Treatment Advances for Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer

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Disclosure

NCCN Guidelines Version 4.2023

National Comprehensive Cancer Network®

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Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Addtional targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal[m,n] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

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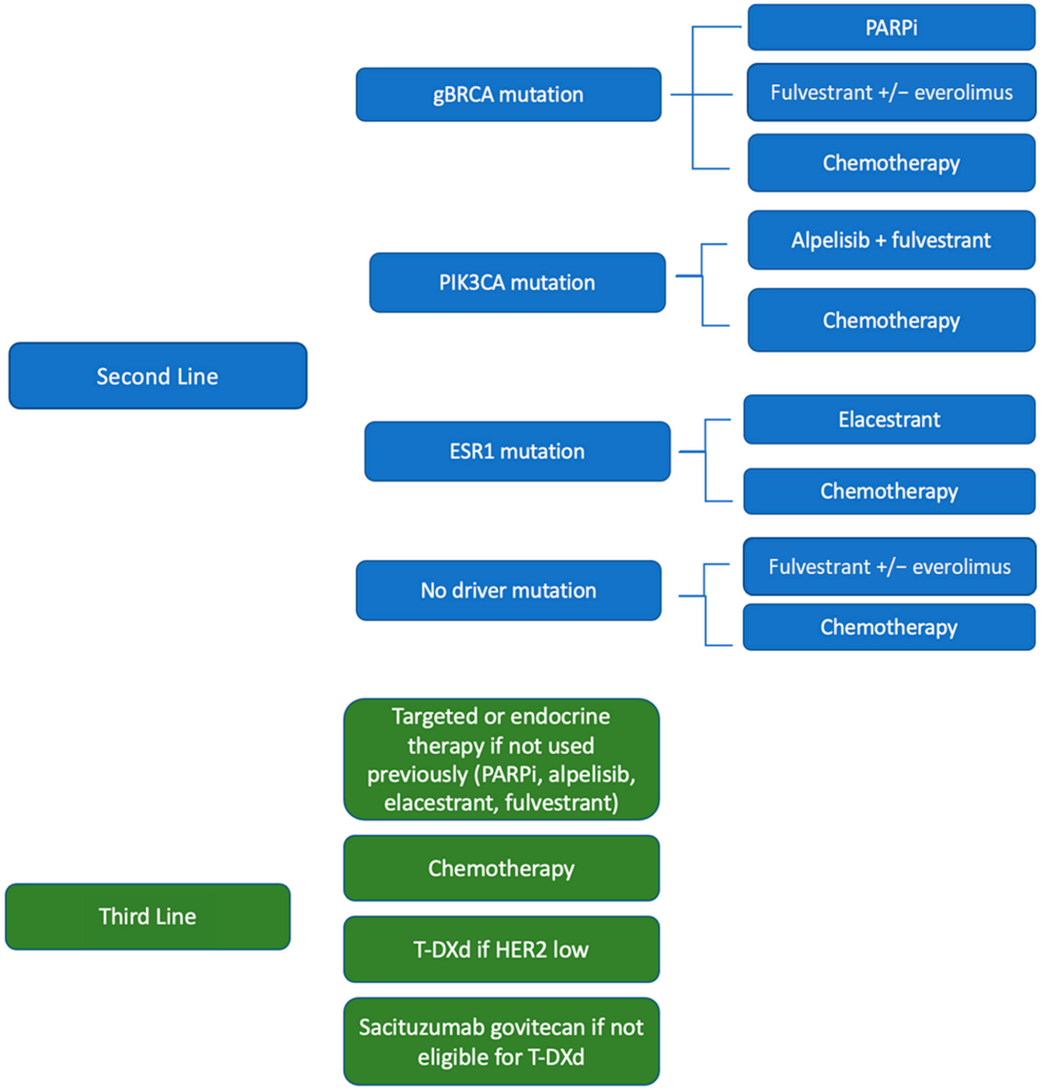
Post-CDK 4/6 Inhibitor Therapy for HR+ HER2-Negative Metastatic Breast Cancer

- CDK4/6 inhibitors (CDK4/6i) with endocrine therapy are the established first-line treatment for hormone receptor-positive HER2-negative metastatic breast cancer. Recently, there has been an expansion in available next lines of therapy.
- When considering second-line therapy, patients' overall health and tumor biology should be considered.
- Second-line therapy (and beyond) options for patients
  - gBRCA: Olaparib or talazoparib (PARP inhibitors); approved first through third-line
  - PIK3CA mutation: Alpelisib (PI3 kinase inhibitor) and fulvestrant; PFS 5.6-7.3 months
  - Fulvestrant, IM selective estrogen receptor degrader (SERD); limited PFS 1.9 months
  - Exemestane and everolimus (mTOR inhibitor)
  - ESR1 mutation: Elacestrant (oral SERD)
  - Trastuzumab deruxtecan (antibody drug conjugate) requires progression on endocrine therapy and one chemotherapy
  - Sacituzumab govitecan (antibody drug conjugate) requires progression on endocrine therapy and two lines of chemotherapy

Suggested Post-First-Line CDK4/6i Sequencing of Therapy



Ashai N and Swain SM. Cancer (Basel). 2023; 15: 1855

HORMONE RECEPTOR SIGNALING

Fig1 (1)

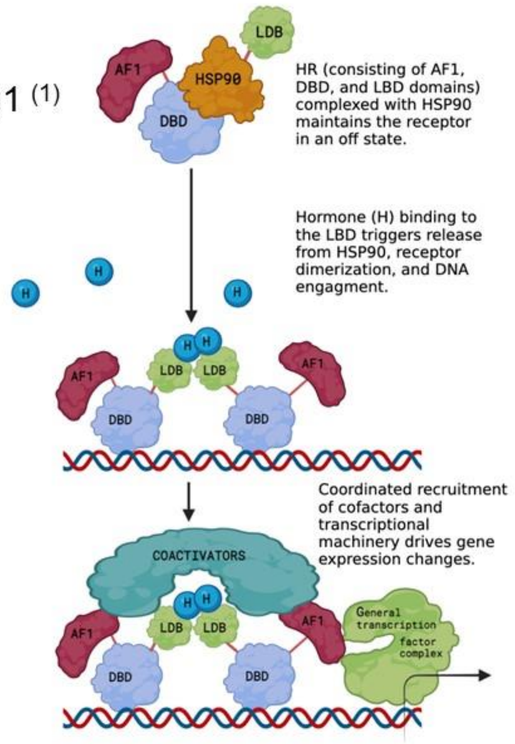
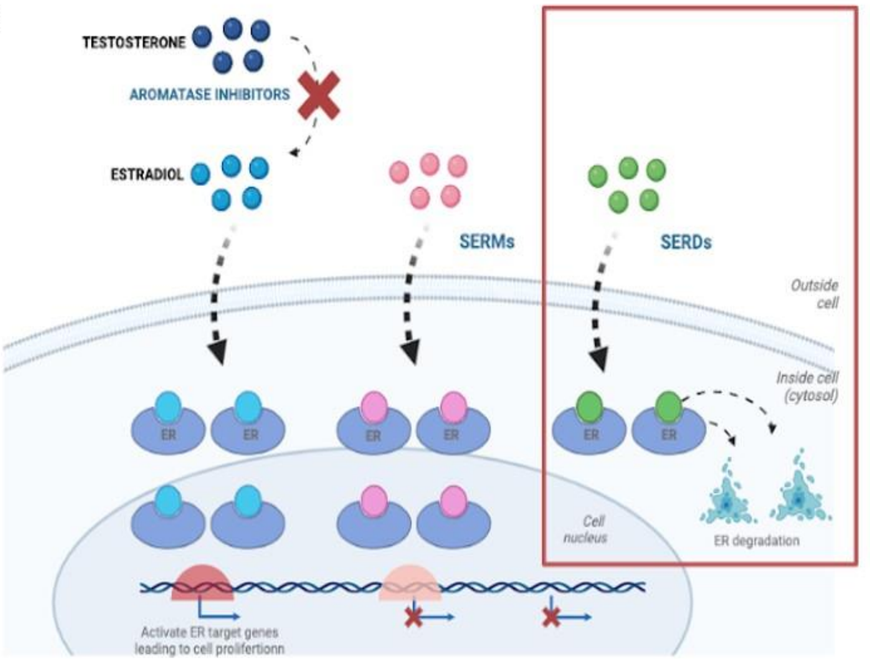


Fig2 (2)



AROMATASE INHIBITORS
(Letrozole, Anastrozole, Exemestane) (3,4)

- Exacerbate menopausal symptoms, vaginal dryness, arthralgias, and accelerated bone loss
- 20-40% of patients develop *ESR1*-mut

SERMs
(Tamoxifen) (5)

- Competitive antagonism ER (Partial agonist)
- Estrogen-like effects in the uterus, bone, liver, and coagulation system

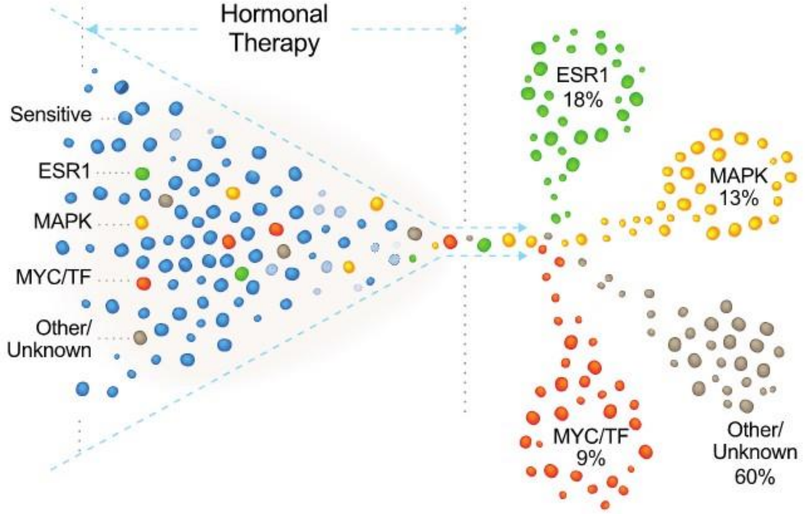
1st SERDs
(Fulvestrant) (6,7,8,9)

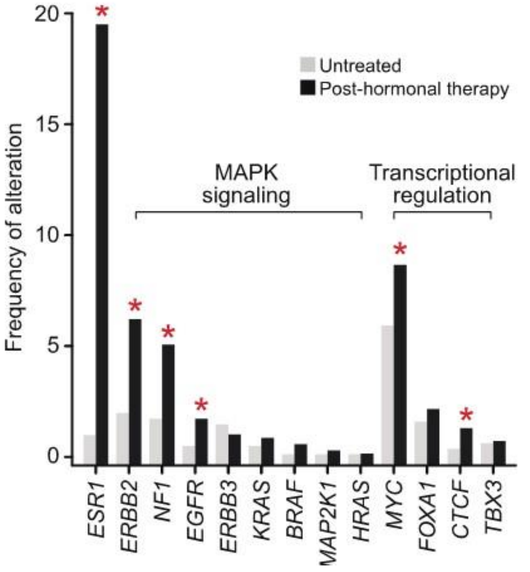
- Poor oral bioavailability
- Efficacy is dose - dependent
- Limited efficacy in ESR1-mut BC (Y537S)
- Limited efficacy in monotherapy post CDK 4/6i

