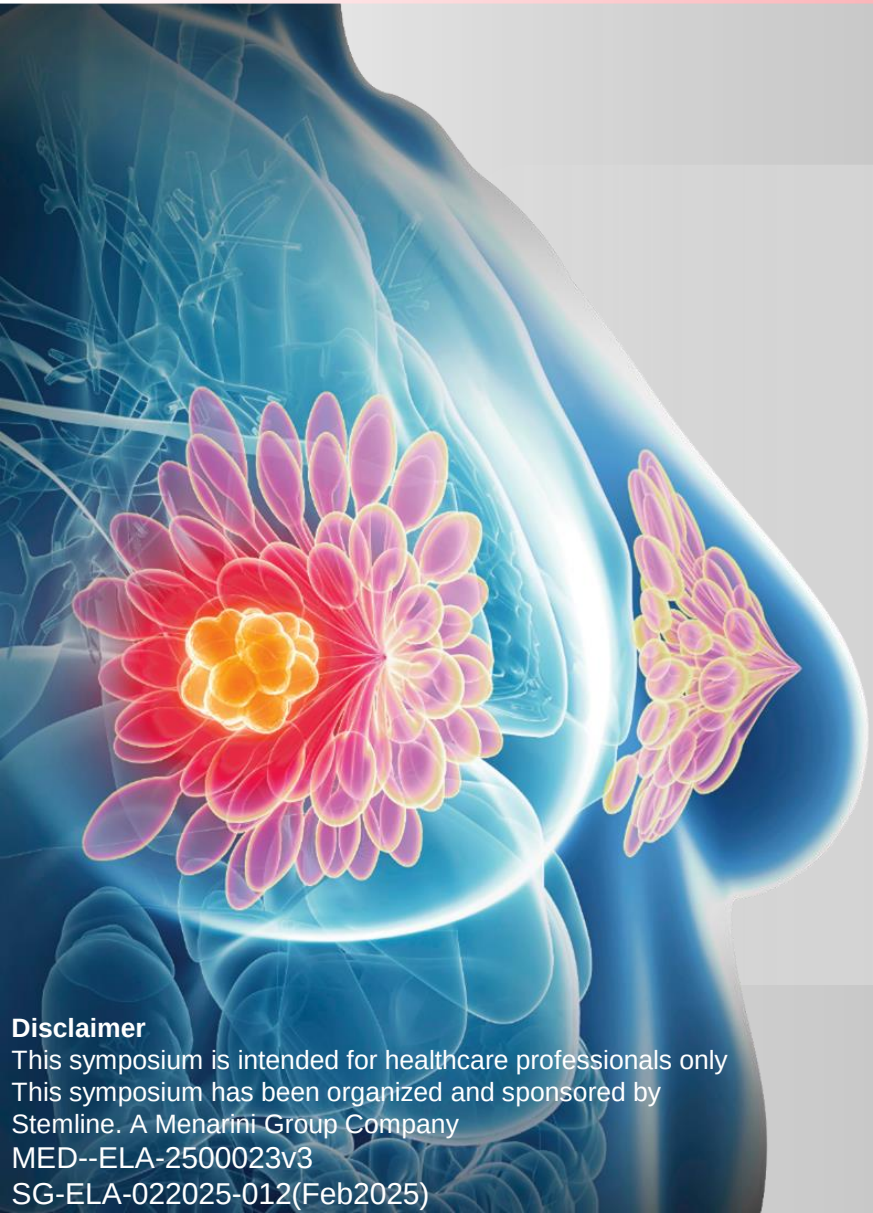


Treatment Strategies and Sequencing After ET + CDK4/6i for Patients With ER+/HER2- Metastatic Breast Cancer

Disclaimer
This symposium is intended for healthcare professionals only
This symposium has been organized and sponsored by Stemline. A Menarini Group Company
MED--ELA-2500023v3
SG-ELA-022025-012(Feb2025)

Faculty

Shaheenah Dawood (Chair) – *Mediclinic City Hospital Dubai*

Consultant medical oncologist and professor in clinical oncology in the United Arab Emirates.

