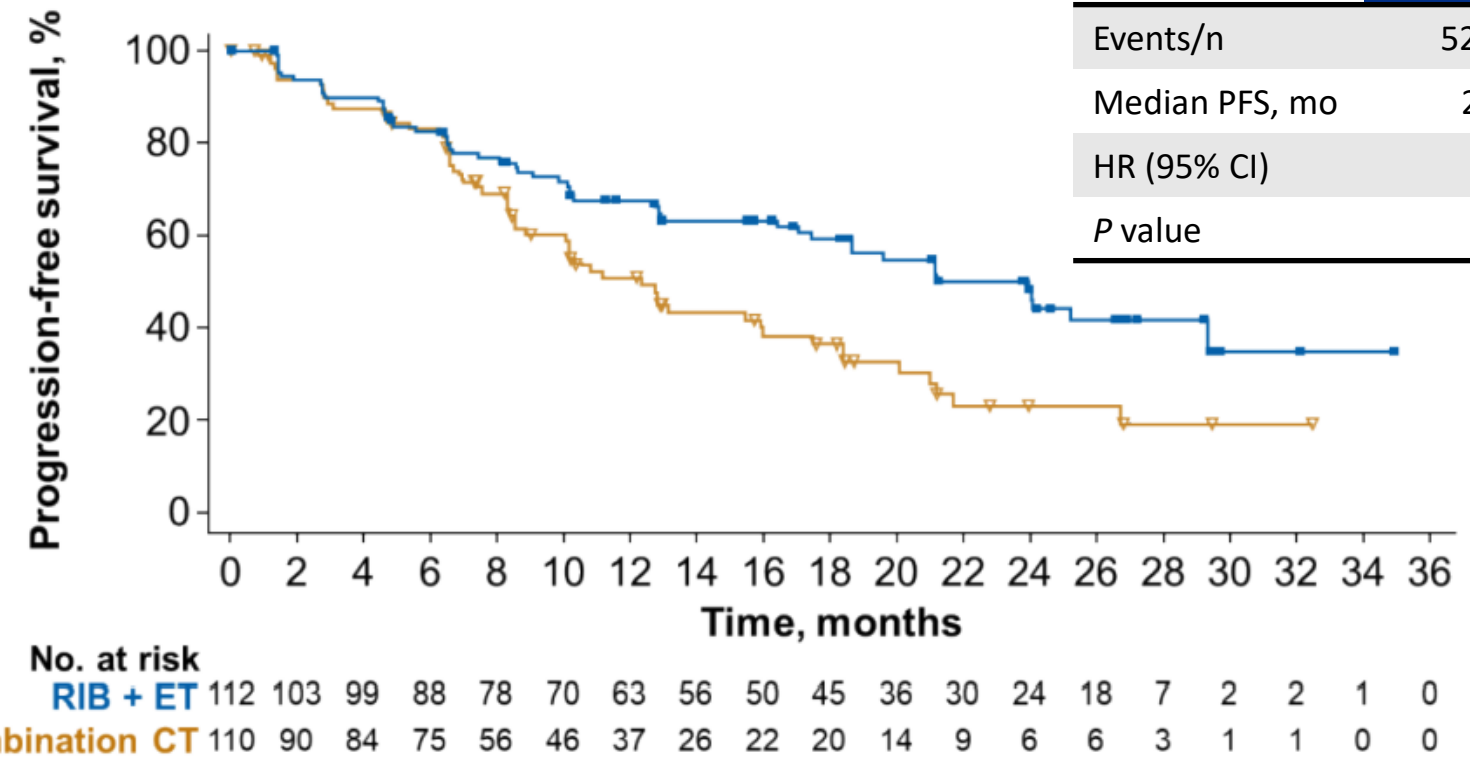
*** In patients who received study treatment (RIB + ET, n = 112; combination CT, n = 100)

Median duration of follow-up was 24.1 months (data cutoff: 12 April 2022)

KEY DATA

RIGHT Choice Clinical Trial

Primary endpoint: PFS



	RIB + ET	Combo CT
Events/n	52/112	58/110
Median PFS, mo	24.0	12.3
HR (95% CI)	**0.54** (0.36-0.70)	
P value	**0.0007**	

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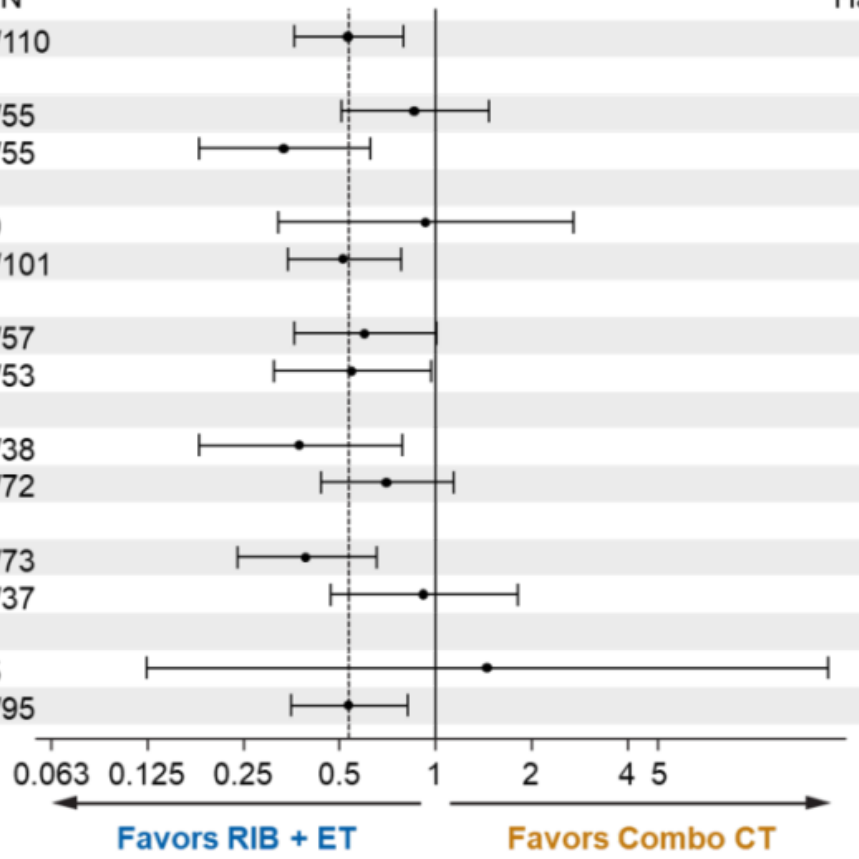
KEY DATA

RIGHT Choice Clinical Trial

PFS by subgroups

Subgroup	RIB + ET n/N	Combo CT n/N	Hazard Ratio (95% CI)
All patients	52/112	58/110	0.54 (0.36-0.79)
Visceral crisis status			
Yes	33/61	26/55	0.87 (0.51-1.47)
No	19/51	32/55	0.34 (0.18-0.63)
Disease free interval			
<2 years	9/13	6/9	0.94 (0.32-2.73)
≥2 years	43/99	52/101	0.52 (0.34-0.78)
Presence of liver metastasis			
Yes	29/56	31/57	0.60 (0.36-1.01)
No	23/56	27/53	0.55 (0.31-0.97)
Age			
<40 years	12/32	25/38	0.38 (0.18-0.79)
≥40 years	40/80	33/72	0.71 (0.44-1.15)
De novo			
Yes	29/71	42/73	0.40 (0.24-0.66)
No	23/41	16/37	0.92 (0.47-1.82)
Estrogen receptor status			
<50	2/8	3/5	1.46 (0.12-17.08)
≥50	47/95	50/95	0.54 (0.35-0.82)



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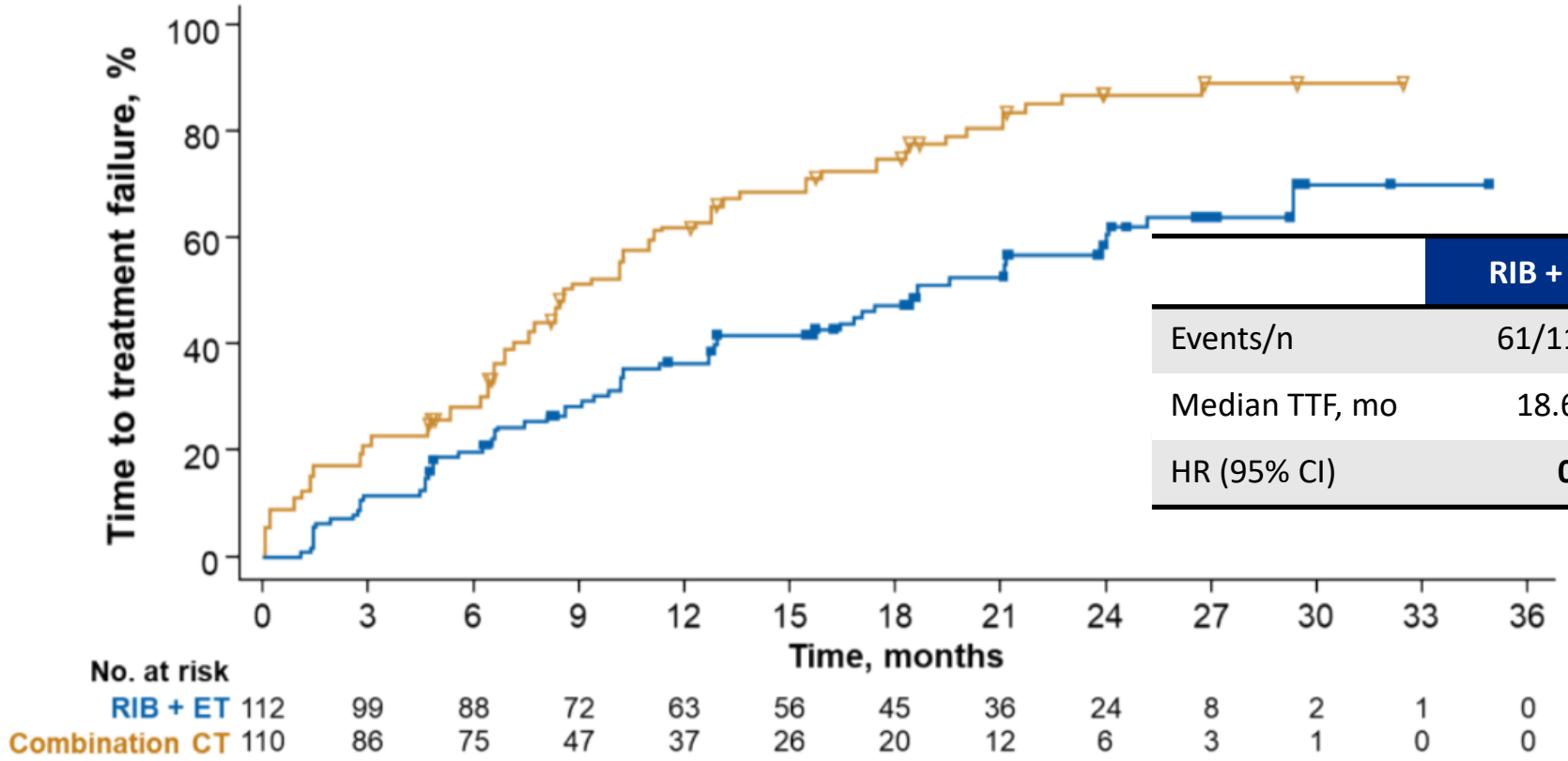
KEY DATA

RIGHT Choice Clinical Trial

Time to Treatment Failure



	RIB + ET	Combo CT
Events/n	61/112	84/110
Median TTF, mo	18.6	8.5
HR (95% CI)	**0.45** (0.32-0.63)	

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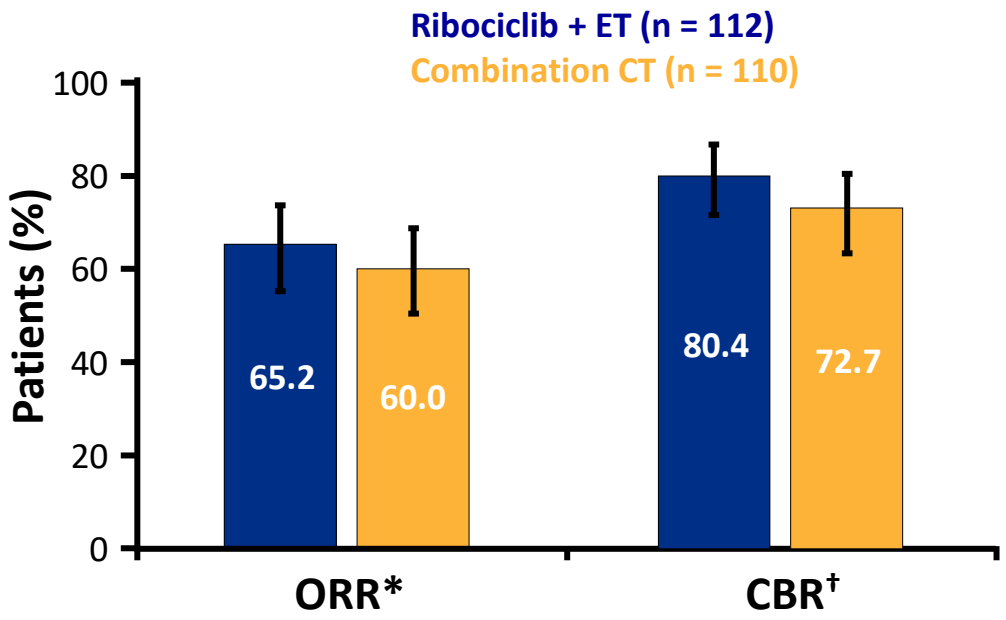
RIGHT Choice Clinical Trial

Overall Response Rate, Clinical Benefit Rate, and Time to Response



	RIB + ET	Combo CT
Events/n	73/112	66/110‡
Median TTR, mo	4.9	3.2
HR (95% CI)	**0.78** (0.56-1.09)	

‡10 patients in CT arm did not receive treatment.

*Confirmation imaging was not required per study protocol.
†CR or PR without confirmation or SD or non-CR/non-PD ≥24 wk.

KEY DATA

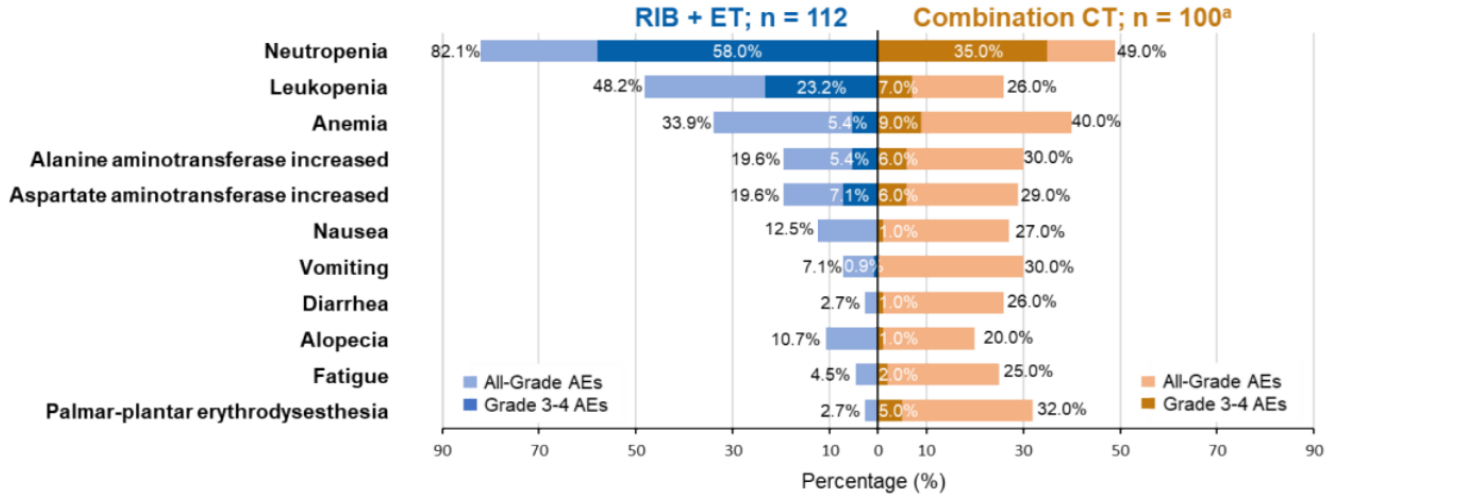
RIGHT Choice Clinical Trial

Safety

AE Parameter, n (%)	Ribociclib + ET (n = 112)		Combo CT (n = 100)*	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Total AEs	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
TRAEs leading to discontinuation†	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)

*10 patients in CT arm excluded from safety set due to failure to receive any treatment.
†Includes discontinuation of any treatment component.

AEs irrespective of causality (≥20% incidence in either RIB or combination CT arms)



- The median duration of exposure to study treatment was 15.0 months (Q1-Q3, 7.4-24.5 months) in the RIB arm and 8.6 months (Q1-Q3, 6.1-15.0 months) in the combination CT arm
- Fewer dose reductions observed with RIB + ET compared to combination chemotherapy

Dose Reductions, n (%)	Ribociclib + ET (n = 112)	Combo CT (n = 100)*
0	81 (72.3)	54 (54.0)
1	27 (24.1)	12 (12.0)
2	4 (3.6)	14 (14.0)
≥3	0	20.0 (20.0)

SUMMARY

RIGHT Choice Clinical Trial

- First prospective demonstration of PFS benefit from CDK4/6 inhibitor plus ET vs combination chemotherapy in pre/perimenopausal patients with HR+/HER2- advanced breast cancer with aggressive, rapidly progressing or highly symptomatic disease
  - Front line ribociclib + ET versus combination CT Median PFS: 24.0 vs 12.3 mo (HR: 0.54) respectively
  - TTF longer for ribociclib + ET vs combination CT
  - Similar TTR and ORR
- No new safety signals observed

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RIGHT Choice Clinical Trial

Ribociclib plus ET provides a non-chemotherapy treatment option for patients with clinically aggressive advanced HR+/HER2- breast cancer and should be considered in the front-line setting

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CLINICAL QUESTION

PACE Clinical Trial

Will palbociclib with or without fulvestrant provide benefit after progression on prior CDK4/6i and ET for pts with HR+/HER2- metastatic BC?

KEY DATA

PACE Clinical Trial

Study Design: Multicenter, randomized, open-label phase II study

- Adults with HR+/HER2- MBC
- Progression on CDK4/6i and ET with ≥6 mo SD on prior tx
- ≤2 prior lines of ET for MBC
- No prior fulvestrant exposure
- ≤1 prior CT for MBC

(N = 220)

Stratified by exposure to CT between CDK4/6 inhibition and trial entry

R
1:2:1

Fulvestrant* alone
n=55

Fulvestrant + Palbociclib
n=111

Fulvestrant + Palbociclib + Avelumab
n=54

Primary endpoints: RECIST-confirmed PFS for fulvestrant + palbociclib vs fulvestrant alone

Secondary endpoints: PFS of fulvestrant + palbociclib + avelumab vs fulvestrant alone, ORR, safety, outcomes in predefined molecular subgroups

Fulvestrant 500 mg IM on Days 1 and 15 of cycle 1, then monthly thereafter.
Palbociclib 125 mg PO QD on Days 1-21 (lower starting dose to match prior tx could be considered).
Avelumab 10 mg/kg IV every 14 days.

- Between September 2017 and February 2022, 220 patients were enrolled from 13 centers; 216 initiated treatment.
- Median follow-up is 23.6 months; at time of datalock in July 2022, 18 patients continue on protocol therapy.
- Efficacy ITT population: n=220
- Safety population: n=216

KEY DATA

PACE Clinical Trial

Baseline Characteristics and Prior Treatments

	Fulvestrant alone n=55	Fulvestrant + Palbociclib n=111	Fulvestrant + Palbociclib + Avelumab n=54
Female, n (%)	55 (100)	109 (98.2)	54 (100)
Median age, yr (range)	58 (36-77)	55 (28-77)	58 (25-83)
Race			
White	47 (85.5)	88 (79.3)	44 (81.5)
Black	3 (5.5)	13 (11.7)	4 (7.4)
Asian	0	4 (3.6)	3 (5.6)
Other	5 (9.1)	6 (5.4)	3 (5.6)
Post-menopausal	47 (85.5)	87 (78.4)	44 (81.5)
De novo MBC	28 (50.9)	40 (36.0)	20 (37.0)
Visceral disease	29 (52.7)	70 (63.1)	33 (61.1)
Bone only disease	4 (7.3)	18 (16.2)	8 (14.8)
Measurable disease	37 (67.3)	73 (65.8)	39 (72.2)

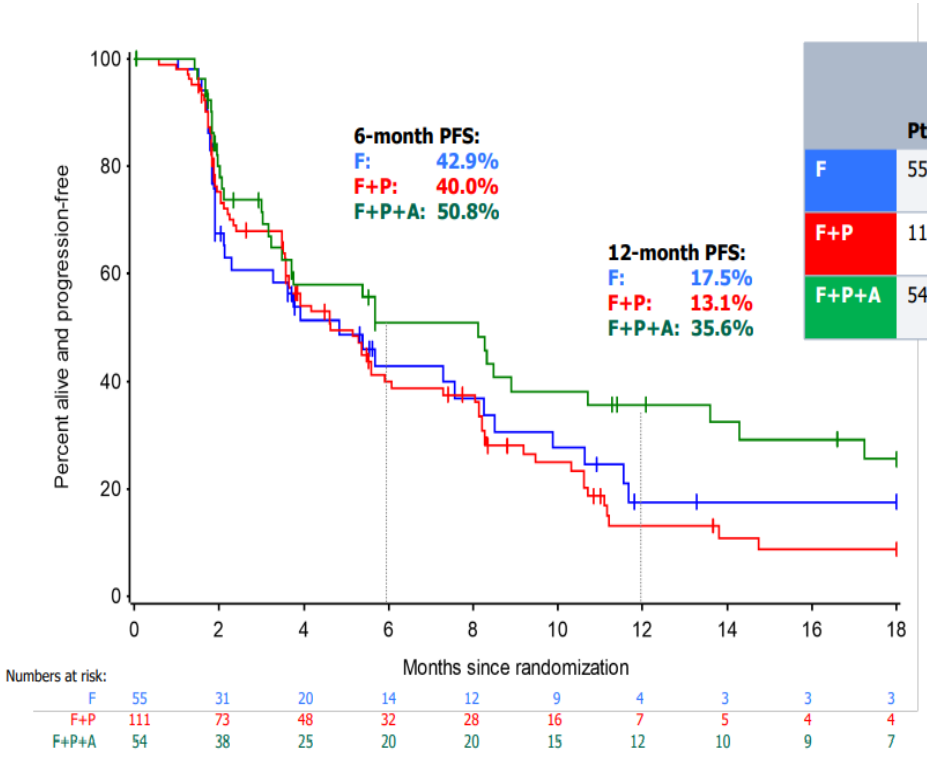
	Fulvestrant alone n=55	Fulvestrant + Palbociclib n=111	Fulvestrant + Palbociclib + Avelumab n=54
Prior adjuvant endocrine exposure*			
Endocrine resistant	10 (18.2)	32 (28.8)	16 (29.6)
Endocrine sensitive	45 (81.8)	78 (70.3)	37 (68.5)
Prior CDK4/6i			
Palbociclib	52 (94.5)	102 (91.9)	46 (85.2)
Ribociclib	1 (1.8)	5 (4.5)	4 (7.4)
Abemaciclib	2 (3.6)	3 (2.7)	4 (7.4)
Duration of prior CDK4/6i + ET	10 (18.2)	26 (23.4)	16 (29.6)
6-12 months	45 (81.8)	84 (75.7)	38 (70.4)
> 12 months	11 (20.0)	16 (14.4)	9 (16.7)
Prior chemotherapy for MBC	11 (20.0)	16 (14.4)	9 (16.7)
Line of MBC therapy initiated in PACE			
First line	3 (5.5)	5 (4.5)	2 (3.7)
Second Line	42 (76.4)	83 (74.8)	44 (81.5)
> Second Line	10 (18.2)	21 (18.9)	7 (13.0)
Any systemic therapy between prior CDK4/6i and randomization	5 (9.1)	16 (14.4)	5 (9.3)

*Endocrine resistant: recur <1y of adj ET. Endocrine sensitive: de novo MBC, or no adj ET, or recur >1y after adj ET. Adapted from ESO-ESMO guidelines, Ann Oncol 2020