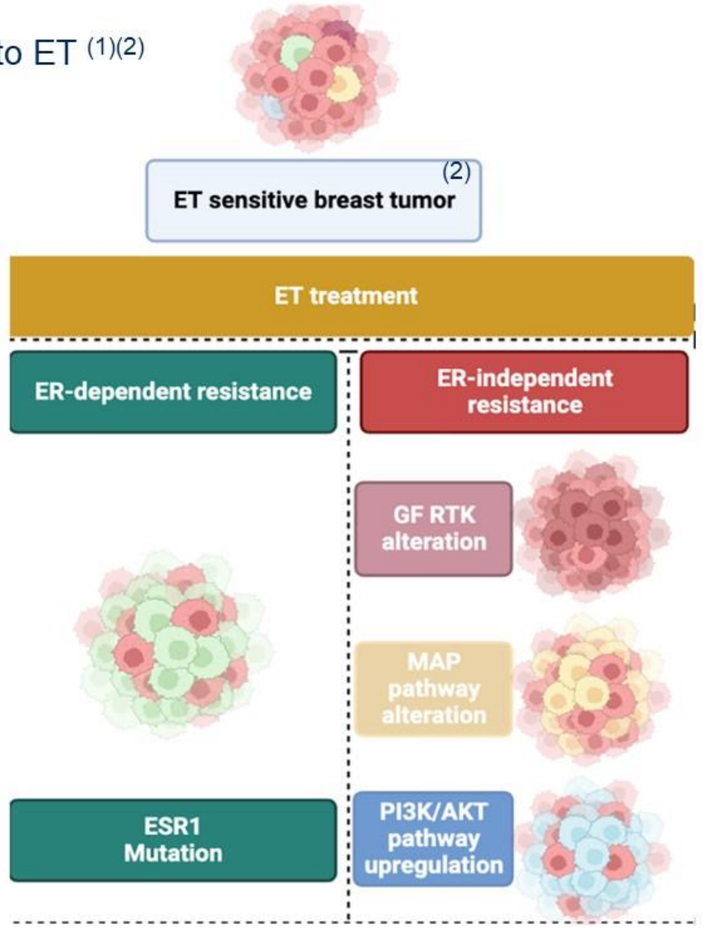
(1) Adapted from Metcalfe, C. *Annual Review of Cancer Biology*, 2, 291-312
(2) Adapted from Hernando C *Int J Mol Sci*. 2021;22(15):7812
(3) Lloyd MR *Ther Adv Med Oncol*. 2022;14:17588359221113694.
(4) Fribbens C *J Clin Oncol*. 2016;34(25):2961-2968.
(5) Osborne CK. N Engl J Med. 1998 Nov 26;339(22):1609-18
(6) Wardell SE *Biochem Pharmacol*. 2011;82(2):122-130
(7) Harrod A *Oncogene*. 2017;36(16):2286-2296.
(8) Hartkopf AD *Breast Care (Basel)*. 2020;15(4):347-354
(9) Ferraro E *Cancer Treat Rev*. 2022;109:102432

ENDOCRINE THERAPY RESISTANCE

- **Molecular pathways** involved in ER functionality and evolving **mechanisms of resistance** to ET [1][2]
  - **Genomic landscape** of **endocrine resistance after treatment** [1]



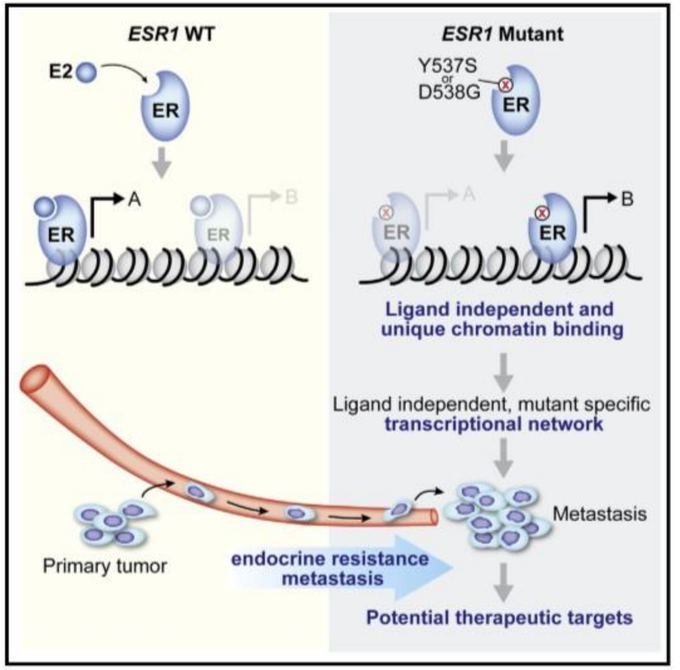


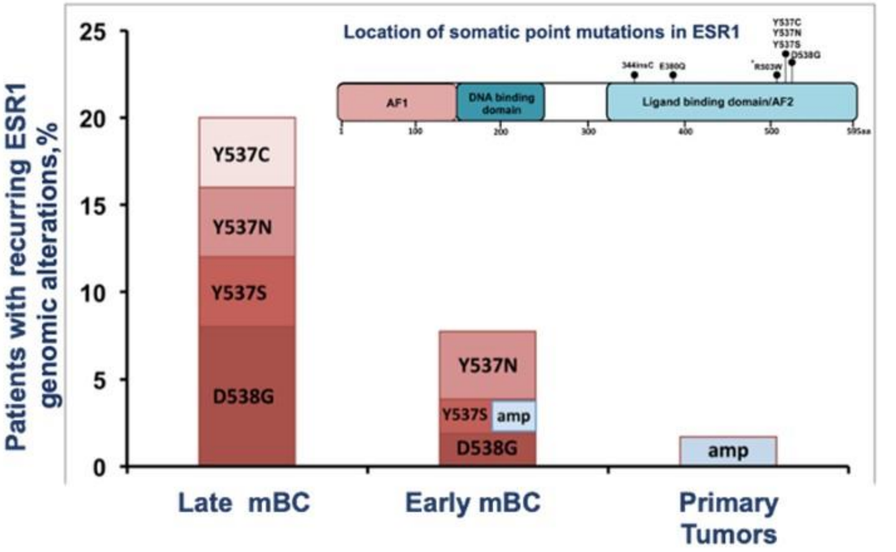


(1) Razavi P *Cancer Cell*. 2018;34(3):427-438.e6
(2) Adapted from Lloyd MR *Therapeutic Advances in Medical Oncology*. 2022;14

ESR1 MUTATIONS

- ***ESR1*** mutations allow **ERα to be activated in the absence of estradiol** (1)

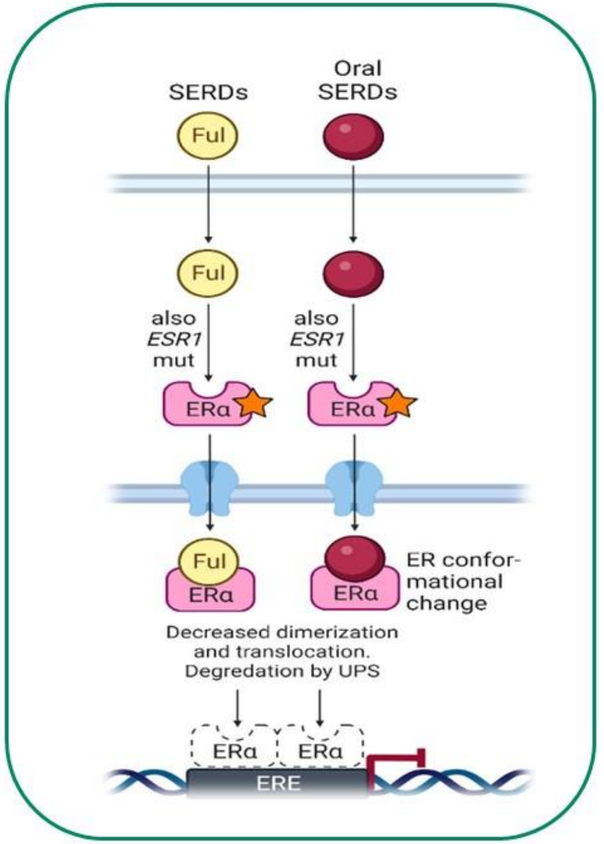




- **Major cause of endocrine resistance** (2)
  - Primary tumors: not detectable
  - First relapse: rare (< 5%)
  - **Progression on AI**: frequent **(30-40%)** (3)
- **Poor prognostic** factor (BOLERO-2) (4)
- Predicts **poor response** to AI therapy (SoFEA/EFECT) (5)
  - Less resistance to fulvestrant, however, limited

(1) Jeselsohn R *Cancer Cell*. 2018;33(2):173-186.e5
(2) Allouchery V *Breast Cancer Res*. 2018;20(1):40
(3) Jeselsohn R *Clin Cancer Res*. 2014;20(7):1757-1767
(4) Chandarlapaty S *JAMA Oncol*. 2016;2(10):1310-1315
(5) Turner NC *Clin Cancer Res*. 2020;26(19):5172-5177

NEW ORAL SERDs



- **Non-steroidal** analogues
- **Side chain**
  - Acrylic acid (Rintodestrant)
  - Basic amino acid (elacestrant, giredestrant, imlunestrant, amcenestrant, camizestrant)
- **Oral** availability
- **High potency**
- Active **against *ESR1*** – mut (Y537S)

Adapted from Chiara Corti Cancer Treatment Reviews, 2023, 102569

Hancker A. Cancer Cell 2020
Pagliuca M Crit Rev Onc Hem 2022

SINGLE-AGENT SERDs IN PHASE I – II

- Efficacy of select single-agent antiestrogen therapies in phase I and phase I–II non-randomized studies

Class	Drug	Phase Trial	*N*	Median lines for mBC	Prior CDK 4/6i	Prior Fulvestrant	ESR1 mutation	ORR	CBR	PFS (months)	References
Hybrid SERM/SERD	**ELACESTRANT** (RAD1901)	I RAD1901-005	50	3 (1-7)	**52%**	52%	50%	19.4%	**42.6%**	4.5	Bardia et al. *J. Clin. Oncol. 39, 1360–1370 (2021)*
SERD	**GIREDESTRANT** (GDC-9545)	Ia/Ib	111	1 (0-3)	**64%**	21%	47%	15%	**52%**	7.2	Jhaveri et al. *J. Clin Oncol. 39, 1017-1017 (2021)*
SERD	**CAMIZESTRANT** (AZD9833)	I SERENA 1	98	3 (0-7)	**62%**	53%	43%	10%	**35.3%**	5.4	Baird et al. *Cancer Res. 81, PS11-05–PS11-05 (2021)*
SERD	**IMLUNESTRANT** (LY348356)	I EMBER 1	114	2 (0-8)	**92%**	51%	49%	8%	**42%**	4.3	Jhaveri et al. *J. Clin. Oncol. 40, 1021–1021 (2022)*
SERD	**RINTODESTRANT** (G1T84)	I	67	2 (0-9)	**69%**	64%	43%	5%	**30%**	2.6-3.6	Aftimos et al. *Cancer Res. 81, PS12-04 (2021)*
SERD	**ZN-c5**	I/II 565TiP	56	2 (0-9)	**70%**	46%	41%	5%	**38%**	3.8	Kalinsky et al. *Cancer Res. 82, P1-17-02–P11-17-02 (2022)*

Table adapted from Patel R *NPJ Breast Cancer*. 2023;9(1):20. Published 2023 Apr 5