Leader of the oncology clinical trials program at Mediclinic City Hospital Dubai, president of the Excellence in Oncology Summit that is held annually in Dubai and co president of the Asia Pacific Breast Cancer Summit (APBCS)

Heather McArthur (Speaker)– *UT Southwestern Medical Center*

Professor of internal medicine at UT Southwestern Medical Center and a member of the Division of Hematology and Oncology. Clinical Director of the Breast Cancer Program at Simmons Cancer Center and specializes in breast cancer research and treatment.

Javier Cortés (Speaker) – *International Breast Cancer Center*

Head of the International Breast Cancer Centre (IBCC) in Barcelona, founding partner of Medica Scientia innovation Research (MedSIR), a company involved in the clinical development of clinical trials. Member of the Scientific Committee of the ESMO and EBCC.

Frédérique Penault-Llorca (Speaker) – *University of Clermont-Ferrand*

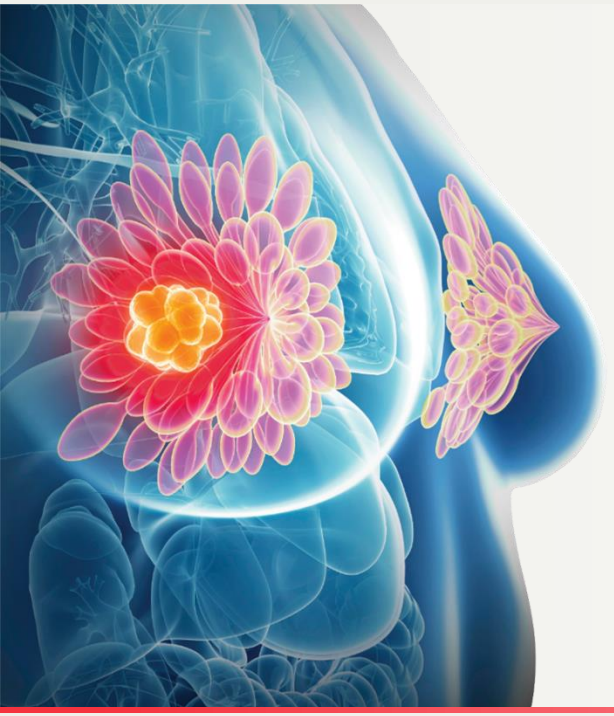
Professor of pathology at the University of Clermont-Ferrand in France. CEO of the Comprehensive Regional Cancer Institute Centre Jean PERRIN, Clermont-Ferrand, France, deputy director of the research team INSERM 1240 IMoST, and head of the Molecular Biology Plateform at Centre Jean Perrin

Acknowledgement and disclosures

This Symposium has been sponsored by Menarini Stemline and is intended for healthcare professionals only

Expert disclosures:

- **Shaheenah Dawood** has received financial support/sponsorship for research support, consultation, or speaker fees from MSD, Roche, BMS, New Bridge, Novartis, Lilly, Pfizer, Caris, Merck, Janssen, Ipsen, Astrazeneca, Zulleg Pharma
- **Heather McArthur** has received financial support/sponsorship for research support, consultation, or speaker fees from Amgen, AstraZeneca, BeiGene, Boston Scientific, Bristol-Myers Squibb, Calithera, Celgene, Daiichi-Sankyo, Delcath Systems Inc., Eli Lilly, Genentech/Roche, Gilead, Immunomedics, Merck, Moderna, Novartis, OBI Pharma, Peregrine, Pfizer/Seattle Genetics, Puma, Spectrum Pharmaceuticals, Stemline Therapeutics, Syndax Pharmaceuticals,TapImmune, Bristol-Myers Squibb, MedImmune, LLC/AstraZeneca; BTG; and Merck.
- **Javier Cortés** has received financial support/sponsorship for research support, consultation, or speaker fees from Roche , AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, BridgeBio, Biontech, Biocon, Circle Pharma, Delcath Systems, Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, Astrazeneca, Gilead, Stemline Therapeutics.
- **Frédérique Penault-Llorca** has received financial support/sponsorship for research support, consultation, or speaker fees from AbbVie, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Genomic Health, Gilead, GSK, Lilly, Menarini Stemline, MERCK, MSD, Myriad, NanoString Technologies, Novartis, Pfizer, Pierre-Fabre, Roche, Seagen, Servier, Tesaro; Institutional research grants from AbbVie, Agendia, AstraZeneca, Bayer, BMS, Genomic Health, MSD, Myriad, NanoString Technologies, Roche; Congress invitations from AbbVie, AstraZeneca, BMS, MSD, Novartis, Pfizer, Roche



