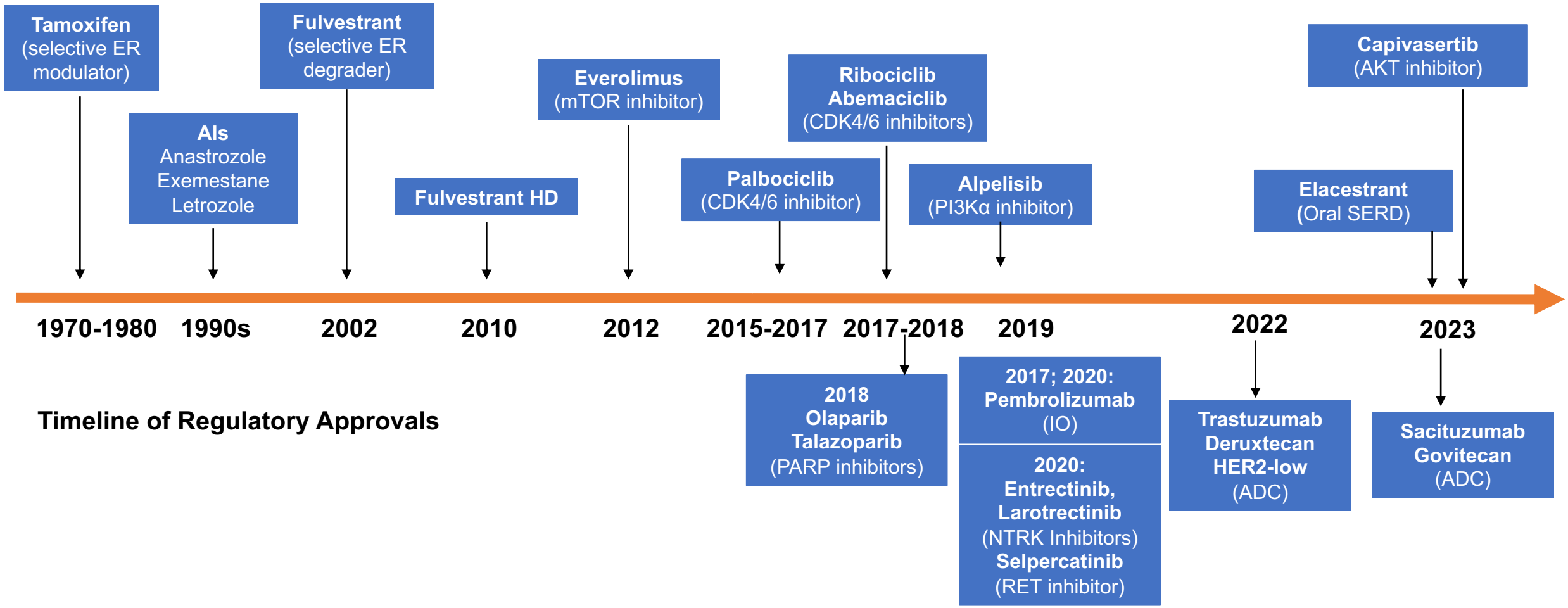
Sequencing Endocrine Therapy and Targeted Agents for the Treatment of Hormone Receptor Positive Metastatic Breast Cancer

Komal Jhaveri, MD, FACP
Patricia and James Cayne Chair for Junior Faculty
Associate Attending, Breast Medicine and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Memorial Sloan Kettering Cancer Center

Associate Professor
Weill Cornell Medical College
New York, New York

@jhaveri_komal

Treatment Landscape of HR+ Advanced MBC



Timeline of Regulatory Approvals

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; ET, endocrine therapy; HD, high dose; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3Kα, phosphoinositide 3-kinase α. Anastrozole [PI]. Approved 1995. Revised November 2022; Exemestane [PI]. Approved 1999. Revised May 2018; Letrozole [PI]. Approved 1997. Revised January 2014; Fulvestrant [PI]. Approved 2002. Revised July 2011; Everolimus [PI]. Approved 2012. Revised October 2010; Palbociclib [PI]. Approved 2015. Revised April 2019; Ribociclib [PI]. Approved 2017. Revised March 2017; Abemaciclib [PI]. Approved 2017. Revised October 2021; Alpelisib [PI]. Approved 2019. Revised May 2019; Brufsky AM. Cancer Treat Rev. 2017;59:22-32; Lim E, et al. Oncology (Williston Park). 2012;26:688-694; Croxtall JD, et al. Drugs. 2011;71:363-380; Carlson RW, et al. J Clin Oncol. 2010;28:3917-3921; NCCN. Breast cancer (v4.2023). 2023. Accessed May 1, 2023. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

PFS in 1st and 2nd Line Treatment With CDK4/6 Inhibitors + ET

	1st LINE TREATMENT				≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	MONALEESA-3
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	521	669	726
Primary Endpoint = PFS (CDK4/6 inhibitor + ET vs. ET)							
HR	0.58	0.56	0.54	0.55	0.46	0.55	0.59
Median PFS, months	27.6 vs 14.5 (13.1 mo)	25.3 vs 16 (9.3 mo)	28.2 vs 14.8 (13.4 mo)	23.8 vs 13 (10.8 mo)	9.5 vs 4.6 (4.9 mo)	16.4 vs 9.3 (7.1 mo)	20.5 vs 12.8 (7.7 mo)
Secondary Endpoint = OS (CDK4/6 inhibitor + ET vs. ET)							
HR	0.956	0.76	0.804	0.76	0.81	0.78	0.75
Median OS, months	53.9 vs 51.2	63.9 vs 51.4	66.8 vs 53.7	58.7 vs 40.9	34.9 vs 28.0	45.8 vs 37.25	52.2 vs 41.5

Cristofanilli et al, Lancet Oncology 2016; Finn et al, NEJM 2016; Hortobagyi et al, NEJM 2016; Tripathy et al, Lancet 2018; Sledge et al, JCO 2017; Goetz et al, ESMO 2022; Slamon et al, JCO 2018; Turner et al NEJM 2018; Sledge GW et al - JAMA Oncol. 2019; Slamon DJ, et al NEJM. Feb 2020; Rugo HS et al., Brain Cancer Res Treat. 2019; Finn et al ASCO2022, Neven et al ESMO Breast 2022 , Sledge et al SABCS 2022; Slamon et al JCO 2024; Goetz et al SABCS 2023

What are the Differences Among the CDK4/6 Inhibitors, and are They Significant and Relevant?[1-4]

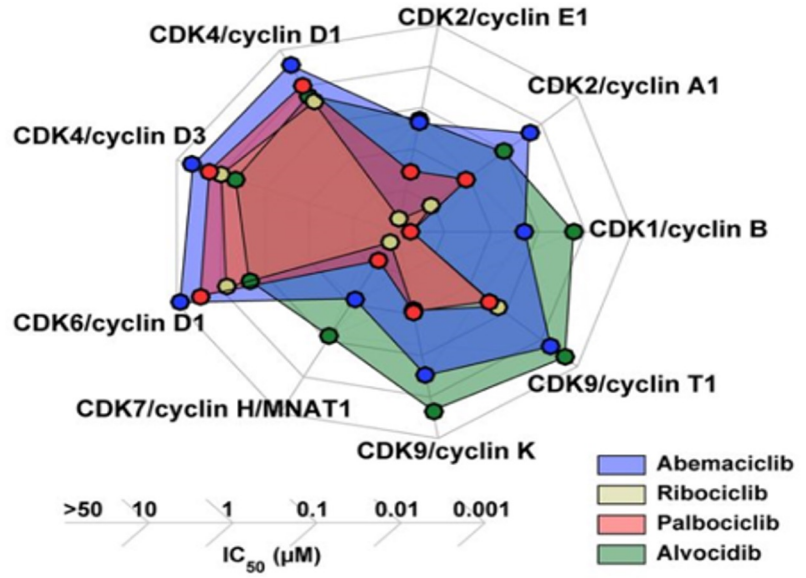
All Inhibit CDK4/6 complexes

- While palbociclib and ribociclib both have high selectivity for CDK4 and CDK6, ribociclib has a higher CDK4:CDK6 inhibition ratio (~4) given its weaker potency for inhibition of CDK6
- Abemaciclib has a different chemical structure and exhibits the highest inhibitory effect on CDK4/6 with a CDK4:CDK6 inhibition ratio of 5, and additional activity on multiple kinases, making it more potent and inducing a potent and sustained apoptotic effect; has cyclin B–CDK1, cyclin A/E–CDK2, and cyclin T–CDK9 inhibition
- Different acquired resistance mechanisms, demonstrated in a high-resolution analysis of pre-clinical models

IC_{50} Inhibition Values (nmol/L) Against Cyclin-CDK Complexes

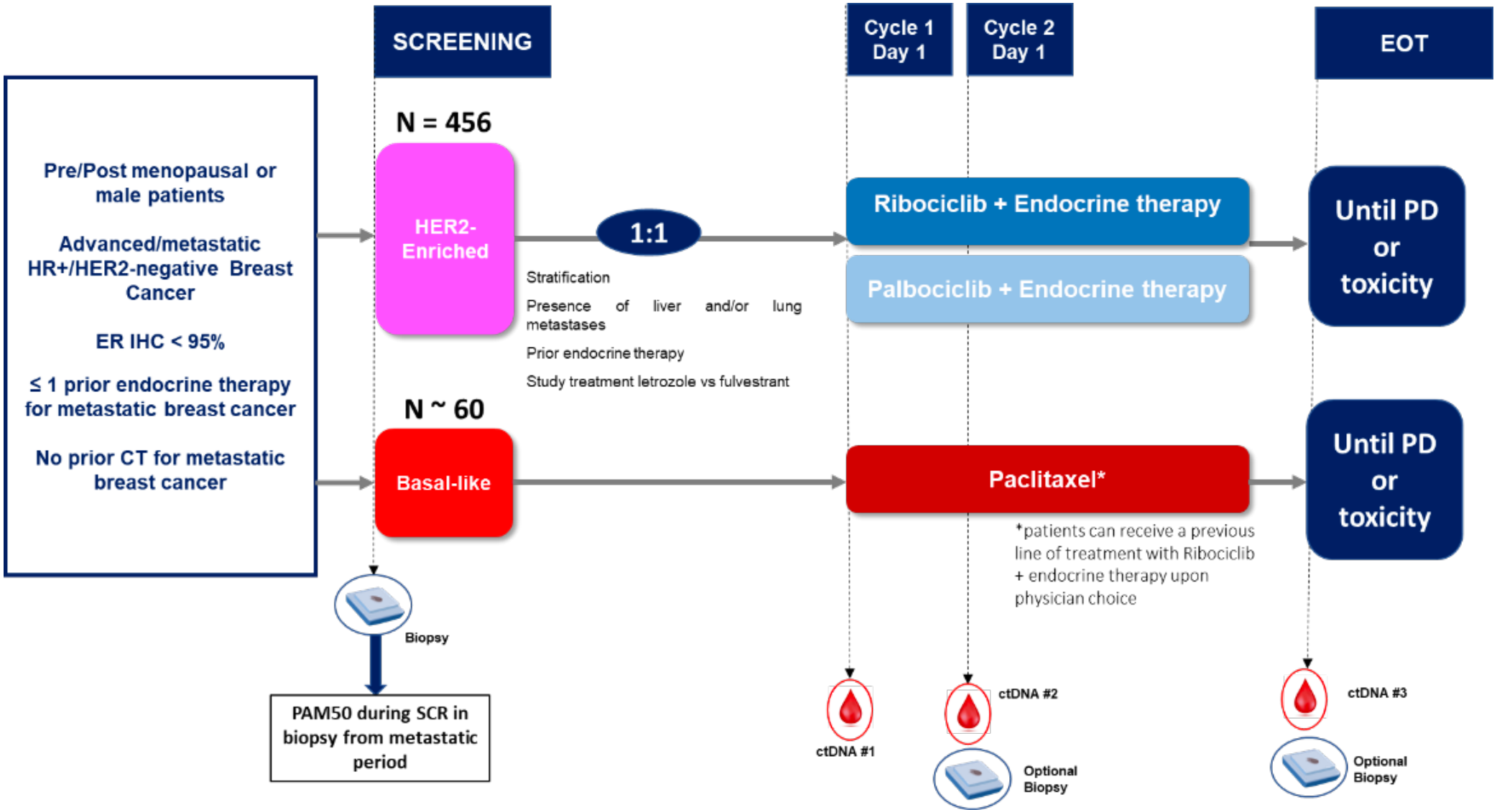
	Cyclin D1-CDK4	Cyclin D1/2/3-CDK4	CDK4:CDK6 Inhibition Ratio	Cyclin B-CDK1	Cyclin A/E-CDK2	Cyclin T-CDK9
Palbociclib	11	16	1:1.5	>10,000	>10,000	NR
Ribociclib	10	39	1:4	113,000	76,000	NR
Abemacib	2	10	1:5	1,627	504	57

Extent of Inhibition of CDK/Cyclin Complexes By Abemaciclib, Palbociclib, or Ribociclib