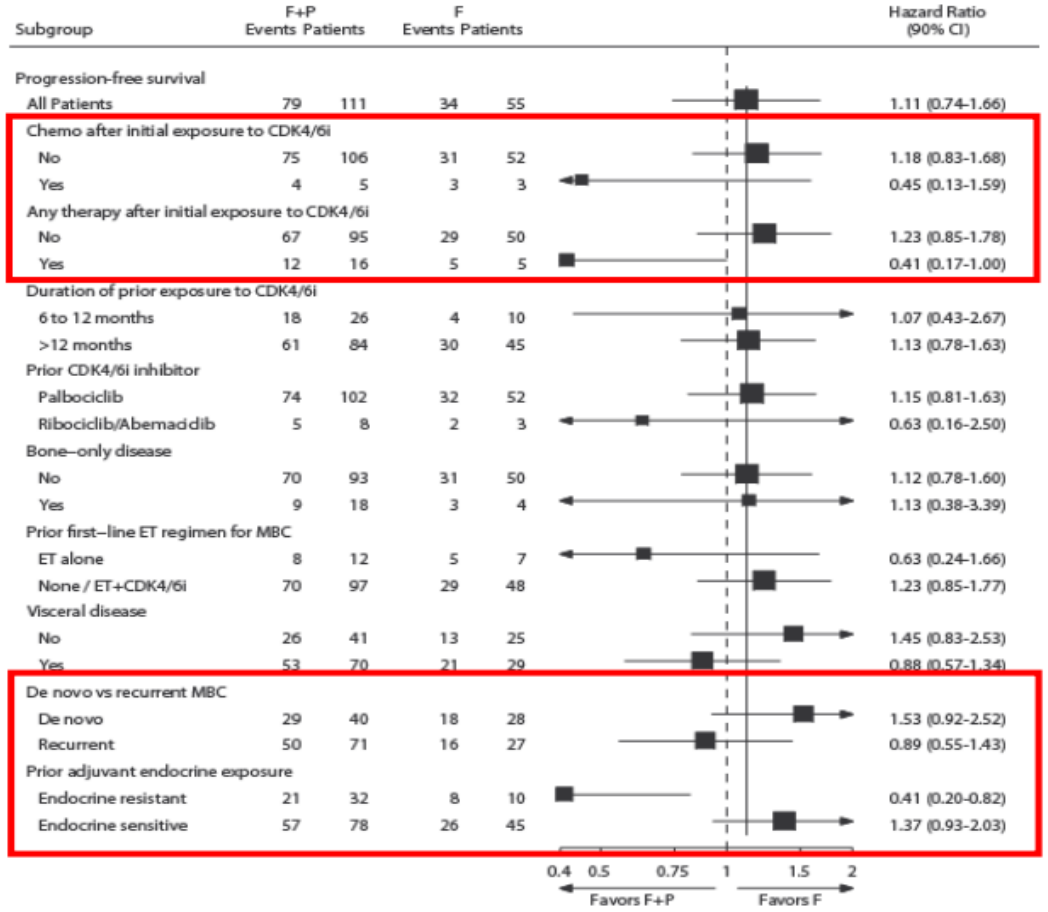
KEY DATA

PACE Clinical Trial

PFS (primary and secondary endpoint and by subgroup analysis)



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

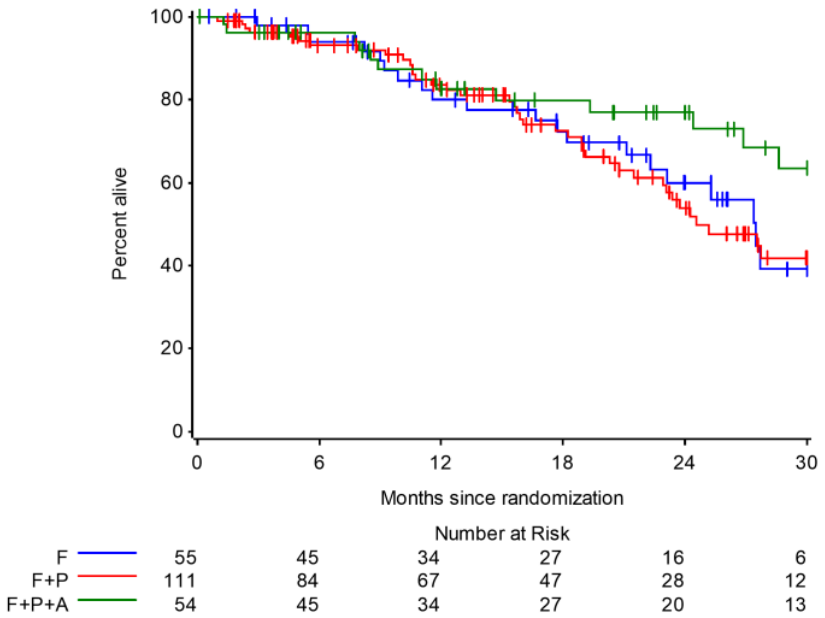


Primary endpoint: RECIST-confirmed PFS for fulvestrant + palbociclib vs fulvestrant alone
Secondary endpoint: PFS of fulvestrant + palbociclib + avelumab vs fulvestrant alone

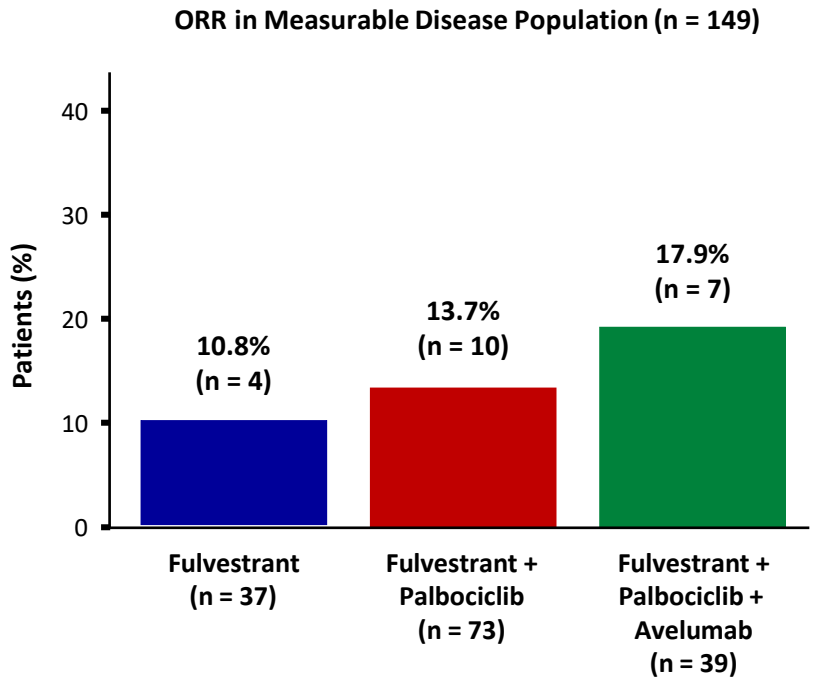
KEY DATA

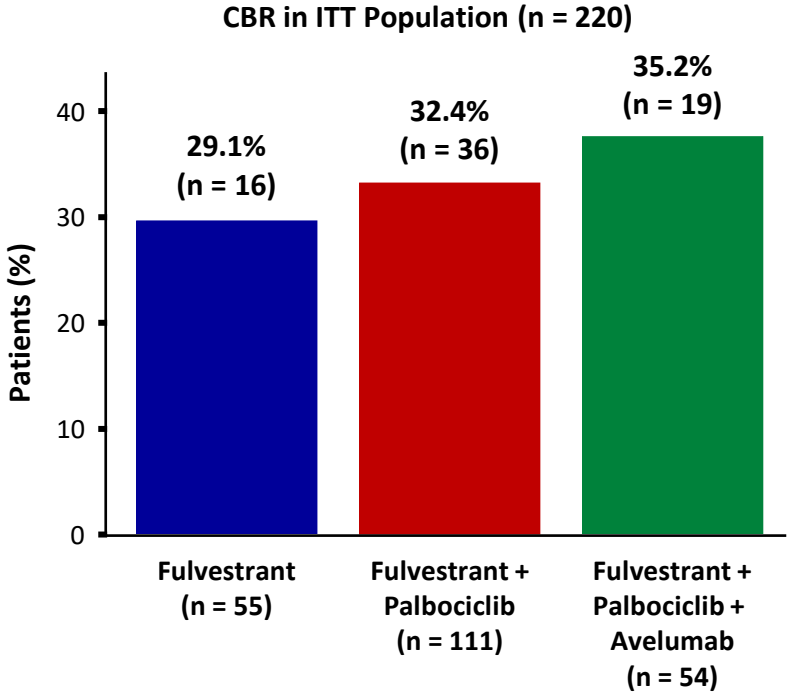
PACE Clinical Trial

Overall survival and Response Endpoints



	Pts	OS Events	Median OS, mo (90% CI)	HR vs F (90% CI)
F	55	23	**27.5** (21.1, 38.0)	--
F+P	111	43	**24.6** (21.5, 33.3)	1.02 (0.67-1.56)
F+P+A	54	17	**42.5** (26.8, 46.0)	0.68 (0.40-1.15)

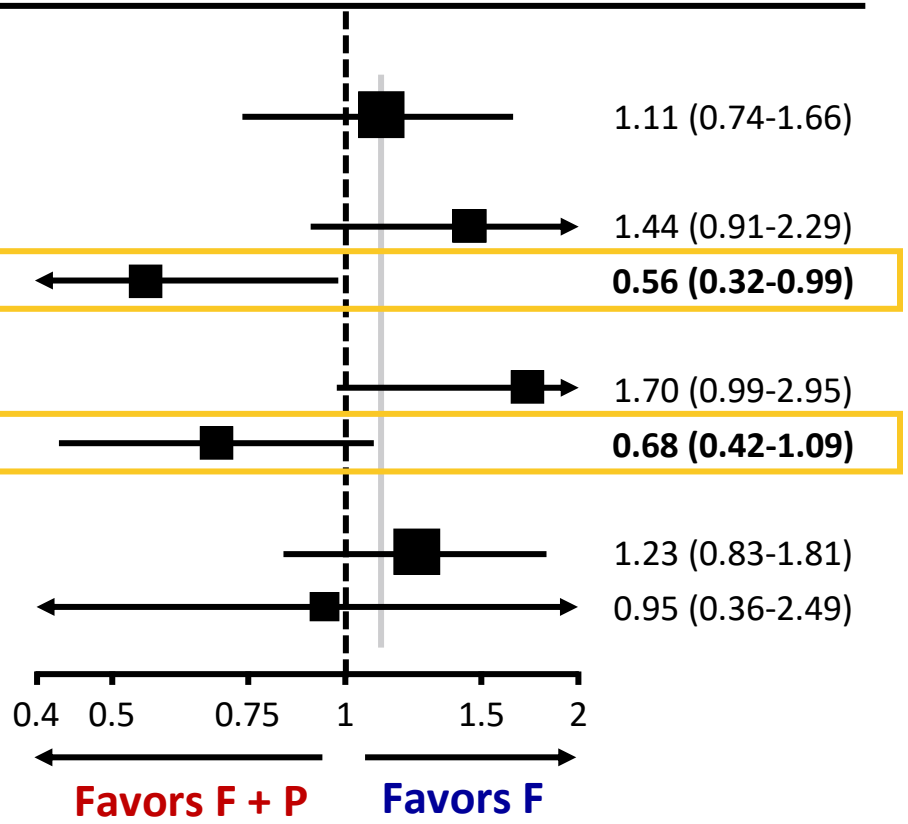




PACE Clinical Trial

Exploratory Analysis of Baseline mutation and outcomes

Subgroup	F + P Events	F + P Patients	F Events	F Patients	HR (90% CI)
PFS					
All patients	79	111	34	55	1.11 (0.74-1.66)
Any *PIK2CA* mutation					
WT	45	63	18	36	1.44 (0.91-2.29)
Mutation	29	**39**	12	**12**	**0.56 (0.32-0.99)**
Any *ESR1* mutation					
WT	31	47	13	25	1.70 (0.99-2.95)
Mutation	43	**55**	17	**23**	**0.68 (0.42-1.09)**
Any *Rb1* mutation					
WT	67	92	25	42	1.23 (0.83-1.81)
Mutation	7	**10**	5	**6**	0.95 (0.36-2.49)



PACE Clinical Trial

Safety: TRAEs in ≥10% of Patients

TRAE, n (%)	Fulvestrant (n = 53)		Fulvestrant + Palbociclib (n = 110)		Fulvestrant + Palbociclib + Avelumab (n = 53)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Hematologic						
▪ Neutropenia*	2 (3.8)	NR	72 (65.5)	36 (32.7)	39 (73.6)	26 (49.1)
▪ Anemia	2 (3.8)	NR	24 (21.8)	5 (4.5)	18 (34.0)	2 (3.8)
▪ Decreased PLTC	1 (1.9)	NR	16 (14.5)	1 (0.9)	17 (32.1)	2 (3.8)
Nonhematologic						
▪ Fatigue	18 (34.0)	NR	38 (34.5)	2 (1.8)	34 (64.2)	3 (5.7)
▪ Nausea	5 (9.4)	NR	13 (11.8)	NR	10 (18.9)	NR
▪ Diarrhea	0 (0)	NR	11 (10.0)	NR	9 (17.0)	2 (3.8)
▪ Anorexia	2 (3.8)	NR	4 (3.6)	NR	9 (17.0)	1 (1.9)
▪ Mucositis	0 (0)	NR	10 (9.1)	1 (0.9)	8 (15.1)	1 (1.9)
▪ AST increase	6 (11.3)	NR	6 (5.5)	1 (0.9)	8 (15.1)	1 (1.9)
▪ Extremity pain	1 (1.9)	NR	NR	NR	8 (15.1)	NR
▪ Pruritis	1 (1.9)	NR	5 (4.5)	NR	7 (13.2)	1 (1.9)
▪ Constipation	2 (3.8)	NR	7 (6.4)	NR	7 (13.2)	NR
▪ Injection-site reaction	6 (11.3)	NR	12 (10.9)	NR	3 (5.7)	NR

*There were no episodes of febrile neutropenia. There were no Grade 5 toxicity events.
NR: not reported

PACE Clinical Trial

Safety: Potential Immune-related Adverse Events

IRAE, n (%)	Fulvestrant + Palbociclib + Avelumab (n = 53)	
	All Grades	Grade 3/4
AST increase	6 (11.3)	1 (1.9)
ALT increase	5 (9.4)	1 (1.9)
Cardiac troponin T increased	1 (1.9)	1 (1.9)
Hypoxia	1 (1.9)	1 (1.9)
Bullous dermatitis	1 (1.9)	1 (1.9)
Infusion-related reaction	4 (7.5)	1 (1.9)
Hypothyroidism	4 (7.5)	0 (0)
Fever	4 (7.5)	0 (0)
CPK increase	4 (7.5)	0 (0)
Arthralgia	4 (7.5)	0 (0)
Hyperglycemia	3 (5.7)	0 (0)
Rash maculopapular	3 (5.7)	0 (0)

IRAE, n (%)	Fulvestrant + Palbociclib + Avelumab (n = 53)	
	All Grades	Grade 3/4
Colitis	2 (3.8)	0 (0)
Skin hypopigmentation	2 (3.8)	0 (0)
Alkaline phosphatase increase	2 (3.8)	0 (0)
Hyperthyroidism	2 (3.8)	0 (0)
Adrenal insufficiency	1 (1.9)	0 (0)
Rectal hemorrhage	1 (1.9)	0 (0)
Blood bilirubin increase	1 (1.9)	0 (0)
Acneiform rash	1 (1.9)	0 (0)

SUMMARY

PACE Clinical Trial

- Th addition of palbociclib to fulvestrant did not significantly improve PFS compared with fulvestrant alone in patients with HR+/HER2- MBC who experienced progression on prior CDK4/6 inhibitor therapy
    - Improvement in PFS was observed with PD-L1 inhibition when (avelumab) added to fulvestrant and palbociclib
- No new safety signals observed

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PACE Clinical Trial

Palbociclib plus fulvestrant does not provide additional benefit after prior CDK4/6i and ET to patients with HR+/HER2- metastatic breast cancer

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

cornerstone specialty network™

CLINICAL QUESTION

POSITIVE Clinical Trial

Will temporarily interrupting ET impact women with HR+ Breast Cancer that desire pregnancy?

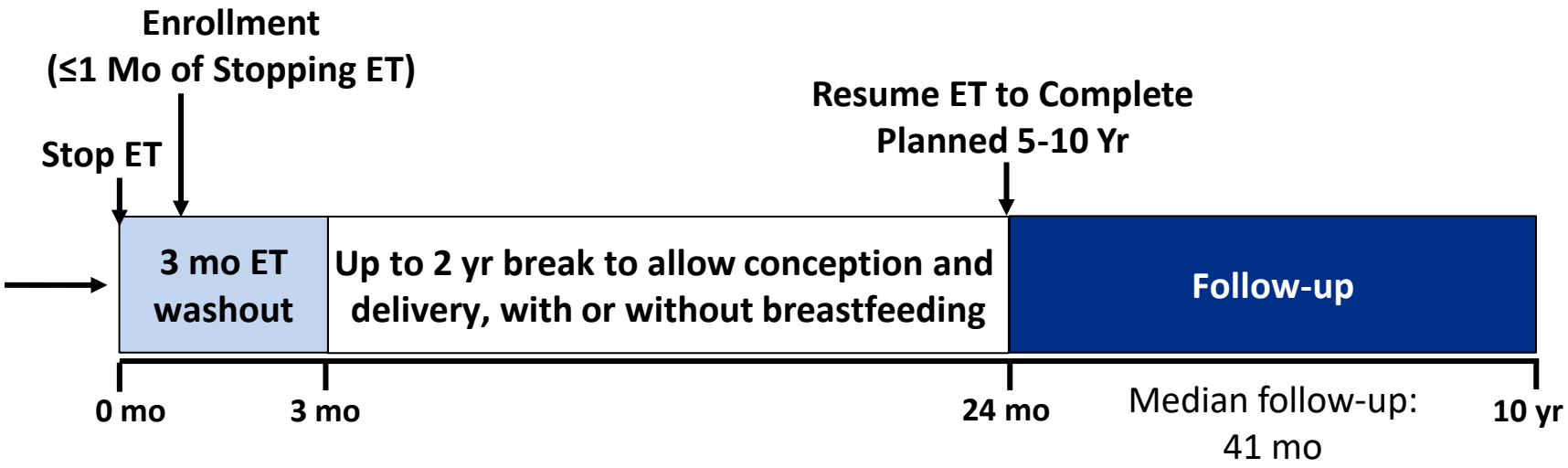
KEY DATA

POSITIVE Clinical Trial

Study Design: International, prospective, single-arm trial

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

(N = 516)



- A cohort of 1499 SOFT/TEXT patients used as external control

Primary endpoints: BCFI defined as time from enrollment (after 18-30 months of ET) to first invasive disease [ipsilateral, contralateral, or locoregional] or distant recurrence

Secondary endpoints: pregnancy outcomes, offspring outcomes, breastfeeding, assisted reproductive technology use, adherence to ET, DRFI (defined as time from enrollment to first distant recurrence of BC)

KEY DATA

POSITIVE Clinical Trial

Baseline Characteristics and Treatments

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

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

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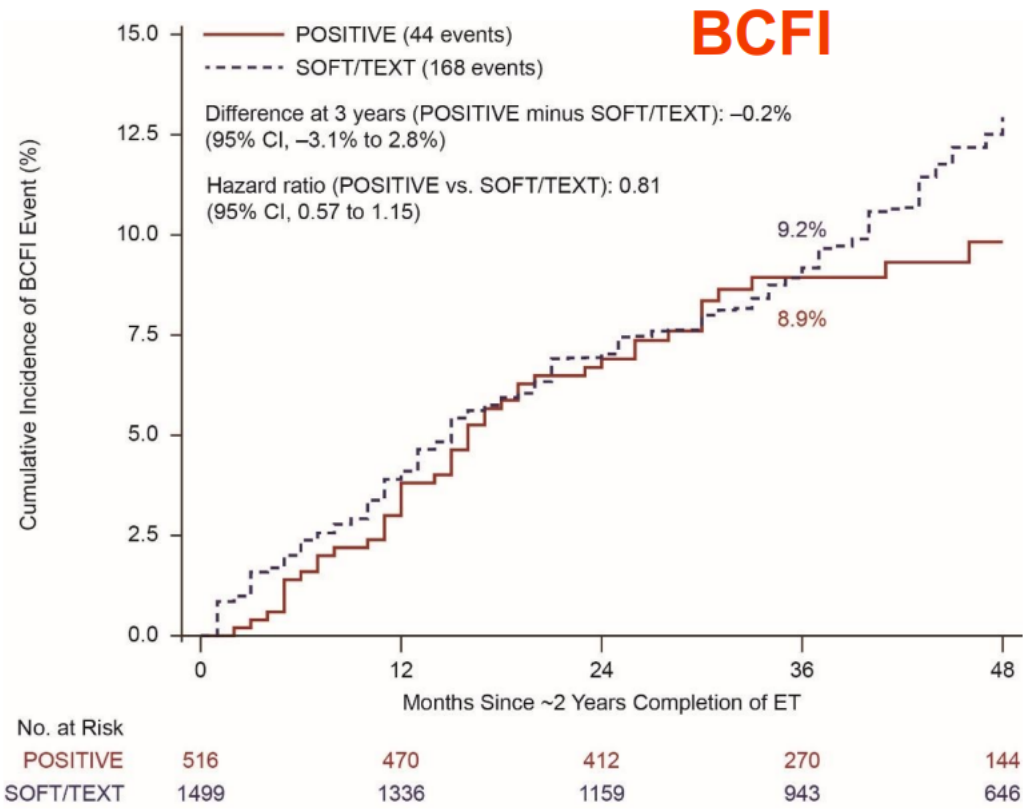
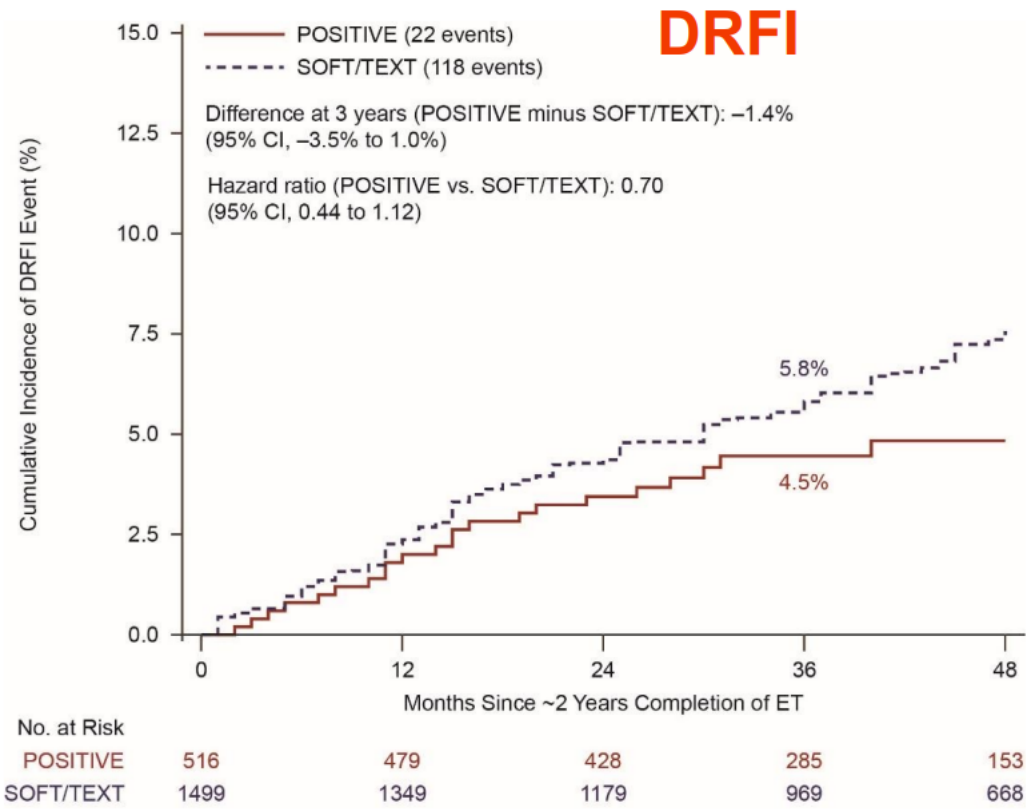
KEY DATA