ADVERSE EVENTS IN PHASE I – II

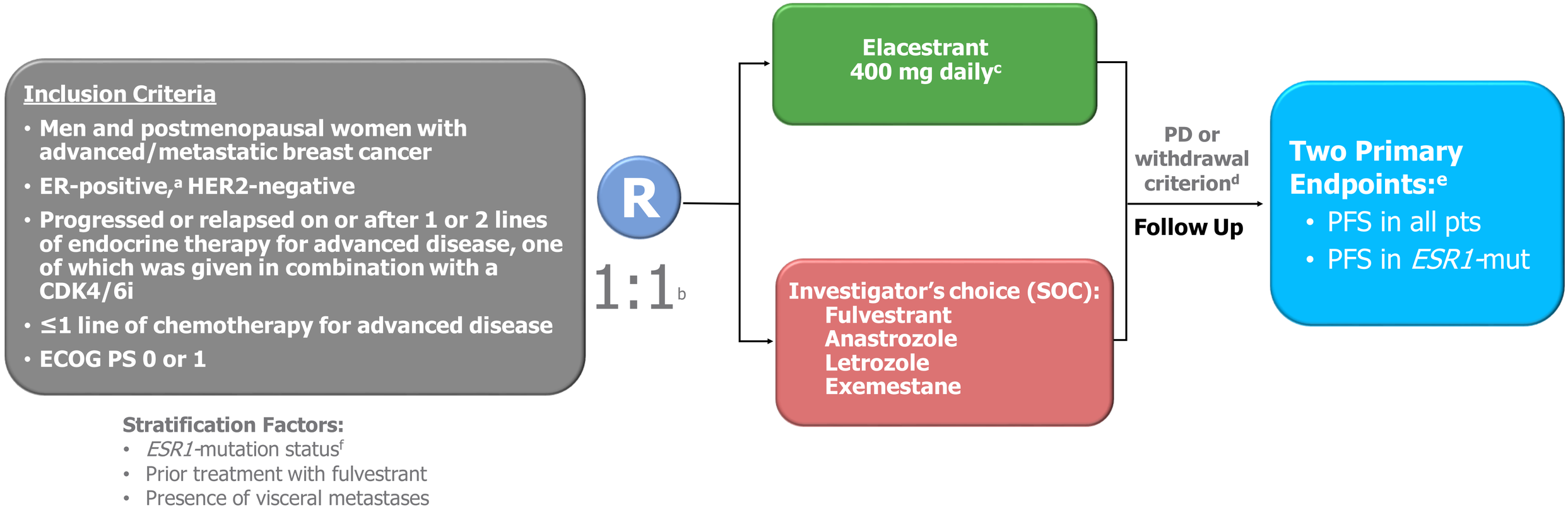
- AEs and recommended phase II doses

Class	Drug	DLTs in phase I	Recommended phase II monotherapy dose	Adverse events >10% monotherapy	References
Hybrid SERM/SERD	**ELACESTRANT** (RAD1901)	None	**400 mg** oral daily	**Nausea**, **fatigue**, vomiting, decrease appetite, **arthralgia**	Bardia et al. *J. Clin. Oncol. 39, 1360–1370 (2021)*
SERD	**GIREDESTRANT** (GDC-9545)	None	**30 mg** oral daily	**Fatigue**, **arthralgia**, **back pain**, nausea, diarrhea, cough, constipation	Lim et al. *J. Clin. Oncol. 38, 1023–1023 (2020)* Jhaveri et al. *J. Clin. Oncol. 39, 1017–1017 (2021)*
SERD	**CAMIZESTRANT** (AZD9833)	QTc prolongation, vomiting, visual disturbance	**75 mg** oral daily	**Visual disturbances**, **bradycardia**, nausea, fatigue, vomiting, dizziness, asthenia	Hamilton et al. *J. Clin. Oncol. 38, 1024–1024 (2020)* Baird et al. *Cancer Res. 81, PS11-05–PS11-05 (2021)*
SERD	**IMLUNESTRANT** (LY348356)	None	**400 mg** oral daily	Nausea, **diarrhea**, fatigue, arthralgia, **urinary tract infection**, headache, constipation	Jhaveri et al. *J. Clin. Oncol. 40, 1021–1021 (2022)*
SERD	**RINTODESTRANT** (G1T84)	None	**800 mg** oral daily	**Hot flashes**, fatigue, nausea, diarrhea, vomiting	Aftimos et al. *Cancer Res. 81, PS12-04 (2021)* Maglakelidze et al. *J. Clin. Oncol. 39, 1063–1063 (2021)*
SERD	**ZN-c5**	None	Final dose pending (25 mg and 50 mg oral daily)	Hot flashes, fatigue, nausea	Kalinsky et al. *Cancer Res. 82, P1-17-02–P11-17-02 (2022)*

Table adapted from Patel R *NPJ Breast Cancer*. 2023;9(1):20. Published 2023 Apr 5

GI toxicity is a common adverse event

EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	 233 (97.5) 6 (2.5)	 115 (100) 0	 238 (99.6) 1 (0.4)	 113 (100) 0
ECOG PS, n (%) 0 1 >1	 143 (59.8) 96 (40.2) 0	 67 (58.3) 48 (41.7) 0	 135 (56.5) 103 (43.1) 1 (0.4)	 62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	**163 (68.2)**	**81 (70.4)**	**170 (71.1)**	**84 (74.3)**
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 142 (59.4) 97 (40.6)	 69 (61.1) 44 (38.9)
Type of prior endocrine therapy,** n (%) Fulvestrant AI Tamoxifen	 70 (29.3) 193 (80.8) 19 (7.9)	 27 (23.5) 101 (87.8) 9 (7.8)	 75 (31.4) 194 (81.2) 15 (6.3)	 28 (24.8) 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	 191 (79.9) 48 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.3) 59 (24.7)	 81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

All Patients: PFS by Duration of CDK4/6i

	Duration on CDK4/6i in the metastatic setting					
	At Least 6 Months (87.5%)		At Least 12 Months (66.7%)		At Least 18 Months (46.7%)	
	Elacestrant (n=202)	SOC Hormonal Therapy (n=205)	Elacestrant (n=150)	SOC Hormonal Therapy (n=160)	Elacestrant (n=98)	SOC Hormonal Therapy (n=119)
Median PFS, months (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)
PFS rate at 6 months, % (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)
PFS rate at 12 months, % (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)
PFS rate at 18 months, % (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)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

	Duration on CDK4/6i in the metastatic setting					
	At Least 6 Months (92.3%)		**At Least 12 Months (71.6%)**		**At Least 18 Months (50.0%)**	
	Elacestrant (n=103)	**SOC Hormonal Therapy (n=102)**	**Elacestrant (n=78)**	**SOC Hormonal Therapy (n=81)**	**Elacestrant (n=55)**	**SOC Hormonal Therapy (n=56)**
Median PFS, months (95% CI)	**4.14** (2.20 - 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)
PFS rate at 6 months, % (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)
PFS rate at 12 months, % (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)
PFS rate at 18 months, % (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 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Safety Summary

Updated safety data were consistent with previously reported results:

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Elacestrant for ER-Positive, HER2-Negative, ESR-1 Mutated Advanced or Metastatic Breast Cancer

- On January 27, 2023, the FDA approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

- FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

- The recommended elacestrant dose is 345 mg taken orally with food once daily until disease progression or unacceptable toxicity.

- Longer duration of prior CDK4/6i therapy correlated with longer PFS with subsequent elacestrant vs SoC, especially for patients with *ESR1* mutation
    - mPFS was 8.6 mo vs 2.1 mo with elacestrant vs SoC, respectively, for patients with *ESR1* mutation who had ≥18 mo of prior CDK4/6i

Table 1: ORSERDU Dose Reduction Levels for Adverse Reactions

Dose Reduction	Dosage	Number and Strength of Tablets
First-dose reduction	258 mg once daily	Three 86 mg tablets
Second-dose reduction	172 mg once daily[1]	Two 86 mg tablets

[1]If further dose reduction below 172 mg once daily is required, permanently discontinue ORSERDU.

MONOTHERAPY AFTER CDK4/6i

	EMERALD [1] Elacestrant (phase III)	SERENA-2 [2] Camizestrant (phase II)	aceIERA [3] Giredestrant (phase II)	AMEERA-3 [4] Amcenestrant (phase II)
Sample size	478	240	303	**367**
Control Arm	Fulvestrant (69%) AI (31%)	Fulvestrant (100%)	Fulvestrant (75%) AI (25%)	Fulvestrant (89.8%) AI (6.8%) Tamoxifen (3.4%)
ESR1 mutant	Elacestrant (48%) Fulvestrant (47.2%)	Camizestrant 75 mg (29.7%) Camizestrant 150 mg (35.6%) Fulvestrant (47.9%)	Giredestrant (33.8%) Fulvestrant (25.7%)	Amcenestrant (45%) Fulvestrant (37.4%)
Prior Fulvestrant	Elacestrant (29.3%) Fulvestrant (31.5%)	**Not Allowed**	Giredestrant (20%) Fulvestrant (18%)	Amcenestrant (10.4%) Fulvestrant (10.2%)
Prior CDK 4/6i	**100%**	49.6%	42%	79.7%
Prior ChT	Elacestrant (20.1%) Fulvestrant (24.4%)	Camizestrant 75 mg (21.6%) Camizestrant 150 mg (12.3%) Fulvestrant (26%)	Giredestrant (31%) Fulvestrant (32%)	Amcenestrant (9.8%) Fulvestrant (12.9%)
Visceral Disease	Elacestrant (68.2%) Fulvestrant (71%)	Camizestrant 75 mg (58.1%) Camizestrant 150 mg (58.9%) Fulvestrant (58.9%)	Giredestrant (69%) Fulvestrant (68%)	Amcenestrant (63.6%) Fulvestrant (63.9%)
PFS	**2.8 vs1.9 mths** *0.70(0.55-0.88)* **Δ 1.0**	Camizestrant 75 mg **7.2 vs 3.7 mths** *0.58(0.41-0.91)* **Δ 3.5** Camizestrant 150 mg **7.7 vs 3.7 mths** *0.67(0.48-0.92)* **Δ 4.0**	5.6 vs 5.4 mths *0.81 (0.60-1.10)* **NEGATIVE**	3.6 vs 3.7 mths *1.051 (0.789-1.4)* **NEGATIVE** **DISCONTINUATION DEVELOPMENT PROGRAM OF AMCENESTRANT**
PFS (*ESR1* mut)	**3.78 vs 1.82 mths** *0.55 (0.39-0.77)* **Δ 2.0** FDA approved	Camizestrant 75 mg **6.3 vs 2.2mths** *0.33 (0.18-0.58)* **Δ 4.1** Camizestrant 150 mg **9.2 vs 2.2 mths** *0.55 (0.0.33-0.89)* **Δ 7.0**	5.3 vs 3.2 mths *0.60 (0.35-1.03)* **NEGATIVE**	3.7 vs 2 mths *0.90 (0.6-1.4)* **NEGATIVE**

- **Heterogeneous patient population**
  - Efficacy in AI-induced endocrine resistance
  - Efficacy in the post-CDK4/6i setting
- **PFS benefit in the ESR1-mut population**
  - Across all studies

Table adapted from Chiara Corti Cancer Treatment Reviews, 2023, 102569

(1) Bardia A et al, Cancer Res. 2022;82:GS2-02
(2) Oliveira M et al, GS3-02 SABCS 2022
(3) Jimenez MM et al, Ann Oncol Sep 2022. 33 (suppl_7): S88-S121
(4) Tolaney S et al, Chan A, *Ann Oncol* 2022;33: S634-5

IN COMBINATION WITH CDK4/6i

- **Efficacy** oral SERDs with **CDK4/6i** in phase I trials

Drugs	N	Prior CDK4/6i (%)	ORR (%)	CBR(%)	References
CAMIZESTRANT PALBOCICLIB	48	**69**	6.3	**50**	*Baird et al.SABCS 2020 (PS 11-05)*
AMCENESTRANT PALBOCICLIB	35	5.1	34.3	74.3	*Chandarlapaty S et al. ASCO 2021 (abs 1058)*
GIREDESTRANT PALBOCICLIB	48	0	33	**81**	*Lim E et al. ASCO 2020 (abs 1023)*
IMLUNESTRANT ABEMACICLIB	42	0	32	**71**	*Jhaveri K et al. SABCS 2022 (abs PD 13-12)*
RINTODESTRANT PALBOCICLIB	40	0	5	**61**	*Maglakelidze M et al. ASCO 2021 (abs 1023)*