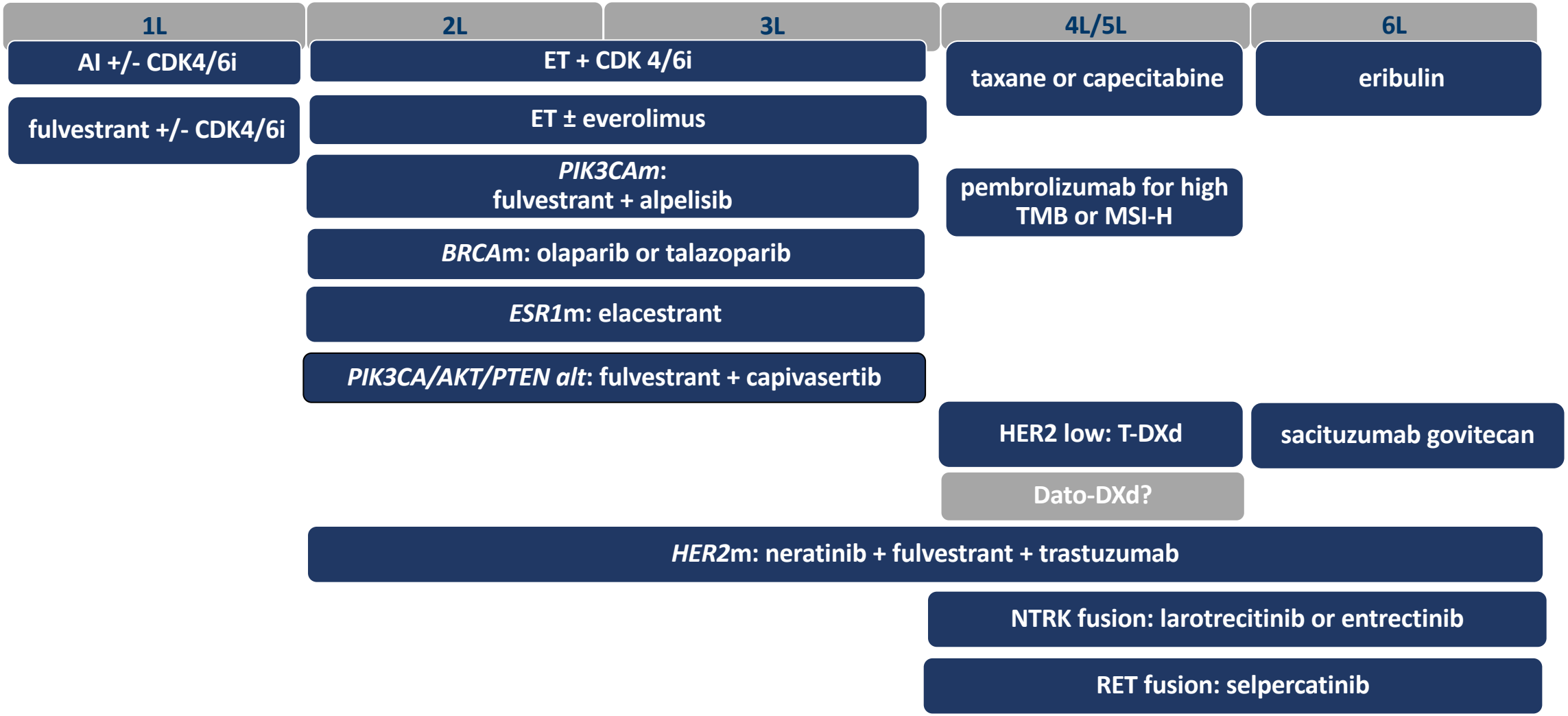
1. Hafner. Cell Chem Biol. 2017. 2. Sammons SL et al. Curr Cancer Drug Targets. 2017;17:637-649. 3. Sammons S et al. ASCO 2022. 4. Guarducci, C et al. *Cancer Res.* 83, GS3-07 (2023).

HARMONIA: Ribociclib vs Palbociclib in HER2E BC



PI: Aleix Prat

Approach to HR+/HER2- MBC Post-CDK4/6 Inhibitor: Move to Personalization

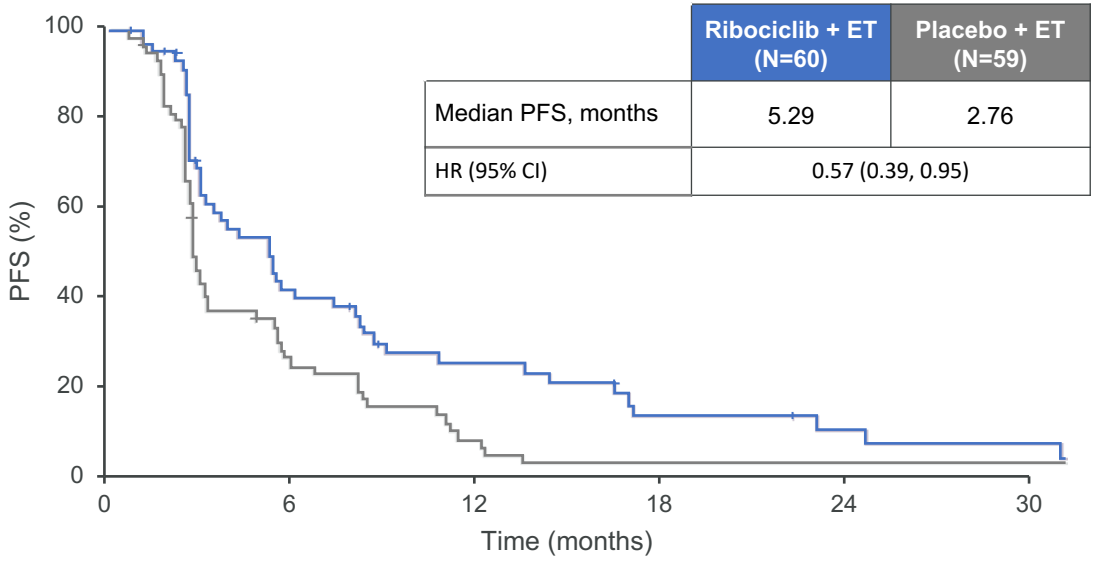


Adapted from NCCN Clinical Practice Guidelines in Oncology. Breast Cancer V4.2023.
Howell SJ et al. *Lancet Oncol*. 2022;23(7):851-864.

CDK4/6i rechallenge: PACE results conflict with those seen in MAINTAIN

MAINTAIN[1]

PFS

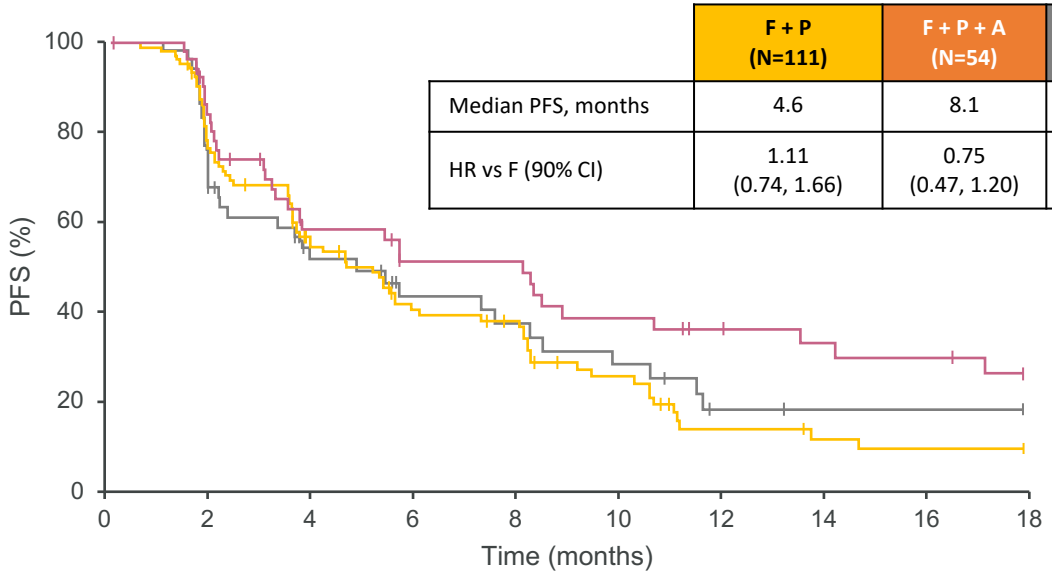


	Ribociclib + ET (N=60)	Placebo + ET (N=59)
Median PFS, months	5.29	2.76
HR (95% CI)	0.57 (0.39, 0.95)	

Palbociclib was the prior CDK4/6i in **~87%** of patients

PACE[2]

PFS



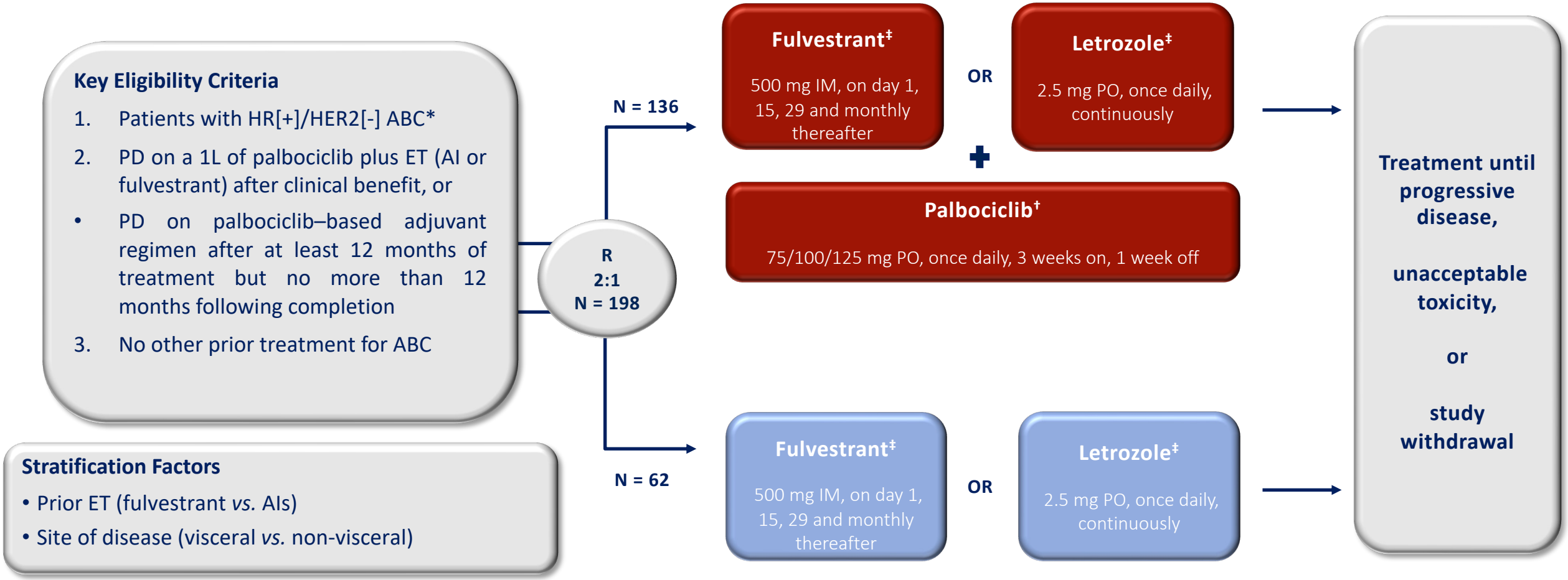
	F + P (N=111)	F + P + A (N=54)	F (N=55)
Median PFS, months	4.6	8.1	4.8
HR vs F (90% CI)	1.11 (0.74, 1.66)	0.75 (0.47, 1.20)	–

Palbociclib was the prior CDK4/6i in **~91%** of patients

A, avelumab; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; ET, endocrine therapy; F, fulvestrant; HR, hazard ratio; P, palbociclib; PFS, progression-free survival

1. Kalinsky K, et al. JCO 2023 2. Mayer E, et al. Oral presentation at SABCS 2022 (Abstract GS3-06)

PALMIRA Study Design (NCT03809988)



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.

*If pre-menopausal, ovarian function suppression method required.

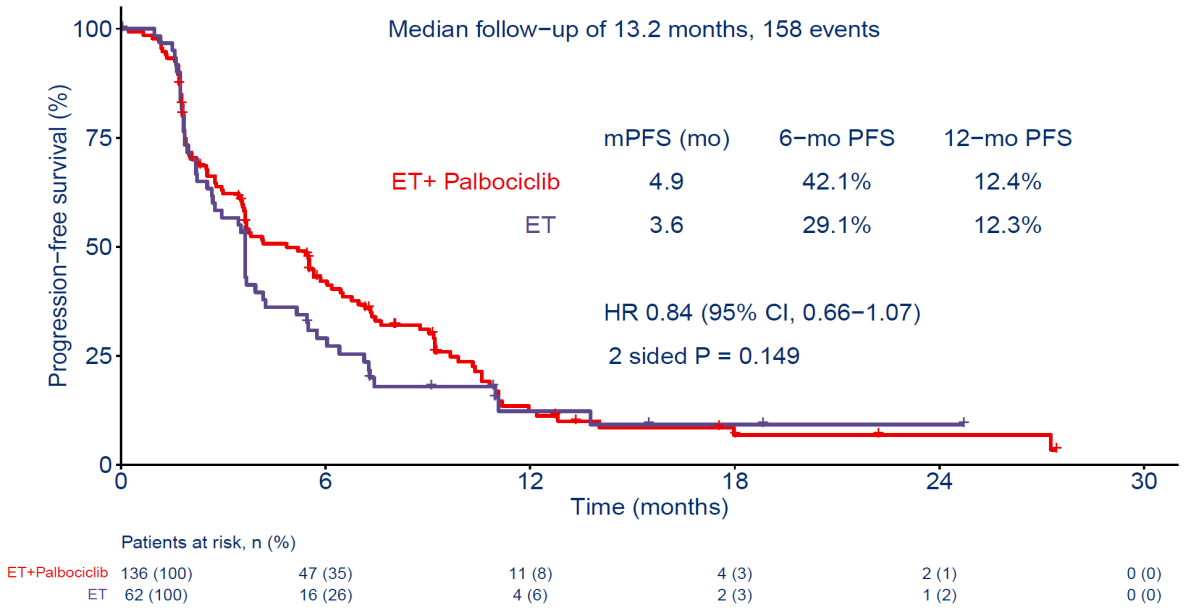
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.

‡Administration of endocrine therapy was chosen depending on the prior administered agent.

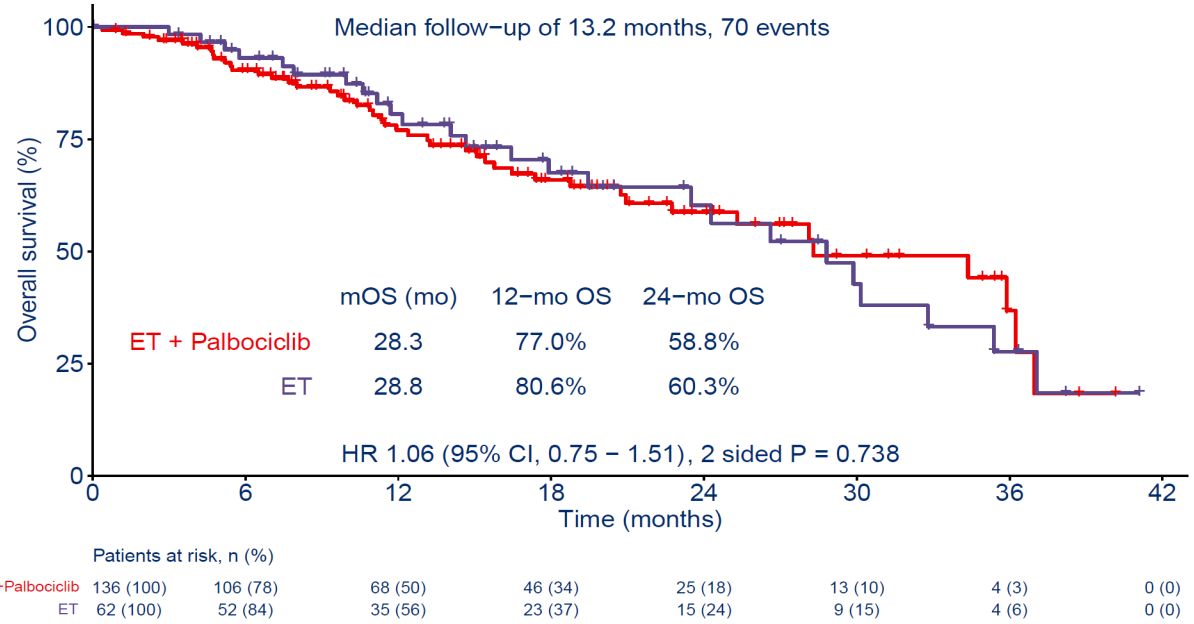
Llombart Cussac et al ASCO 2023

PALMIRA: Investigator-assessed PFS and OS (ITT)

PFS



OS



CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Other Key Phase 3 Trials Assessing Continuation of CDK4/6 Inhibition Beyond Progression

postMONARCH (NCT05169567)[1]

Does abemaciclib + fulvestrant improve outcomes after adjuvant or first-line CDK4/6i + ET?