POSITIVE Clinical Trial

BCFI, Breast cancer–free interval and DRFI, distant recurrence–free interval



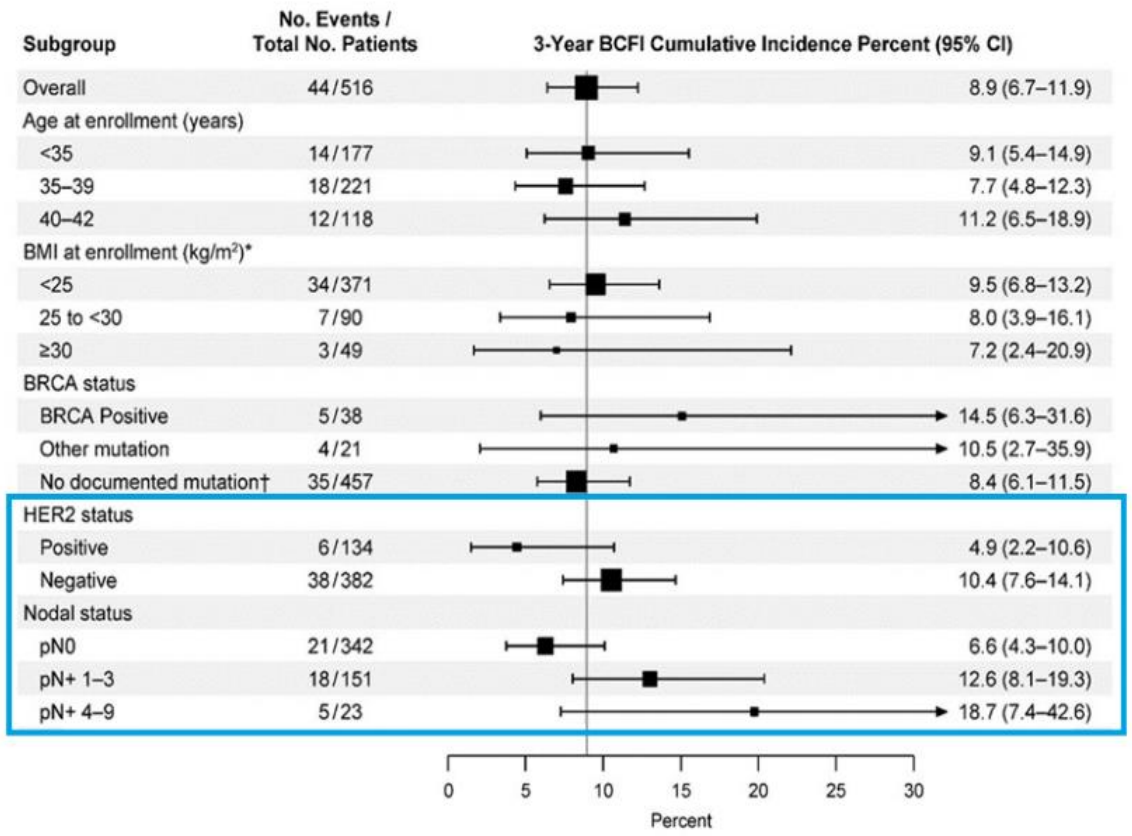


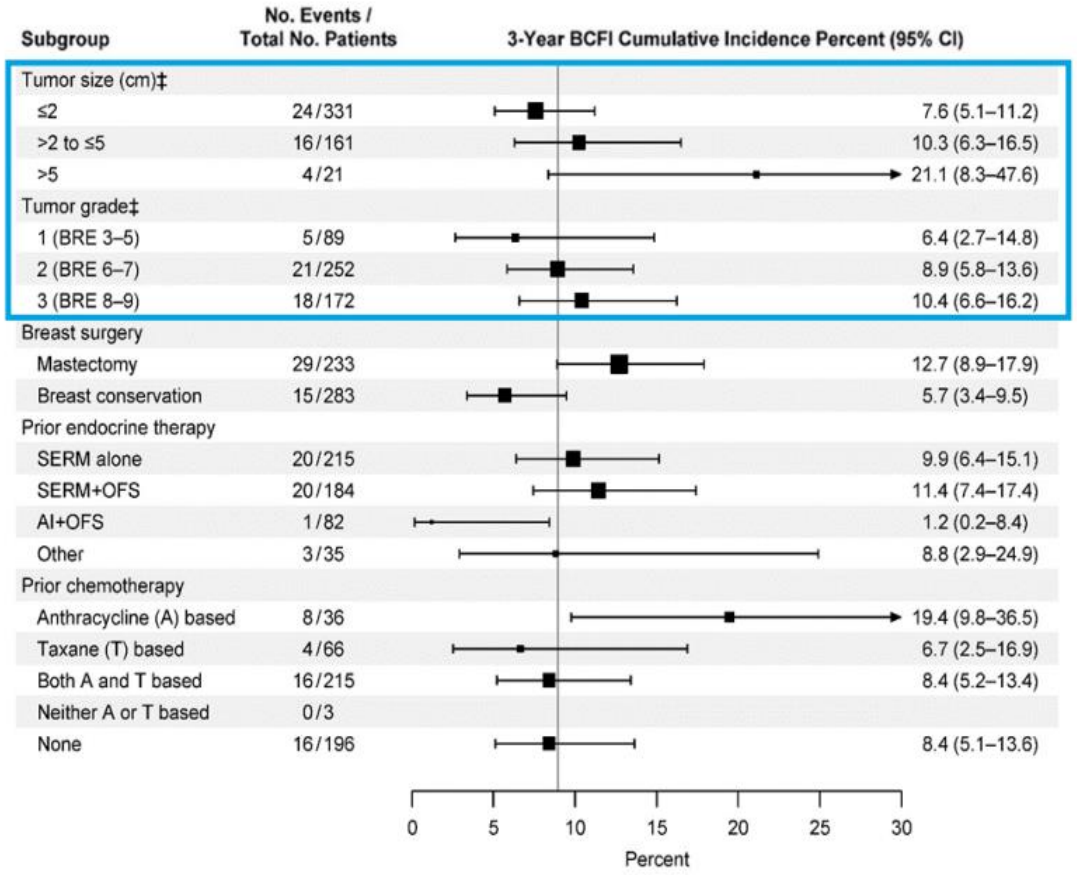
1638 patient-years of follow-up (41 months median follow-up)

KEY DATA

POSITIVE Clinical Trial

3-Yr BCFI Cumulative Incidence

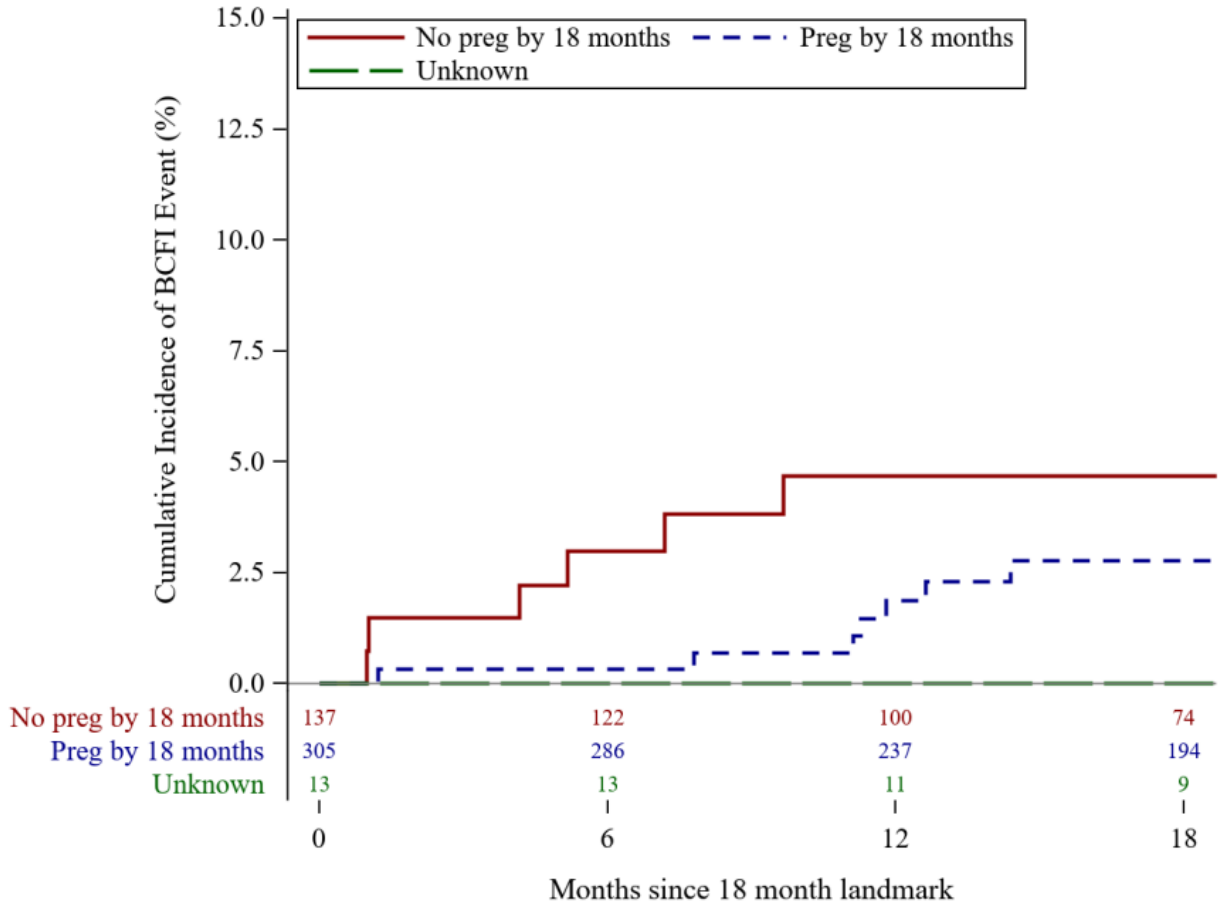




KEY DATA

POSITIVE Clinical Trial

BCFI For Pregnant Vs Non Pregnant Patients



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

*Including BMI, lymph node status, age, prior AI, prior chemo

SABCS 2022. Abstract GS4-09

KEY DATA

POSITIVE Clinical Trial

Pregnancy and Offspring Outcomes

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

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

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

- 350 live births among 317 women who had at least 1 live birth
  - 62% of women reported breastfeeding
- Total 365 offspring
  - 335 singleton births and 15 sets of twins

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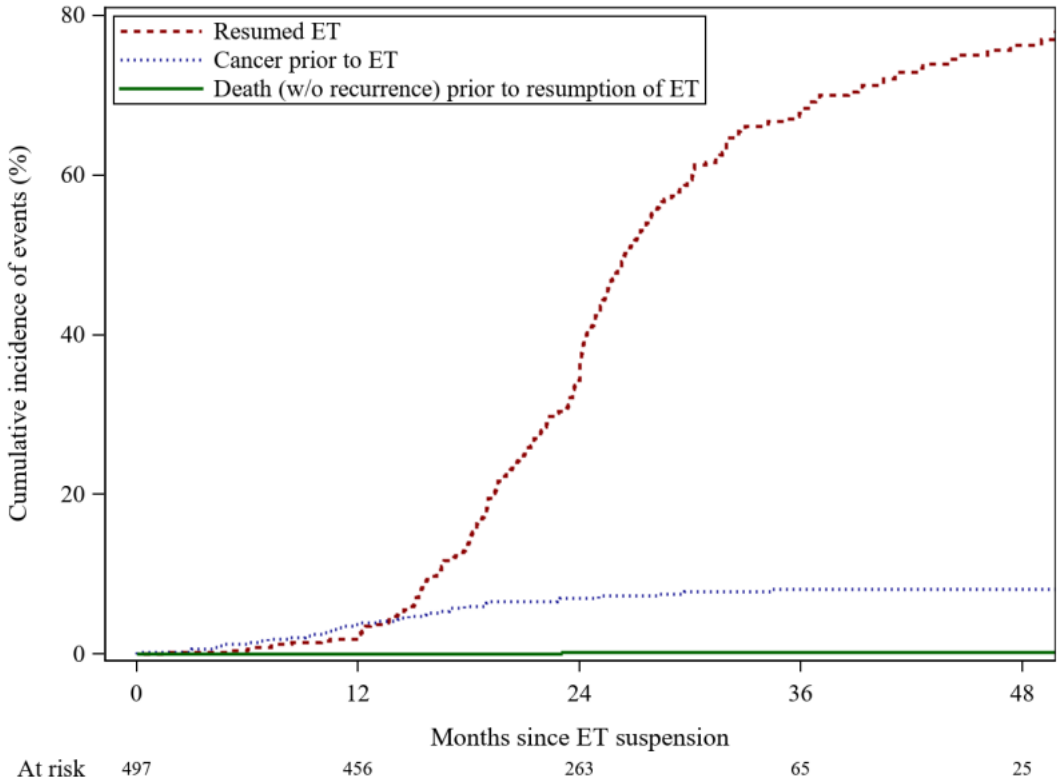
POSITIVE Clinical Trial

Competing Risk Analysis of ET Resumption



Cumulative incidence at 48 mo

- 8% experienced cancer recurrence/death prior to ET resumption
- 76% resumed ET
- 15% had not yet resumed ET

79% of women who were disease free at 2 yr had not yet resumed ET due to

- Active or recent pregnancy
- Breastfeeding
- In pursuit of pregnancy

POSITIVE Clinical Trial

Temporary interruption of ET does not impact short-term disease outcomes for women who desire pregnancy

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE
- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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KEY QUESTION

HR+ Breast Cancer

What role will SERMs/SERDs play in the treatment of patients with HR+ breast cancer?

Should ESR1 mutation monitoring become standard?

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CLINICAL QUESTION

EMERALD Clinical Trial

Will use of elacestrant, an investigational oral selective estrogen receptor degrader (SERD) benefit pts with ER+/HER2- advanced or metastatic BC following tumor progression on prior endocrine and CDK4/6 inhibitor therapy?

Updated analysis

KEY DATA

EMERALD Phase 3 Clinical Trial: Comparing a new oral SERD vs hormonal SOC

Inclusion Criteria

- Men and postmenopausal women with advanced or metastatic breast cancer
- ER+[a], HER2-
- Progression or relapse on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6 inhibitor
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

Stratification factors:

- ESR1-mutation status
- Prior treatment with fulvestrant
- Presence of visceral metastases

R 1:1
N = 477[b]

Elacestrant
400mg daily[c]
N=239

Investigators choice (SOC):
Fulvestrant, Anastrozole, Letrozole, or Exemestane
N=238

Primary Endpoints:

- PFS in all patients
- PFS in pts with mESR1[d]

Secondary Endpoint:

- Overall survival

[a] ER+ tumor with ≥ 1% staining by IHC; [b]Recruitment from Feb 2019 to Oct 2020; [c]Protocol-defined dose reductions permitted; Blinded Independent Central Review. [d]ESR1-mutation status was determined by ctDNA analysis using the Guardant360 assay; Restaging CT scans every 8 weeks

Stats: ≥90% power to evaluate a PFS hazard ration (HR) of 0.667 in all pts and ≥80% power for a PFS HR of 0.610 in the mESR1 subset

KEY DATA

EMERALD Clinical Trial

Baseline Characteristics

	All Patients		Patients With ESR1 Mutation	
	Elacestrant (n = 239)	SoC (n = 239)	Elacestrant (n = 115)	SoC (n = 113)
Median age, yr (range)	63.0 (24-89)	63.0 (32-83)	64.0 (28-89)	63.0 (32-83)
Female, n (%)	233 (97.5)	238 (99.6)	115 (100)	113 (100)
ECOG PS, n (%)				
▪ 0	143 (59.8)	135 (56.5)	67 (58.3)	62 (54.9)
▪ 1	96 (40.2)	103 (43.1)	48 (41.7)	51 (45.1)
▪ >1	0	1 (0.4)	0	0
Visceral metastasis,* n (%)	163 (68.2)	170 (71.1)	81 (70.4)	84 (73.5)
Prior CDK4/6i, n (%)	239 (100)	239 (100)	115 (100)	113 (100)
Prior lines of ET,† n (%)				
▪ 1	129 (54.0)	142 (59.4)	73 (63.5)	69 (61.1)
▪ 2	110 (46.0)	97 (40.6)	42 (36.5)	44 (38.9)
Type of prior ET, † n (%)				
▪ Fulvestrant	70 (29.3)	75 (31.4)	27 (23.5)	28 (24.8)
▪ AI	193 (80.8)	194 (81.2)	101 (87.8)	96 (85.0)
▪ Tamoxifen	19 (7.9)	15 (6.3)	9 (7.8)	9 (8.0)
Prior lines of CT,† n (%)				
▪ 0	191 (79.9)	180 (75.3)	89 (77.4)	81 (71.7)
▪ 1	48 (20.1)	59 (24.7)	26 (22.6)	32 (28.3)

EMERALD Clinical Trial

All Patients: PFS by Duration (≥6, ≥12, and ≥18 Mo) of Prior CDK/6i

PFS Outcomes	CDK4/6i ≥6 Mo (87.5%)		CDK4/6i ≥12 Mo (66.7%)		CDK4/6i ≥18 Mo (46.7%)	
	Elacestrant (n = 202)	SoC (n = 205)	Elacestrant (n = 150)	SoC (n = 160)	Elacestrant (n = 98)	SoC (n = 119)
Median PFS, mo (95% CI)	**2.79** (1.94-3.78)	**1.91** (1.87-2.14)	**3.78** (2.33-6.51)	**1.91** (1.87-3.58)	**5.45** (2.33-8.61)	**3.29** (1.87-3.71)
HR (95% CI)	**0.688** (0.535-0.884)		**0.613** (0.453-0.828)		**0.703** (0.482-1.019)	
6-mo PFS rate, % (95% CI)	34.40 (26.70-42.10)	19.88 (12.99-26.76)	41.56 (32.30-50.81)	21.72 (13.65-29.79)	44.72 (33.24-56.20)	25.12 (15.13-35.10)
12-mo PFS rate, % (95% CI)	21.00 (13.57-28.43)	6.42 (0.75-12.09)	25.64 (16.49-34.80)	7.38 (0.82-13.94)	26.70 (15.61-37.80)	8.23 (0.00-17.07)
18-mo PFS rate, % (95% CI)	16.24 (8.75-23.74)	3.21 (0.00-8.48)	19.34 (9.98-28.70)	3.69 (0.00-9.77)	21.03 (9.82-32.23)	4.11 (0.00-11.33)

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EMERALD Clinical Trial

ESR1-mut Tumors: PFS by Duration (≥6, ≥12, and ≥18 Mo) of Prior CDK4/6i

PFS Outcomes	CDK4/6i ≥6 Mo (92.3%)		CDK4/6i ≥12 Mo (71.6%)		CDK4/6i ≥18 Mo (50.0%)	
	Elacestrant (n = 103)	SoC (n = 102)	Elacestrant (n = 78)	SoC (n = 81)	Elacestrant (n = 55)	SoC (n = 56)
Median PFS, mo (95% CI)	**4.14** (2.02-7.79)	**1.87** (1.87-3.29)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)	**8.61** (5.45-16.89)	**2.10** (1.87-3.75)
HR (95% CI)	**0.517** (0.361-0.738)		**0.410** (0.262-0.634)		**0.466** (0.270-0.791)	
6-mo PFS rate, % (95% CI)	42.43 (31.15-53.71)	19.15 (9.95-28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
12-mo PFS rate, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
18-mo PFS rate, % (95% CI)	20.70 (9.77 - 31.63)	0.00	28.49 (14.08 - 42.89)	0.00	30.68 (13.94 - 47.42)	0.00

SABCS 2022. Abstract GS3-01.

KEY DATA

EMERALD Clinical Trial: Safety Summary

Safety Outcome, n (%)	Elacestrant (n = 237)	SoC (n = 230)
Grade 3 nausea, n (%)	6 (2.5)	2 (0.9)
Dose reduction due to nausea, n (%)	3 (1.3)	NA
Discontinuation due to nausea, n (%)	3 (1.3)	0 (0)
Antiemetic use, %	8	10.3 (AI) 1.3 (fulvestrant)

- 3.4% of patients receiving elacestrant and 0.9% of patients receiving SoC discontinued treatment due to TRAE
- Most AEs grade 1/2; no grade 4 or 5 TRAEs
- No hematologic safety signals
- No cases of sinus bradycardia

SABCS 2022. Abstract GS3-01.

SUMMARY

EMERALD Clinical Trial

- Elacestrant extended PFS versus SOC
  - The benefit was stronger for people who had spent more time on CDK4/6 inhibitors and for those with *ESR1* mutations
  - ESR1-mut and prior CDK4/6i for at least 12 months: PFS 8.6 mo with elacestrant vs 1.9 mo for SOC
- Elacestrant was well tolerated with a safety profile consistent with previously reported
- Elacestrant is taken as a daily pill

SABCS 2022. Abstract GS3-01.

EMERALD Clinical Trial

Elacestrant continues to demonstrate positive results for the treatment of ER+/HER2- advanced or mBC that no longer responds to CDK4/6i or other hormonal therapies with limited side effects

More to come: potential approval by regulatory agencies with or without recommendation for ESR1 testing…

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE
- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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CLINICAL QUESTION

SERENA-2 Clinical Trial

Will camizestrant, a next-generation oral selective estrogen receptor degrader (SERD) compared to fulvestrant benefit post-menopausal pts with ER+/HER2- advanced or metastatic BC?

KEY DATA

SERENA-2 Clinical Trial

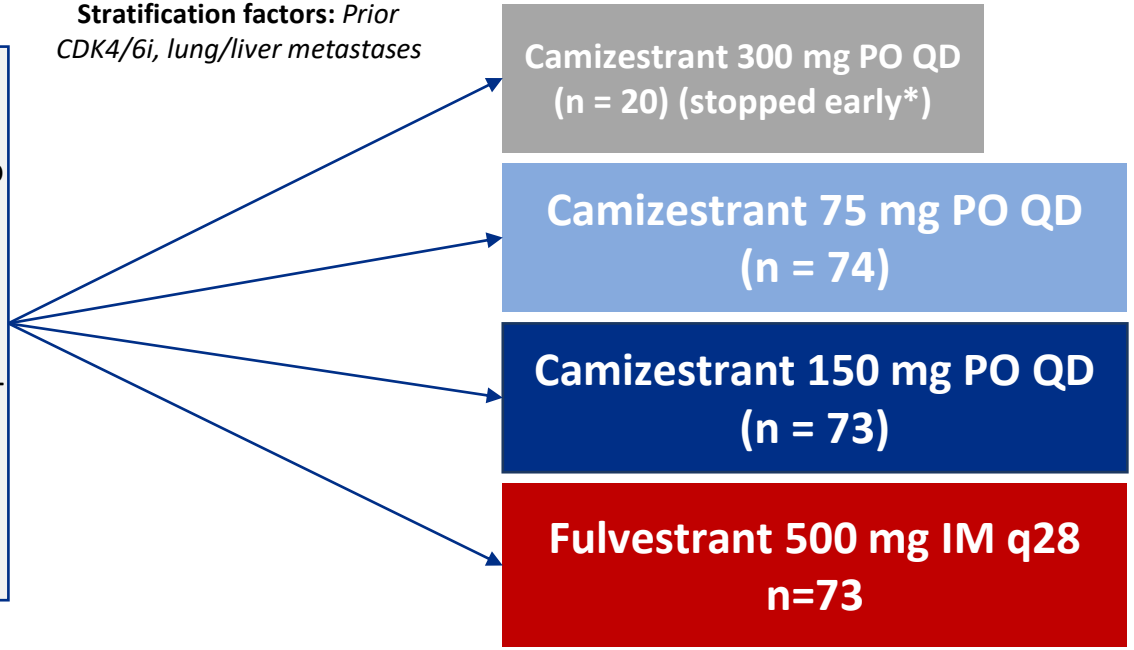
Study Design: Randomized, multi-dose Phase 2 trial

Inclusion Criteria

- Postmenopausal women with ER+/HER2- advanced breast cancer who are candidates for fulvestrant monotherapy
- Measurable and nonmeasurable disease
- Recurrence/progression on ≥1 line of ET
- ≤1 line of ET or chemotherapy
- Without prior fulvestrant or oral SERD in advanced setting

(N = 240)

Stratification factors: *Prior CDK4/6i, lung/liver metastases*



Primary Endpoints:

- investigator-assessed PFS

Secondary endpoints:

- CBR24, ORR, OS, safety

Translational endpoints:

- serial analysis of ctDNA, including *ESR1* mutations, and serial CTC analysis

August 2022: Primary analysis when 108 progression events (75% maturity) had occurred in the best performing pair (camizestrant 75 or 150 mg versus fulbestrant)

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KEY DATA

SERENA-2 Clinical Trial

Baseline Characteristics

Characteristic	Camizestrant 75 mg (n = 74)	Camizestrant 150 mg (n = 73)	Fulvestrant 500 mg (n = 73)
Median age, yr (range)	61.0 (37-89)	60.0 (42-84)	60.0 (35-84)
White race, %	95.9	95.9	89.0
PgR+, %	81.1	84.9	79.5
ECOG PS 0, %	62.2	57.5	58.9
Lung/liver metastasis, %	58.1	58.9	58.9
Liver metastasis, %	31.1	41.1	47.9
Bone-only disease, %	14.9	19.4	17.8
ESR1 mutation detectable, %	29.7	35.6	47.9