SERENA – 4
N=1342
No prior tx for ABC
PFS
NCT04711252

1:1

Camizestrant 75 mg
Palbociclib 125 mg
Anastrozole – matched PLA

Anastrozole 1 mg
Palbociclib 125 mg
Camizestrant – matched PLA

persevERA
N=978
No prior tx for ABC
PFS
NCT04546009

1:1

Giredestrant 30 mg
Palbociclib 125 mg
Letrozole – matched PLA

Letrozole 1 mg
Palbociclib 125 mg
Giredestrant – matched PLA

EMBER-3
N=869
No prior fulvestrant
Allowed tx CDK4/6i
PFS
NCT04188548

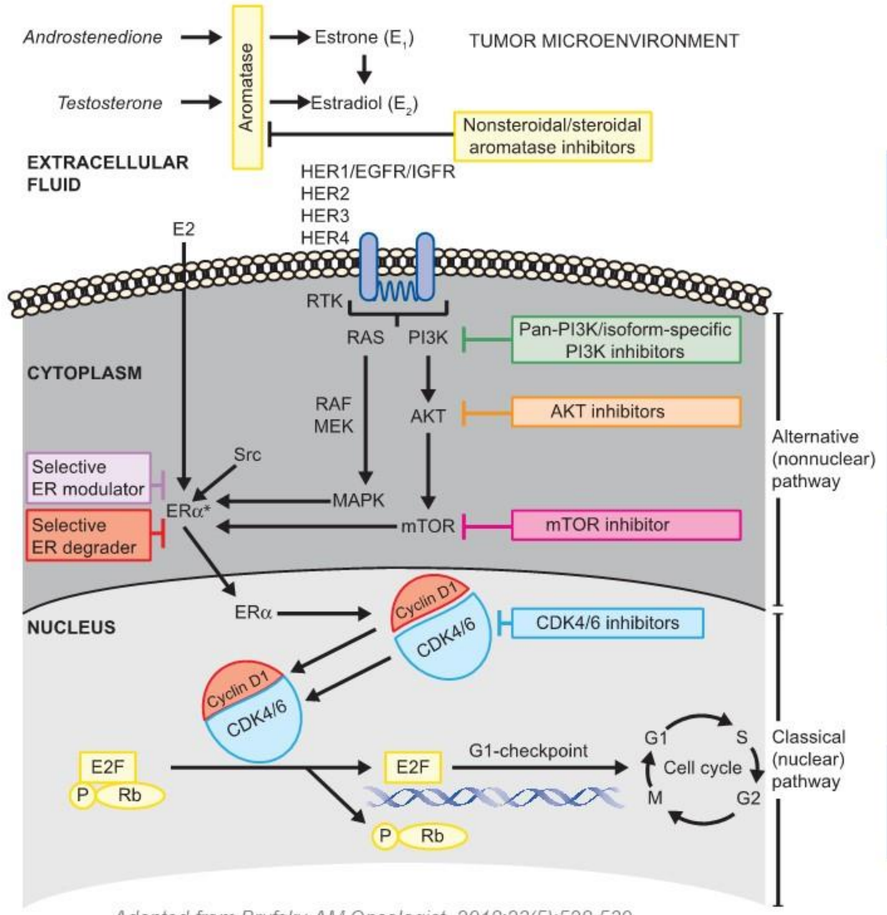
1:1:1

Imlunestrant 400 mg

Investigator´s choice ET
(Fulvestrant or exemestane)

Imlunestrant 400 mg
Abemaciclib 150 mg BD

IN COMBINATION WITH TARGETED AGENTS

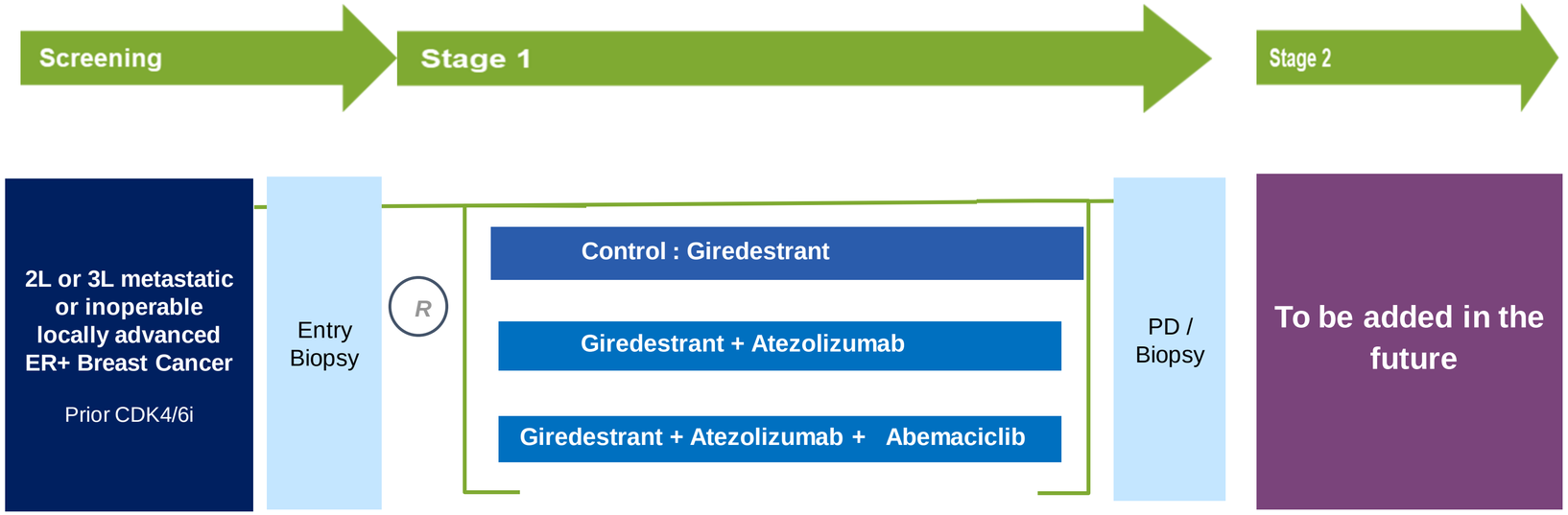


Adapted from Brufsky AM Oncologist. 2018;23(5):528-539

Drug	Trial ID	Combination drugs	Primary endpoint	Patient population
ELACESTRANT (RAD1901)	ELEVATE Phase Ib/II (NCT05563220)	Alpelisib,Everolimus, Abemaciclib	DLT RP2D	mBC, ≥ 1L ET
GIREDESTRANT (GDC-9545)	MORPHEUS Phase Ib/II (NCT04802759)	Abemaciclib, Palbociclib, ribociclib, ipatasertib, inavolisib, everolimus, samuraciclib, atezolizumab, PH FDC SC	ORR	mBC, 2nd/3rd line
GIREDESTRANT (GDC-9545)	evERA PhaseIII (NCT053063340)	Combined with everolimus vs everolimus + exemestane	PFS	mBC, 2nd/3rd line
CAMIZESTRANT (AZD9833)	SERENA-1 Phase I (NCT4214288)	Abemaciclib, everolimus, capivasertib, anastrozole	DLT	mBC, ≥ 2L ET
IMLUNESTRANT (LY348356)	EMBER-1 Phase I (NCT 4188548)	Alpelisib, abemaciclib, everolimus trastuzumab, trastuzumab-abemaciclib, trastuzumab	DLT	mBC, HER2-positive or negative

CO42867: Phase Ib/II, Open-label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations In Patients with Breast Cancer (MORPHEUS Breast Cancer)

Cohort 1



Disease progression during or after 1st or 2nd line hormonal therapy containing a CDK4/6 inhibitor for locally advanced or metastatic disease

Note: At least one line of therapy must have contained a CDK4/6i administered for a minimum of 8 weeks prior to disease progression

Prior fulvestrant therapy is allowed. For patients who have progressed on prior fulvestrant-containing therapy, clinical benefit (i.e., stable disease) for a minimum of six months or objective response to fulvestrant is required

MORPHEUS HR+BC. NCT04802759. Updated June 22, 2023. Accessed July 10, 2023.

ADJUVANT TRIALS

- Oral SERDs: **more potent inhibitors of ER vs TAM and AI** (both *ESR1*-mut and *ESR1*-wt)
  - Expecting same efficacy in adjuvant setting

lidERA

N=4100
- Stage I-III HR+/HER2-
- Medium- or high-risk (clinical and/or biological)
- Completed (neo)adjuvant CT and/or surgery <12months prior enrollment

NCT04961996

1:1

Giredestrant 30mg QD

iDFS

Physician's choice of adjuvant endocrine therapy

CAMBRIA-1

N=4300
- Intermediate or high-risk of recurrence (clinical and/or biological)
- No relapse after 2-5 years of ET
- Prior CDK4/6i allowed

NCT05774951

1:1

Camizestrant 150mg QD

iBCDS

Standard endocrine therapy of investigator´s choice

TREAT ctDNA

- ER+/HER2-
- Stage IIb-III
- Female (pre, post), Male
- **At least 2 years and up to 7 years of ET**
- Adj CDKi, PARPi allowed
- No prior SERD or ER investigational agents

NCT05512364

ctDNA screening phase N 1960

ctDNA + RaDaR assay (+ no recurrence)

Phase III, open label N 220

1:1

Experimental Arm Elacestrant

OP -Distant metastasis free survival (DMFS)
OS - ctDNA elimination rate at month 1

Control Arm EOT - AI, TMX

EMBER-4

N=6000
- **24 months, but not more than 60 months, of any adjuvant endocrine therapy (ET) from time of adjuvant ET initiation**
- Neoadjuvant chemotherapy and/or targeted therapy with a CDK4/6i or PARPi

NCT05514054

1:1

Imlunestrant

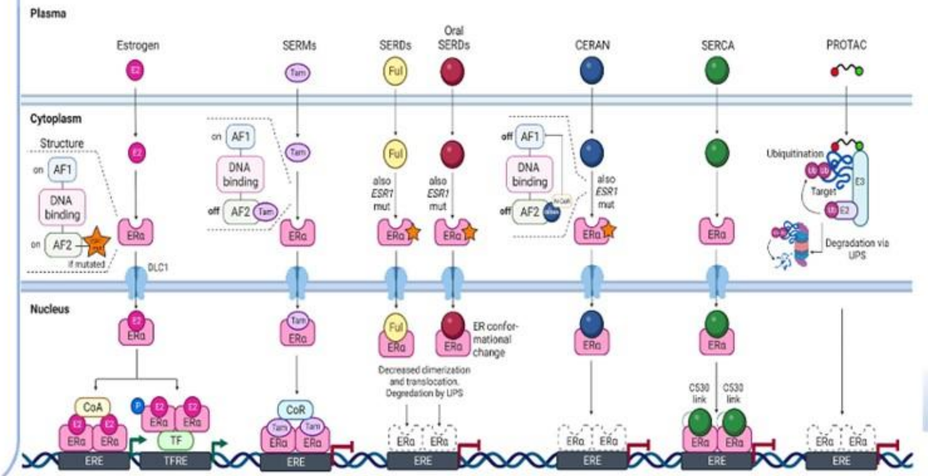
iDFS

Exemestane, letrozole, anatrozole, tamoxifen

* All studies: (LHRH) agonist will be administered to male participants and premenopausal/perimenopausal participants

EMERGING ER-TARGETING AGENTS

ORAL SERDs Selective Estrogen Receptors Degraders	NOVEL SERMs Selective Estrogen Receptors Modulators	SERCA Selective Estrogen Receptor Covalent Antagonist	PROTAC Proteolysis Targeting Chimera	CERAN Complete Estrogen Receptor Antagonist
ELACESTRANT * (RAD1901) GIREDESTRANT (GDC-9545) CAMIZESTRANT (AZD9833) AMCENESTRANT (SAR4399859) IMLUNESTRANT (LY3484356) RINTONESTRANT (G1T48) BORESTRANT (ZB-716) ZN-C5	LASOFOXIFENE BAZEDOXIFENE *	H3B-6545	ARV-471	OP-1250



Novel ER-DRIVEN agents differing in potency as **degraders** vs. **antagonistic activity**, which are in **different stages of development** and **different disease contexts**

Adapted from Chiara Corti Cancer Treatment Reviews, 2023, 102569

* Hybrid SERM/SERD

Lasofoxifene (LAS) Plus Abemaciclib (Abema) for Treating *ESR1*-mutated, ER+/HER2- Metastatic Breast Cancer (mBC) after Progression on Prior Therapies: ELAINE 2 Study Update

Senthil Damodaran, MD, PhD; Halle C. F. Moore, MD; Ian C. Anderson, MD; Mathew Cherian, MBBS; Ciara C. O'Sullivan, MB, BCh, BAO; Paul V. Plourde, MD; David J. Portman, MD; and Matthew P. Goetz, MD

Introduction

- Endocrine therapy (ET), particularly aromatase inhibitors (AIs), for estrogen receptor (ER)-positive breast cancer can lead to acquired *ESR1* mutations (*mESR1*), which drive endocrine resistance and tumor progression[1-4]
- LAS, a breast ER antagonist, was studied in patients with *mESR1* mBC that progressed on ET and CDK4/6 inhibitors

	ELAINE 1[5]			ELAINE 2[6]
Endpoint	LAS	Fulvestrant	p-value	LAS+Abema
Progression-free survival (PFS; median)	5.6 mos	3.7 mos	0.138	~13 mos
Clinical benefit rate (CBR)	37%	22%	0.117	33%
Objective response rate (ORR)	13%	3%	0.124	62%

Objective: To report longer follow up of ELAINE 2 safety and efficacy data

Methods

- Women (≥18 years) with acquired *mESR1* in ER+/HER2- mBC that progressed on prior ET for mBC (≤2 lines) took oral LAS 5 mg/day and Abema (supplied by Eli Lilly and Co) 150 mg BID until disease progression, death, toxicity, or withdrawal
- Primary endpoint: safety/tolerability; secondary endpoints: PFS, CBR, ORR, duration of response, and time to response
- *ESR1* mutant allele fractions (MAF) were analyzed in circulating tumor DNA (ctDNA) at baseline and wk 4 using Sysmex-Inostics SafeSeq assay; Guardant 360 was used to identify other genomic alterations

1. De Santo I, et al. *Cancers (Basel)*. 2019;11:1894. **2.** Brett JO, et al. *Breast Cancer Res*. 2021;23:85. **3.** Robinson DR, et al. *Nat Genet*. 2013;45:1446. **4.** Toy W, et al. *Nat Genet*. 2013;45:1439. **5.** Goetz MP, et al. *Ann Oncol*. 2022;33:S1387. **6.** Damodaran S, et al. *J Clin Oncol*. 2022;40:1022.