Treatment Landscape for ER+/HER2- Metastatic Breast Cancer

Heather McArthur

UT Southwestern Medical Center

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

MENARINI group

Stemline® A Menarini Group Company

Current factors affecting treatment choices for patients with ER+/HER2- mBC

Disease characteristics

ER+/HER2- mBC is a complex, heterogeneous disease[1]

As disease progresses, most tumors develop endocrine resistance[2]

Patient characteristics

Key factors:
Performance status, imminent organ failure, menopausal status, prior lines of therapy[1]

Genomic landscape

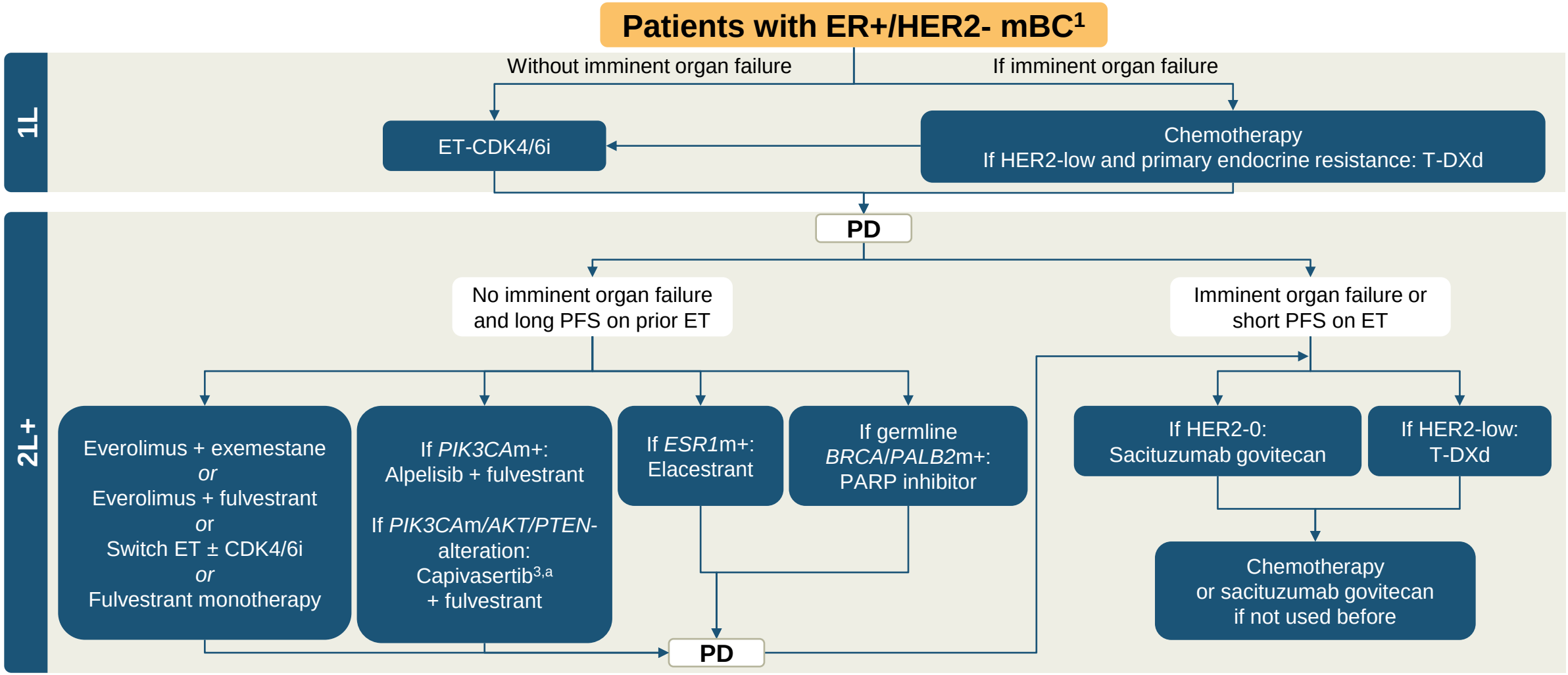
Molecular mechanisms underlying endocrine sensitivity and resistance are multifold[1-3]