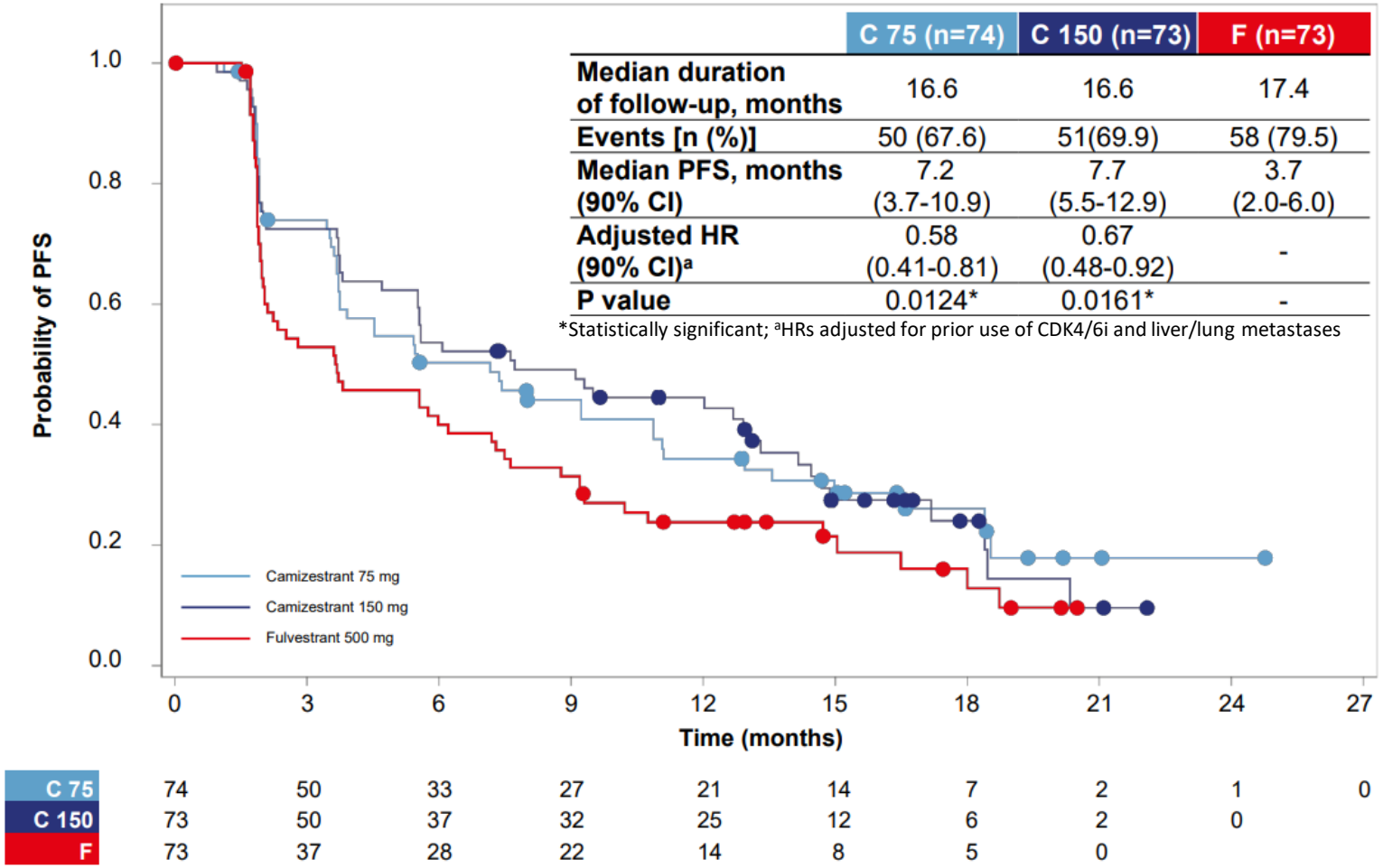
Characteristic	Camizestrant 75 mg (n = 74)	Camizestrant 150 mg (n = 73)	Fulvestrant 500 mg (n = 73)
CT adjuvant, %	54.1	53.4	52.1
CT in ABC, %	21.6	12.3	26.0
Overall lines ET, %			
• 0	1.4	1.4	0
• 1	81.1	72.6	76.7
• 2	16.2	24.7	19.2
• 3	1.4	1.4	4.1
Adjuvant ET, %	66.2	71.2	60.3
• AI/SERM, %	40.5/32.4	35.6/45.2	31.5/43.8
Lines of ET in ABC, (%)			
• 0/1	37.8/62.2	28.8/71.2	26.0/74.0
• AI/SERM	55.4/6.8	67.1/2.7	67.1/6.8
Prior CDK4/6i, %*	51.4	50.7	50.7
• Palbociclib	21.6	31.5	30.1
• Ribociclib	23.0	19.2	16.4
• Abemaciclib	5.4	1.4	4.1

*Missing or not specified in 3 patients

KEY DATA

SERENA-2 Clinical Trial

Primary Endpoint PFS By investigator



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

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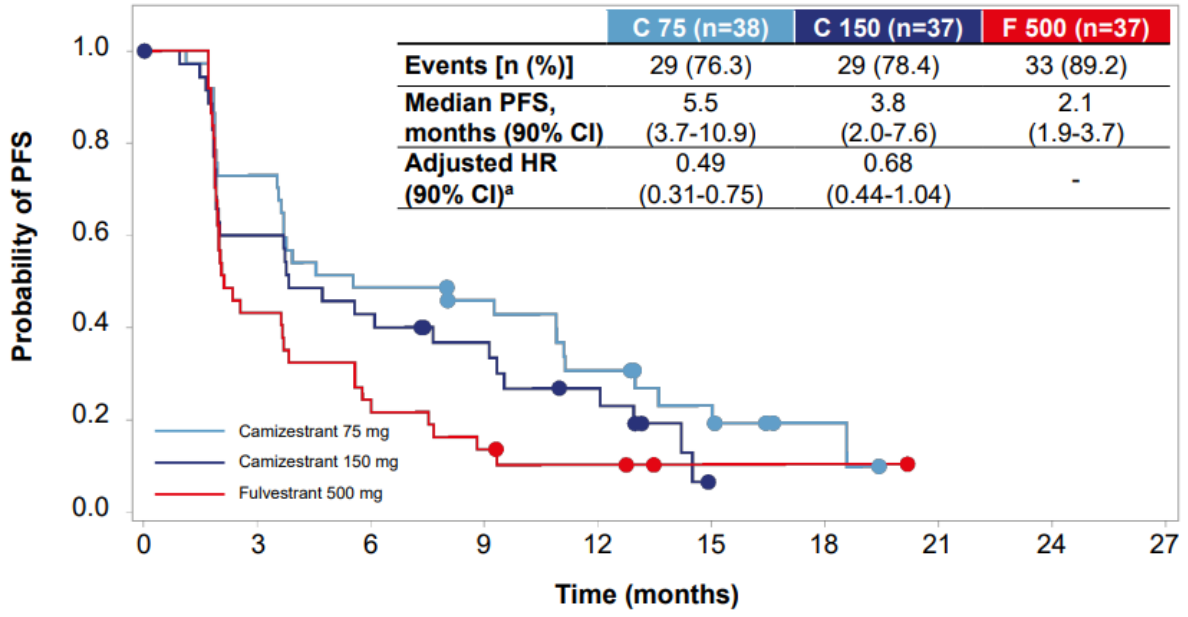
KEY DATA

SERENA-2 Clinical Trial

PFS By Prior Use of CDK4/6i

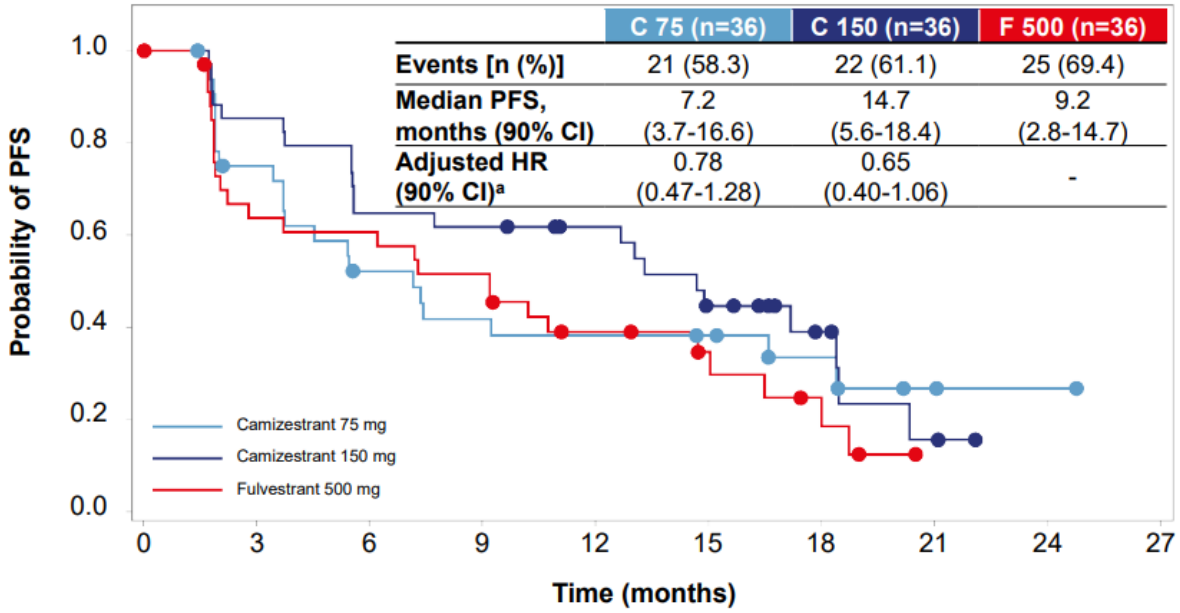
Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

C 75	38	27	18	15	10	5	2	0
C 150	37	21	15	11	7	0		
F	37	16	8	5	3	1	1	0

No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

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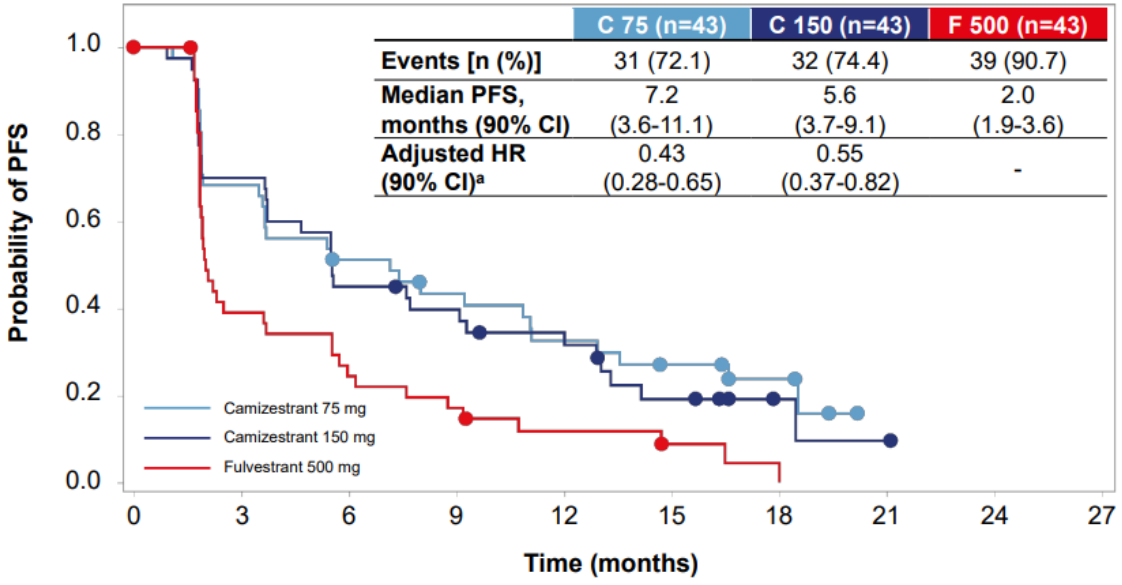
KEY DATA

SERENA-2 Clinical Trial

PFS By lung and/or liver metastases

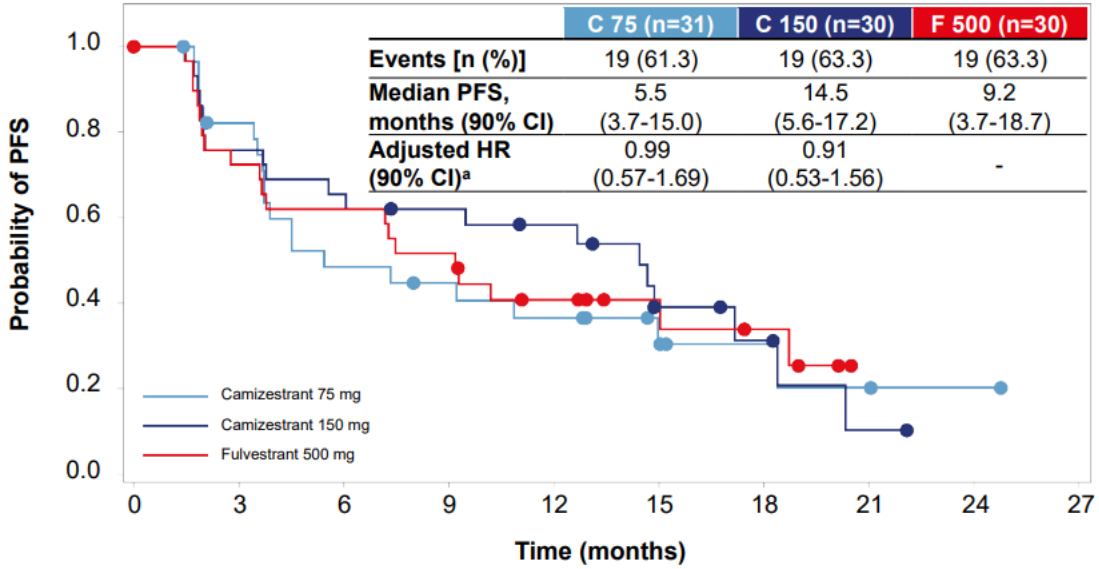
Presence of lung and/or liver metastases



	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-

C 75	43	28	20	16	12	9	4	0		
C 150	43	28	18	15	12	6	2	1	0	
F	43	16	10	7	4	2	1	0		

No lung or liver metastases



	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

C 75	31	22	13	11	9	5	3	2	1	0
C 150	30	22	19	17	13	6	4	1	0	
F	30	21	18	15	10	6	4	0		

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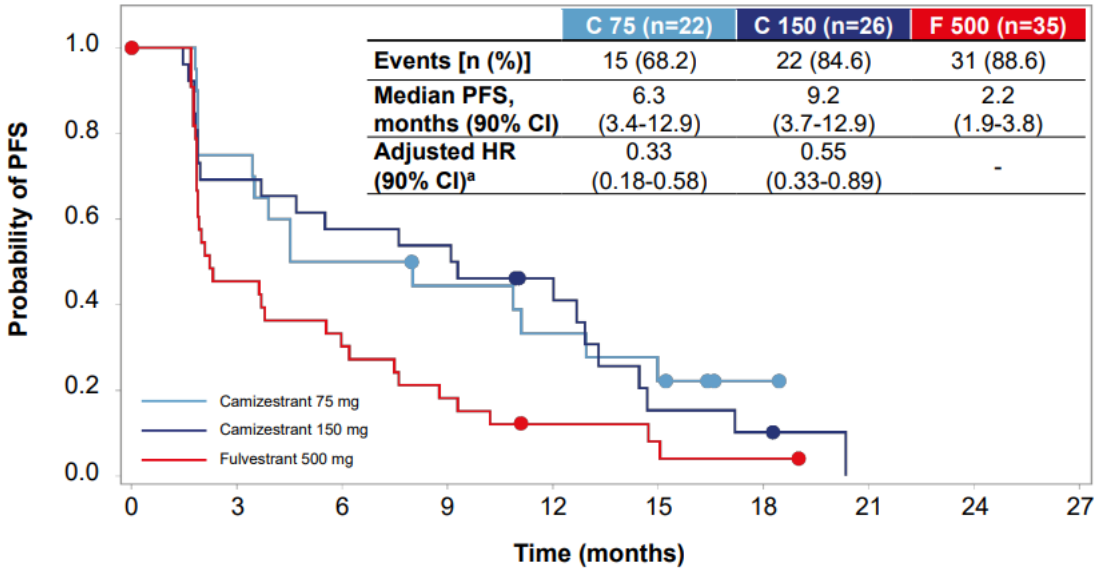
KEY DATA

SERENA-2 Clinical Trial

PFS By Detectable *ESR1*-mutation

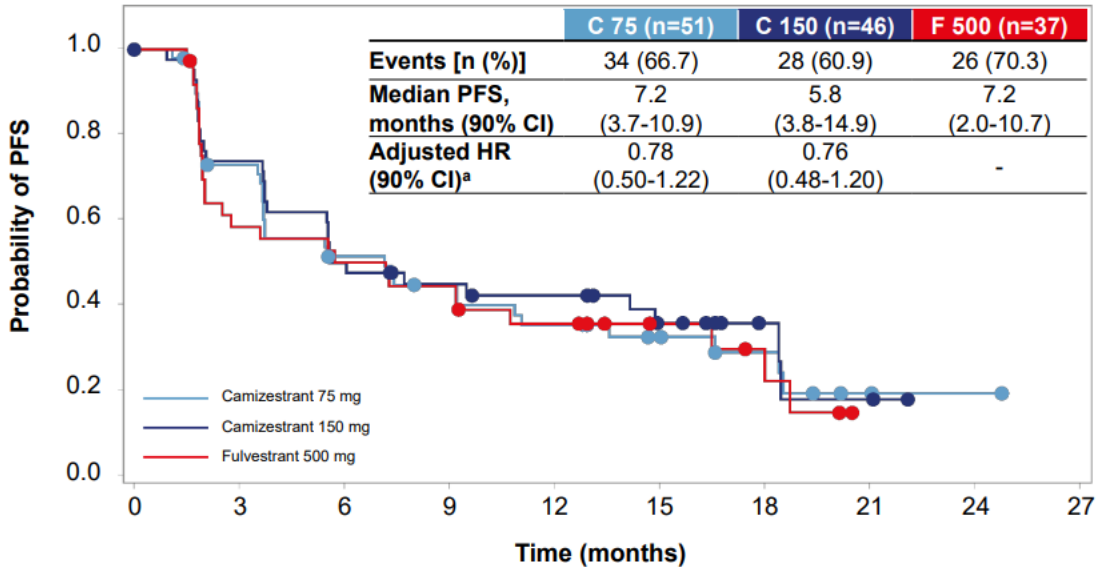
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

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KEY DATA

SERENA-2 Clinical Trial

Overall Response Rate and Clinical Benefit Rate at 24 weeks

Group	n	No. of Patients With Response, n (%)	Adjusted Response Rate, %	Comparison Against Fulvestrant		
				Odds Ratio	90% CI	2-sided P Value
ORR*						
Camizestrant 75 mg	70	11 (15.7)	15.7	1.43	0.63-3.33	0.4789
Camizestrant 150 mg	65	13 (20.0)	20.3	1.96	0.88-4.51	0.1675
Fulvestrant	68	8 (11.8)	11.5	–	–	–
CBR24†						
Camizestrant 75 mg	74	35 (47.3)	48.8	1.48	0.84-2.64	0.2554
Camizestrant 150 mg	73	36 (49.3)	51.0	1.62	0.91-2.89	0.1658
Fulvestrant	73	28 (38.4)	39.1	–	–	–

*Objective response determined only for patients with measurable disease.
†Clinical benefit was defined as patients with best objective response of CR or PR in first 25 wk or patients with stable disease for ≥23 wk after randomization.

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KEY DATA

SERENA-2 Clinical Trial

Safety

	Camizestrant 75 mg (n = 74)	Camizestrant 150 mg (n = 73)	Camizestrant 300 mg (n = 20)	Fulvestrant 500 mg (n = 73)
Total duration in mo, mean (SD)	8.27 (6.59)	8.91 (6.78)	9.26 (8.19)	7.34 (6.09)
Any TEAE, n (%)	57 (77.0)	66 (90.4)	19 (95.0)	50 (68.5)
Any TRAE, n (%)	39 (52.7)	49 (67.1)	14 (70.0)	13 (17.8)
• CTCAE grade ≥3	1 (1.4)	2 (2.7)	1 (5.0)	1 (1.4)
• Serious	3 (4.1)	2 (2.7)	1 (5.0)	0
• Fatal	0	0	0	0
• Leading to treatment discontinuation	2 (2.7)	0	0	0
TEAE leading to dose reduction, n (%)	1 (1.4)	9 (12.3)	4 (20.0)	0
TEAE leading to dose interruption, n (%)	11 (14.9)	16 (21.9)	4 (20.0)	3 (4.1)
• TRAE leading to dose interruption, n (%)	7 (9.5)	8 (11.0)	3 (15.0)	0
• Median duration of dose interruption, days	7.0	7.5	7.0	--

- TRAEs of Grade 3 or higher and TRAEs leading to discontinuation were infrequent across all treatment arms
- TRAEs leading to dose interruptions were numerically similar for camizestrant 75 and 150 mg, and of short duration
- All camizestrant doses are well tolerated

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KEY DATA

SERENA-2 Clinical Trial

Safety: TEAEs

All TEAEs, n (%)	Camizestrant 75 mg (n = 74)		Camizestrant 150 mg (n = 73)		Camizestrant 300 mg (n = 20)		Fulvestrant (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**57 (77.0)**	**9 (12.2)**	**66 (90.4)**	**16 (21.9)**	**19 (95.0)**	**3 (15.0)**	**50 (68.5)**	**10 (13.7)**
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0
AST increased	2 (2.7)	0	6 (8.2)	0	2 (10.0)	0	5 (6.8)	1 (1.4)
ALT increased	1 (1.4)	0	6 (8.2)	1 (1.4)	3 (15.0)	0	4 (5.5)	1 (1.4)
COVID-19	4 (5.4)	0	4 (5.5)	0	3 (15.0)	0	3 (4.1)	0
Diarrhea	4 (5.4)	0	4 (5.5)	0	3 (15.0)	1 (5.0)	2 (2.7)	1 (1.4)
Pain in extremity	1 (1.4)	0	4 (5.5)	1 (1.4)	2 (10.0)	0	3 (4.1)	0
Dyspepsia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Insomnia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Hyponatremia	0	0	3 (4.1)	1 (1.4)	2 (10.0)	0	1 (1.4)	1 (1.4)
Blood pressure increased	2 (2.7)	1 (1.4)	1 (1.4)	1 (1.4)	2 (10.0)	1 (5.0)	0	0
Cataract	2 (2.7)	0	0	0	2 (10.0)	0	0	0
Vitreous floaters	2 (2.7)	0	0	0	2 (10.0)	0	0	0

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SUMMARY

SERENA-2 Clinical Trial

- Camizestrant at both 75 and 150 mg doses provides statistically and clinically meaningful PFS benefit over fulvestrant in post-menopausal women with ER+/HER2- ABC
  - PFS benefit was maintained across the prespecified subgroups (postCDK4/6i, lung/liver metastases, ESR1m and evidence of ER-driven disease)
- Camizestrant was well tolerated, with infrequent Grade ≥3 TRAEs, dose reductions and discontinuations
- Recruitment is ongoing to two Phase 3 studies of camizestrant in advanced breast cancer
  - SERENA-4a and SERENA-6b

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SERENA-2 Clinical Trial

Camizestrant demonstrated positive PFS benefit for the treatment of postmenopausal women with ER+/HER2- advanced or mBC and could provide another treatment option

More to come…

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2

- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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CLINICAL QUESTION

CAPItello-291 Clinical Trial

Does capivasertib and fulvestrant provide benefit to patients with aromatase inhibitor-resistant *HR+/HER2-* advanced BC?