Patient disposition and demographics

- 6 of 29 enrolled patients continue treatment
  - 17 disease progression, 1 AE discontinuation, 3 patient withdrawal, 2 other causes

Patient characteristics	Median or %
Age, median	60 yrs
Visceral disease	55%
Prior ET lines for mBC, median	2
Prior CDK4/6i	97%
Duration, median	2 yrs
Prior fulvestrant	79%
Prior chemotherapy for mBC	48%
Most frequent *ESR1* mutations	
Y537S	66%
D538G	45%
Y536N	28%
Y537C	10%
Polyclonal *ESR1* mutations	48%

Safety

- LAS/Abema was well tolerated: primarily grade 1/2 TEAEs, mostly diarrhea, nausea, fatigue, and vomiting
- Three patients (10%) had scan-identified VTE; all three achieved clinical benefit
- One patient discontinued treatment due to grade 2 diarrhea
- No deaths occurred on treatment

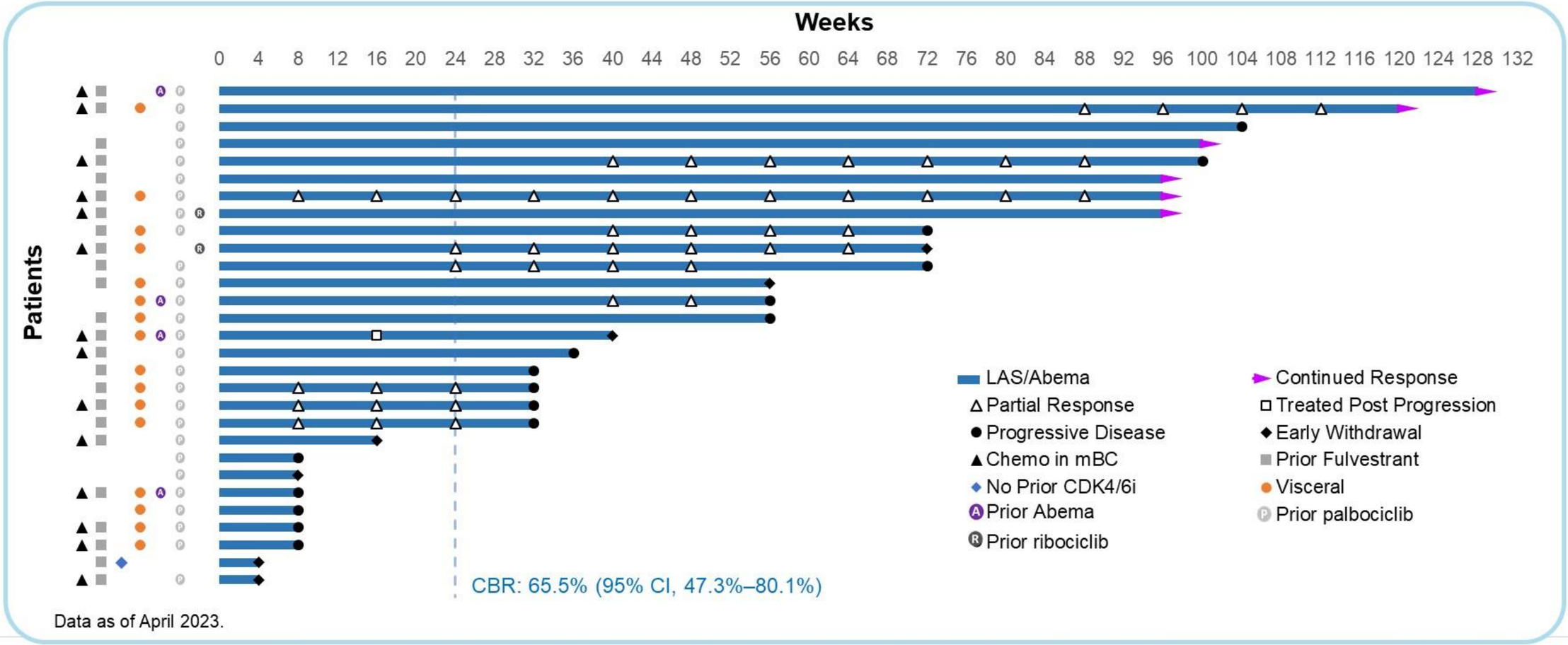
Most frequently reported TEAEs (in ≥12% of patients)* (N=29)

TEAE, n (%)	Grade 2	Grade 3	Grade 4	All grades
Diarrhea	5 (17.2)	0	0	24 (82.8)
Nausea	5 (17.2)	0	0	15 (51.7)
Fatigue	3 (10.3)	1 (3.4)	0	11 (37.9)
Vomiting	2 (6.9)	1 (3.4)	0	9 (31.0)
Anemia	1 (3.4)	3 (10.3)	0	8 (27.6)
Dyspnea	4 (13.8)	0	0	8 (27.6)
WBC count decreased	6 (20.7)	0	0	8 (27.6)
Blood creatinine increased	4 (13.8)	0	0	7 (24.1)
Constipation	0	1 (3.4)	0	6 (20.7)
Cough	1 (3.4)	0	0	6 (20.7)
Decreased appetite	2 (6.9)	0	0	6 (20.7)
Hypokalemia	0	3 (10.3)	0	5 (17.2)
Muscle spasm	0	0	0	5 (17.2)
Alopecia	0	0	0	4 (13.8)
Dehydration	2 (6.9)	0	0	4 (13.8)
Dizziness	2 (6.9)	0	0	4 (13.8)
Fall	1 (3.4)	2 (6.9)	0	4 (13.8)
Hot flush	1 (3.4)	0	0	4 (13.8)
Hypoalbuminemia	0	0	0	4 (13.8)
Myalgia	0	0	0	4 (13.8)
Edema peripheral	0	0	0	4 (13.8)
Pain in extremity	0	0	0	4 (13.8)
Pruritus	1 (3.4)	0	0	4 (13.8)
Stomatitis	1 (3.4)	0	0	4 (13.8)
Urinary tract infection	4 (13.8)	0	0	4 (13.8)

*Patients' maximum grade was counted. AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; mBC, metastatic breast cancer; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism; WBC, white blood cell.

Efficacy

- CBR was 66%; 8 (28%) patients were progression free over 96 wks
- Of the 4 patients who had prior Abema exposure, two achieved clinical benefit, and one had RECIST progression at wk 16 but remained on study with stable disease until wk 40

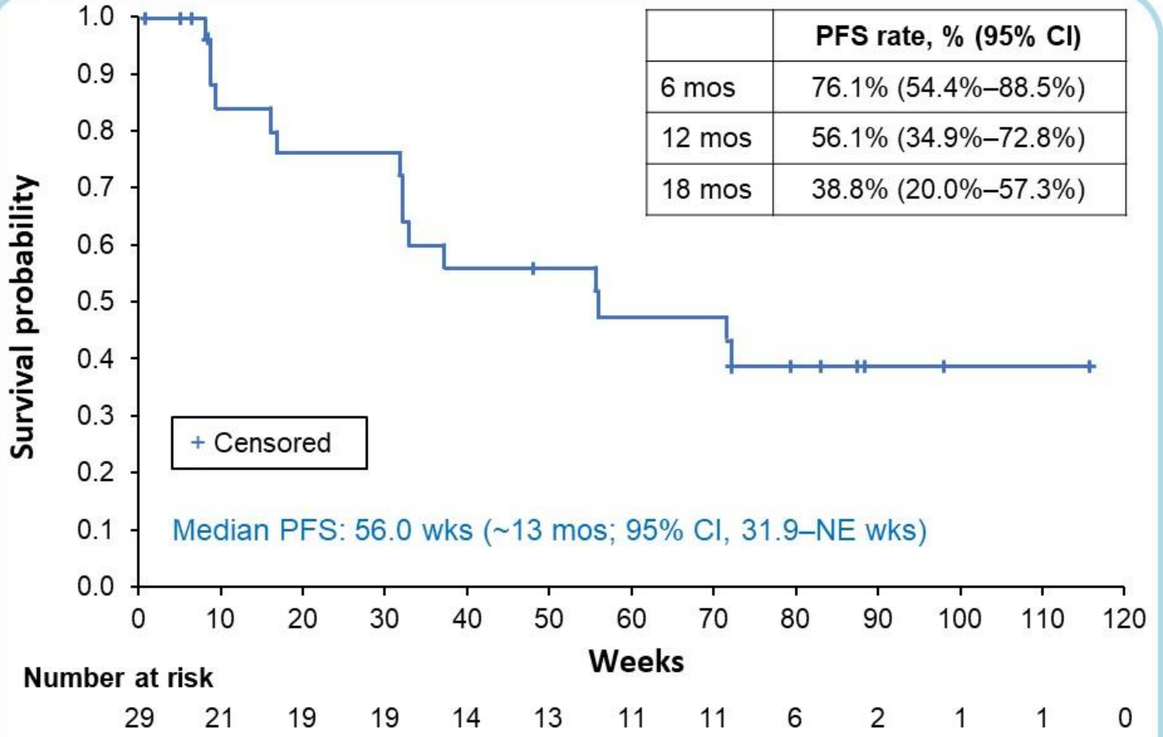


Data as of April 2023.

Abema, abemaciclib; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; LAS, lasofoxifene.

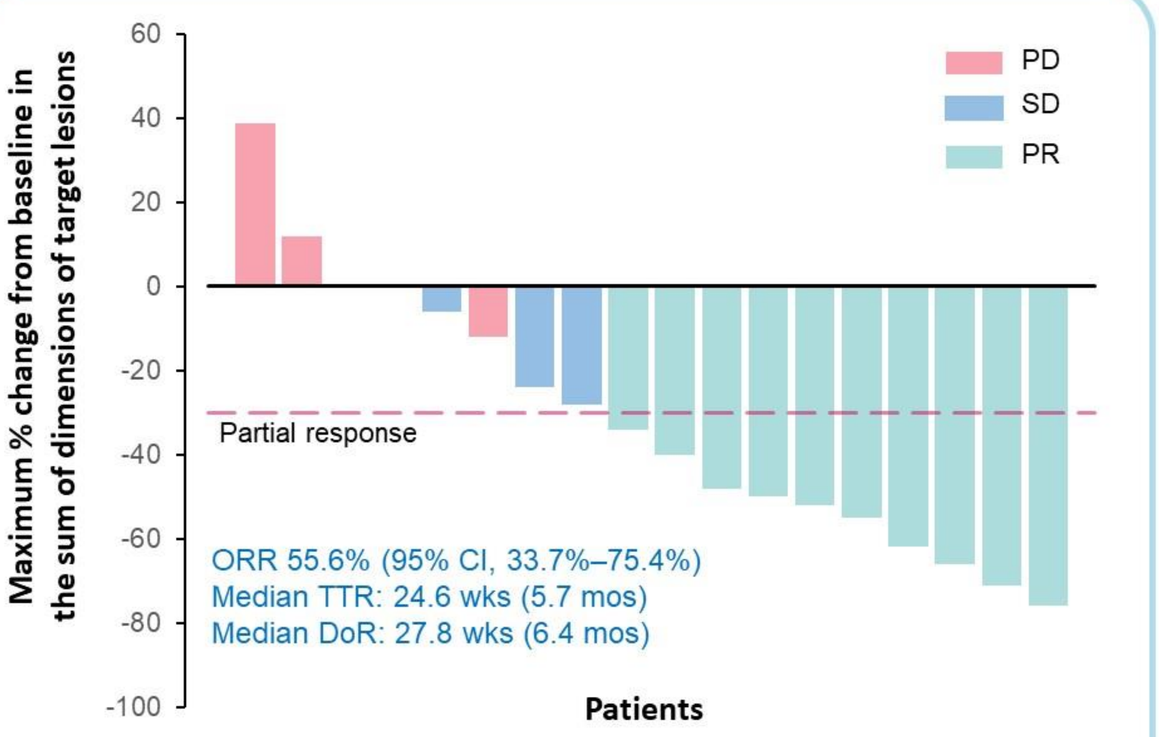
Efficacy

- Median censored PFS was approximately 13 mos and ORR was 56% (Figures)
- *ESR1* MAF decreased at wk 4 in 21 (81%) patients, including 14 (54%) whose *ESR1* MAF was undetectable, in 26 patients with evaluable baseline and wk 4 ctDNA
- Antitumor activity of LAS/Abema was not compromised by concurrent alterations that confer endocrine resistance