Key biomarkers:
PIK3CA, ESR1, BRCA/PALB2[1–3]

mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; ER, estrogen receptor; *ESR1*, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; *PALB2*, partner and localizer of BRCA2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

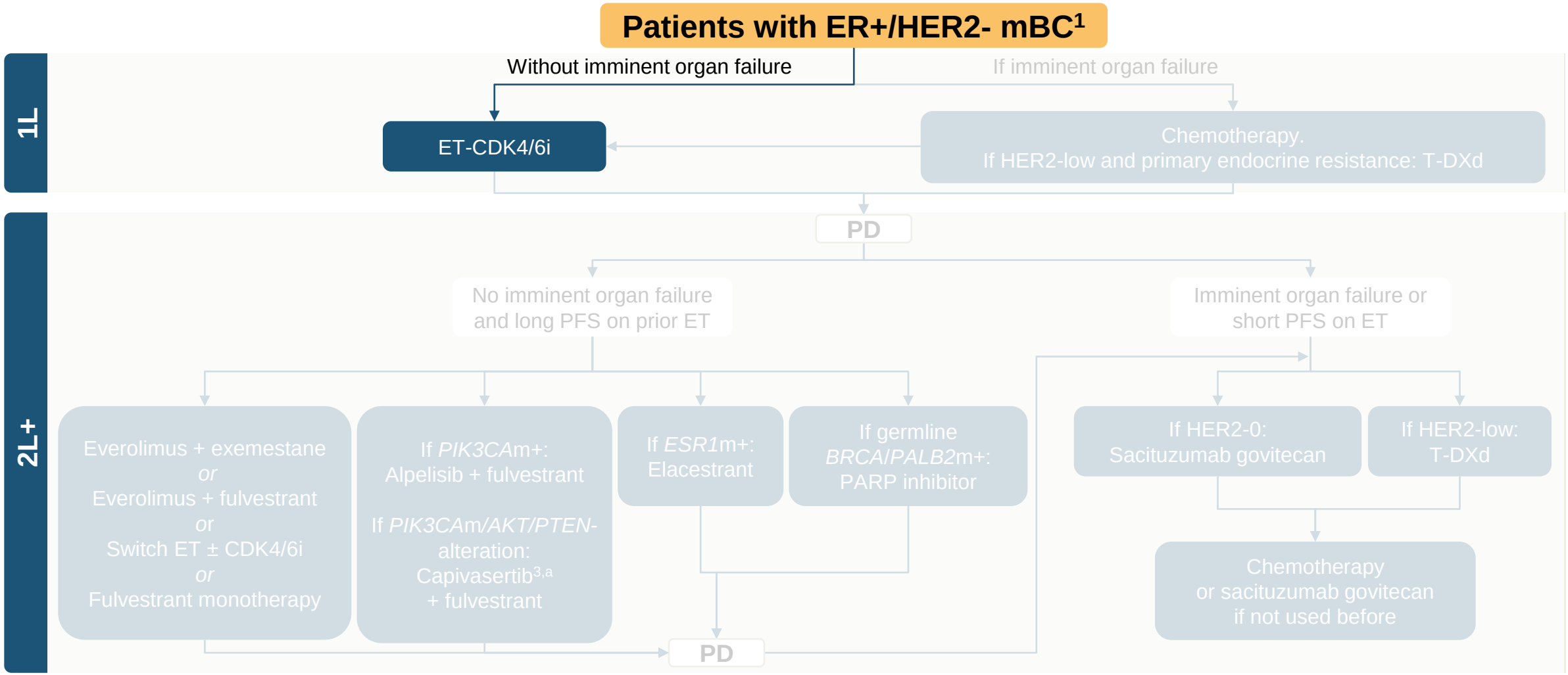
1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Hartkopf A, et al. *Breast Care (Basel)* 2020;15:347-354; 3. Bennett C, et al. *Cancers* (Basel) 2022;14:3046.