Capivasertib, an investigational oral inhibitor of AKT1/2/3, in combination with fulvestrant, significantly prolonged PFS and OS in postmenopausal women with AI-resistant HR+/HER2- ABC and no prior CDK4/6i in phase II FAKTION trial

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KEY DATA

CAPItello-291 Clinical Trial

Study Design: Phase III, randomized, double-blind, placebo-controlled study

Stratification by liver mets (yes vs no), prior CDK4/6i (yes vs no), region

- Men and pre/postmenopausal women with HR+/HER2- ABC
- Recurred on or <12 mo from end of adjuvant AI, or PD on prior AI for ABC
- ≤2 lines of ET and ≤1 line of CT for ABC
- No prior SERD, mTORi, PI3Ki, or AKTi
- A1C <8.0% and diabetes not requiring insulin permitted
- Prior CDK4/6i permitted (required in ≥51%)
- FFPE sample available from primary/recurrent tumor

(N = 708)

R 1:1

Capivasertib 400 mg PO BID (4 days on, 3 days off) + Fulvestrant 500 mg IM on D1,15 of cycle 1, then Q4W (n = 355)

Placebo PO BID (4 days on, 3 days off) + Fulvestrant 500 mg IM on D1,15 of cycle 1, then Q4W (n = 353)

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–

Dual primary endpoints: investigator-assessed PFS in overall population and in those with AKT pathway–altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints: OS and ORR in overall and AKT pathway–altered tumor populations

KEY DATA

CAPItello-291 Clinical Trial

Baseline Characteristics: Overall population

Alteration, n (%)	Capivasertib + FULV (n = 355)	Placebo + FULV (n = 353)
Any AKT pathway alteration	155 (43.7)	134 (38.0)
Any PIK3CA	116 (32.7)	103 (29.2)
• PIK3CA only	110 (31.0)	92 (26.1)
• PIK3CA and AKT1	2 (0.6)	2 (0.6)
• PIK3CA and PTEN	4 (1.1)	9 (2.5)
AKT1 only	18 (5.1)	15 (4.2)
PTEN only	21 (5.9)	16 (4.5)
Nonaltered	200 (56.3)	219 (62.0)
• AKT pathway alteration not detected	142 (40.0)	171 (48.4)
• Unknown	58 (16.3)	48 (13.6)
○ No sample available	10 (2.8)	4 (1.1)
○ Preanalytical failure	39 (11.0)	34 (9.6)
○ Postanalytical failure	9 (2.5)	10 (2.8)

Characteristic, n (%)	Capivasertib + FULV (n = 355)	Placebo + FULV (n = 353)
Female	352 (99.2)	349 (98.9)
Median age, years (range)	59 (26-84)	58 (26-90)
Postmenopausal	287 (80.8)	260 (73.7)
Metastatic sites		
• Bone only	51 (14.4)	52 (14.7)
• Liver	156 (43.9)	150 (42.5)
• Visceral	237 (66.8)	241 (68.3)
Prior ET for ABC		
• 0	40 (11.3)	54 (15.3)
• 1	286 (80.6)	252 (71.4)
• 2	29 (8.2)	47 (13.3)
Prior CDK4/6i for ABC	245 (69.0)	244 (69.1)
Prior Chemotherapy		
• Neo/adjuvant	180 (50.7)	170 (48.2)
• ABC	65 (18.3)	64 (18.1)

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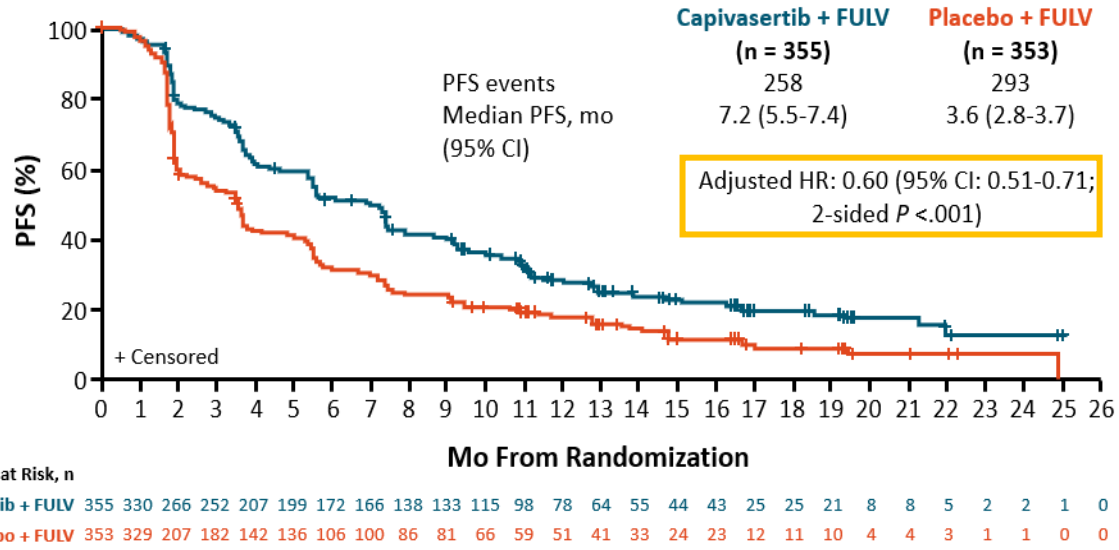
KEY DATA

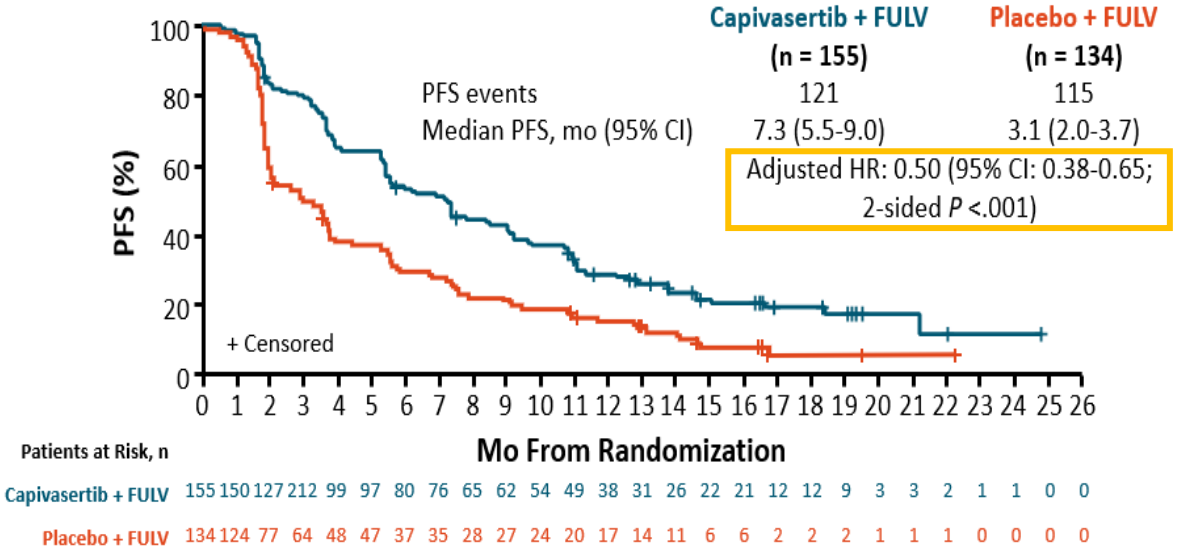
CAPItello-291 Clinical Trial

Investigator assessed PFS

Overall population



AKT-Pathway Altered Population



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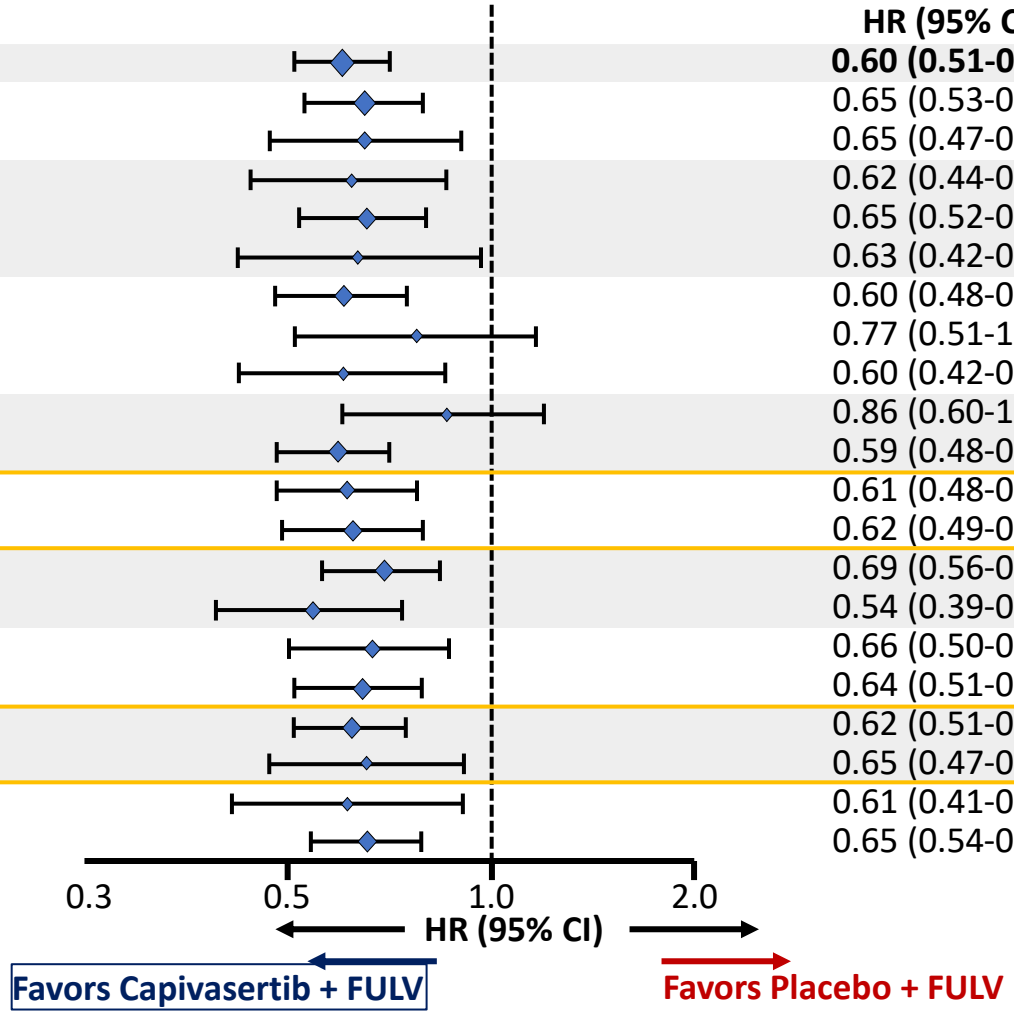
KEY DATA

CAPItello-291 Clinical Trial

Overall population: Investigator assessed PFS by subgroup

		No. Patients	HR (95% CI)
All Patients		**708**	**0.60 (0.51-0.71)**
Age	<65 yr	491	0.65 (0.53-0.79)
	≥65 yr	217	0.65 (0.47-0.90)
Race	Asian	189	0.62 (0.44-0.86)
	White	407	0.65 (0.52-0.80)
	Other	112	0.63 (0.42-0.96)
Region	1	395	0.60 (0.48-0.75)
	2	136	0.77 (0.51-1.16)
	3	177	0.60 (0.42-0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60-1.20)
	Post	547	0.59 (0.48-0.71)
Liver metastases	Yes	306	0.61 (0.48-0.78)
	No	402	0.62 (0.49-0.79)
Visceral metastases	Yes	478	0.69 (0.56-0.84)
	No	230	0.54 (0.39-0.74)
Endocrine resistance	Primary	262	0.66 (0.50-0.86)
	Secondary	446	0.64 (0.51-0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51-0.75)
	No	212	0.65 (0.47-0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41-0.91)
	No	579	0.65 (0.54-0.78)



SABCS 2022. Abstract GS3-04

CAPItello-291 Clinical Trial

Overall Response Rate

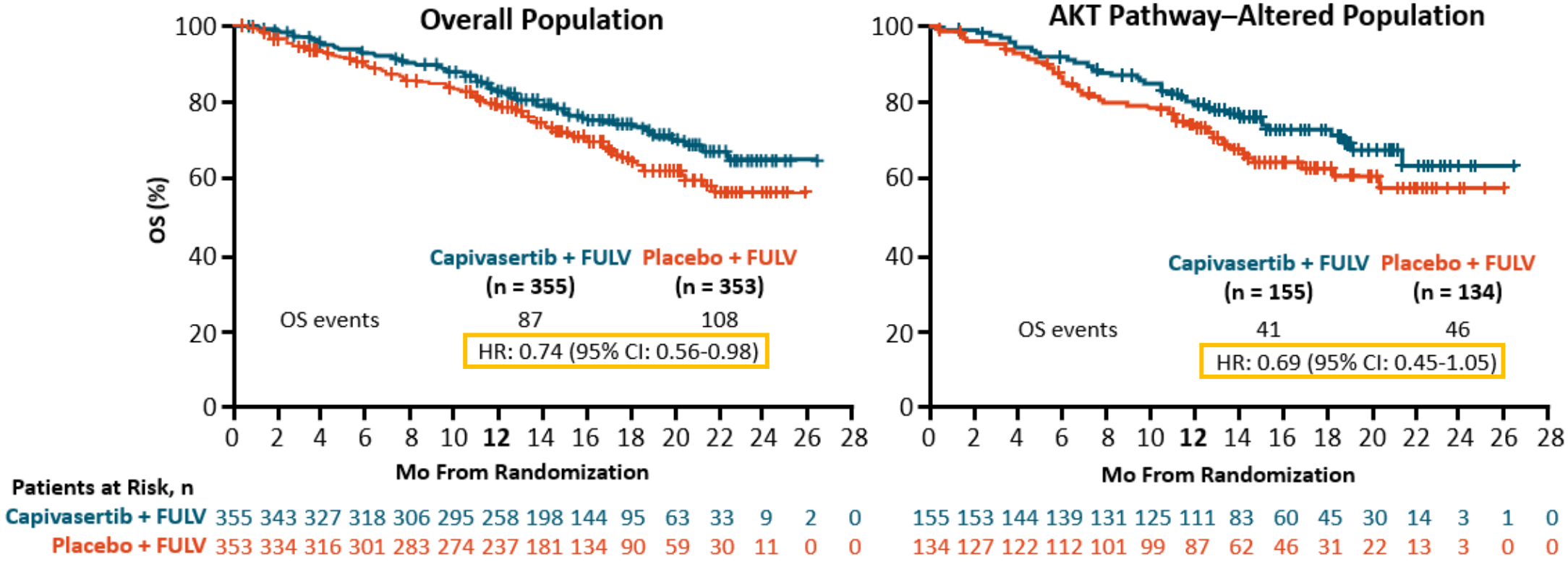
Response, n (%)	Overall		AKT Pathway Altered	
	Capivasertib + FULV	Placebo + FULV	Capivasertib + FULV	Placebo + FULV
Measurable disease at baseline	n = 310	n = 320	n = 132	n = 124
• ORR	**71 (22.9)**	**39 (12.2)**	**38 (28.8)**	**12 (9.7)**
• Odds ratio (95% CI)	2.19 (1.42 – 3.36)		3.93 (1.93 – 8.04)	
Best objective response in all patients	n = 355	n = 353	n = 155	n = 134
• CR	4 (1.1)	1 (0.3)	3 (1.9)	0
• PR	68 (19.2)	38 (10.8)	35 (22.6)	12 (9.0)
• SD (≥8 wk)	187 (52.7)	152 (43.1)	84 (54.2)	55 (41.0)
• PD	83 (23.4)	149 (42.2)	31 (20.0)	62 (46.3)
• Not evaluable	13 (3.7)	13 (3.7)	2 (1.3)	5 (3.7)

SABCS 2022. Abstract GS3-04

KEY DATA

CAPItello-291 Clinical Trial

Overall Survival



Note: OS data at 28% maturity in overall population

SABCS 2022. Abstract GS3-04

CAPItello-291 Clinical Trial

Safety

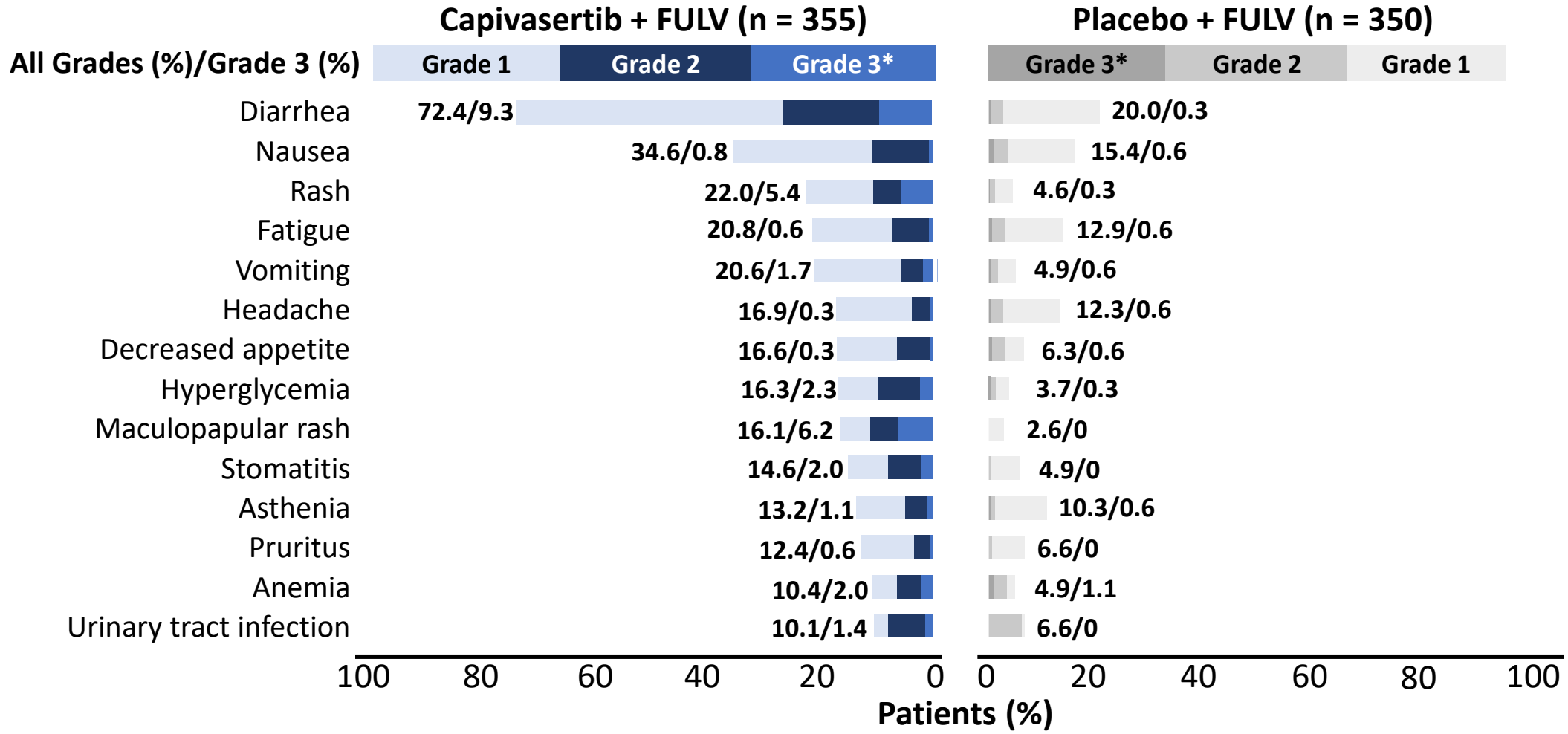
AE, n (%)	Capivasertib + FULV (n = 355)	Placebo + FULV (n = 350)
Any AE	343 (96.6)	288 (82.3)
Any serious AE	57 (16.1)	28 (8.0)
Any AE leading to death	4 (1.1)	1 (0.3)
Any AE leading to discontinuation	46 (13.0)	8 (2.3)
• Capivasertib/placebo only	33 (9.3)	2 (0.6)
• Both capivasertib/placebo and FULV	13 (3.7)	6 (1.7)
Any AE leading to dose interruption of capivasertib/ placebo only	124 (34.9)	36 (10.3)
Any AE leading to dose reduction of capivasertib/placebo only	70 (19.7)	6 (1.7)

- n = 5 grade 5 events, none deemed related to capivasertib/placebo by local investigator
  - Capivasertib + FULV: n = 1 each of acute MI, cerebral hemorrhage, pneumonia aspiration, sepsis
  - Placebo + FULV: COVID-19, n = 1
- Safety profile comparable for overall vs AKT pathway–altered populations

KEY DATA

CAPItello-291 Clinical Trial

AEs in >10% of Overall Population



SABCS 2022. Abstract GS3-04

SUMMARY

CAPItello-291 Clinical Trial

- Capivasertib plus fulvestrant significantly prolonged PFS vs placebo plus fulvestrant in overall and AKT pathway–altered patient populations
  - PFS benefit generally consistent across subgroups, including those with prior CDK4/6 inhibitor treatment and those with liver metastases
  - OS data immature

SABCS 2022. Abstract GS3-01.

CAPItello-291 Clinical Trial

Capivasertib plus fulvestrant has the potential to be a future treatment option for patients with HR+ advanced BC who have progressed on an endocrine-based regimen

More to come…potential approval of first AKT inhibitor

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE
- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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TROPiCS-02

Does sacituzumab govitecan provide benefit to patients with previously treated *HR+/HER2-* mBC?

Trop-2 Subgroup Analysis

On April 7, 2021, the Food and Drug Administration granted regular approval to sacituzumab govitecan (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease

cornerstone specialty network™

KEY DATA

TROPiCS-02

Study Design: Randomized, multicenter, open-label phase III study

Stratification by visceral metastases (yes vs no), ET in metastatic setting ≥6 mo (yes vs no), prior lines of chemotherapy (2 vs 3/4)

- Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression
- At least 1 ET, taxane, and CDK4/6 inhibitor in any setting
- 2-4 previous lines of chemotherapy for metastatic disease (neo/adjuvant therapy qualified as a prior line if disease recurred within 12 mo)
- Measurable disease by RECIST v1.1

(N = 543)

R 1:1

Sacituzumab Govitecan
10 mg/kg IV d1 and 8, q 21 days
(n = 272)

Until PD or unacceptable toxicity

Physician's Choice of Treatment
(Capecitabine, vinorelbine, gemcitabine, or eribulin)
(n = 271)

Primary endpoint:
- PFS (BICR)

Secondary endpoints:
- OS
- ORR
- DoR
- CBR (by LIR and BICR)
- PRO
- Safety

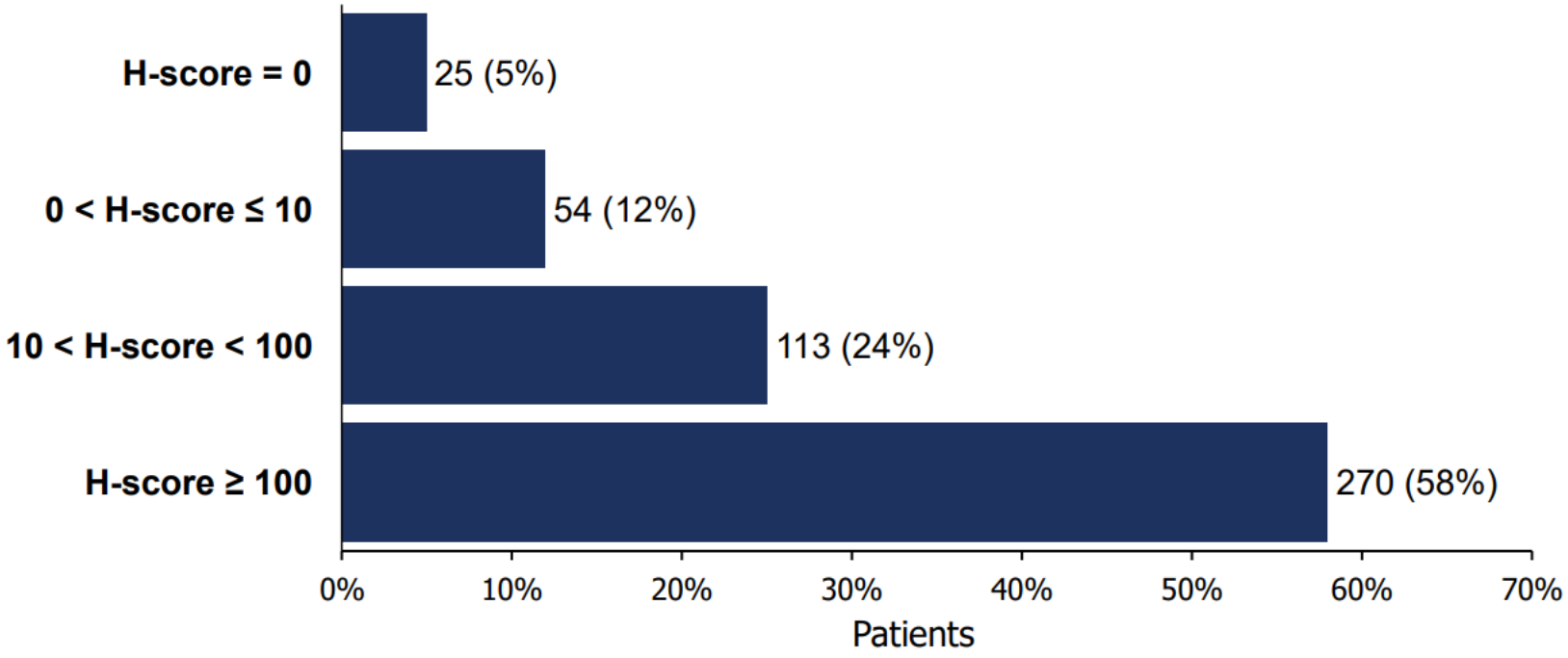
Trop-2 Subgroup Analysis: to evaluate the potential impact of Trop-2 expression on efficacy outcomes in TROPICS-02
- Trop-2 expression was not required to determine patient eligibility and was not a stratification factor in TROPICS-02
- Trop-2 expression was determined on primary or metastatic archival tumor tissue requested at study entry
- Median time from tumor tissue collection to study entry was 7.7 months (range, 0.03-177.9)
- Membrane Trop-2 expression was assessed by a validated research IHC assay at a CAP/CLIA central laboratory

SABCS 2022. Abstract GS1-11.