	PFS rate, % (95% CI)
6 mos	76.1% (54.4%–88.5%)
12 mos	56.1% (34.9%–72.8%)
18 mos	38.8% (20.0%–57.3%)

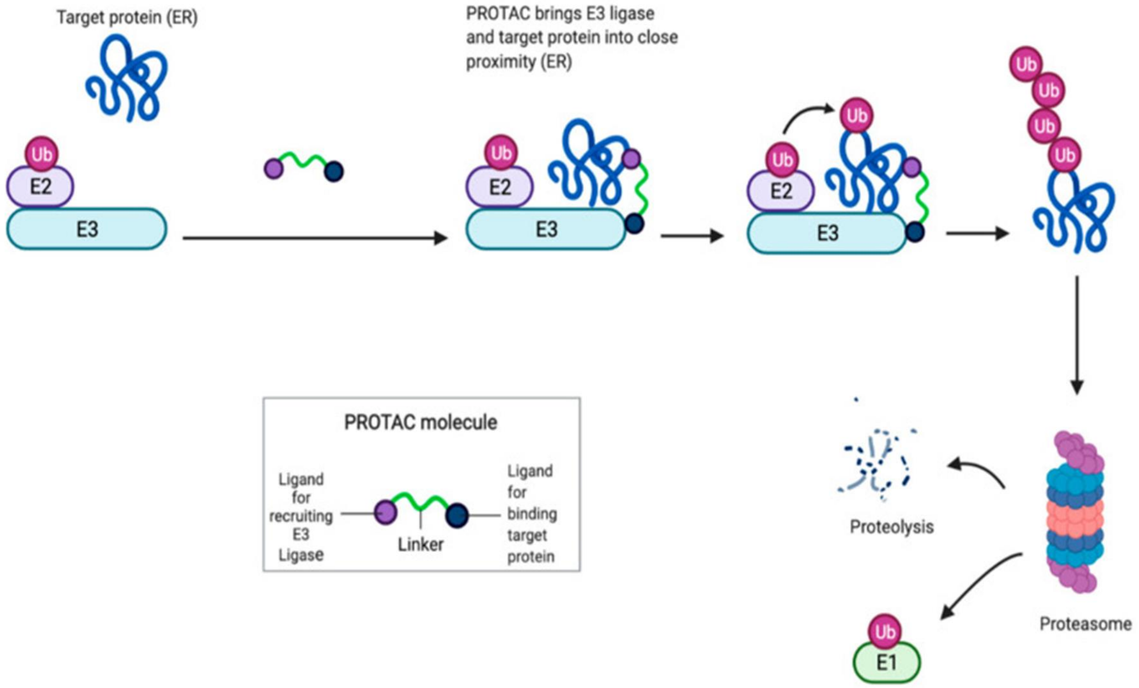
Data as of January 2023.



Data as of April 2023.

Abema, abemaciclib; CI, confidence interval; ctDNA, circulating tumor DNA; DoR, duration of response; LAS, lasofoxifene; MAF, mutant allele fraction; NE, not estimable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

PROTAC Protein Degrader



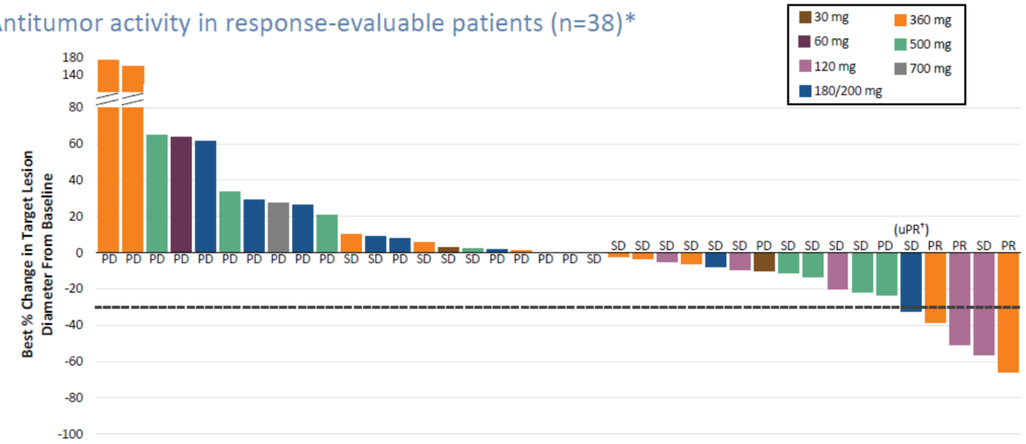
Hernando C et al. Int J Mol Sci. 2021; 22:7812

First-in-Human Safety and Activity of ARV-471, a Novel PROTAC Estrogen Receptor Degrader, in ER+/HER2-negative Locally Advanced or Metastatic Breast Cancer

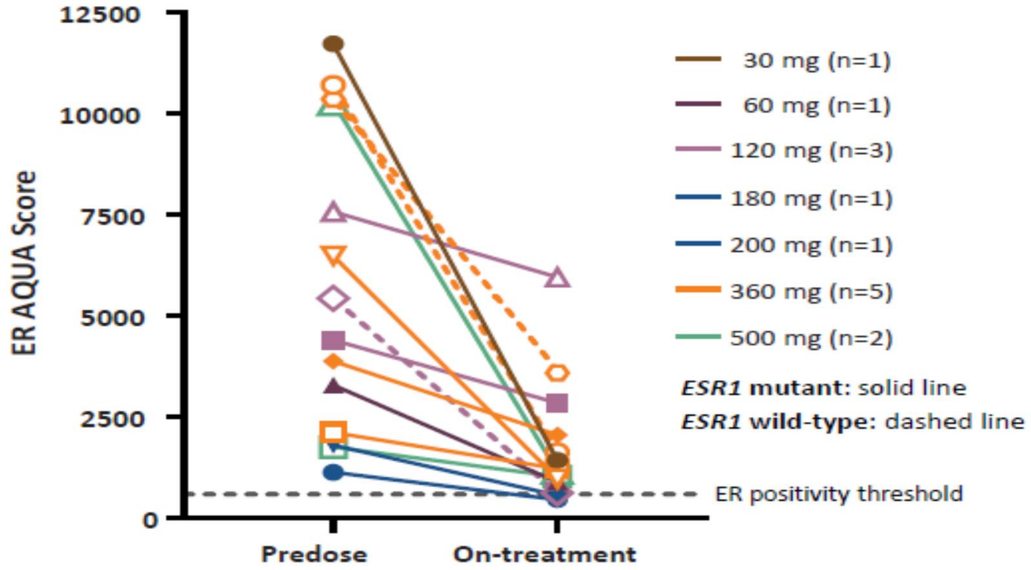
- ARV-471 showed antitumor activity in CDK4/6 inhibitor–pretreated patients with ER+/HER2-breast cancer, with a clinical benefit rate (CBR) of 40% (95% CI: 26%–56%)
- ARV-471 was well tolerated at all dose levels, with no dose-limiting toxicities reported
- Most treatment-related adverse events were grade 1/2
- Dose-related increases AUC_{24} and C_{max} were seen at doses up to 500 mg daily
- ARV-471 demonstrated robust ER degradation (up to 89%) at all doses up to 500 mg daily in paired biopsy samples

ARV-471 demonstrates promising anti-tumor activity in late-line patients

Antitumor activity in response-evaluable patients (n=38)*



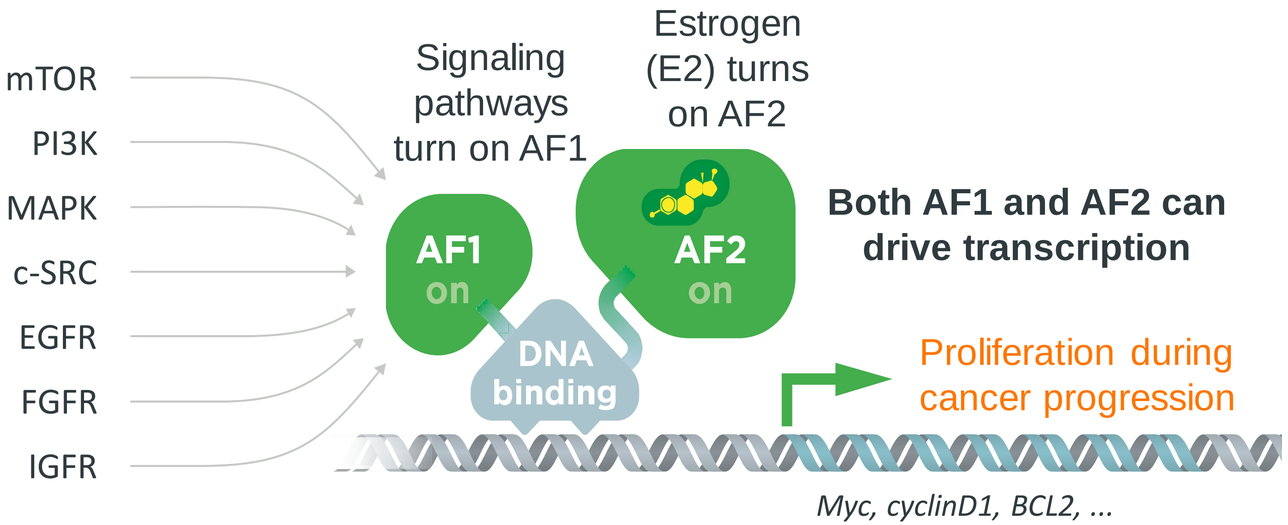
ER degradation in paired tumor biopsies* (n=14)



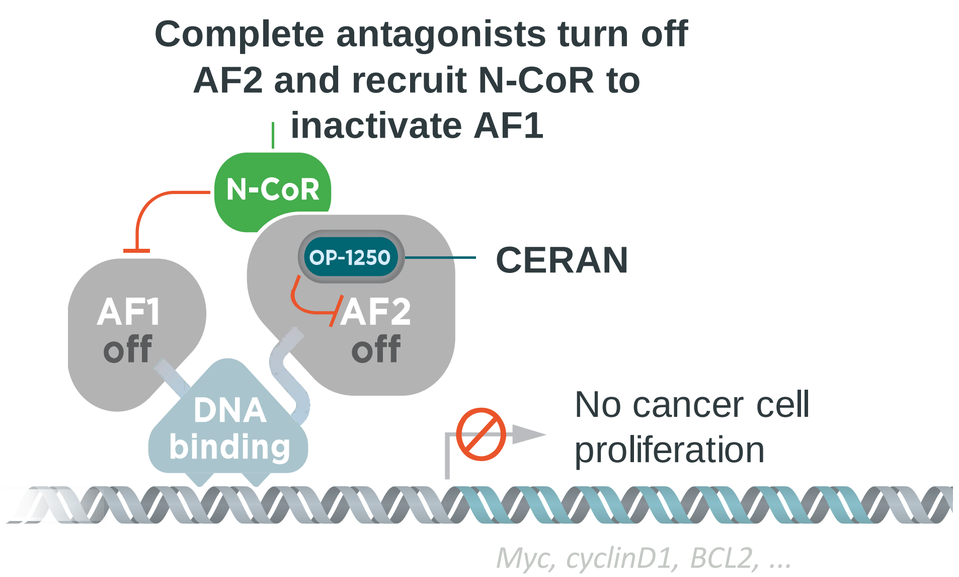
Hamilton, E et al. SABCS 2021; abstract 2343