- HR+/HER2- MBC pre- and postmenopausal adults (women and men)
- Prior therapy:
  - Advanced setting: Disease progression on CDK4/6i plus an AI as initial therapy, or
  - Adjuvant setting: Disease recurrence on or after CDK4/6i + ET

(N = 350)

R 1:1

- **Abemaciclib + fluvestrant** (n = 175)
- **Placebo + fulvestrant** (n= 175)

EMBER-3 (NCT04975308)[2]

How well does imlunestrant ± abemaciclib work compared with standard hormone therapy?

HR+, HER2- locally ABC or MBC

- If female, postmenopausal
- ECOG PS 0 or 1
- Measurable disease (per RECIST v1.1)
- Adequate organ function

R 1:1:1

- **Imlunestrant**
- **Exemestane** or **fulvestrant**
- **Imlunestrant + abemaciclib**

1. https://clinicaltrials.gov/study/NCT05169567. 2. https://clinicaltrials.gov/study/NCT04975308.

Elacestrant Monotherapy Post-CDK4/6 inhibitor

EMERALD: First Phase III, multicenter, international oral SERD Study

Inclusion Criteria
- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤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[b]

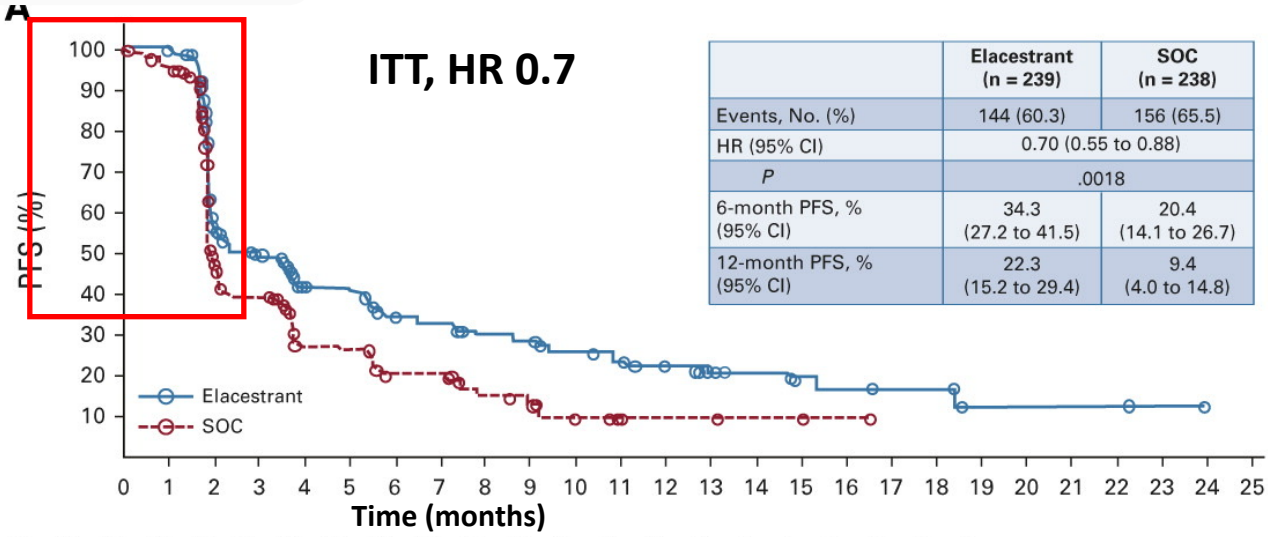
- Elacestrant 400 mg daily[c]
- Investigator's choice (SOC): Fulvestrant, Anastrozole, Letrozole, Exemestane

PD or withdrawal criterion[d] → Follow Up

Two Primary Endpoints:[e]
- PFS in all pts
- PFS in m*ESR1*

Demographics
- ~70% visceral mets
- ~57% Second Line
- ~40% 2 lines prior ET for mBC
- ~24% one line of chemotherapy
- 100% prior CDK4/6i

A



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

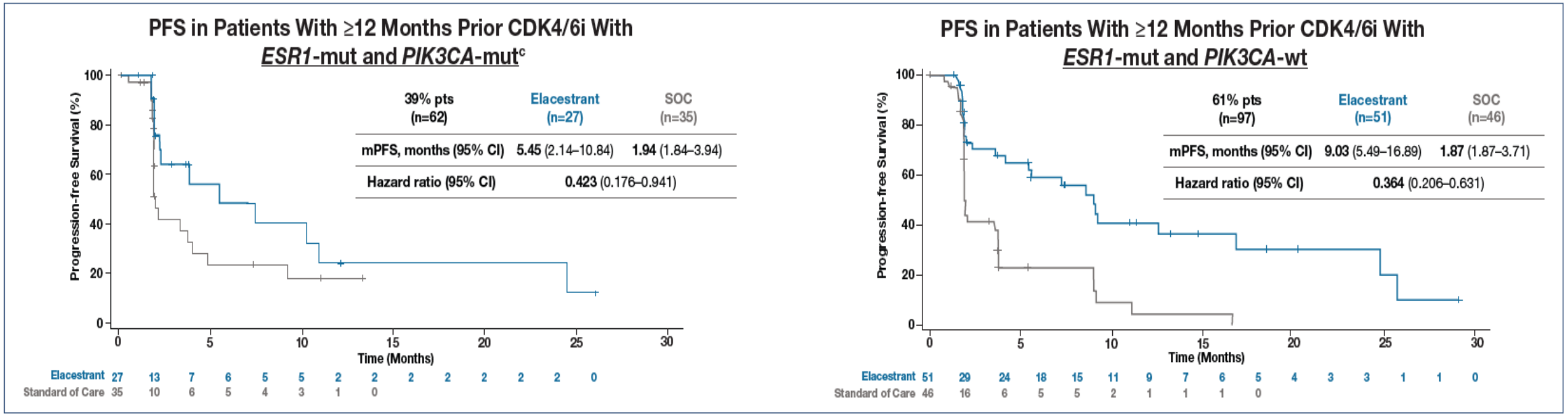
Bardia et al SABCS 2021; FC Bidard et al JCO 2022

Elacestrant Alone Shows Respectable Disease Control in *ESR1*m with Long CDK4/6 Exposure

Trial Enrollment: Elacestrant (n=239) or SOC (n=238)

	>12m on CDK4/6 in ITT				> 12m on CDK4/6 in *ESR1* mutant pts			
	At least 12 mo		At least 18 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=150)	SOC (n=160)	Elacestrant (n=98)	SOC (n=119)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
mPFS	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
6m PFS	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
12m PFS	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
18m PFS	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
HR	**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Elacestrant in *ESR1* and *PIK3CA* Mutant Population and >12 Months on CDK4/6i



EMERALD: Safety and Summary

Safety Summary

- Most AEs, including nausea, were grade 1-2
- No grade 4 TRAEs were reported
- Discontinuations of therapy due to TRAEs:
  -Elacestrant arm: 3.4%
  -SOC arm: 0.9%
- No hematologic safety signal was observed
- None of the patients in either treatment arm experienced 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)	N/A
Discontinuation rate due to nausea, n (%)	3 (1.3)	0
Antiemetic use, %	8	10.3 (AI) 1.3 (fulvestrant)

Bardia A, et al. SABCS 2022. Abstract GS3-01; Bidard FC et al. *J Clin Oncol*. 2022;JCO2200338.

Randomized Trials of Novel SERDs/SERM Monotherapy

	EMERALD (NCT03778931)	acelERA (NCT04576455)	SERENA-2 (NCT04214288)	ELAINE 1 (NCT03781063)
N	Phase III, 477	Phase II, 303	Phase II, 288	Phase II, 103
Prior CDK 4/6i	100%	Allowed	50%	100%
Treatment Arms	Elacestrant vs ET (AI or Fulvestrant)	Giredestrant vs ET (AI or Fulvestrant)	Camizestrant (various doses) vs Fulvestrant	Lasofoxifene vs Fulvestrant
Primary Endpoint	PFS in ITT and *ESR1* mutant	PFS	PFS	PFS
% *ESR1*m	48%	39%	34%	100%
Results	2.8m vs 1.9m HR 0.7, **+ study**	HR 0.8 **- study**	7.2m (75mg) vs 3.7m HR 0.58, **+ study**	
***ESR1*mut**	*ESR1m*: 3.78m vs 1.87m HR 0.55	*ESR1*m: HR 0.6	*ESR1m*: 6.3m (75mg) vs. 2.2m, HR 0.3	*ESR1m*: 6m vs 4m, HR 0.7, **- study**

FC Bidarad JCP 2022: Jimenez MM et al ESMO 2022; Olivera SABCS 2022; Jhaveri ASCO 2022; Goetz et al ESMO 2022

Recent Updates In the Novel Endocrine Agents Landscape

	Monotherapy		PI3K Pathway Combinations		CDK4/6i Combinations		
	Imlunestrant	OP-1250 (CERAN)	Imlunestrant + alpelisib	Imlunestrant + everolimus	Vepdegestrant (PROTAC) + palbociclib	OP-1250 (CERAN) + palbociclib	Imlunestrant + abemaciclib
N	114	86	21	42	31	19	42
ESR1 mutant	49%	48%	47%	48%	43%	52%	7%
Median Prior Tx	2	2	1	1	4	1	0
% Prior CDK4/6i	93%	97%	100%	100%	87%	72%	0%
% Prior Fulv	52%	66%	43%	31%	80%	11%	5%
% Prior chemo	25%	31% (met)	14%	19%	76% (46% met)	22%	10%
ORR	**8%**	**3%**	**58%**	**21%**	**42%**	**10.5%** (21% incl. uPR)	**32%**
CBR	**42%**	**40%**	**62%**	**62%**	**63%**	**46%**	**71%**
PFS	**4.3** (6.5 2L post CDK4/6i)	**4.6** (7.2 2L/3L)	**9.2**	**15.9**	**11.1**	N/R	**19.2**

N/R = not reported.

1.Jhaveri et al ASCO 2022; 2. Lin et al ESMO 2023 #382MO, 3. Jhaveri et al ESMO 2023 #383MO, 4. Hurvitz et al SABCS 2023 PS-15-03, 5. Chan et al SABCS 2023 PS-15-04, 6. Jhaveri et al SABCS 2023 PS15-09

Selected Ongoing Clinical Trials of SERDs + Targeted Agents in HR+/HER2- ABC

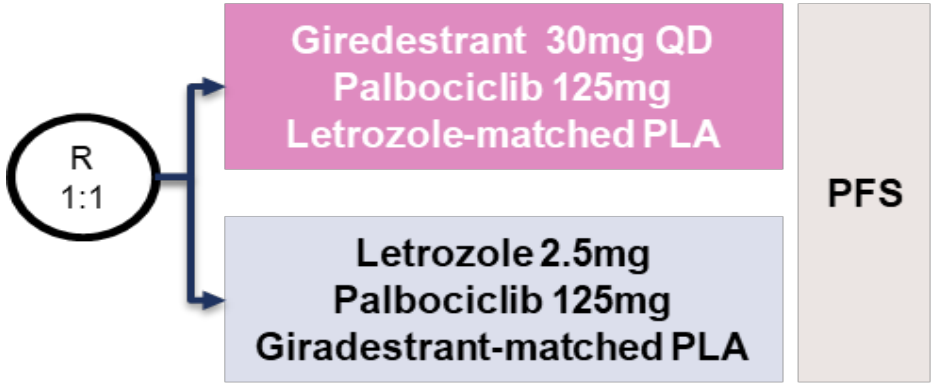
Trial (NCT Identifier)	Intervention	Study Population	Primary Endpoint(s)	Secondary Endpoint(s)	Enrollment (Estimated)	Recruiting (Yes/No)*
ELEVATE (NCT05563220)	Elacestrant **+** • Abemaciclib • Ribociclib • Palbociclib • Alpelisib • Everolimus	≤ 2 ET, one of which is in combination with CDK4/6i	RP2D of elacestrant in combination with each of the other study drugs	Safety, PK, Efficacy (ORR, CBR, PFS, OS)	322	Yes
pionERA Breast Cancer (NCT06065748)	Giredestrant + CDK4/6i vs. Fulvestrant + CDK4/6i	Resistance to prior adjuvant ET; prior use of neo/adjuvant CDK4/6i allowed	PFS in *ESR1m* subgroup and full analysis set	PFS in the *ESR1nmd* subgroup, OS, cORR, DoR, CBR, time to chemotherapy, TTCD in PROs, AEs, vital sign and clinical laboratory test abnormalities	1050	Not yet recruiting
evERA Breast Cancer (NCT05306340)	Giredestrant + Everolimus vs. Physician's choice of ET + Everolimus	Prior ET in combination with CDK4/6i (metastatic or adjuvant setting)	PFS in *ESR1m* subgroup and ITT population	OS, ORR, DoR, CBR, TTCD pain severity, presence, and interference, TTCD in PROs, AEs, vital sign and clinical laboratory test abnormalities, plasma concentration of giredestrant	320	Yes

Ongoing Trials of Oral SERDs in Combination With CDK4/6i in the 1st-L Metastatic Setting

persevERA (NCT04546009)