TROPiCS-02

Trop-2 Expression in Tumor Tissue Samples

- 238 patients (88%) in the SG and 224 patients (83%) in the TPC group had samples evaluable for Trop-2 expression



SABCS 2022. Abstract GS1-11.

KEY DATA

TROPiCS-02: Demographics

Sacituzumab govitecan for refractory HR+/HER2 neg breast cancer

Characteristic	Sacituzumab Govitecan (n = 238)		Physician's Choice (n = 224)	
	H-Score <100 (n = 96)	H-Score ≥100 (n = 142)	H-Score <100 (n = 96)	H-Score ≥100 (n = 128)
Median age, yr (range)	55 (36-78)	58 (29-86)	56 (27-78)	56 (32-75)
Race/ethnicity, n (%)				
▪ White	65 (68)	97 (68)	64 (67)	87 (68)
▪ Non-White	8 (8)	7 (5)	8 (8)	8 (6)
▪ Other or not reported	23 (24)	38 (27)	24 (25)	33 (26)
ECOG PS, n (%)				
▪ 0	36 (38)	69(47)	49 (51)	50 (39)
▪ 1	60 (63)	73(51)	47 (49)	78 (61)

Characteristic, n (%)	Sacituzumab Govitecan (n = 238)		Physician's Choice (n = 224)	
	H-Score <100 (n = 96)	H-Score ≥100 (n = 142)	H-Score <100 (n = 96)	H-Score ≥100 (n = 128)
Visceral mets				
▪ Yes	92 (96)	135 (95)	91 (95)	122 (95)
▪ No	4 (4)	7 (5)	5 (5)	6 (5)
Prior lines of CT for MBC				
▪ 2	33 (34)	68 (48)	40 (42)	57 (45)
▪ 3-4	63 (66)	74 (52)	56 (58)	71 (55)
Prior ET use in MBC setting ≥6 mo	82 (85)	125 (88)	81 (84)	114 (89)
Prior CDK4/6i use				
▪ ≤12 mo	53 (55)	91 (64)	57 (59)	86 (67)
▪ >12 mo	43 (45)	46 (32)	38 (40)	40 (31)
▪ Unknown	0	5 (4)	1 (1)	2(2)

SABCS 2022. Abstract GS1-11.

KEY DATA

TROPiCS-02: PFS, OS, & ORR (previously reported)

PFS and OS in the ITT Population

PFS by BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median PFS, mo (95% CI)	**5.5** (4.2-7.0)	**4.0** (3.1-4.4)
• Stratified hazard ratio (95% CI)	**0.66** (0.53-0.83)	
• Stratified log-rank *P* value	**0.0003**	
6-mo PFS, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo PFS, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo PFS, % (95% CI)	**21.3** (15.2-28.1)	**7.1** (2.8-13.9)

OS at second interim analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Number of events	191	199
Median OS, mo (95% CI)	**14.4** (13.0 – 15.7)	**11.2** (10.1 – 12.7)
• Stratified hazard ratio (95% CI)	**0.79** (0.65-0.96)	
• Stratified log-rank *P* value	**0.020**	
12-mo OS, % (95% CI)	**61** (55 – 66)	**47** (41–53)

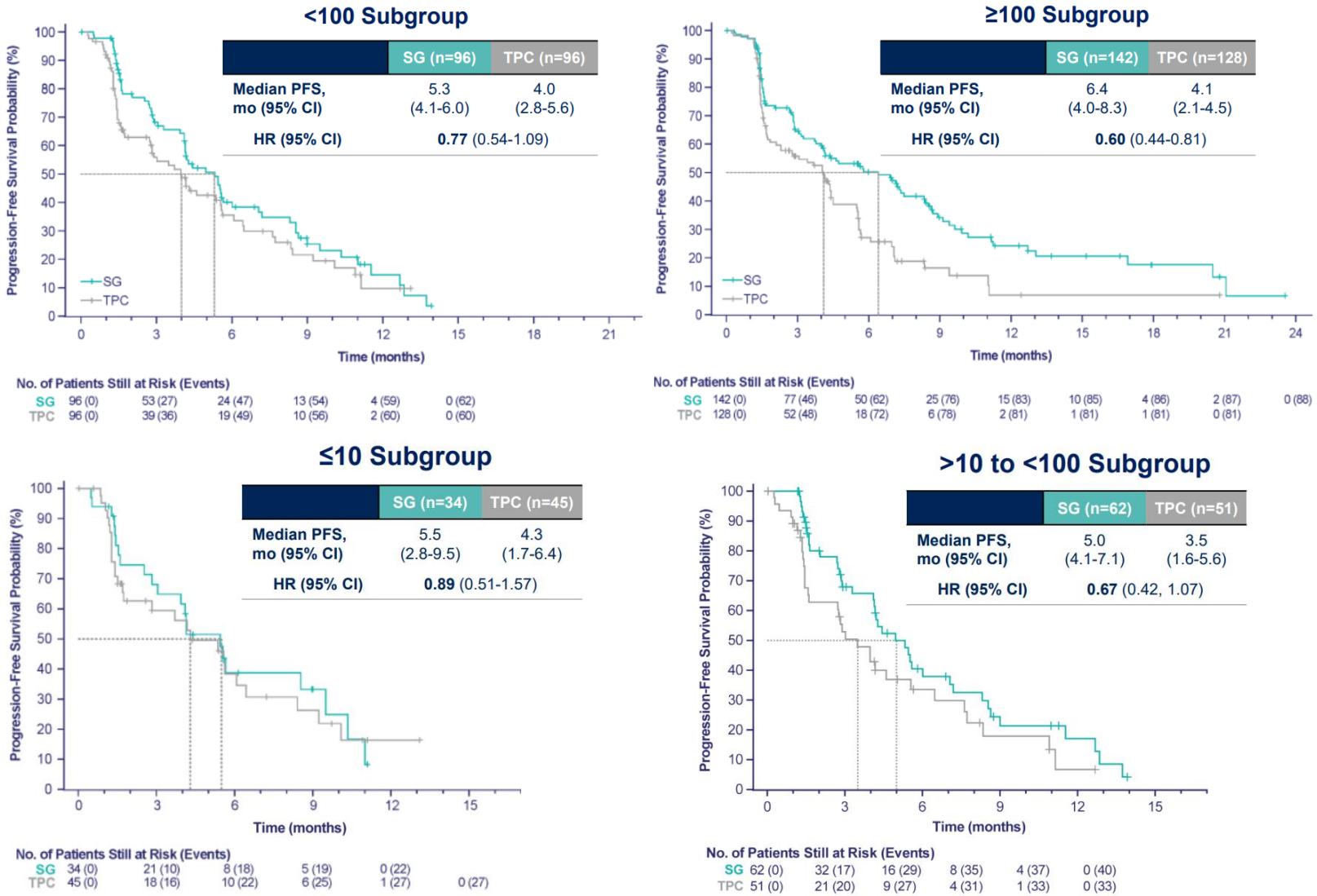
Response Rates in the ITT Population

BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
ORR, n (%)	57 (21)	38 (14)
• Odds ratio (95% CI)	1.63 (1.03 – 2.56), *P* = 0.035	
Best overall response, n (%)		
• CR	2 (1)	0
• PR	55 (20)	38 (14)
• SD	142 (52)	106 (39)
• SD ≥6 mo	35 (13)	21 (8)
• PD	58 (21)	76 (28)
• NE	15 (6)	51 (19)
CBR,* n (%)	92 (34)	60 (22)
• Odds ratio (95% CI)	1.80 (1.23 – 2.63), *P* = 0.003	
Median DoR, mo (95% CI)	**8.1** (6.7-9.1)	**5.6** (3.8-7.9)

SABCS 2022. Abstract GS1-11.

KEY DATA

TROPiCS-02: PFS, Trop-2

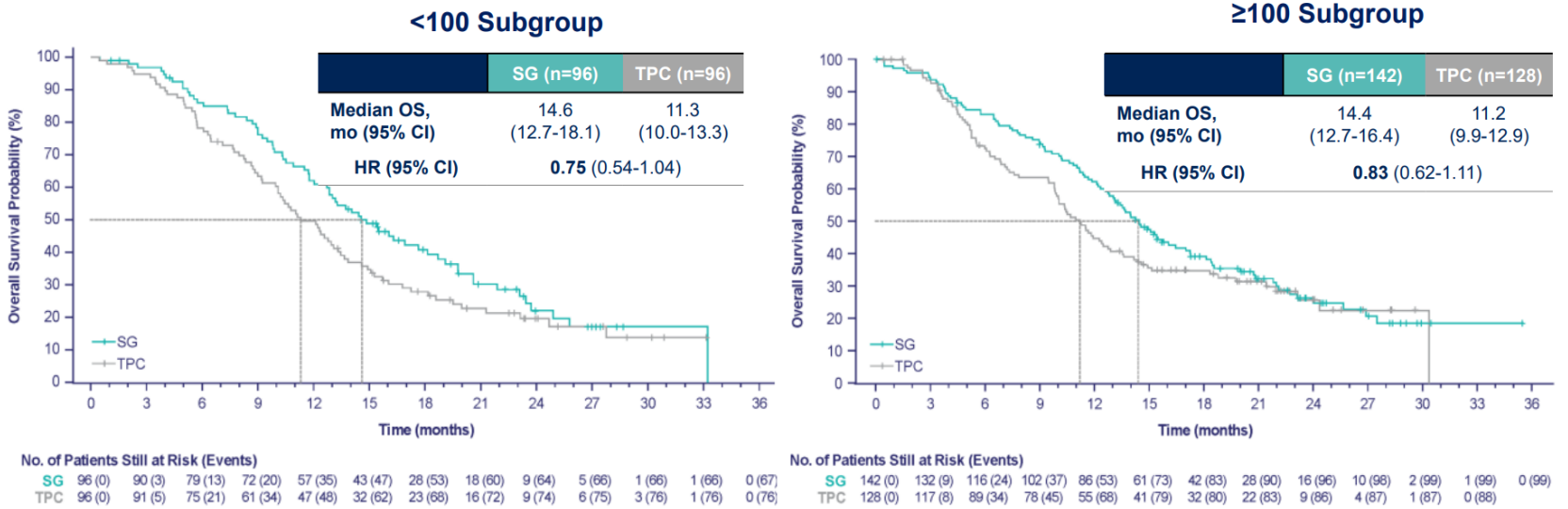


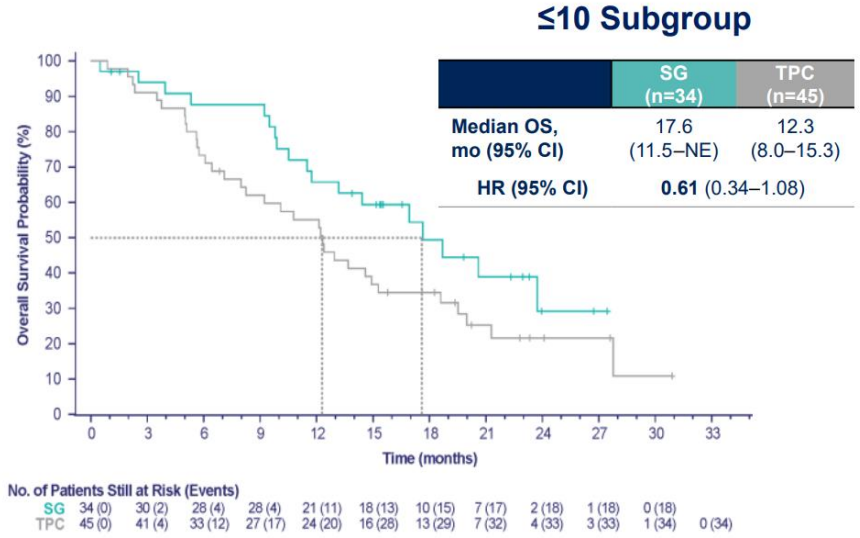
- PFS outcome favored SG over TPC across all Trop-2 H-score subgroups, including those with very low Trop-2 expression (H-score ≤10)

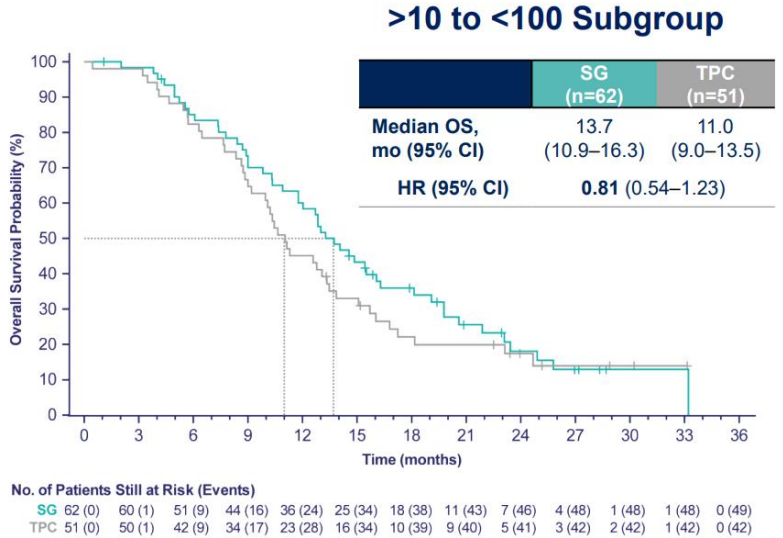
SABCS 2022. Abstract GS1-11.

KEY DATA

TROPiCS-02: OS, Trop-2







- OS benefit with SG over TPC was consistently observed across all Trop-2 H-score subgroups, including those with very low Trop-2 expression (H-score ≤10)

SABCS 2022. Abstract GS1-11.

TROPiCS-02: OS, Trop-2

Objective Response Rates

Response to SG are observed in all Trop-2 subgroups, including those with very low Trop-2 expression (H-score ≤10)

Response	H-Score		
	≤10 (n = 34)	**>10 to <100 (n = 62)**	**≥100 (n = 142)**
ORR, n (%)	8 (24)	11 (18)	33 (23)
CBR, n (%)	11 (32)	17 (27)	55 (39)
Median DoR, mo (95% CI)	7.5 (2.5-NR)	7.4 (4.1-NR)	8.5 (5.9-16.9)

SABCS 2022. Abstract GS1-11.

KEY DATA

TROPiCS-02: OS, Trop-2

Safety Summary

Safety Outcome, n (%)	Sacituzumab Govitecan (n = 268)		Physician's Choice (n = 249)	
	H-Score <100 (n = 96)	H-Score ≥100 (n = 140)	H-Score <100 (n = 94)	H-Score ≥100 (n = 123)
Grade ≥3 TEAEs	76 (79)	103 (74)	58 (62)	78 (63)
TEAEs leading to treatment discontinuation	2 (2)	11 (8)	5 (5)	5 (4)
TEAEs leading to dose delay	68 (71)	93 (66)	43 (46)	52 (42)
TEAEs leading to dose reductions	32 (33)	51 (36)	37 (39)	35 (28)
TE SAEs	25 (26)	42 (30)	18 (19)	27 (22)
TEAEs leading to death*	1 (1)	4 (3)	0	0
• Treatment related	1 (1)	0	0	0
Select TEAEs (grade ≥3)				
• Neutropenia**	56 (58)	76 (54)	43 (46)	43 (35)
• Febrile neutropenia	7 (7)	9 (6)	4 (4)	6 (5)
• Diarrhea	10 (10)	13 (9)	1 (1)	1 (1)

*Five of the 6 participants who experienced a TEAE leading to death had a known H-score. Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. On detailed review of the TEAEs leading to death, there were no patterns identified.

**Neutropenia includes combined terms of neutropenia, neutrophil count decreased, and febrile neutropenia.

SABCS 2022. Abstract GS1-11.

SUMMARY

TROPiCS-02 Clinical Trial

- Continued demonstration of modest clinical benefit in PFS and OS with sacituzumab govitecan compared to TPC in patients with pretreated, endocrine-resistant HR+/HER2– mBC
  - PFS and OS benefit of SG over TPC was observed across Trop-2 subgroups (H-score <100 and ≥100)
  - Benefit from SG was also observed in patients whose tumors had very low Trop-2 expression, including those with H-score ≤10
- Caution should be exercised in data interpretation given the small sample size in this Trop-2 subgroup
- SG demonstrated a manageable safety profile, which was not impacted by Trop-2 expression

TROPiCS-02 Clinical Trial

Exploratory analysis confirmed modest efficacy of sacituzumab govitecan across all Trop-2 expression levels, even those with very low expression in HR+/HER2- advanced breast cancer

Trop-2 testing is not required for sacituzumab govitecan treatment

KEY QUESTIONS

HER2+ Breast Cancer

What role do ADCs play in the treatment of patients with HER2-positive and HER2-low breast cancer?

Should HER2-low be considered a separate entity?

What % of HER2 positive cells are needed to see a therapeutic effect?

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2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2

- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

cornerstone specialty network™

CLINICAL QUESTION

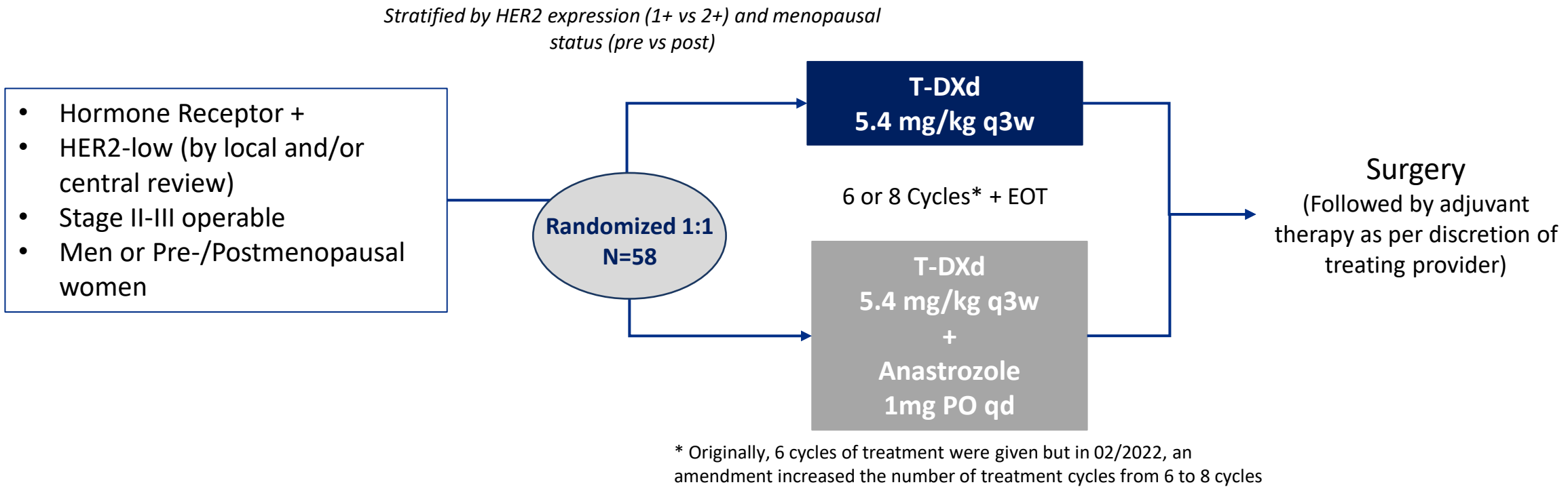
TALENT Clinical Trial

Does the use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) with or without anastrozole in the neoadjuvant setting benefit pts with HER2-low, HR+ early stage breast cancer?

KEY DATA

TALENT Clinical Trial

Study Design: Investigator-initiated multicenter, randomized, open-label phase II trial



* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 cycles

Primary End Point: pCR rate in breast and LNs (ypT0/is ypTN0; RCBI = 0)
Secondary Endpoints: ORR, Tumor biomarkers including change in HER2, Safety

Simon's minimax two-stage study design:
- 58 participants randomly assigned 1:1 to one of two treatment arms
- No formal statistical comparison between the arms
- pCR ≤ 5% as statistical benchmark

KEY DATA

TALENT Clinical Trial

Baseline Characteristics

	T-DXd (n=29)	T-DXd + Anastrozole (n=29)
Age, Median (range), years	59 (33 – 87)	55(32 – 83)
Post Menopausal status, n (%)	17 (60.7)	17 (58.6)
Stage, n (%)		
• IIA	8 (27.6)	11 (37.9)
• IIB	13 (44.8)	15 (51.7)
• IIIA	7 (24.1)	3 (10.3)
• IIIB	1 (2.4)	0 (0)
HER2 Status (IHC, %)*		
• 0	2 (6.9)	2 (6.9)
• 1+	22 (75.9)	25 (86.2)
• 2+	4 (13.8)	2 (6.9)
• 1+ & 2+**	1 (3.4)	0 (0)
HR status, ER+ and PR+, n (%)	24 (82.8)	26 (89.7)
Lymph node positive, n (%)	15 (51.7)	16 (55.2)
Histology, n (%)		
• Invasive ductal / invasive lobular	25 (86.2) / 4 (13.8)	26 (89.7) / 3 (10.3)***

	T-DXd (n=29)	T-DXd + Anastrozole (n=29)
Baseline Ki67 Scores, n (%)		
• <10%	1 (3.4)	0 (0)
• ≥10% and < 30%	12 (41.4)	10 (34.5)
• ≥30%	16 (55.2)	19 (65.5)
Tumor Grade, n (%)		
• Grade 1	4 (13.8)	1 (3.4)
• Grade 2	14 (48.3)	16 (55.2)
• Grade 3	11 (37.9)	11 (37.9)
• Not reported	0 (0)	1 (3.4)

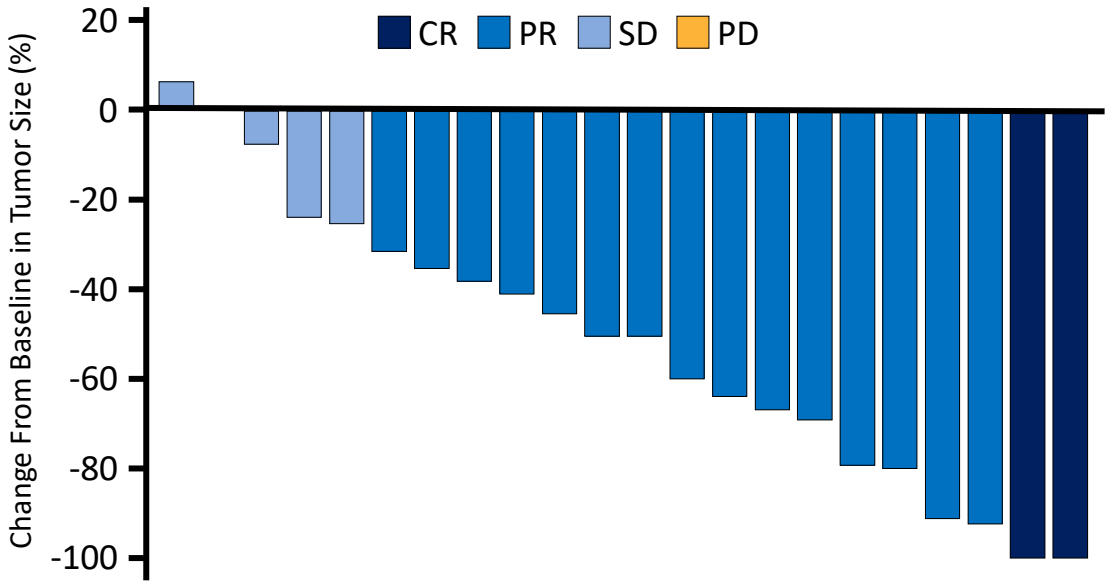
- * Patients were eligible if HER2 IHC was 1+ or 2+ by local or central review **1 multicentric lesion ***1 mixed ductal/lobular
- 4 patients had HER2 IHC 1+ by local assessment which was determined as IHC 0 by central assessment
- 1 patient with single lesion and multiple grades (2 & 3) included in Grade 3 only
- 2 patients with 2 masses and multiple grades (2 & 3) included in Grade 3 only