OP-1250, CERAN, Mechanism of Action

Activation of AF1 and AF2 domains results in gene transcription that induces cancer cell proliferation



OP-1250 blocks both AF1 and AF2 blocking transcription of genes which induce cancer cell proliferation



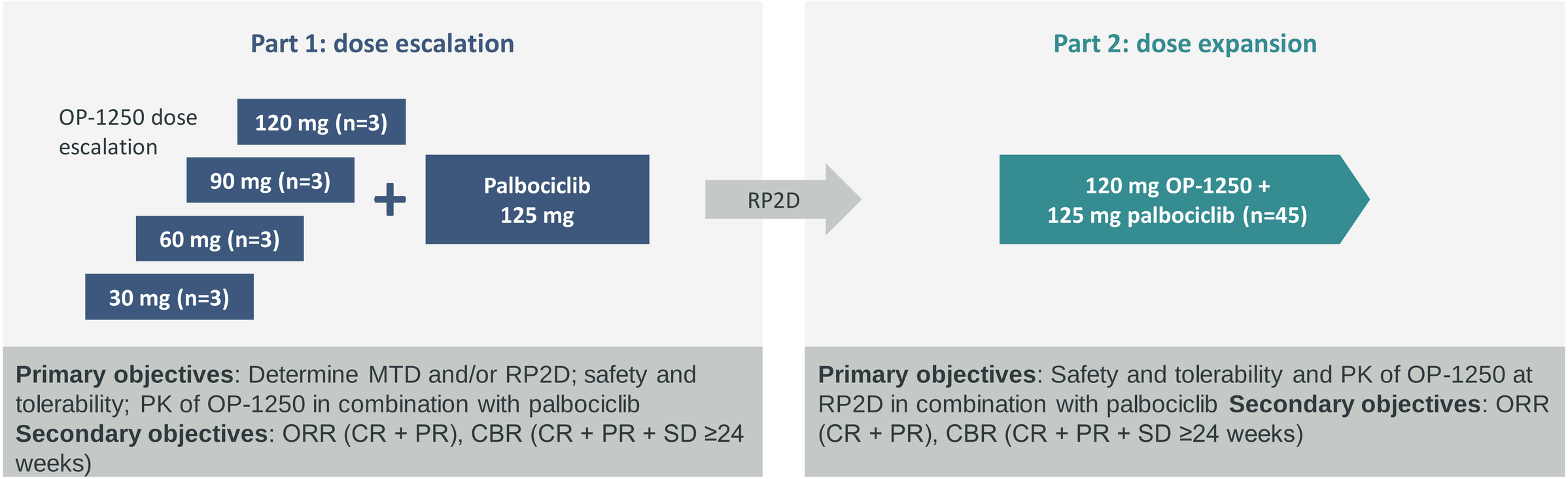
AF, activation function; **CERAN**, complete estrogen receptor antagonist; **N-CoR**, nuclear receptor corepressor.

Shang Y, et al. Science. 2002;295:2465–8
Webb P, et al. J Biol Chem. 2003;278:6912–2

Study Design

- This two-part study is comprised of a dose-escalation phase followed by a dose-expansion phase

OP-1250-002 study design



CBR, clinical benefit rate; **CR**, complete response; **MTD**, maximum tolerated dose; **ORR**, overall response rate; **PK**, pharmacokinetics; **PR**, partial response; **RP2D**, recommended phase 2 dose; **SD**, stable disease.

OP-1250-003: A Phase 1b Open-Label Multicenter Study of OP-1250 in Combination with the CDK4/6 Inhibitor Ribociclib or with the PI3K Inhibitor Alpelisib in Adult Subjects with Advanced and/or Metastatic HR Positive, HER2 Negative Breast Cancer

Study Design and Plan

This is a Phase 1b open-label, 2-part study in 2 treatment groups

Treatment Group 1		Treatment Group 2	
OP-1250	**Ribociclib** (KISQALI®, Novartis Pharmaceuticals Corporation)	**OP-1250**	**Alpelisib** (PIQRAY®, Novartis Pharmaceuticals Corporation)

The investigator will determine the treatment group to which an individual subject is assigned on a case-by-case basis based on the subject's treatment history, the best interest of the subject, and the subject's phosphoinositide 3-kinase alpha catalytic subunit (PIK3CA) mutation status.

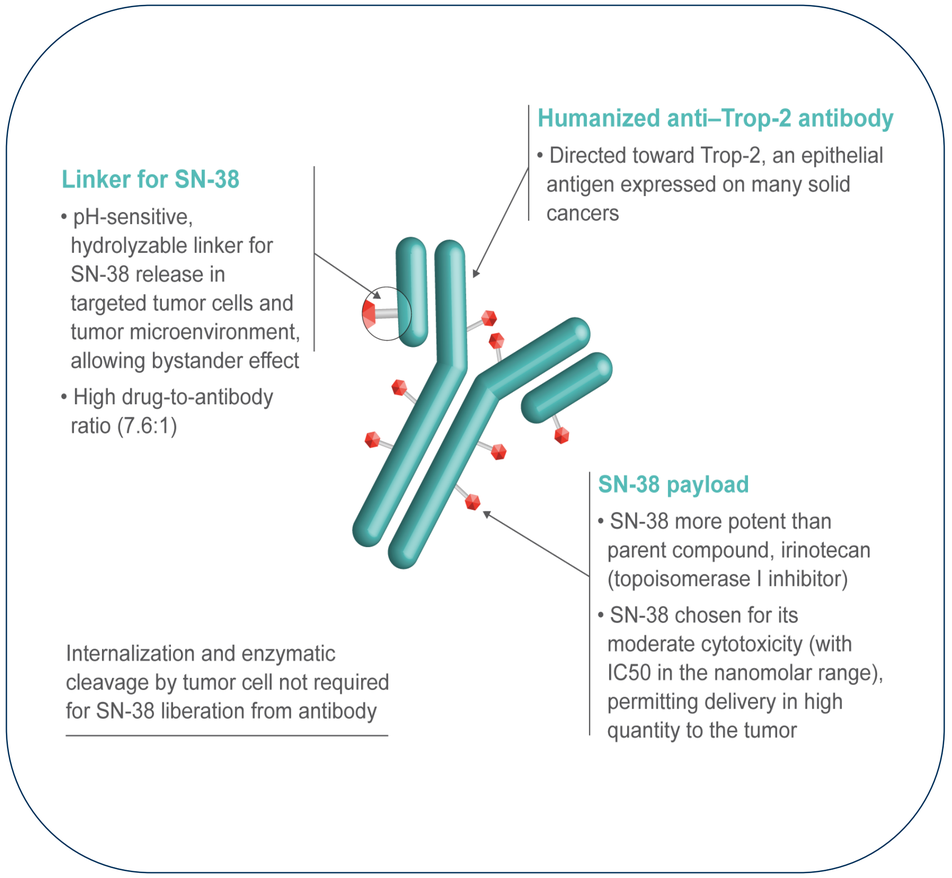
A subject may participate in only 1 treatment group and in only 1 part of the study.

OP-1250-003. NCT05508906. Updated May 25, 2023. Accessed July 25, 2023.

Sacituzumab Govitecan Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate[1-5]

- Trop-2 is an epithelial antigen that is highly expressed in ~85-90% of all subtypes of breast cancer, including HR+ breast cancer[6,7]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[8,9]
- In the TROPiCS-02 study, in patients with pretreated, endocrine-resistant HR+/HER2– mBC, SG demonstrated:
  - Statistically significant improvement in PFS, with a 34% reduction in the risk of disease progression or death (HR, 0.66; *P*=0.0003; median 5.5 vs 4.0 mo)[10]
  - Statistically significant improvement in OS at the second planned interim analysis (14.4 vs 11.2 mo; HR, 0.79; *P*=0.020)[11]
- SG demonstrated clinical benefit versus TPC in previously treated mTNBC, irrespective of level of Trop-2 expression[12]

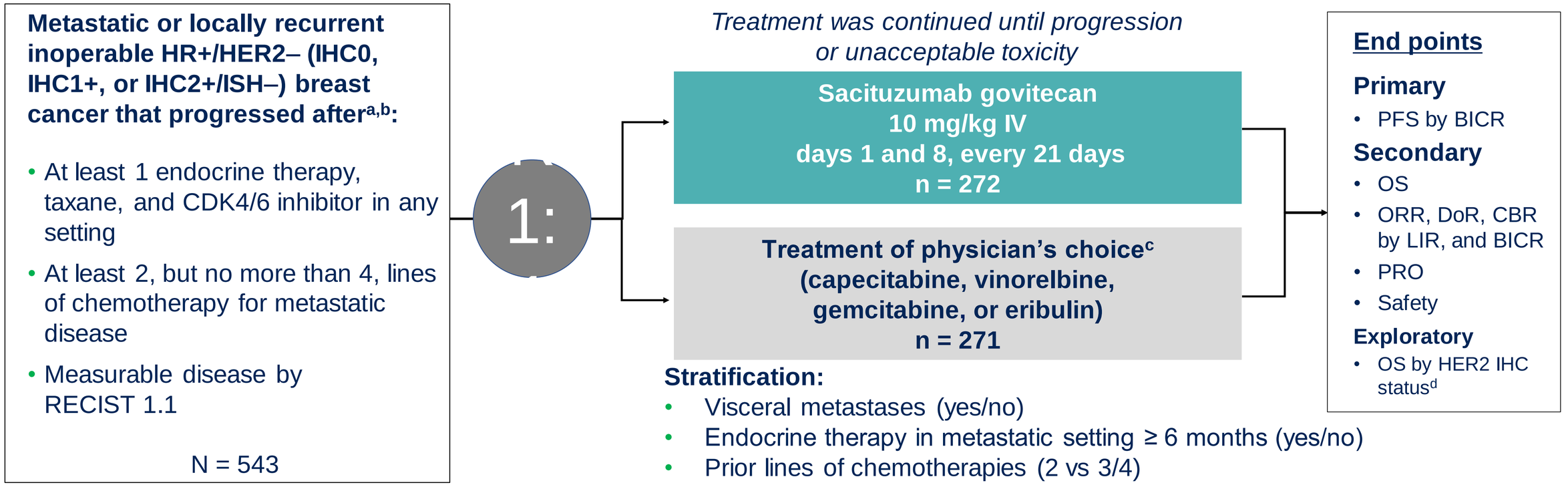
Here, we compare clinical outcomes for SG versus TPC by Trop-2 expression in TROPiCS-02



HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

1. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512. 4. Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. 5. Govindan SV, et al. *Mol Cancer Ther*. 2013;12:968-978. 6. Coates JT et al. *Cancer Discov.* 2021;11:2436-2445. 7. Vidula N et al. *Breast Cancer Res and Treat*. 2022;194:569-575. 8. TRODELVY (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2022. 9. European Medicines Agency: Trodelvy, INN-sacituzumab govitecan. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf. March 2022. Accessed November 23, 2022. 10. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. 11. Rugo HS, et al. ESMO 2022. Oral LBA76. 12. Bardia A, et al. *Ann Oncol.* 2021;32:1148-1156.

TROPiCS-02: A Phase 3 Study of SG in Patients with HR+/HER2– mBC[1]



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.