N=978

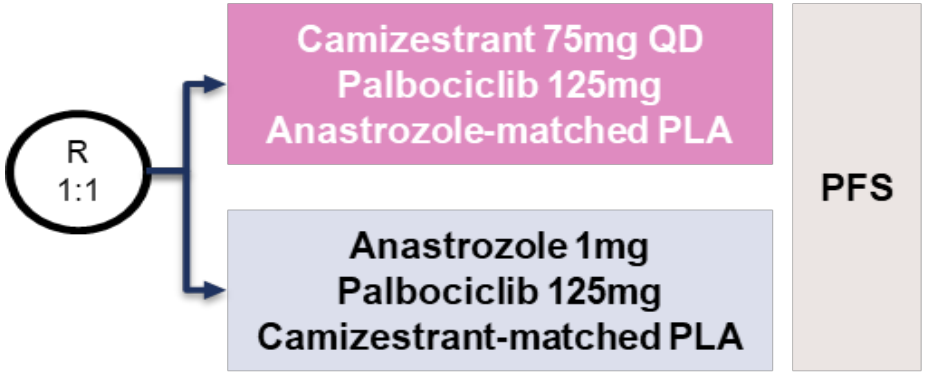
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



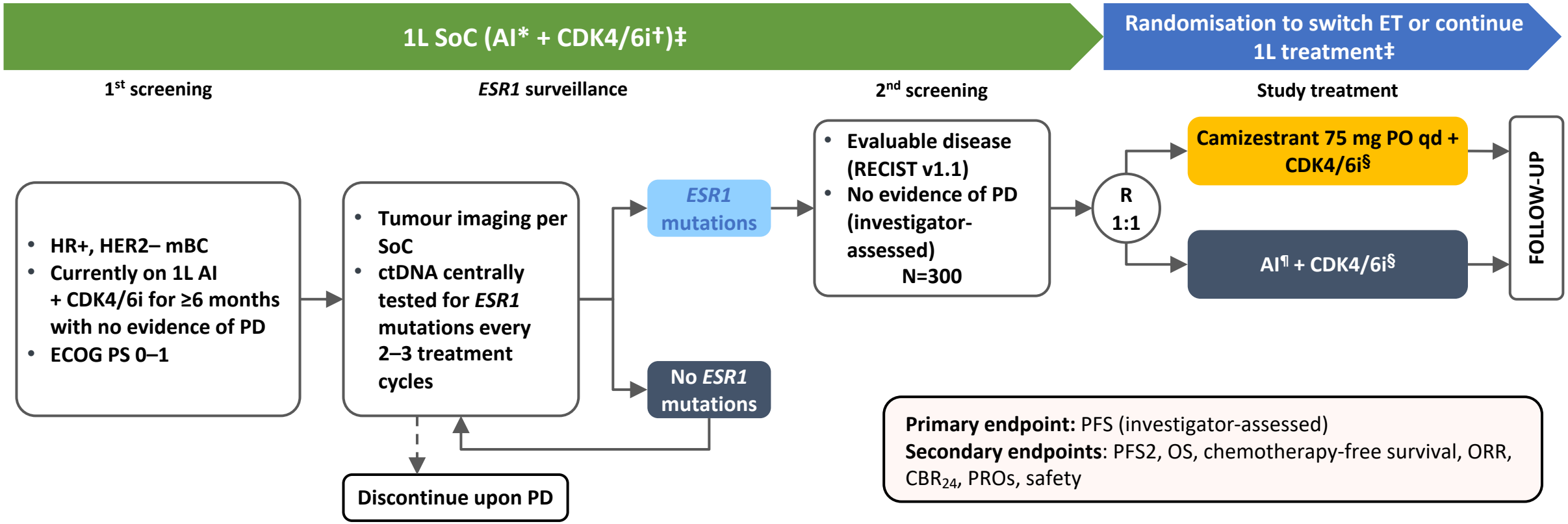
SERENA-4 (NCT04711252)

N=1342

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



SERENA-6: ctDNA *ESR1* Mutation-Guided Therapy[1,2]



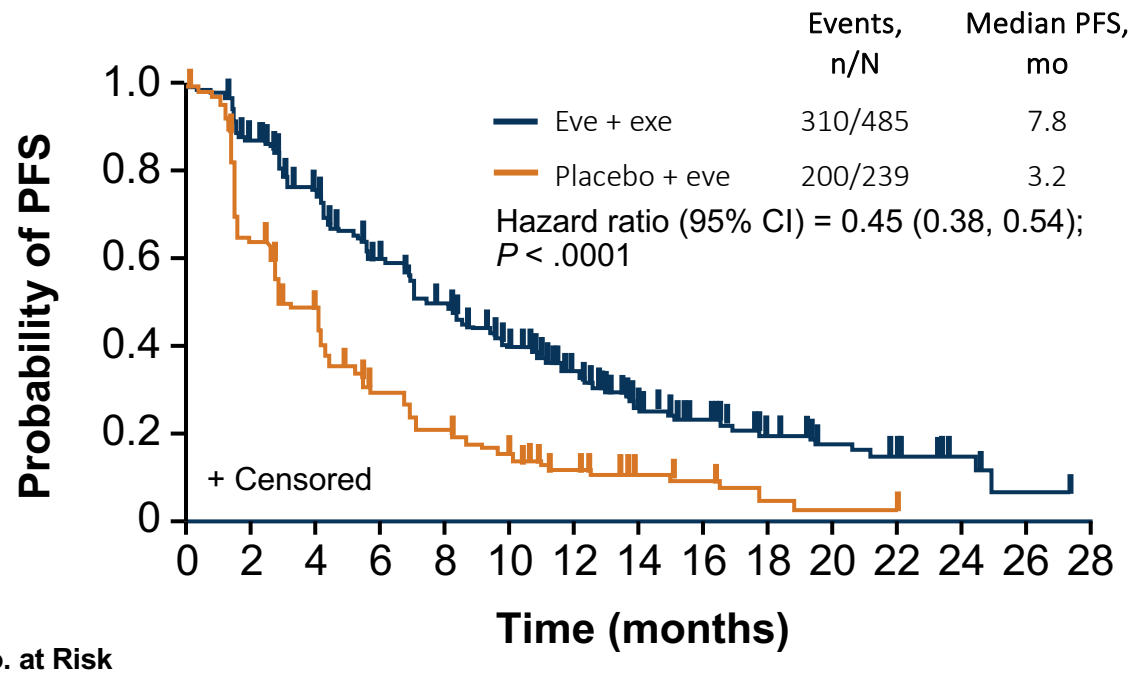
The SERENA-6 trial is currently recruiting

Letrozole or anastrozole. † Palbociclib or abemaciclib. ‡ Pre-/peri-menopausal women and men receive LHRH agonist as applicable. § Maintain same CDK4/6i as 1L treatment; ¶ Maintain same AI as 1L treatment.
1L, first line; AI, aromatase inhibitor; CBR_{24}, clinical benefit rate at 24 weeks; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumour DNA; ET, endocrine therapy; HR, hormone receptor; LHRH, luteinising hormone-releasing hormone; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PFS2, time to second progression or death; PO, orally; PRO, patient-reported outcome; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Bidard FC et al. SABCS 2021. Abstract OT2-11-05. 2. SERENA-6. Accessed August 2023. https://clinicaltrials.gov/ct2/show/NCT04964934

Improved PFS With mTOR Inhibition
BOLERO-2 and PrE0102 Trials

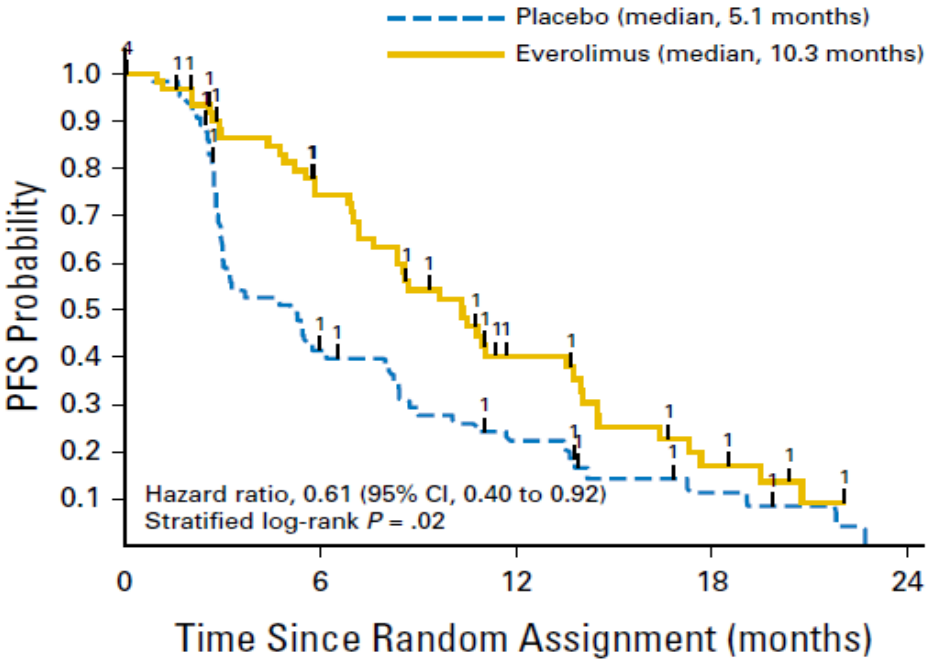
Local Assessment[a,b]



No. at Risk

Eve + exe	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
Placebo + eve	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Investigator-Assessed PFS[c]



No. at risk:

Placebo	65	25	12	4	0
Everolimus	66	41	17	6	1

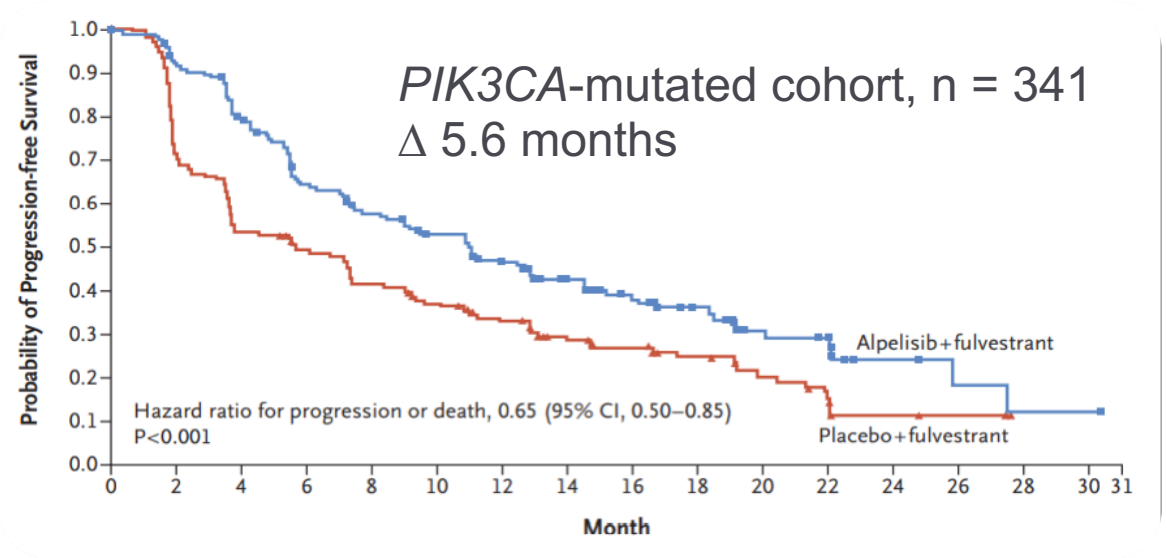
Improved PFS with mTOR inhibition regardless of *PIK3CA* mutation[a-c]; similar results with tamoxifen + everolimus[d]; no OS benefit

a. Yardley DA, et al. Adv Ther. 2013;30:870-884; b. Baselga J, et al. N Engl J Med. 2012;366:520-529; c. Kornblum N, et al. J Clin Oncol. 2018;36:1556-1563; d. Bachelot T, et al. J Clin Oncol. 2012;30:2718-2724.

Option for Patients Whose Tumors Harbor *PIK3CA* Mutations
Fulvestrant + *Alpelisib*

SOLAR-1 (Phase 3): Fulvestrant ± Alpelisib

(Progression on or after AI)



- Numerical improvement in median OS of 7.9 months in the mutated cohort[b]
- Discontinuation rate was 25% in FUL + ALP arm vs 4.2% in the FUL arm[a]
- Most common side effects (grade 3): hyperglycemia (36%), rash (10%), and diarrhea (7%)[a]
- **6% had prior CDK4/6 inhibitor**

Median PFS[a]

- 11.0 months (ALP + FUL) vs 5.7 months (FUL)
- HR = 0.65 (95% CI: 0.50, 0.85); *P* < .001

ALP, alpelisib; FUL, fulvestrant.

a. Andre F, et al. N Engl J Med. 2019;380:1929-1940; b. Andre F, et al. Ann Oncol. 2021;32:208-217

Activity With PI3K Inhibitors and Various Endocrine Partners

- **PFS benefit in 2L metastatic setting after progression on CDK4/6i is ~ 5 to 7 months**

	BYLieve: PI3Ki + ET in HR+/HER2– BC With *PIK3CA* Mutation and PD on CDK4/6 Inhibition		
	Cohort A[a] (n = 121)	Cohort B[b] (n = 115)	Cohort C[c] (n = 115)
Cohort population	CDK4/6i + AI as immediate prior tx	CDK4/6i + fulvestrant as immediate prior tx	Chemo or ET as immediate prior tx
Endocrine partner	Fulvestrant	Letrozole	Fulvestrant
PI3Ki	Alpelisib	Alpelisib	Alpelisib
Median PFS, mo	7.3	5.7	5.6
HR (PI3Ki vs control)	NA	NA	NA

PD, progressive disease; tx, treatment.