KEY DATA

TALENT Clinical Trial

Overall Response Rate

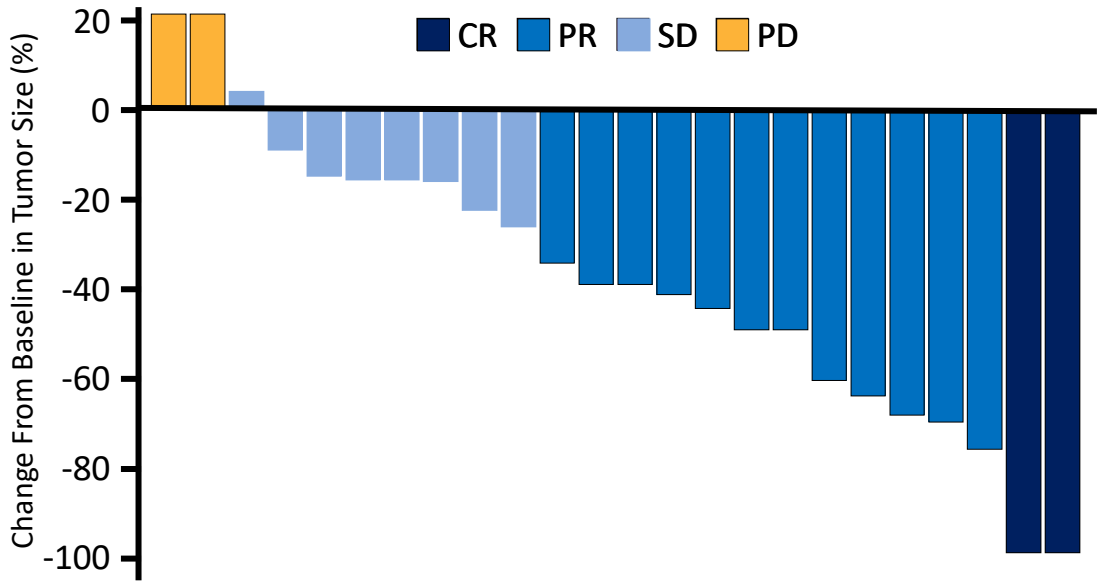
Arm A: T-DXd (n = 25)



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

- 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in ITT denominator for ORR analysis per protocol

Arm B: T-DXd + Anastrozole (n = 24)



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

- 5 patients still on treatment

KEY DATA

TALENT Clinical Trial

Change in HER2 IHC with T-DXd by Central Review

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

Change From Baseline to Surgery in HER2 IHC Staining

- **Decreased**
- **Remained stable**
- **Increased**

TALENT Clinical Trial

Residual cancer burden after T-DXd

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

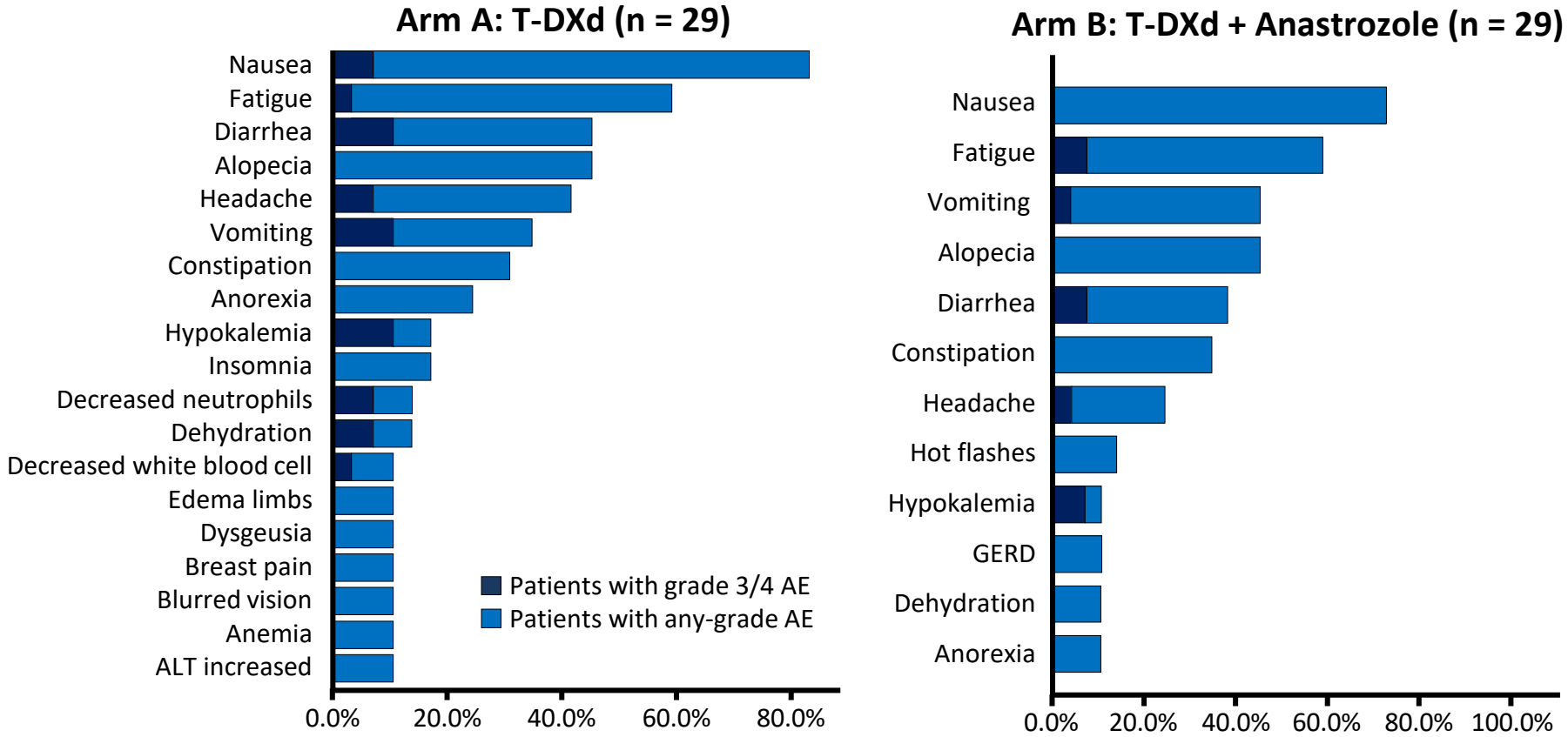
As of data cutoff 11/25/2022: surgical outcomes pending for 24% (7/29) patients being treated in Arm A and 31% (9/29) in Arm B.
*4 pts discontinued early Arm A
**3 pts discontinued early (included in denominator for intention to treat analysis) Arm B
RCBi = Residual cancer burden index; RCB 0 = pCR; Histology or IHC Status did not appear to be associated with RCB response

KEY DATA

TALENT Clinical Trial

Safety

T-DXd–Related AEs in ≥10% of Patients



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

SUMMARY

TALENT Clinical Trial

- Neoadjuvant T-DXd was associated with clinical activity in HR+/HER2-low early breast cancer
  - ORR: T-DXd alone, 68%
    T-DXd + anastrozole, 58%
- No new safety concerns
- Supports further study of ADCs in early disease

TALENT Clinical Trial

Use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the neoadjuvant setting shows potential as a treatment option with or without anastrozole

More to come…

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

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CLINICAL QUESTION

DESTINY-Breast03 Clinical Trial

Does the use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 2L setting benefit pts with HER2+ MBC, when compared with T-DM1?

Updated OS Analysis

(Overall survival data had not been reached in the first interim analysis).

May 6, 2022: The U.S. Food and Drug Administration (FDA) approved ENHERTU® (fam-trastuzumab deruxtecan-nxki) in the U.S. for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or without six months of completing therapy

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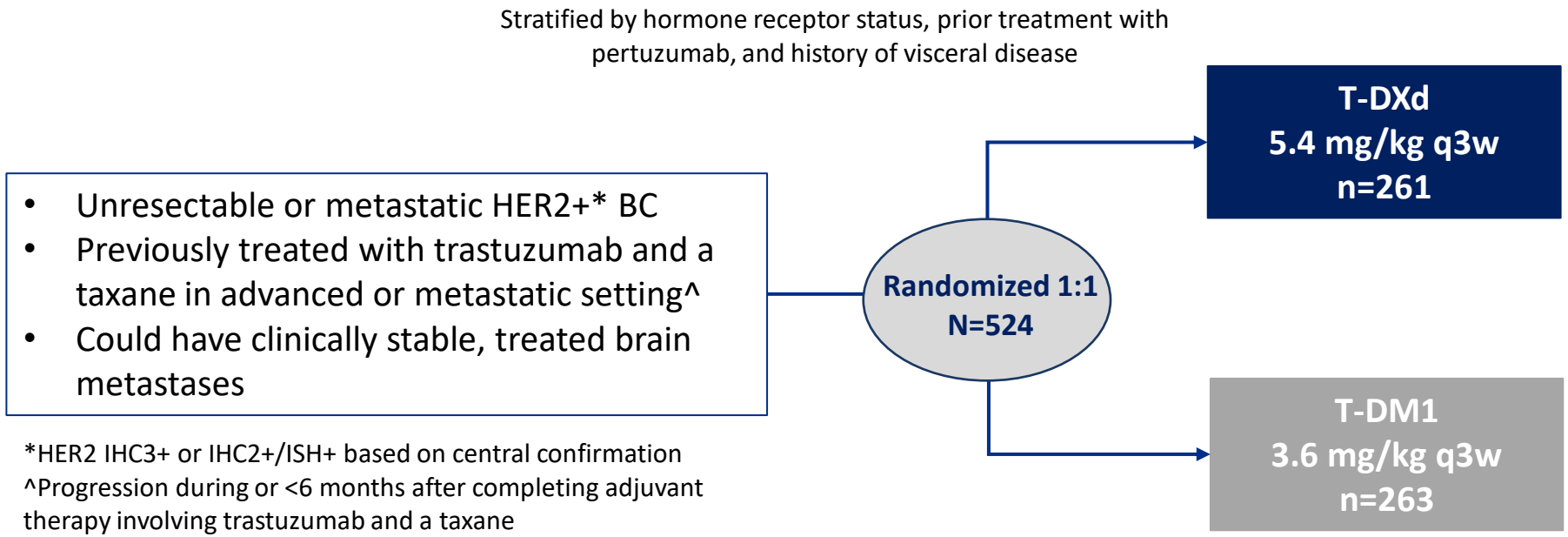
KEY DATA

DESTINY-Breast03 Clinical Trial

Study Design: Phase 3 open-label, multicenter study



Primary End Point:

- PFS (Blinded ICR)

Secondary Endpoints:

- OS
- ORR (BICR and investigator)
- DoR (BICR)
- Safety

- The prespecified OS interim analysis was planned with 153 events
- At the time of data cutoff (July 25, 2022), 169 OS events were observed and the P value to achieve statistical significance was 0.013
  - Note: Primary data cutoff May 21, 2021

KEY DATA

DESTINY-Breast03 Clinical Trial

Patient Disposition: screened n=699; randomized n=524

	Randomized to T-DXd (n=261) Treated (n=257)	Randomized to T-DM1 (n=263) Treated (n=261)
Ongoing study treatment	**75**	**18**
Discontinued study treatment	**182**	**243**
• Death	4	4
• Adverse Event	54	21
• Progressive Disease	94	178
• Clinical Progression	5	14
• Withdrawal by Subject	17	12
• Physician Decision	2	8
• Other	6	6

Median follow up for T-DXd was 28.4 months and for T-DM1 was 26.5 months

KEY DATA

DESTINY-Breast03 Clinical Trial

Baseline Characteristics

	Randomized to T-DXd (n=261)	Randomized to T-DM1 (n=263)
Age, Median (range), years	54.3 (27.9 – 83.1)	54.2 (20.2 – 83.0)
Female, %	99.6	99.6
Region, %		
• Europe	20.7	19.0
• Asia	57.1	60.8
• North America	6.5	6.5
• Rest of World	15.7	13.7
HER2 Status (IHC, %)		
• 3+	89.7	88.2
• 2+ (ISH amplified)	9.6	11.4
• 1+ / not evaluable	0.4 / 0.4	0 / 0.4
ECOG PS, %: 0 / 1 / missing	59.0 / 40.6 / 0.4	66.5 / 33.1 / 0.4
Hormone Receptor Positive, %	50.2	51.0
Baseline Brain Mets, %	16.5	14.8
Visceral Disease, %	70.5	70.3

KEY DATA

DESTINY-Breast03 Clinical Trial

Prior Therapies

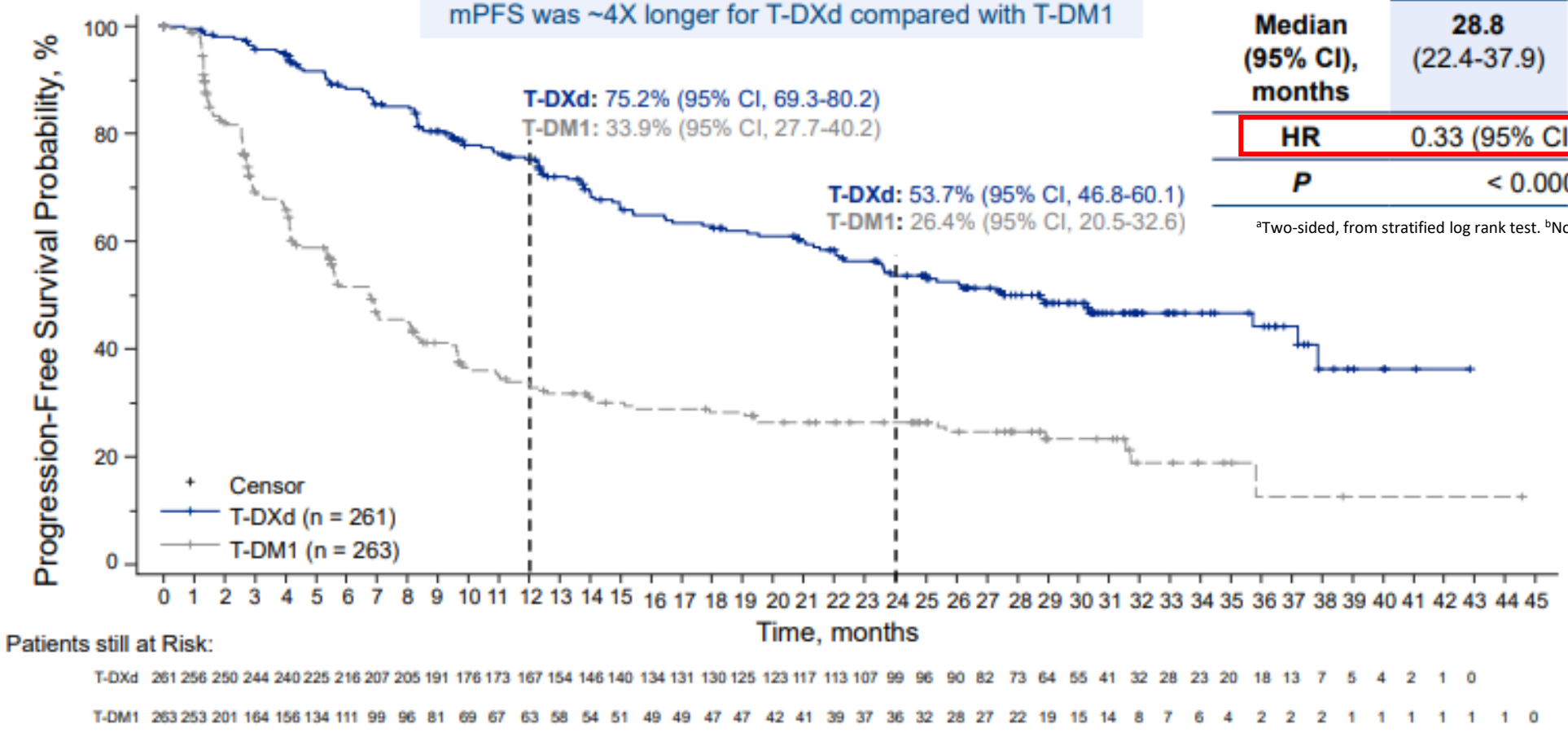
	Randomized to T-DXd (n=261)	Randomized to T-DM1 (n=263)
Any Prior Treatment for mBC, n (%)	260 (99.6)	262 (99.6)
Number of prior lines of therapy in the metastatic setting, median (range)	2 (0-16)	2 (0-15)
Prior Cancer Therapy, n (%)		
• Trastuzumab	260 (99.6)	262 (99.6)
• Pertuzumab	162 (62.1)	158 (60.1)
• Other anti-HER2*	42 (16.1)	38 (14.4)
Prior lines of therapy in the metastatic setting, n (%)		
• 0	1 (0.4)	1 (0.4)
• 1	108 (41.4)	102 (38.8)
• 2	60 (23.0)	64 (24.3)
• 3	44 (16.9)	45 (17.1)
• 4	15 (5.7)	23 (8.7)
• ≥5	33 (12.6)	28 (10.6)

Note: 2 patients (1 in each treatment arm) were randomized in error and the prior cancer systemic therapy case report form was not completed. Prior treatment includes regimens indicated for advanced/metastatic or early progression within 6 months of regimen for (neo)adjuvant (12 months for pertuzumab).
*Includes anti-HER2 TKI and other anti-HER2 antibody or ADC

KEY DATA

DESTINY-Breast03 Clinical Trial

Updated Primary Endpoint: PFS by BICR



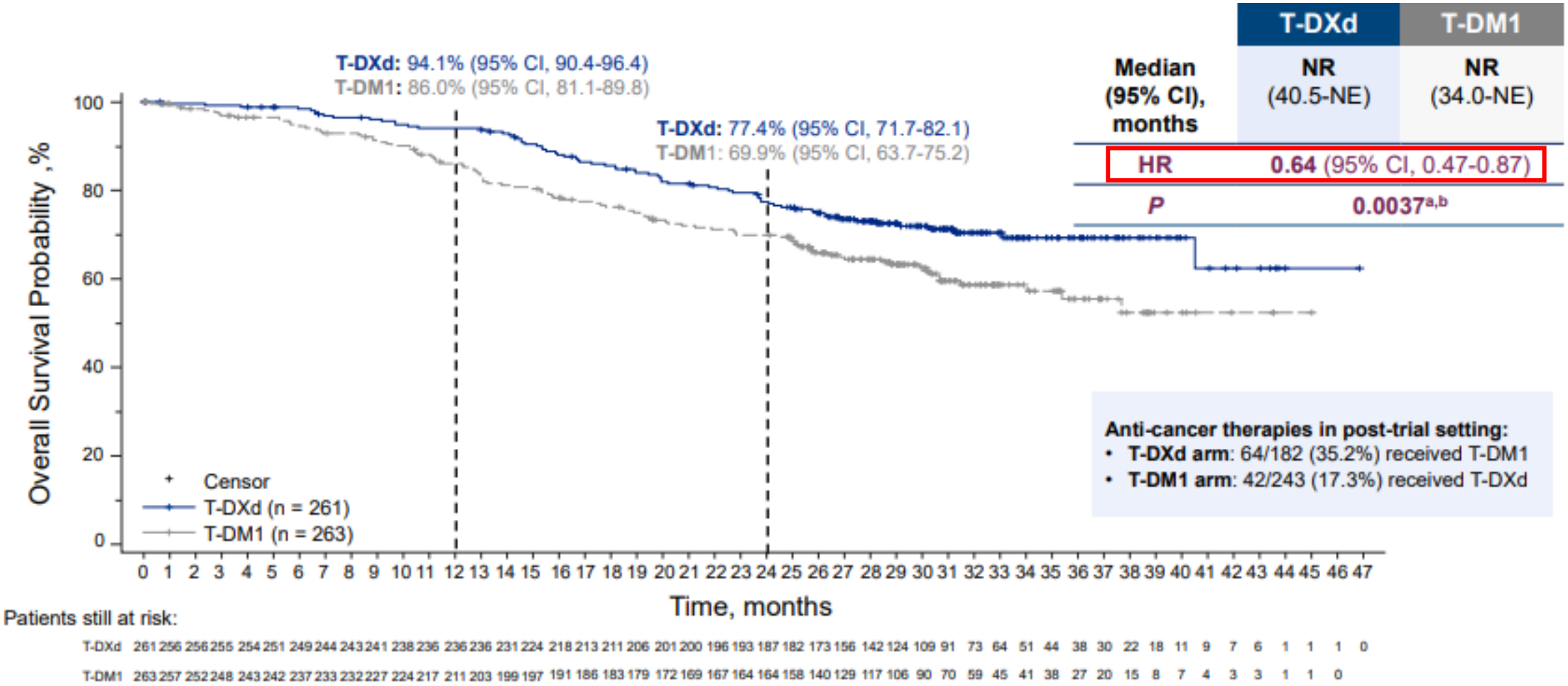
	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

[a]Two-sided, from stratified log rank test. [b]Nominal P value.

KEY DATA

DESTINY-Breast03 Clinical Trial

Updated Key Secondary Endpoint: OS



	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	0.64 (95% CI, 0.47-0.87)	
P	0.0037[a,b]	

Anti-cancer therapies in post-trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

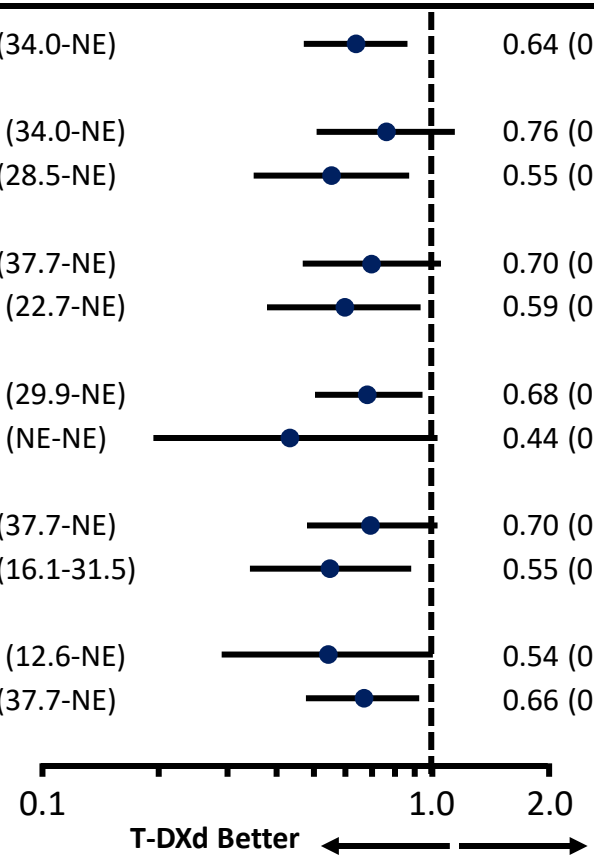
[a]The P value for overall survival crossed the prespecified boundary (P = 0.013) and was statistically significant.
[b]Two-sided from stratified log-rank test.