Demographics and Baseline Characteristics[1]

	SG (n = 272)	TPC (n = 271)
Female, %	99	99
Median age, (range) y	57 (29-86)	55 (27-78)
< 65 y, %	73	75
≥ 65 y, %	27	25
Race or ethnic group, %		
White	68	66
Black	3	5
Asian	4	2
Other[a]/Not reported[b]	25	28
Geographic region, %		
North America	42	42
Europe	58	58
ECOG PS, %		
0	43	46
1	57	54
Visceral metastases at baseline, %	95	95
Liver metastases,[c] %	84	87
De novo metastatic breast cancer, %	29	22

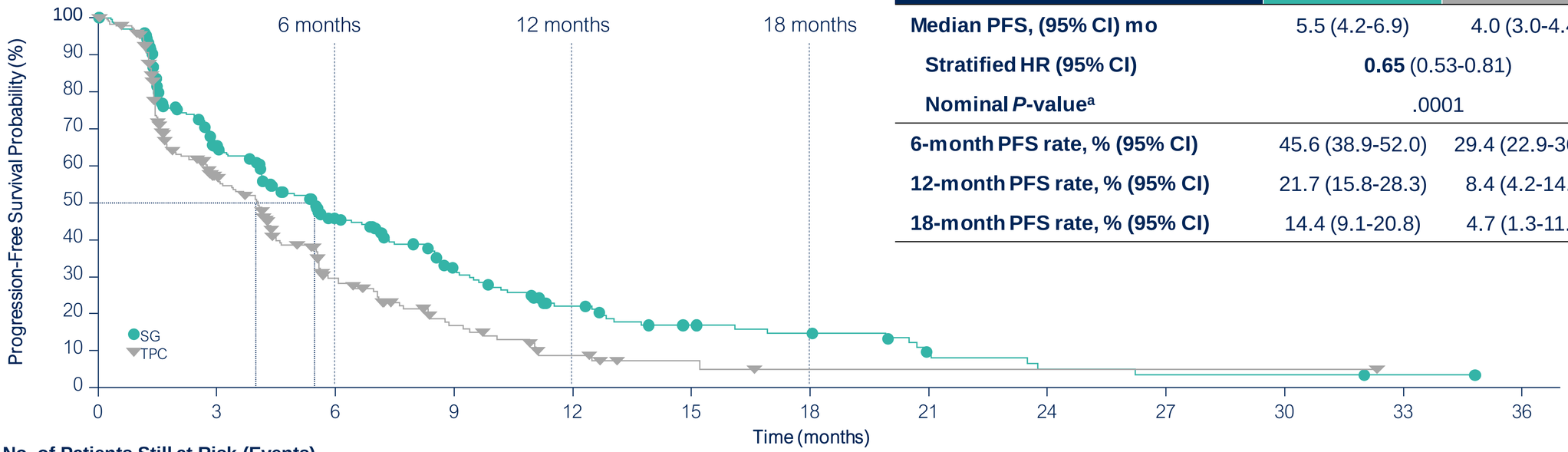
	SG (n = 272)	TPC (n = 271)
Median time from initial metastatic diagnosis to randomization, (range) mo	48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, %	64	68
DFI < 12 mo, %	8	8
Prior endocrine therapy use in the metastatic setting ≥ 6 mo, %	86	86
Prior CDK4/6 inhibitor use, %		
≤ 12 months	59	61
> 12 months	39	38
Unknown	2	1
Number of prior lines of chemotherapy, %		
≤ 2	42	44
≥ 3	58	56
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

CDK, cyclin-dependent kinase; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status, (neo)adjuvant, neoadjuvant or adjuvant; RECIST, Response Evaluation Criteria In Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

[a]Includes American Indian or Alaska native, native Hawaiian or other Pacific Islander. [b]Not reported indicates local regulators did not allow collection of race or ethnicity information. [c]Presence of baseline target/non-target liver metastases per RECIST 1.1 by local investigator review. [d]The reported number of prior therapies was miscounted at screening for some patients; 9 patients received prior chemotherapy regimens in the metastatic setting outside the per-protocol range for inclusion criteria and were included in the intent-to-treat population.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

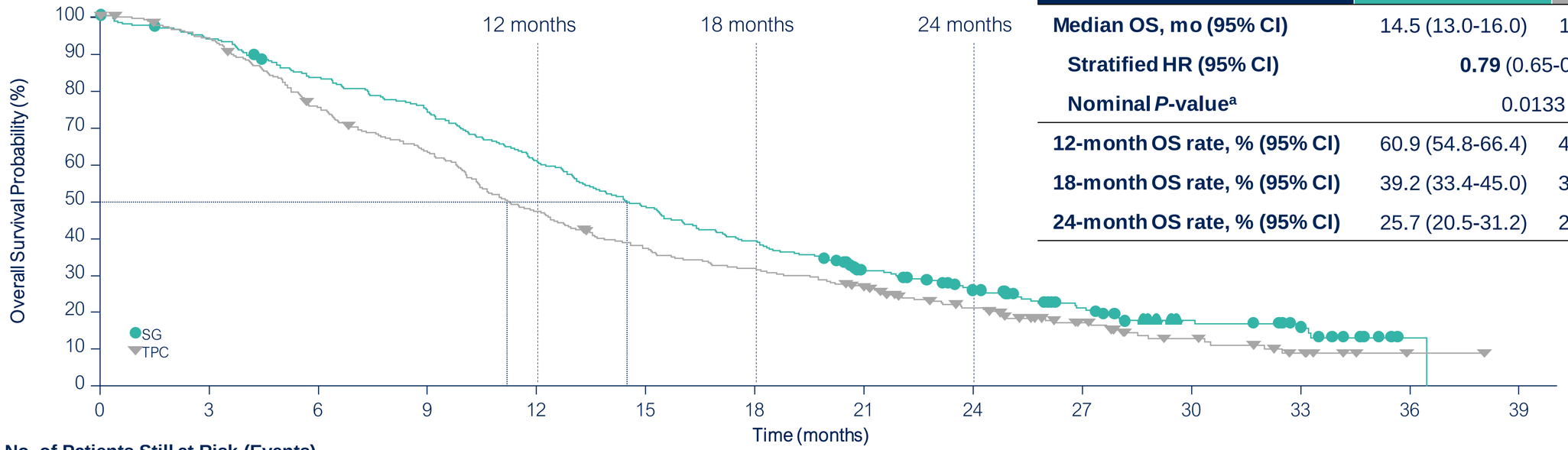
No. of Patients Still at Risk (Events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of Patients Still at Risk (Events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Safety Summary

TEAEs,[a] n (%)		SG (n = 268)		TPC (n = 249)	
		Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hematologic	Neutropenia[b]	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia[c]	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia[d]	17 (6)	1 (<1)	41 (16)	9 (4)
Gastrointestinal	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

The most common grade ≥ 3 TEAEs were neutropenia (52%), diarrhea (10%), and anemia (7%) in the SG group, and neutropenia (39%), thrombocytopenia (4%), fatigue (4%), and dyspnea (4%) in the TPC group

SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 30 days after the last dose of study drug.
[a]Key any-grade and grade ≥ 3 TEAEs were defined as those occurring in ≥ 15% or ≥ 10% of patients in 1 arm, respectively. [b]Combined preferred terms of "neutropenia" and "neutrophil count decreased." [c]Combined preferred terms of "anemia," "hemoglobin decreased," and "red blood cell count decreased." [d]Combined preferred terms of "thrombocytopenia" and "platelet count decreased."

Sacituzumab Govitecan-hziy for HR+ HER2-Negative Metastatic Breast Cancer

- On February 3, 2023, the FDA approved sacituzumab govitecan-hziy (Trodelvy) for patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

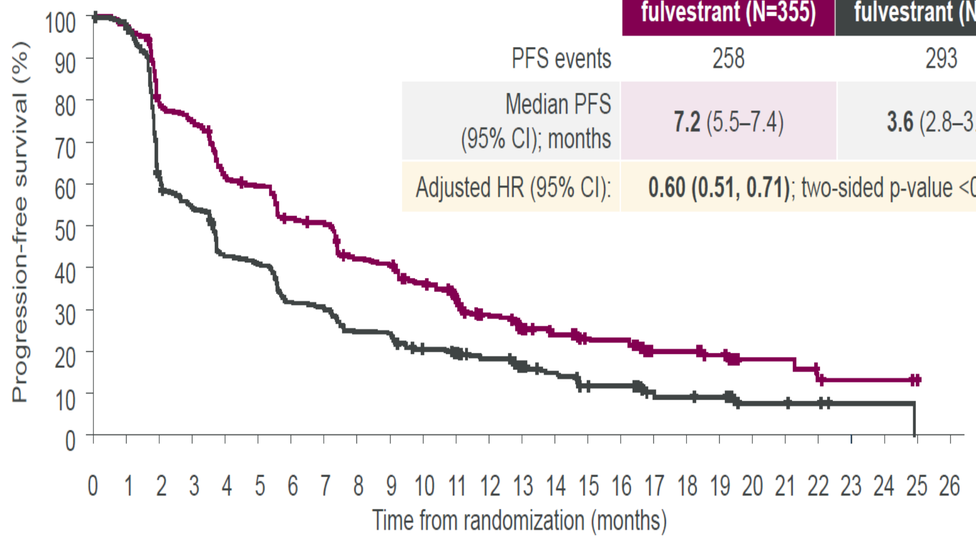
- Recommended dose modifications:
  - First occurrence: 25% dose reduction and administer granulocyte colony-stimulating factor (G-CSF)
  - Second occurrence: 50% dose reduction and administer G-CSF
  - Third occurrence: Discontinue treatment and administer G-CSF

- The first infusion of sacituzumab govitecan must be administered over 180 minutes. If this is well tolerated administer subsequent infusions over 60 to 120 minutes. Patients should be observed for 30 minutes after infusion.

Phase III Capltello-291 Trial: Capivasertib and Fulvestrant for Patients with Aromatase-Inhibitor Resistant Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer

Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



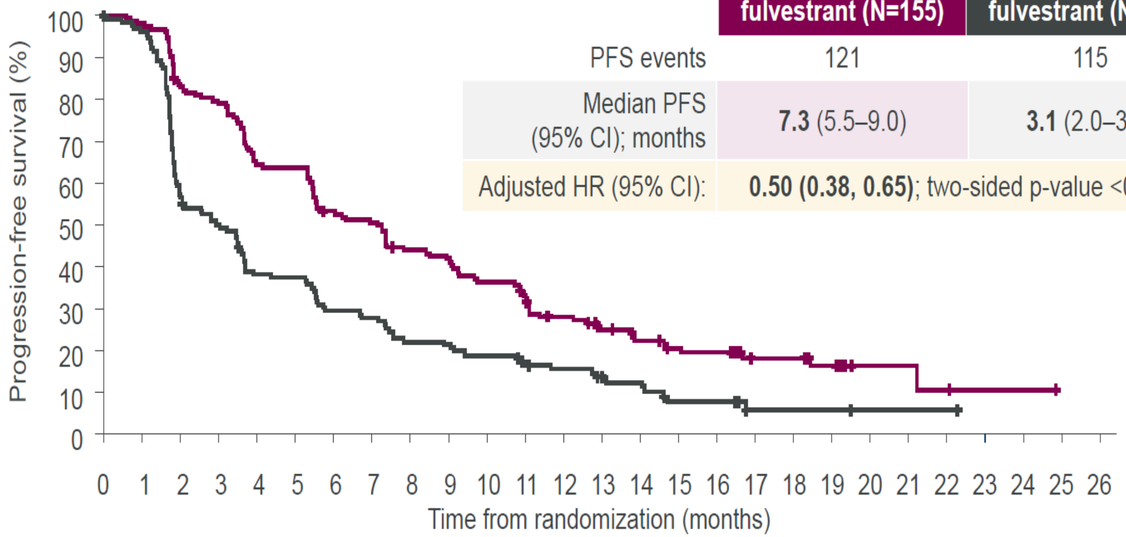
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	



Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Turner NC, et al: Presented at SABCS 2022; abstract GS3-04

Conclusions

- The first-line treatment for HR+ HER2-negative metastatic breast cancer is the combination of a CDK4/6 inhibitor with endocrine therapy.
- Optimal sequencing post-CDK4/6 inhibitor therapy should be tailored to the patient's functional status and tumor biology.
- Targeted or additional endocrine therapy should be considered prior to the use of chemotherapy.
- The oral SERD elacestrant was FDA-approved in patients with ESR1 mutations that have progressed on a prior line of endocrine therapy. Increasing PFS benefit was seen to correlate to the degree of overall endocrine sensitivity.

Conclusions

- Trastuzumab deruxtecan and sacituzumab govitecan have shown impressive OS benefits of 6.4 months and 3.2 months, respectively, over physicians' choice of therapy. In prospective trials showing this benefit, patients had to have prior chemotherapy exposure.

- Earlier use of trastuzumab deruxtecan in patients with HER2 low disease could be considered prior to chemotherapy in patients with a high burden of disease, as it has been associated with an impressive response rate and OS benefit.

- Additional oral SERDs are under investigation as a monotherapy and in conjunction with other agents, such as CDK4/6 inhibitors, alpelisib, or everolimus.

- Other targeted therapies that overcome endocrine resistance or directly target the estrogen receptor have promising efficacy and should be considered for patients through clinical trials.