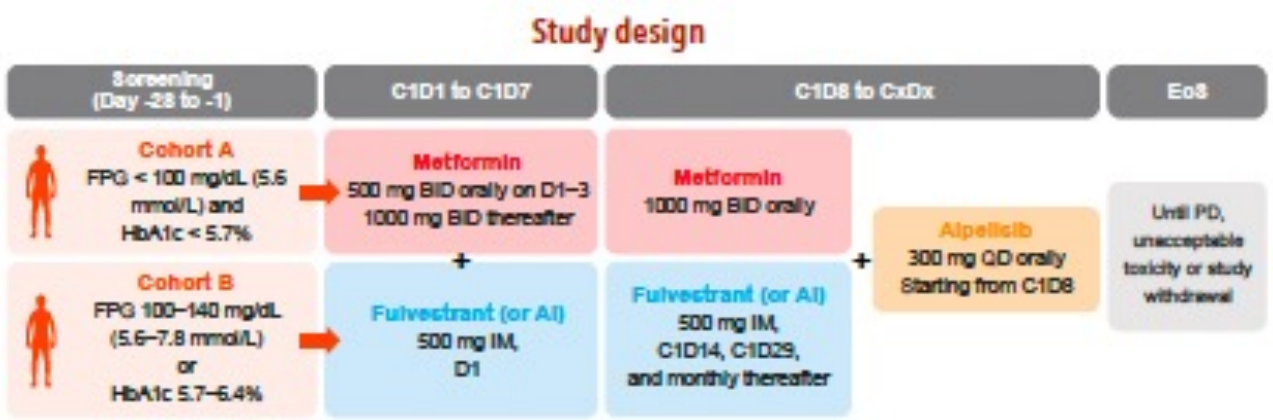
a. Rugo HS, et al. Lancet Oncol. 2021;22:489-498; b. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020; December 8-11, 2020; Virtual. Presentation PD2-07; c. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2021; December 7-10, 2021; San Antonio, TX. Presentation PD13-05.

Potential strategies to improve efficacy of isoform-specific PI3Ki

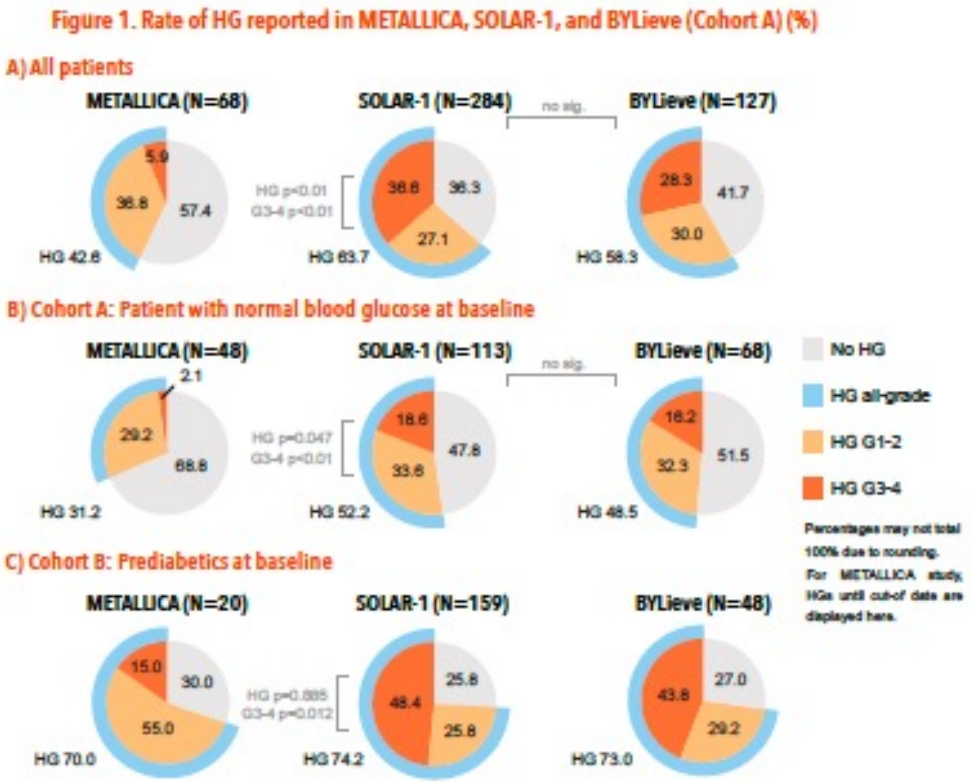
- **Improve toxicity profile**
  - METALLICA trial: prophylactic metformin
  - Role of mutant selective PI3K inhibitors

- **Triplet combination strategies: PI3Ki + CDK4/6i + ET**
  - INAVO120
  - VIKTORIA1

METALLICA Study:
Metformin prophylaxis to prevent hyperglycemia with alpelisib



- Use of prophylactic metformin substantially reduced incidence of severe hyperglycemia with alpelisib exposure
- G3 hyperglycemia 5.9% (METALLICA) versus 36.6% (SOLAR-1)



The Next Frontier

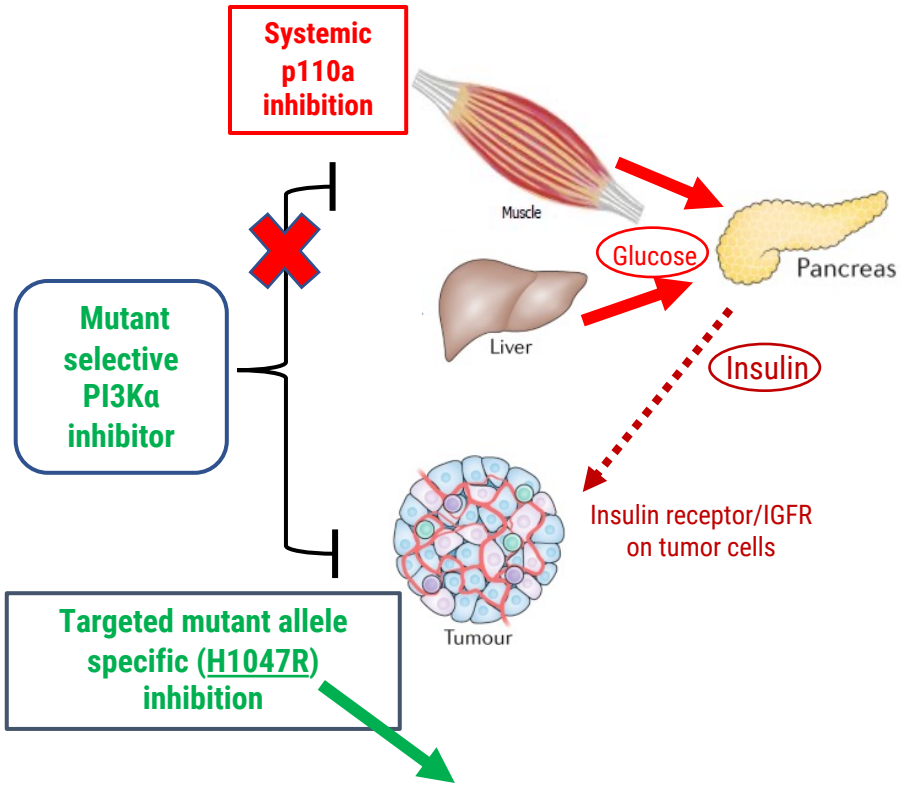
Tumor/Mutant Selective PI3Kα Inhibitors

Selective targeting of oncogenic PI3K activation without inhibiting normal PI3K function in host tissues

Selective tumor targeting of PI3Kα H1047R should:

- Permit higher and uninterrupted dosing
- Permit continuous and more complete target engagement
- Enable long-term dosing with novel combination regimens (CDK4/6 inhibitors, etc)

Increased efficacy and improved safety



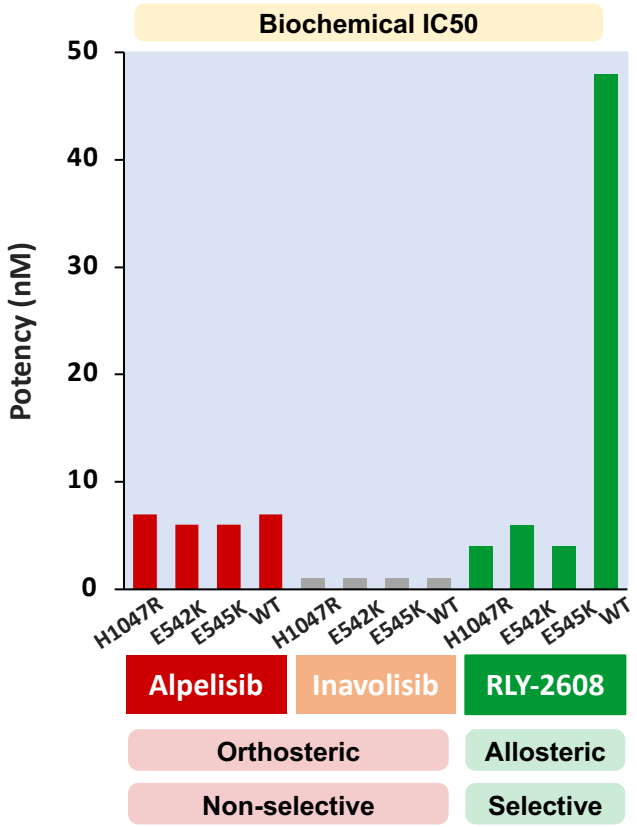
FIH Phase 1 trial LOXO-783 for *PIK3CA*1047R mutant cancer: PIKASSO-01 NCT05307705

p110a kinase (exon 20 p.**H1047R**) domain mutation occurring **~15% of breast cancer**

Dent R. Presented at: ESMO Breast Cancer 2021; May 5-8, 2021; Virtual; Kalinsky K, et al. Clin Cancer Res. 2009;15:5049-5059.

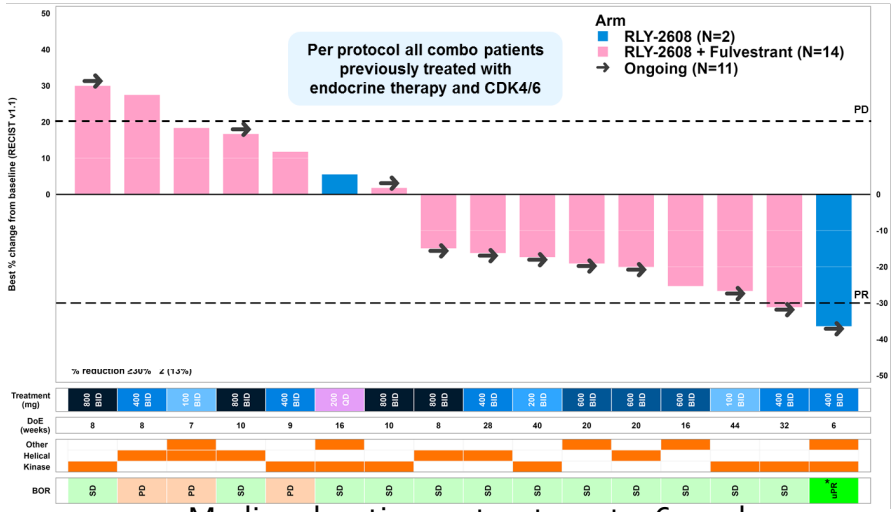
ReDiscover: First-in-Human Study of RLY-2608

RLY-2608 selectively inhibits mutant PI3Kα



Efficacy

Breast Cancer Patients (RECIST Measurable Disease) *N=16*



56% of patients (9/16) exhibit radiographic tumor reductions

81% of patients (13/16) with SD/uPR* across genotypes

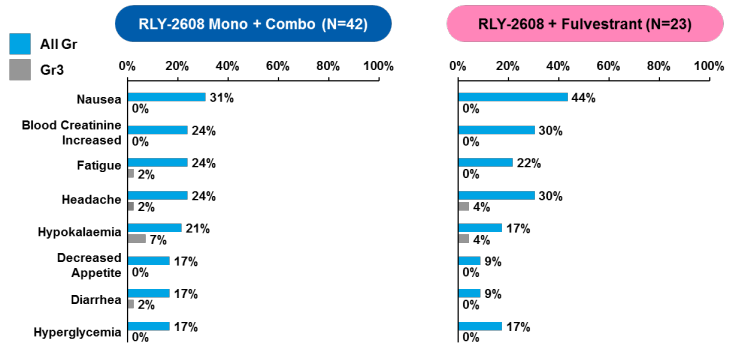
11/16 patients ongoing

BOR = Best Overall Response:
SD Stable Disease
uPR* Unconfirmed Partial Response*
PD Progressive Disease

Median duration on treatment: 16 weeks

Safety

Treatment Emergent Adverse Events (TEAEs) ≥15% Across All Doses (N=42)



AEs leading to alpelisib discontinuation observed with RLY-2608
(for 400mg BID mono, ≥600mg BID combo; N=17)

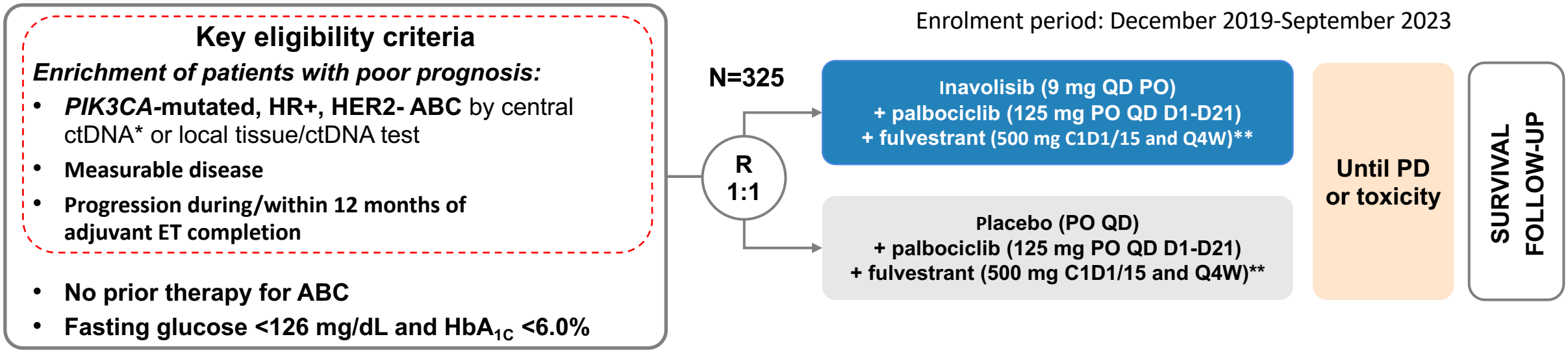
AE	All Gr (Gr3+)
Hyperglycemia	18% (0%)
Diarrhea	0%
Rash	12% (0%)

Most AEs low grade, manageable, reversible
Grade 3 TEAEs 10/42 (24%); No Grade 4-5 AEs
Dose modifications due to AE: Interruptions 31%; Reductions 2%; Discontinuations 0%
Median Relative Dose Intensity: 98%