KEY DATA

DESTINY-Breast03 Clinical Trial

OS in Key Subgroups

	Events, n/N		Median Overall Survival Time, Mo (95% CI)		HR for Death (95% CI)
	Trastuzumab Deruxtecan	Trastuzumab Emtansine	Trastuzumab Deruxtecan	Trastuzumab Emtansine	
All patients	72/261	97/263	NR (40.5-NE)	NR (34.0-NE)	0.64 (0.47-0.87)
Hormone receptor status					
Positive	42/133	51/139	NR (40.5-NE)	37.7 (34.0-NE)	0.76 (0.50-1.14)
Negative	30/126	45/122	NR (NE-NE)	NR (28.5-NE)	0.55 (0.35-0.87)
Previous pertuzumab					
Yes	41/162	50/158	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.46-1.06)
No	31/99	47/105	NR (NE-NE)	31.5 (22.7-NE)	0.59 (0.38-0.93)
Baseline visceral disease					
Yes	64/195	80/189	NR (40.5-NE)	35.4 (29.9-NE)	0.68 (0.49-0.95)
No	8/66	17/74	NR (NE-NE)	NR (NE-NE)	0.44 (0.19-1.02)
Previous lines of systemic therapy*					
<3	44/188	57/191	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.47-1.04)
≥3	28/73	40/72	NR (27.4-NE)	22.8 (16.1-31.5)	0.55 (0.34-0.89)
Baseline brain metastases					
Yes	17/43	22/39	NR (23.8-NE)	25.1 (12.6-NE)	0.54 (0.29-1.03)
No	55/218	75/244	NR (40.5-NE)	NR (37.7-NE)	0.66 (0.47-0.94)

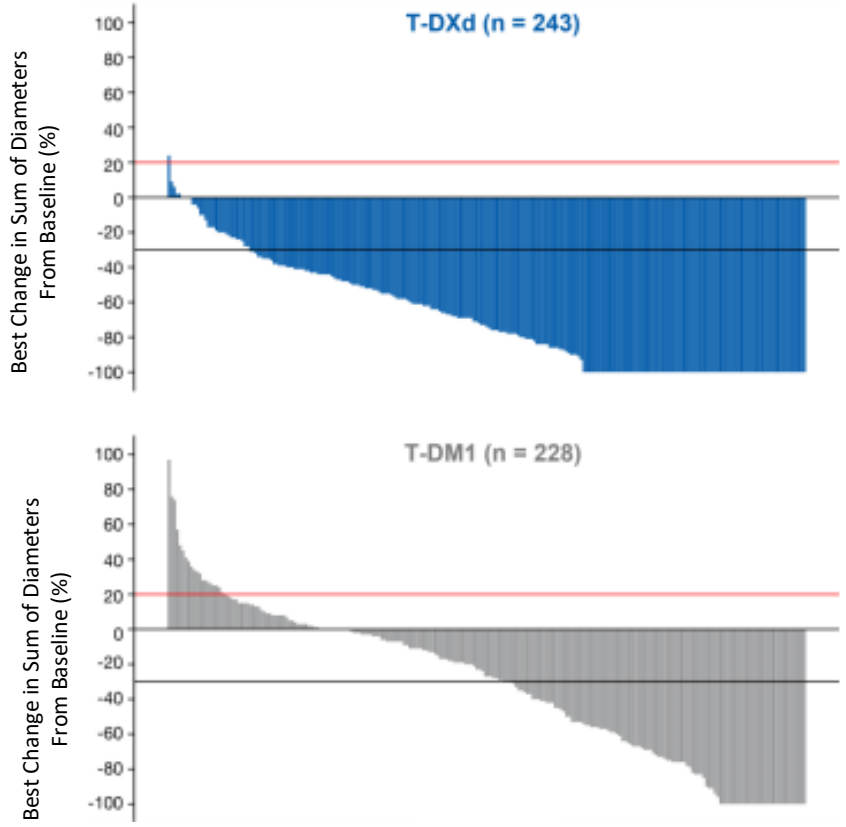


*Not including hormone therapy.

KEY DATA

DESTINY-Breast03 Clinical Trial

Confirmed ORR and Best Overall Response



Note: Red line at 20% indicated progressive disease;
Black line at -30% indicates partial response

Response	T-DXd (n = 261)	T-DM1 (n = 263)
ORR, n(%) (95% CI)	205 (78.5) (73.1-83.4)	92 (35.0) (29.2-41.1)
P value	<.0001	
Best overall response, n (%)		
• CR	55 (21.1)	25 (9.5)
• PR	150 (57.5)	67 (25.5)
• SD	47 (18.0)	110 (41.8)
• PD	3 (1.1)	47 (17.9)
• Not evaluable	6 (2.3)	14 (5.3)
CBR, n (%) (95% CI)	233 (89.3) (84.9-92.8)	122 (46.4) (40.2-52.6)
P value	<.0001	
mDoR, mo (95% CI)	36.6 (22.4-NE)	23.8 (12.6-34.7)

Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included

KEY DATA

DESTINY-Breast03 Clinical Trial

Overall Safety Summary

Median treatment duration was **18.2** months (range, 0.7 – 44.0) for T-DXd and **6.9** months (range 0.7-39.3) for T-DM1

Safety Outcome	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE, n(%)	252 (98.1)	228 (87.4)
• Grade ≥3	121 (47.1)	110 (42.1)
• Serious	33 (12.8)	20 (7.7)
Drug-related TEAE associated with the following, n (%)		
• Discontinuation	51 (19.8)	17 (6.5)
• Dose reduction	65 (25.3)	38 (14.6)
• Drug interruption	108 (42.0)	45 (17.2)
• Outcome of death	0 (0)	0 (0)

The most common drug-related TEAEs associated with treatment discontinuation:

- For T-DXd
  - Pneumonitis (5.8%)
  - ILD (5.1%)
  - Pneumonia (1.9%)
- For T-DM1
  - Platelet count decreased (1.5%)
  - Pneumonitis (1.1%)
  - Thrombocytopenia (1.1%)

DESTINY-Breast03 Clinical Trial

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n=257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n=261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events
- With longer treatment exposure and follow-up the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis to 15.2%
- There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis

SUMMARY

DESTINY-Breast03 Clinical Trial

- After two years of follow-up T-DXd continued to demonstrate clinically meaningful and statistically significant improvement in PFS compared to T-DM1
  - PFS HR 0.33 ($P < 0.00001$)
- Clinically meaningful and statistically significant improvement in OS compared to T-DM1
  - OS HR 0.64 ($P = 0.0037$)
  - Consistent OS benefit across key subgroup and efficacy endpoints
  - Confirmed ORR for T-DXD of 78.5% vs 35.0% for T-DM1 (CR, 21.1% vs 9.5%, respectively)
- Continue to be aware of and monitor for ILD/pneumonitis

DESTINY-Breast03 Clinical Trial

Use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 2L setting continues to show benefit and should be standard of care for patients with HER2+ metastatic breast cancer

2022 SABCS Key Studies

HR+ Breast Cancer & CDK4/6 inhibitors

- monarchE
- RIGHT Choice
- PACE

- POSITIVE

HR+ Breast Cancer

- EMERALD
- SERENA-2
- CAPItello-291
- TROPiCS-02

HER2+ Breast Cancer

- TALENT
- DESTINY-Breast03
- DESTINY-Breast02

cornerstone specialty network™

CLINICAL QUESTION

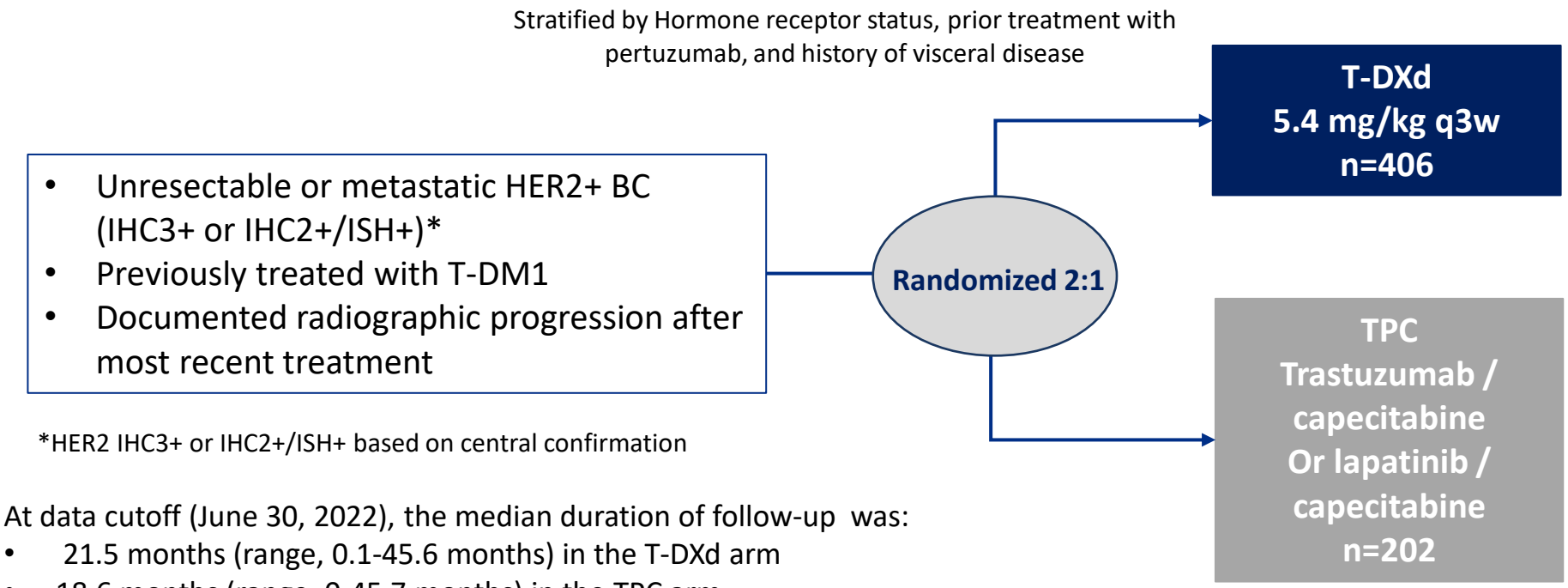
DESTINY-Breast02 Clinical Trial

Does the use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 3L setting benefit pts with HER2+ MBC previously treated with T-DM1?

KEY DATA

DESTINY-Breast02 Clinical Trial

Study Design: Randomized phase 3, open-label, multicenter study



*HER2 IHC3+ or IHC2+/ISH+ based on central confirmation

At data cutoff (June 30, 2022), the median duration of follow-up was:

- 21.5 months (range, 0.1-45.6 months) in the T-DXd arm
- 18.6 months (range, 0-45.7 months) in the TPC arm

Primary End Point:

- PFS (Blinded ICR)

Secondary Endpoints:

- OS, ORR (BICR), DoR (BICR), PFS (investigator), safety

Exploratory Endpoints

- CBR, (BICR), PFS2 (investigator)

- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

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KEY DATA

DESTINY-Breast02 Clinical Trial

Baseline Characteristics

Characteristic	T-DXd (n = 406)	TPC (n = 202)
Median age, yr (range)	54.2 (22.4-88.5)	54.7 (24.7-86.5)
• <65 yr/≥65 yr, n (%)	321 (79.1)/85 (20.9)	164 (81.2)/38 (18.8)
Female, n (%)	403 (99.3)	200 (99.0)
Region, n (%)		
• Asia/Europe	112 (27.6)/152 (37.4)	52 (25.7)/78 (38.6)
• North America/rest of world	41 (10.1)/101 (24.9)	23 (11.4)/49 (24.3)
HER2 status (IHC), n (%)		
• 3+	326 (80.3)	159 (78.7)
• 2+ (ISH+/ISH- or unevaluable)	79 (19.5)/1 (0.2)	41 (20.8)/1 (0.5)
• 1+ (ISH+)	0	1 (0.5)
ECOG PS 0/1/2, n (%)	228 (56.2)/177 (43.6)/1 (0.2)	121 (59.9)/81 (40.1)/0
Hormone receptor status, n (%)		
• Positive	238 (58.6)	118 (58.4)
• Negative	165 (40.6)	83 (41.1)
Brain metastases at baseline, n (%)		
• Yes/no	74 (18.2)/332 (81.8)	36 (17.8)/166 (82.2)
Visceral disease, n (%)		
• Yes/no	316 (77.8)/90 (22.2)	160 (79.2)/42 (20.8)

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DESTINY-Breast02 Clinical Trial

Prior Therapies

Characteristic	T-DXd (n = 406)	TPC (n = 202)
Prior treatment for BC, n (%)	406 (100)	202 (100)
Prior lines of therapy in metastatic setting,* n (%)		
• 0	2 (0.5)	0
• 1	18 (4.4)	12 (5.9)
• 2	192 (47.3)	92 (45.5)
• 3	123 (30.3)	63 (31.2)
• 4	42 (10.3)	13 (6.4)
• ≥5	29 (7.1)	22 (10.9)
Median number of prior lines of systemic therapy in metastatic setting, range	2 (0-10)	2 (1-8)
Prior systemic cancer therapy, n (%)		
• Trastuzumab	404 (99.5)	202 (100)
• T-DM1	404 (99.5)	202 (100)
• Taxane	386 (95.1)	197 (97.5)
• Pertuzumab	318 (78.3)	156 (77.2)
• Other systemic therapy	289 (71.2)	157 (77.7)
• Hormone therapy	164 (40.4)	87 (43.1)
• Anti-HER2 TKI	26 (6.4)	17 (8.4)
• Other anti-HER2 therapy (except HER2 TKI)	11 (2.7)	6 (3.0)

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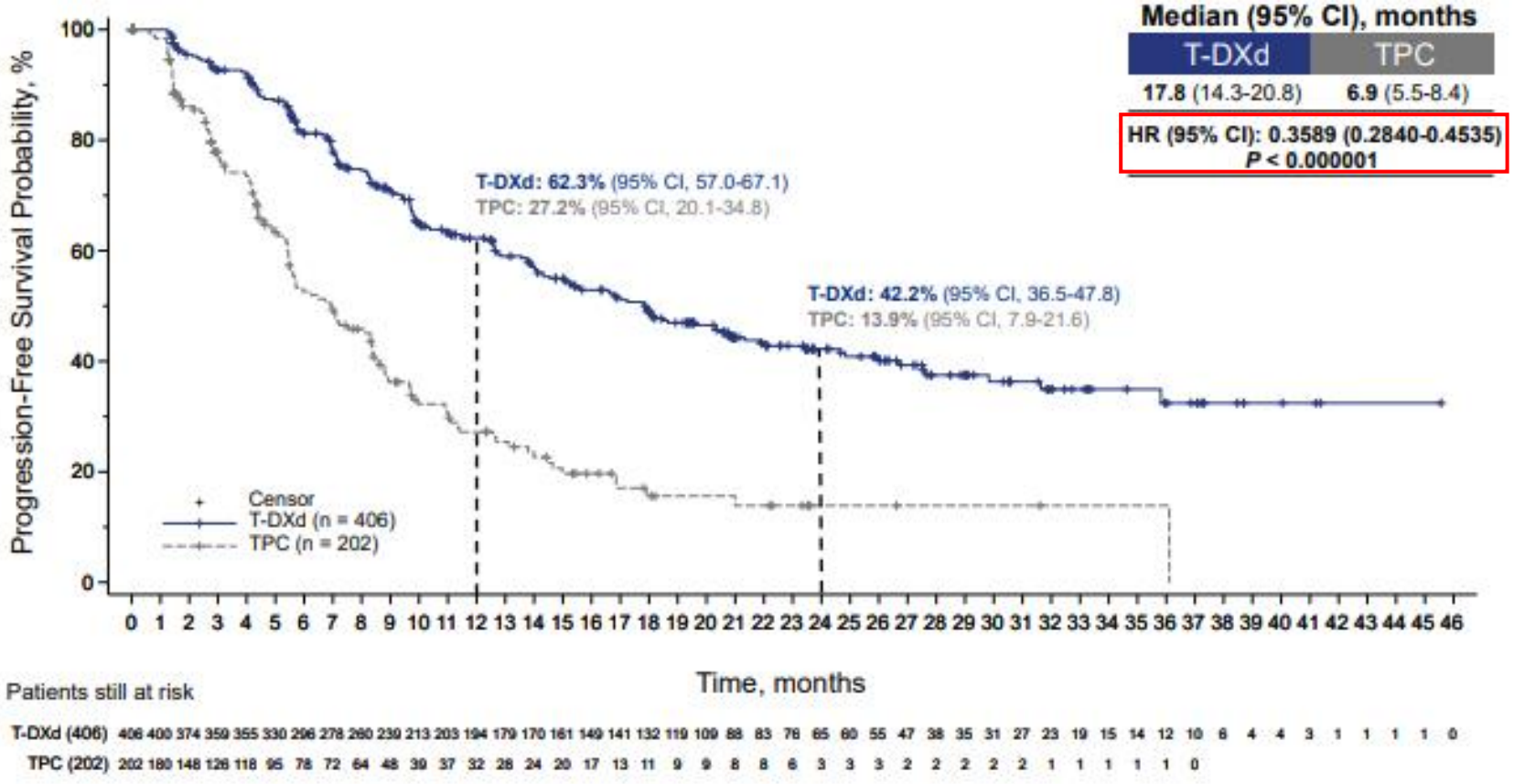
KEY DATA

DESTINY-Breast02 Clinical Trial

Primary Endpoint: PFS by BICR



In the TPC arm

- 69.3% (140/202) of patients received a new systemic anticancer treatment
- 25.7% (52/202) of patients received T-DXd in the post-trial setting

- PFS superior with T-DXd across all assessed subgroups, including among patients with baseline brain metastases
  - Median PFS 13.9 mo with T-DXd vs 5.6 mo with TPC among 74 and 36 patients with baseline brain metastases, respectively

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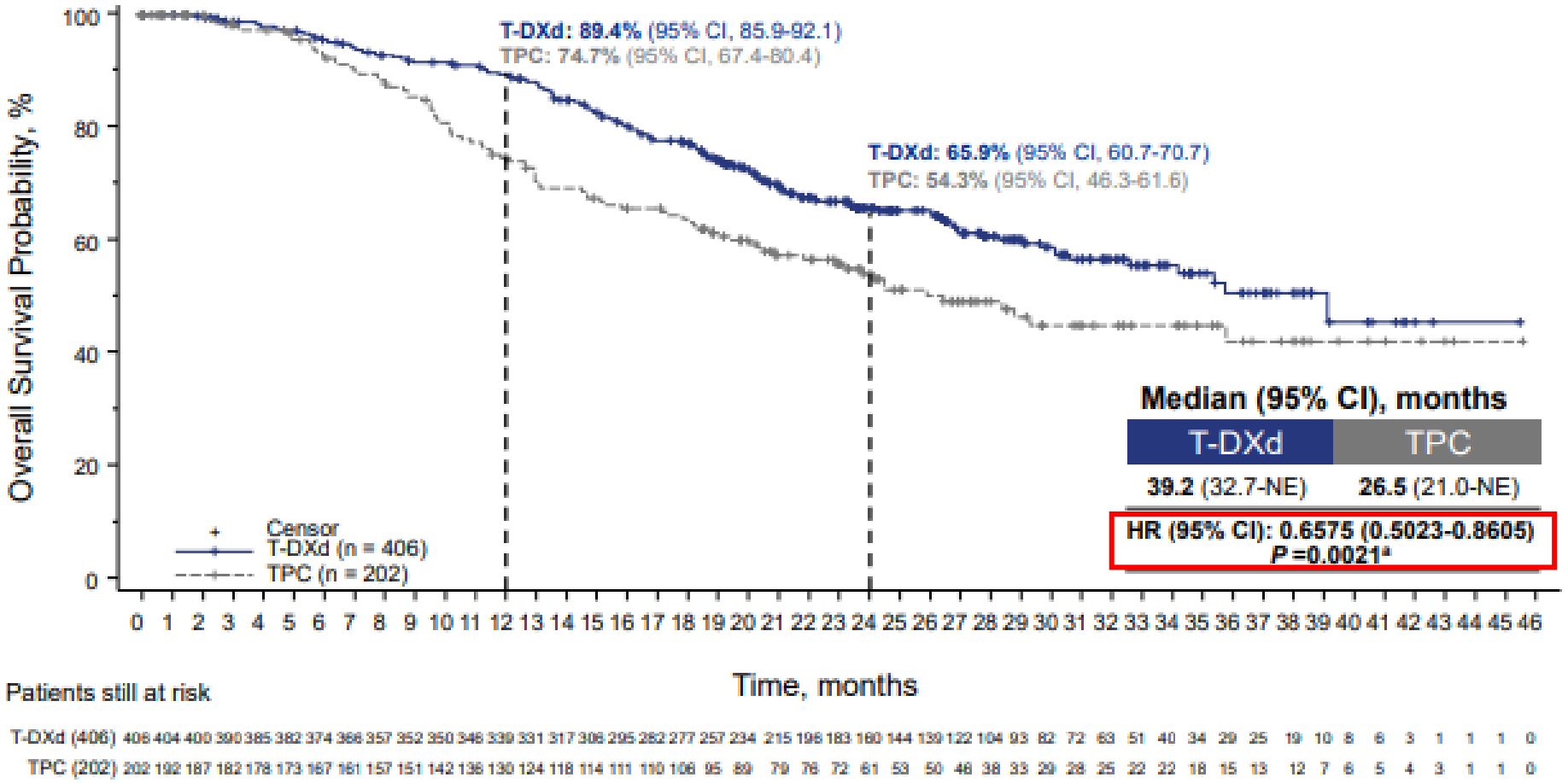
KEY DATA

DESTINY-Breast02 Clinical Trial

Secondary Endpoints: OS



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DESTINY-Breast02 Clinical Trial

Secondary and Exploratory Endpoints

Efficacy Outcome	T-DXd (n = 406)	TPC (n = 202)	P Value
Confirmed ORR by BICR, n (%) • 95% CI	283 (69.7) 65.0-74.1	59 (29.2) 23.0-36.0	<.0001
Confirmed best overall response, n (%)			
• CR	57 (14.0)	10 (5.0)	
• PR	226 (55.7)	49 (24.3)	
• SD	95 (23.4)	94 (46.5)	--
• PD	19 (4.7)	26 (12.9)	
• Not evaluable	9 (2.2)	23 (11.4)	
Median DoR by BICR, mo (95% CI)	19.6 (15.9-NE)	8.3 (5.8-9.5)	--
CBR by BICR, % (95% CI)	82.3 (78.2-85.9)	46.0 (39.0-53.2)	--
Median PFS by investigator, mo (95% CI)	16.7 (14.3-19.6)	5.5 (4.4-7.0)	--
Median PFS2, mo (95% CI)	35.8 (28.4-NE)	15.8 (13.5-21.0)	--

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KEY DATA

DESTINY-Breast02 Clinical Trial

Overall Safety Summary

TEAE, n (%)	T-DXd (n = 404)	TPC (n = 195)
Any	403 (99.8)	185 (94.9)
• Drug related	394 (97.5)	180 (92.3)
Grade ≥3	213 (52.7)	86 (44.1)
• Drug related	167 (41.3)	60 (30.8)
Serious	103 (25.5)	46 (23.6)
• Drug related	46 (11.4)	15 (7.7)
Led to drug discontinuation	80 (19.8)	19 (9.7)
• Drug related	58 (14.4)	10 (5.1)
Led to drug interruption	183 (45.3)	90 (46.2)
• Drug related	132 (32.7)	76 (39.0)
Led to dose reductions	102 (25.2)	89 (45.6)
• Drug related	95 (23.5)	89 (45.6)
Associated with death	11 (2.7)	7 (3.6)
• Drug related	4 (1.0)	0

Median treatment duration:

- T-DXd 11.3 mo
- TPC ~4.5 mo

Most common drug-related TEAEs associated with drug discontinuation

- T-DXd: pneumonitis (6.2%), ILD (3.2%)
- TPC: palmar–plantar erythrodysesthesia (1.5%)

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KEY DATA

DESTINY-Breast02 Clinical Trial

Most Common TEAEs (≥15% of Patients in Either Treatment Arm)

TEAE in ≥15% of Patients, Any Grade/Grade ≥3, (%)	T-DXd (n = 404)	TPC (n = 195)
Nausea	72.5 (6.7)	37.4 (2.6)
Vomiting	37.6 (3.7)	12.8 (1.0)
Alopecia	37.1 (0.2)	4.1 (0)
Fatigue	36.4 (4)	26.7 (0.5)
Constipation	35.1 (0.2)	10.8 (0.5)
Decreased appetite	30.9 (1.7)	17.9 (0.5)
Anemia	28.5 (7.9)	13.8 (0.5)
Diarrhea	27.0 (2.7)	53.8 (7.2)
Asthenia	24.5 (5.0)	9.7 (0.5)

TEAE in ≥15% of Patients, Any Grade/Grade ≥3, %	T-DXd (n = 404)	TPC (n = 195)
Headache	19.8 (0.2)	6.2 (0)
Decreased neutrophils	19.6 (10.6)	7.2 (2.1)
Decreased weight	17.6 (0.2)	3.6 (0)
Increased AST	16.3 (1.0)	11.8 (1.5)
Neutropenia	16.1 (7.7)	5.1 (2.1)
Increased ALT	15.1 (1.0)	10.3 (0.5)
Stomatitis	11.1 (1.0)	18.5 (1.0)
PPE syndrome	1.7 (0.2)	51.3 (10.3)

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DESTINY-Breast02 Clinical Trial

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis, n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n=404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n=195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV Dysfunction

In the T-DXd arm:
- 18 (4.5%) patients experienced an LV dysfunction event
- 2 (0.5%) patients had a grade ≥3 event

In the TPC arm:
- 3 (1.5%) patients experienced an LV dysfunction
  1 (0.5%) patient had a grade ≥3 event

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SUMMARY

DESTINY-Breast02 Clinical Trial

- Clinically meaningful and statistically significant improvement in PFS and OS compared to TPC for patients previously treated with T-DM1
  - PFS HR 0.3589 (95% CI, 0.2840-0.4535; *P* < 0.000001)
  - OS HR 0.6575 (95% CI, 0.5023-0.8605; *P* = 0.0021)
- Consistent benefit across key subgroup and efficacy endpoints
- Overall safety profile was consistent with the established safety of T-DXd, with no new safety signals observed
  - Continue to be aware of and monitor for ILD/pneumonitis

DESTINY-Breast02 Clinical Trial

Use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 3L setting continues to show benefit and provides additional treatment options for patients with HER2+ metastatic breast cancer