NCT05768139 - First-in-Human Study of STX-478 as Monotherapy and in Combination With Other Antineoplastic Agents in Participants With Advanced Solid Tumors

NCT05216432

INAVO120: Triplet combination of Inavolisib + Palbociclib + Fulvestrant *study design*

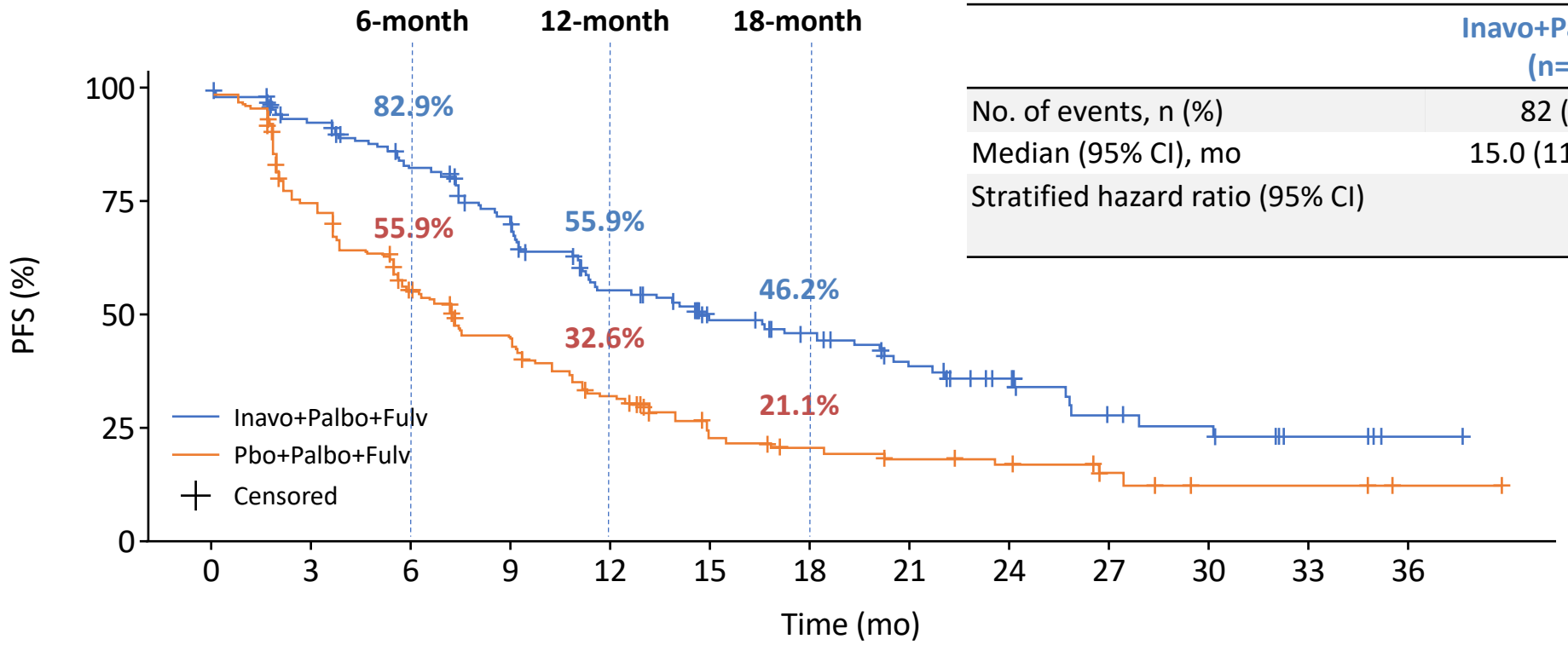


Stratification factors:
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

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

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

INAVO 120: Primary endpoint: PFS (investigator assessed)



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

Patients at risk:

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

Median follow-up:
21.3 months

CCOD: 29th September 2023

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

INAVO120: Adverse Events with Any Grade AEs ≥20% Incidence in Either Treatment Group

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

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

INAVO 120: Overview of adverse events

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

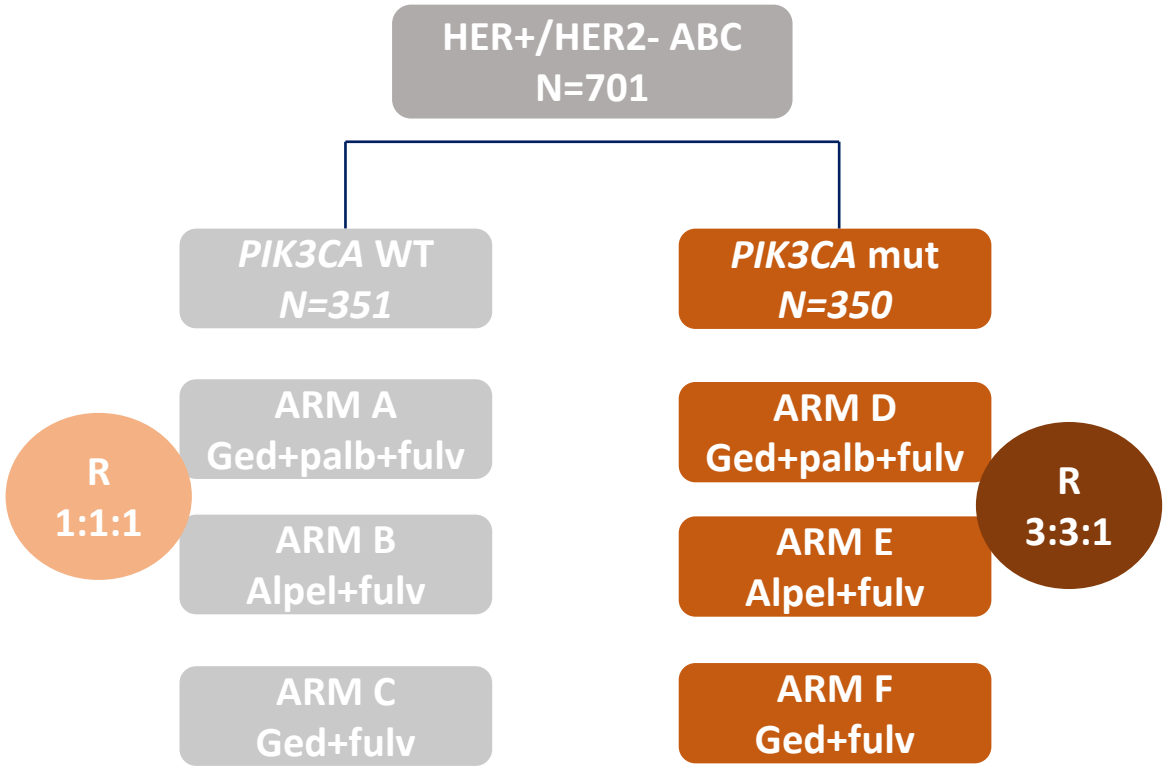
AES were assessed per CTCAE V5

* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral haemorrhage; cerebrovascular accident, gastrointestinal haemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.

AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Gedatolisib Phase 1b Data and Current Ph 3

VIKTORIA-1: Phase 3: Study Schema



Key Inclusion Criteria Include:

- 2 ≤ lines of ET in the met setting
- No prior chemo in the adv setting
- Prior tx with AI+CDK4/6

Phase Ib Data

	Total Expansion Arms (N=103, full analysis set)			
	Expansion			
Arm	**A**	**B**	**C**	**D**
Prior Therapy	1L: CDKi- naive	2L+: CDKi- naive	2L/3L: CDKi -pretreated	2L/3L: CDKi- pretreated
n (Full, response evaluable)	31, 27	13, 13	32, 28	27, 27
Study Treatment	P + L + G	P + F + G	P + F + G	P + F + G
Gedatolisib schedule	weekly	weekly	weekly	3 weeks on/1 week off
Median DOR, months (95% CI)[3]	NR (22.2, NR)	12.2 (3.7, 40.6)	16.6 (3.7, 30.3)	12.6 (7.3, 21.2)
ORR[1] (evaluable)	85%	77%	36%	63%
mPFS[2], mos (range)	NR (16.9, NR)	12.9 (7.6, 38.3)	5.1 (3.3, 7.5)	12.9 (7.4, 16.7)
Median Follow Up[2], mos (range)	33.1 (0.0+, 40.3+)	NE (2.1+, 42.5)	NE (0.0+, 32.1)	29.0 (1.7, 31.6+)
PFS % at 12 mos[2]	72.1%	54.5%	23.6%	53.2%

[1]Response evaluable analysis set per RECIST v1.1 including uPR; [2]full analysis set; [3]Kaplan Meier method and confidence intervals by the Brookmeyer and Crowley Method; Abbreviations: 1L= first line, 2L= second line; mos= months; NR = not reached; NE = could not be estimated per reverse KM method; DOR, duration of response; ORR, objective response rate; PFS, progression free survival; +=censored

Table 3: Treatment Related and Emergent Adverse Events (≥20% of subjects, by SOC and preferred term)

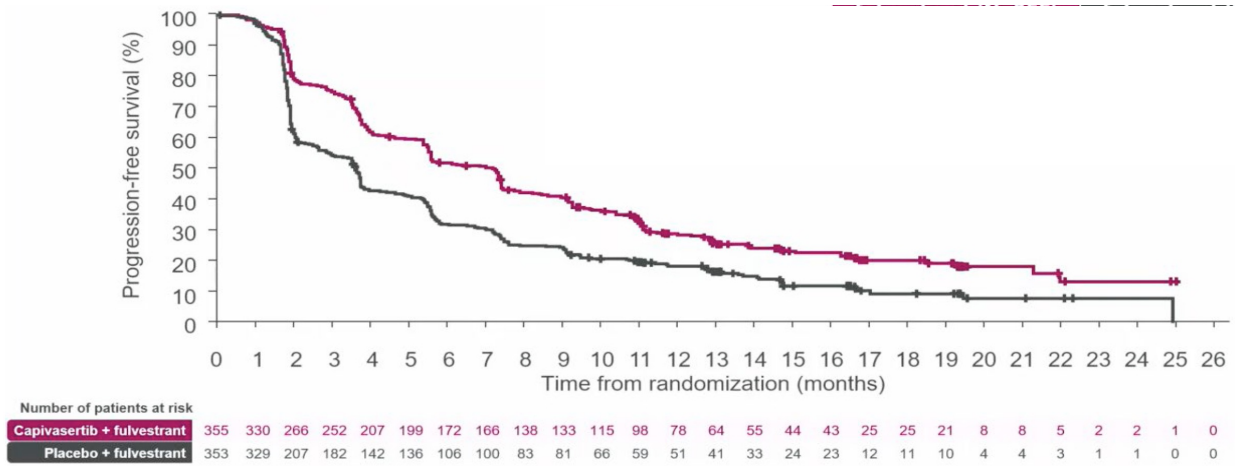
	All Expansion Arms (n=103)			
Adverse Event	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders				
Stomatitis[1]	19.4	41.7	27.2	0
Nausea	42.7	34.0	0	0
Vomiting	32.0	12.6	1.0	0
Diarrhea	23.3	8.7	2.9	0
Dry mouth	25.2	1.9	0	0
Constipation	20.4	4.9	1.0	0
General disorders and administration site conditions				
Fatigue	21.4	35.9	10.7	0
Skin and subcutaneous tissue disorders				
Rash[2,3]	21.4	10.7	20.4	0
Pruritus	13.6	7.8	4.9	0
Metabolism and nutrition disorders				
Decreased appetite	23.3	8.7	0	0
Hyperglycemia	12.6	5.8	3.9	1.9
Injury, poisoning and procedural complications				
Infusion related reaction	16.5	5.8	0	0

There were no Grade 5 treatment related TEAEs

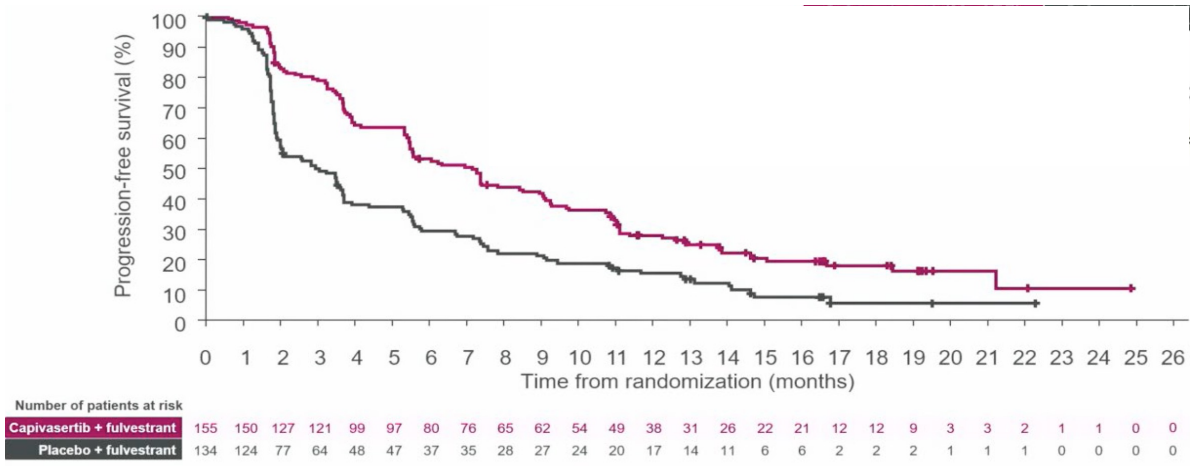
[1]Prophylactic treatment for stomatitis was not implemented; [2]Number of patients with at least one of the terms. If a patient experienced multiple terms, it will be counted once for the highest grade; [3]Rash, Rash maculo-papular, Rash pruritic, Rash pustular, Rash papular, Rash erythematous, or Rash vesicular; [4]Neutropenia and neutrophil count decrease were reported interchangeably for many patients. In this table, neutropenia (SOC-blood and lymphatic system disorders) and neutrophil count decreased (SOC-investigations) were combined

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: PFS

PFS by Investigator in Overall Population



PFS by Investigator in the AKT Pathway-Altered Population



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

AKT Pathway-Altered Population	C+F (n=155)	P+F (n=134)
PFS events	121	115
Median PFS, mo (95% CI)	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	

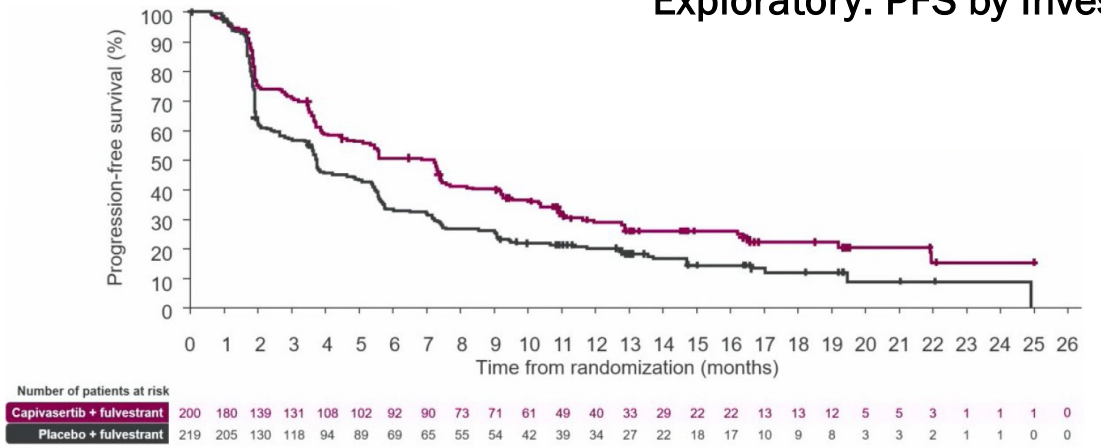
- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6i, and geographic region.

Turner NC, et al. SABCS 2022. Abstract GS3-04; Turner et al NEJM 2023.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: PFS (cont'd) and ORR

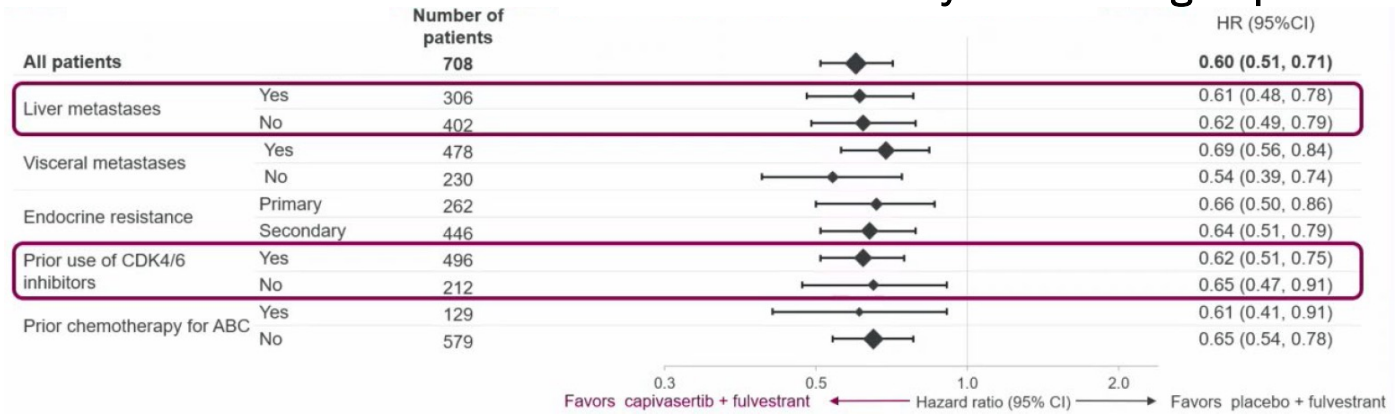
Exploratory: PFS by Investigator in the Nonaltered Population[1]



Nonaltered Population	C+F (n=200)	P+F (n=219)
PFS events	137	178
Median PFS, mo (95% CI)	7.2 (4.5-7.4)	3.7 (3.0-5.0)
Adjusted HR (95% CI)	0.70 (0.56-0.88)	

- The nonaltered population included:
  - AKT pathway alteration **not detected**: C+F arm: 142/355 (40.0%), P+F arm: 171/353 (48.4%)
  - **Unknown**: C+F arm: 58/355 (16.3%), P+F arm: 48/353 (13.6%)

INV-Assessed PFS by Select Subgroups in the Overall Population[1,2]



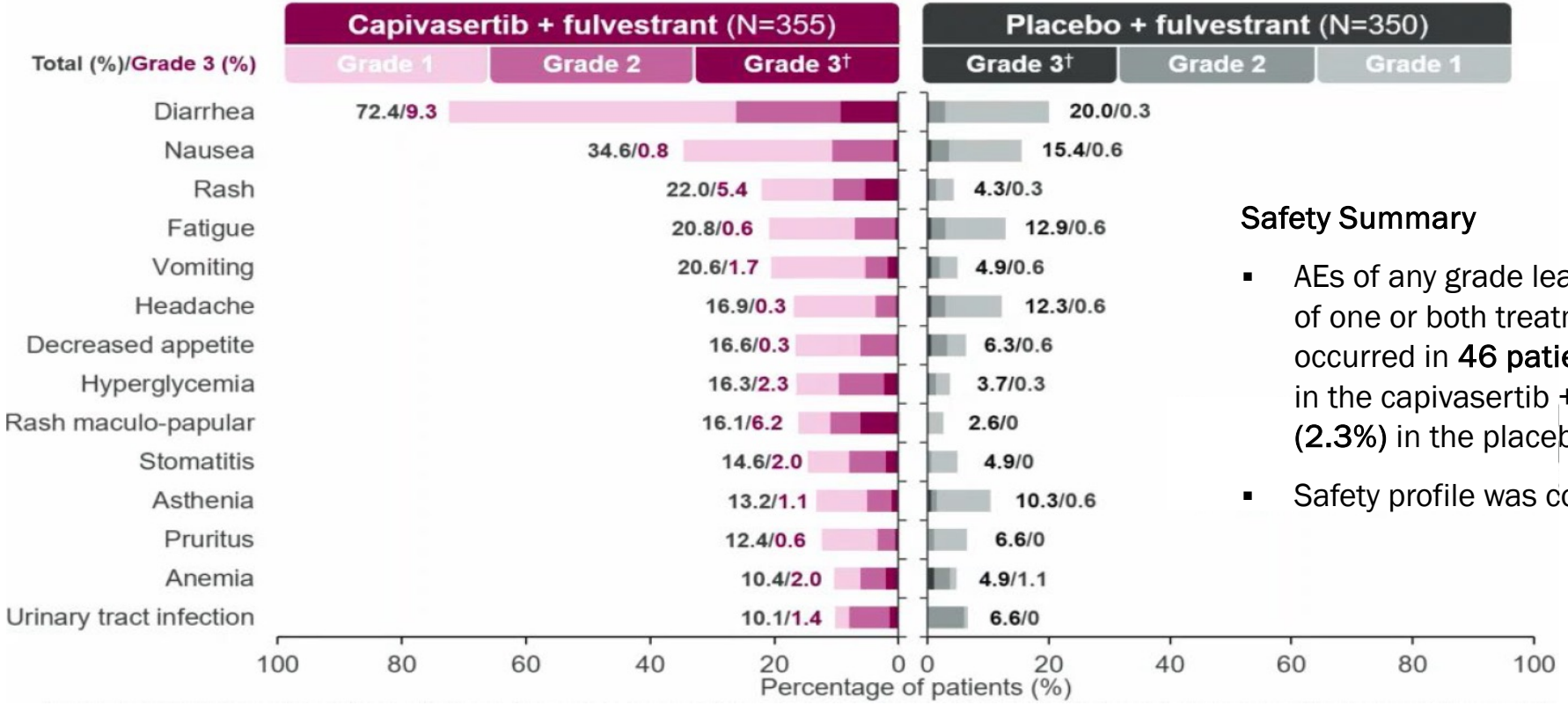
mPFS (95% CI), mo		C+F	P+F
Prior CDK4/6i	Yes (n=496)	5.5 (3.9-6.8)	2.6 (2.0-3.5)
	No (n=212)	10.9 (7.4-13.0)	7.2 (4.8-7.9)
Prior CT for MBC	Yes (n=129)	3.8 (3.0-7.3)	2.1 (1.9-3.6)
	No (n=579)	7.3 (5.6-8.2)	3.7 (3.4-5.1)
Liver metastases	Yes (n=306)	3.8 (3.5-5.5)	1.9 (1.8-1.9)
	No (n=402)	9.2 (7.4-11.1)	5.5 (3.9-5.8)

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6i.

1. Turner NC, et al. SABCS 2022. Abstract GS3-04. 2. Oliveira M, et al. ESMO Breast 2023. Abstract 187O; Turner et al NEJM 2023

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Safety

AEs (>10% of Patients) in Overall Population



Safety Summary

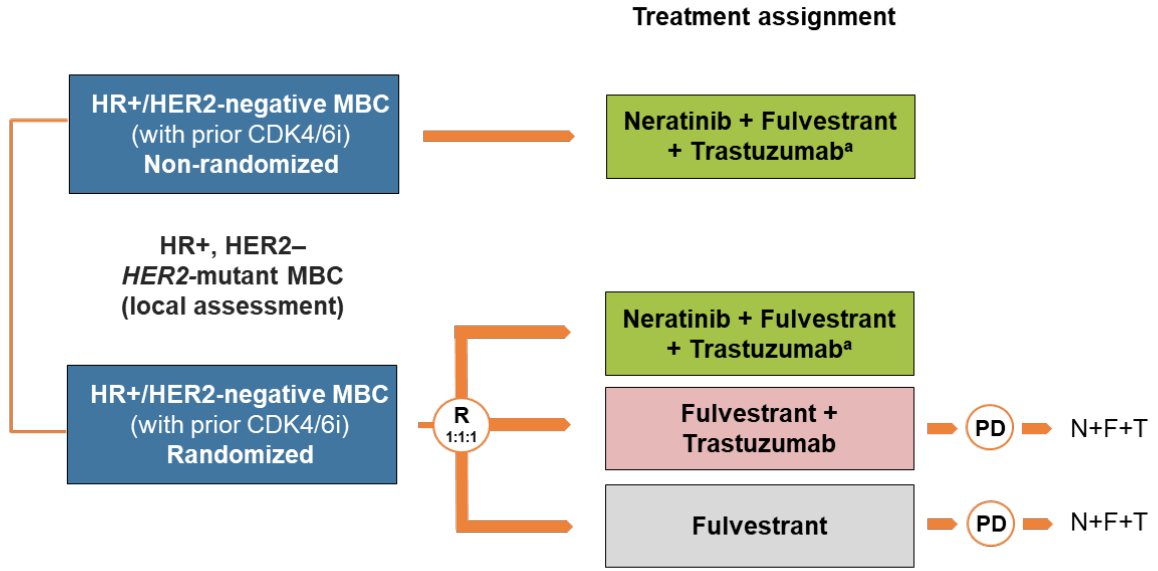
- AEs of any grade leading to discontinuation of one or both treatments in the safety population occurred in **46 patients (13.0%)** in the capivasertib + fulvestrant arm and **8 patients (2.3%)** in the placebo + fulvestrant arm
- Safety profile was consistent with that previously reported

Turner NC, et al. SABCS 2022. Abstract GS3-04; Turner et al NEJM 2023

HER2 Mutation: Combinations needed for improved efficacy and durability

SUMMIT (NCT01953926): ER+ HER2- *ERBB2* mut Cohort

***HER2* mutation: 8% ER+ MBC**
15%: met ILC



[a]Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

***HER2*-mutant MBC**

Primary endpoint

- Confirmed objective response rate (ORR; RECIST v1.1, centrally assessed)

Secondary endpoints

- Confirmed ORR (investigator-assessed)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety and PROs

Treatment Regimen	ORR	PFS (months)	DOR (months)
Neratinib (n=23)	17%	3.6	6.5
Neratinib + Fulvestrant (n=47)	**30%**	**5.4**	**9.2**
Neratinib + Fulvestrant +Trastuzumab (n=51)	**35.3%**	**8.2**	**14.3**

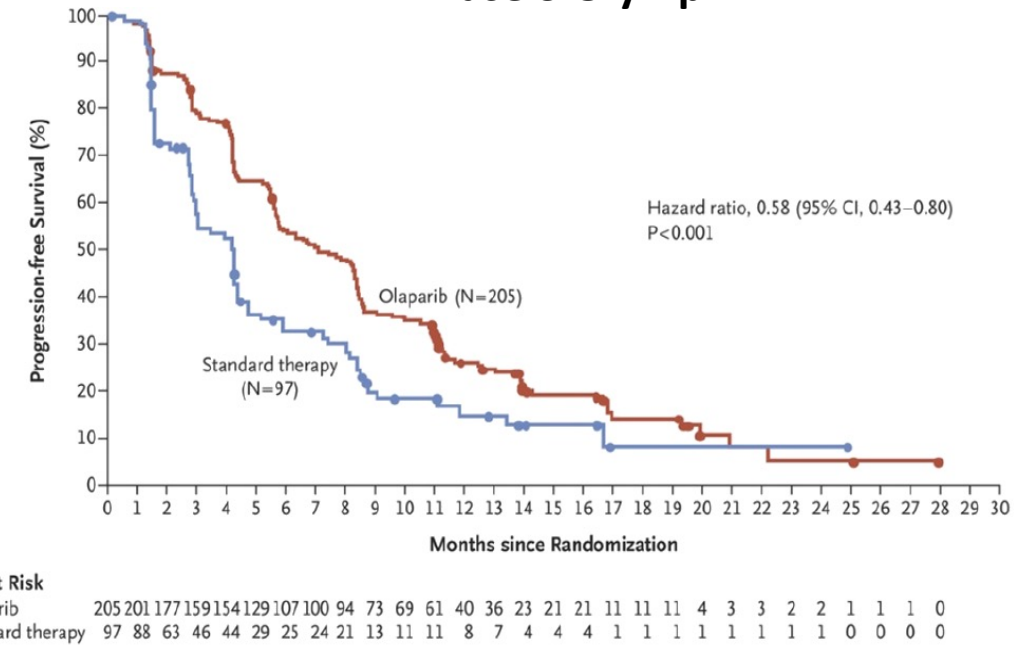
Addition of T to N prolongs suppression of HER3 phosphorylation in HR+, HER2-negative, *HER2*-mutant breast cancer cell line model

- **Tucatinib + Trastuzumab Basket Study (NCT04579380)**
- **BDTX0819 Potent and Selective Inhibitor of the Allosteric Oncogenic ErbB Family (NCT04209465)**
- **Trastuzumab Deruxtecan: DESTINY-pantumor01 (NCT04639219)**

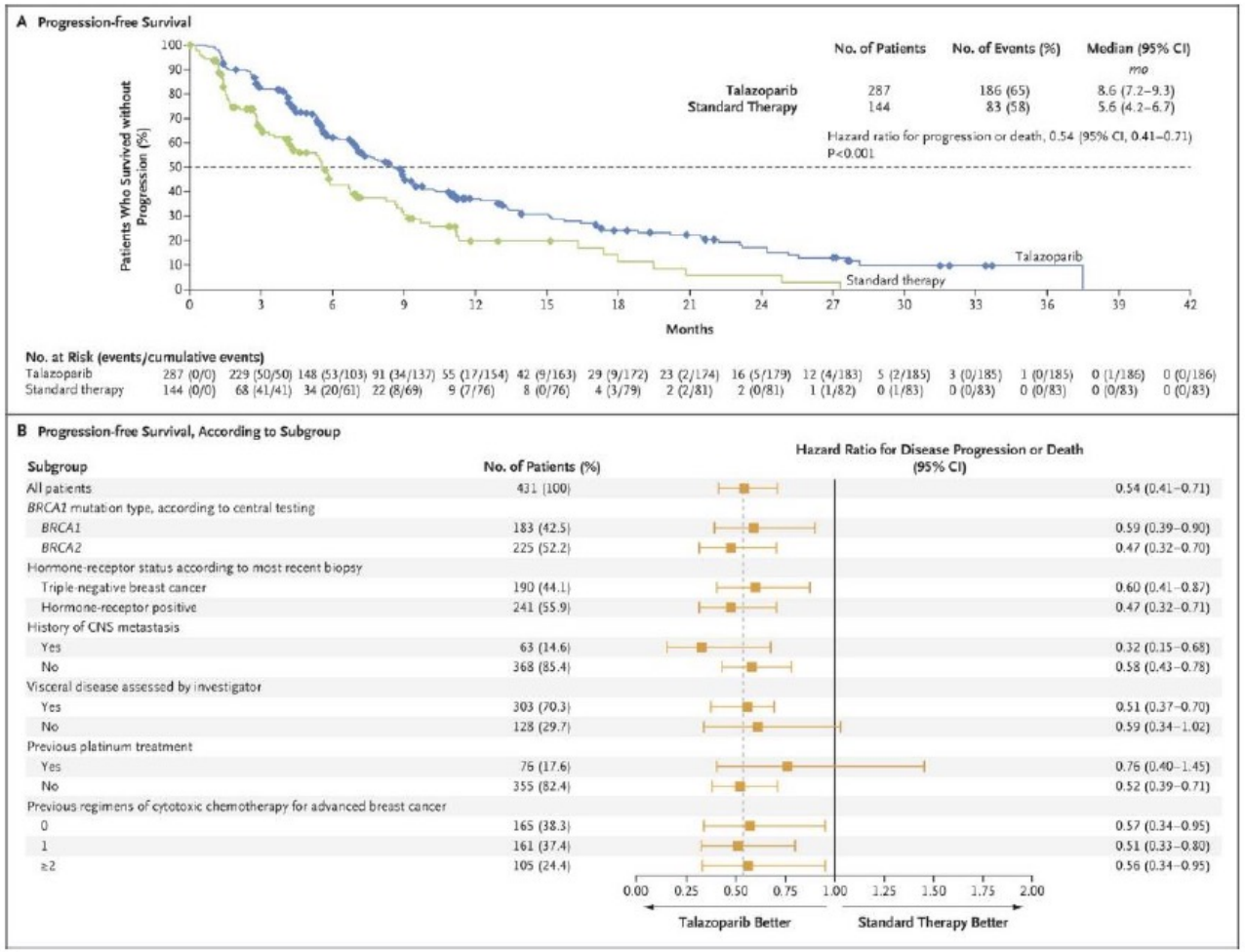
Jhaveri et al SABCS 2021; Jhaveri et al ASCO 2022; Jhaveri Ann of Onc 2023

PARP Inhibitors US FDA Approved for g*BRCA* mutant MBC

Olaparib
Phase 3 OlympiAD



Talazoparib
Phase 3 EMBRACA



Improvement in PFS with PARPi compared with chemotherapy

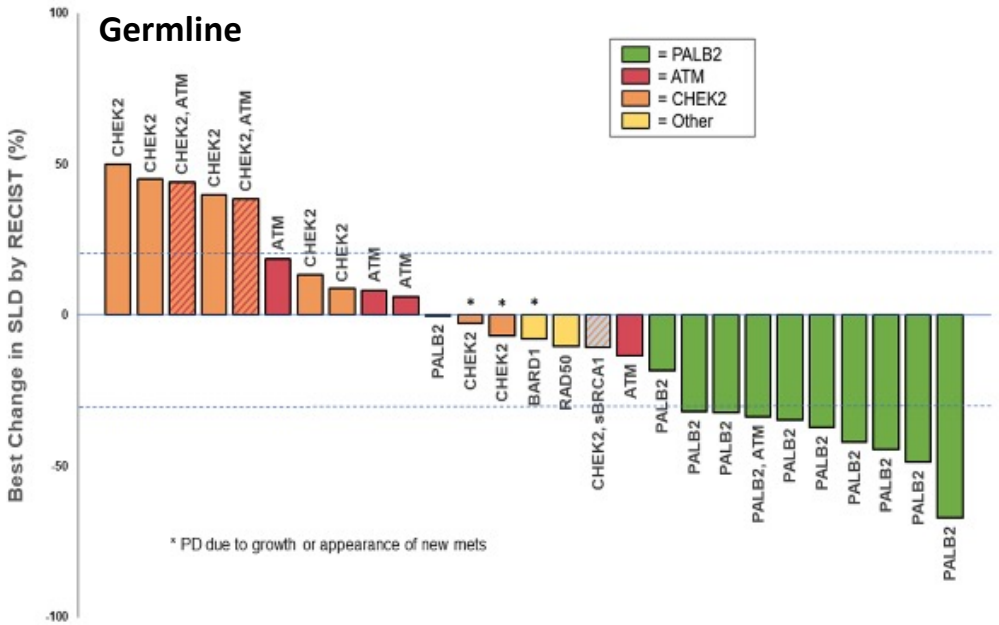
Benefit regardless of subgroup

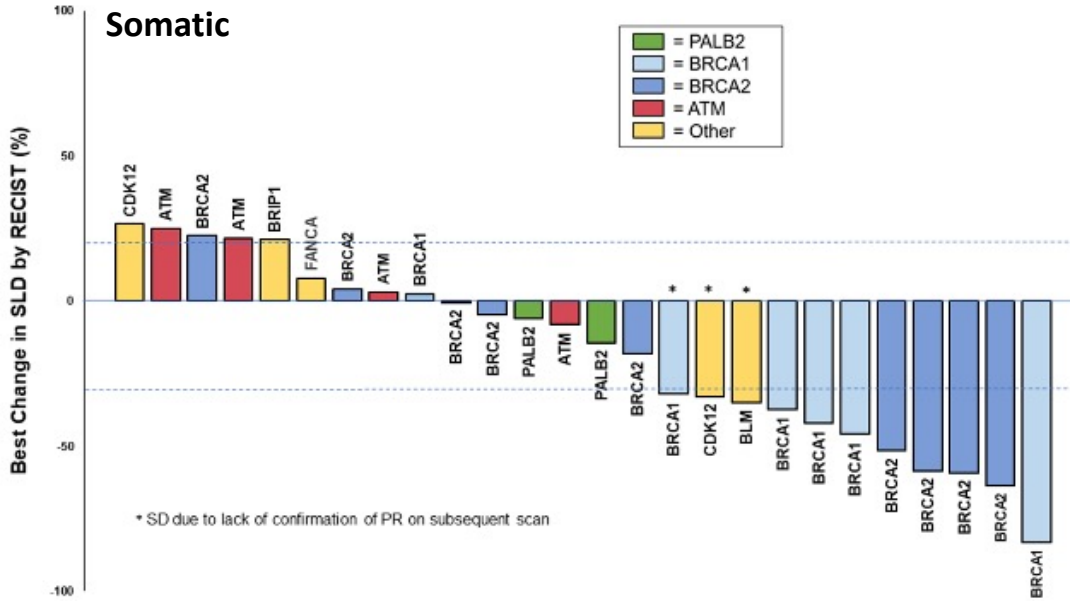
Robson et al NEJM 2017; Litton et al NEJM 2018

TBCRC 048: A Phase 2 Study of Olaparib in MBC With Germline or Somatic Mutations in Homologous Recombination Pathway Genes

Germline (Cohort 1)			Somatic (Cohort 2)[4]		
• *CHEK2*[1,2]	n=8	14 *ATM CHEK2*	• *sBRCA1*[5]	n=6	15 *sBRCA1/2*
• *ATM*	n=4		• *sBRCA2*	n=9	
• *ATM & CHEK2*[1]	n=2		• *ATM*[6]	n=4	
• *PALB2*[3]	n=11		• *PAL2*	n=2	
• *BARD1*	n=1		• *CDK12*	n=2	
• *RAD50*	n=1		• *BRIP1*	n=1	
			• *BLM*	n=1	
			• *FANCA*	n=1	

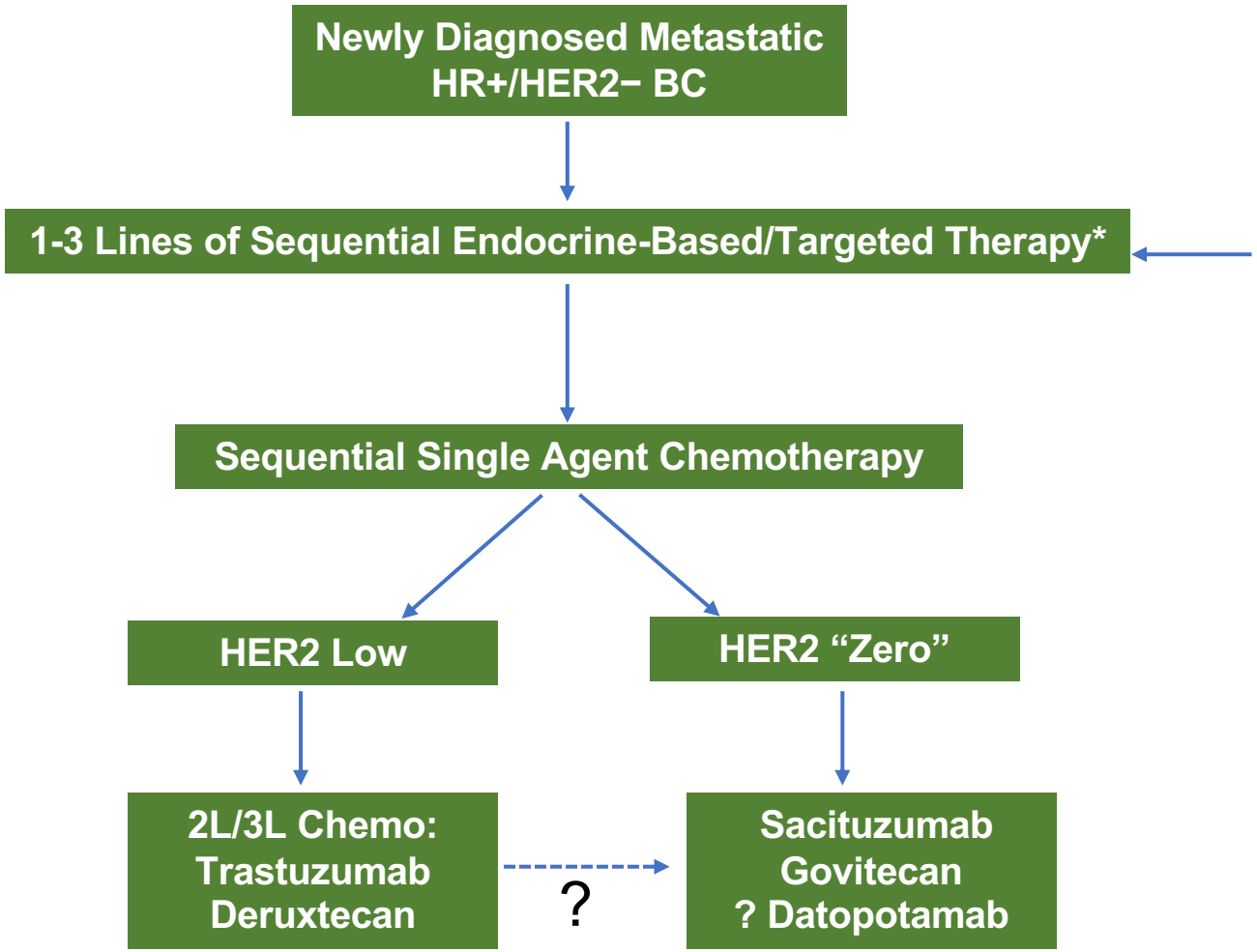
PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic





Tung NM, et al. *J Clin Oncol*. 2020;38:4274-4282

Treatment Roadmap for HR+/HER2− MBC Today in Clinic



1L: - AI/SERD + CDK4/6i

2L or 3L:
- SERD + PI3Ki (*PIK3CA* mutant)
- Oral SERD (*ESR1* mutation)
- ET + mTORi
- ET + AKTi (*PIK3CA/AKT/PTEN* alteration)
- SERD + CDK4/6i
- ET

1L-3L: - *gBRCA1/2+*: *PARPi*

≥ 2L:
- Larotrectinib/Entrectinib (*NTRK* fusion)
- Pembrolizumab (MSI-H/dMMR, high TMB)
- Selpercatanib (RET alterations)

*Chemotherapy for visceral crisis.

Key Messages

- **Approach to treatment post CDK4/6i progression needs further refinement**
  - Elacestrant approved for *ESR1*m
  - PARPi approved for *gBRCAm*
  - Neratinib + trastuzumab + Fulvestrant for HR+ *HER2m* MBC (NCCN category 2b)
  - Alpelisib with ET approved for *PIK3CA*m
  - Capivasertib with Fulvestrant approved for *PIK3CA/AKT/mTOR* alterations
  - Everolimus + ET Approved regardless of pathway mutation status
  - Triplet of Inavolisib + Fulvestrant + Palbociclib might be approved for high risk PIK3CAm in 1L?
  - CDK4/6i beyond progression- phase 3 data awaited
  - Optimal sequencing of these agents?
  - Mechanisms of resistance for mTOR and AKTi?

- **Novel endocrine agents better than prior approved ET**
  - Have a role as monotherapy in ET sensitive *ESR1* mutant
  - Attractive partner of choice with other targeted agents

Acknowledgements

Patients and their families who inspire us everyday

Questions?

@jhaveri_komal