Treatment choices for patients with ER+/HER2- mBC are driven by endocrine sensitivity status and biomarkers[1,2]



[a]Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

Treatment choices for patients with ER+/HER2- mBC are initially driven by endocrine sensitivity[1,2]



[a]Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

ET + CDK4/6i is the first-line standard of care in ER+/HER2- mBC[1–3]

Median duration of treatment with endocrine therapy + CDK4/6 inhibition based on pivotal trials is ~15–21 months[4–6]

	PALOMA-2[7]	MONALEESA-2[8]	MONARCH-2[9]	MONARCH-3[10]	MONALEESA-3[a 11]	MONALEESA-7[b 6]
Phase (n)	Ph3 (666)	Ph3 (668)	Ph3 (669)	Ph3 (493)	Ph3 (726)	Ph3 (672)
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Abemaciclib	Ribociclib	Ribociclib
Endocrine partner	Letrozole	Letrozole	Fulvestrant	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
Patient population	Post-menopausal	Post-menopausal	Pre/post-menopausal	Post-menopausal	Post-menopausal	Pre/peri-menopausal
mPFS, mo	24.8 vs 14.5	25.3 vs 16.0	16.4 vs 9.3	28.2 vs 14.8	20.5 vs 12.8	23.8 vs 13.0
HR (95% CI)	0.58 (0.46–0.72)	0.57 (0.46–0.70)	0.55 (0.45 to 0.68)	0.54 (0.42–0.70)	0.59[c] (0.48-0.73)	0.55 (0.44–0.69)

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a]Includes first and second line; [b]First-line ET; up to 1 previous CT line permitted in advanced setting (14% had received CT); [c]Descriptive analysis; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression free survival; Ph, phase

1. Burstein HJ, et al. *J Clin Oncol.* 2021;39:3959–3977; 2. Cardoso F, et al *Ann Oncol.* 2020;31:1623-1649; 3. Gennari et al. *Ann Oncol.* 2021;32:1475–1495; 4. Pfizer. Ibrance (palbociclib) Summary of Product Characteristics. 2024; 5. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 6. Tripathy D, et al. *Lancet Oncol*. 2018;19:904–915; 7.Finn, et al. *NEJM*. 2016;375-1925; 8.Hortobagyi, et al. *NEJM*. 2016;375-1738; 9. Sledge, et al. *J Clin Oncol*.2017 Sep 1;35(25):2875-2884. 6:116; 10. Johnston S, et al. *NPJ Breast Can*cer.2019. 7:5:5; 11. Goetz, et al. JCO. 2017;35:3638;

INAVO120: Inavolisib demonstrated PFS benefits in combination with first-line SOC treatments in HR+/HER2–, *PIK3CA*-mut mBC

Key eligibility criteria

Enrichment of patients with poor prognosis:

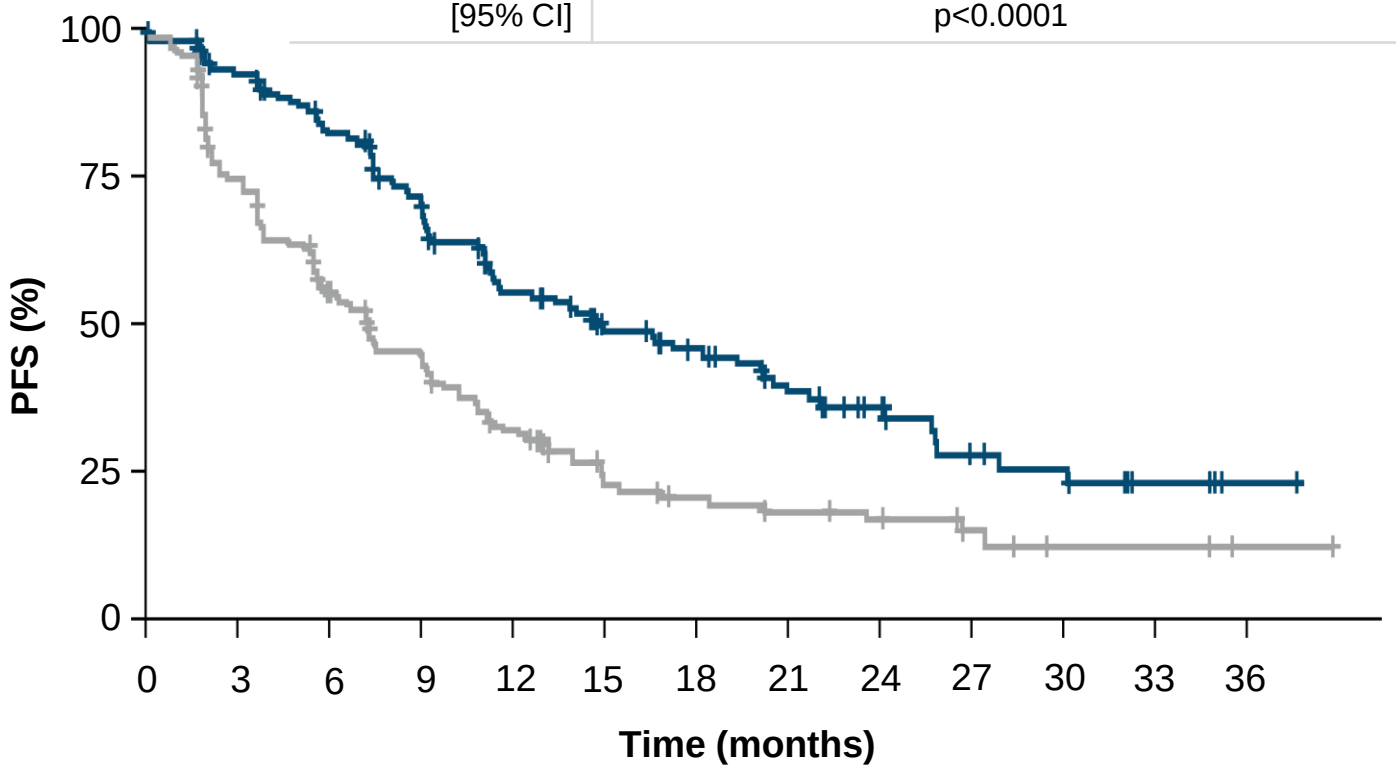
- ***PIK3CA*-mutated, HR+/HER2- LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

N= 325

R 1:1

- Inavolisib[a] + palbociclib[b] + fulvestrant[c]
- Placebo[d] + palbociclib[b] +fulvestrant[c]

	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
mPFS, mo [95% CI]	**15.0** [11.3-20.5]	**7.3** [5.6-9.3]
Stratified HR [95% CI]	**0.43** [0.32-0.59] p<0.0001	



[a]9mg QD PO; [b]PO QD D1-D21; [c]500 mg C1D1/15 and Q4W; [d]PO QD

CI, confidence interval; Fulv, fulvestrant; HR, hazard ratio; Inavo, inavolisib; (m)PFS, (median) progression free survival; mo, months; Palbo, palbociclib; Pbo, placebo

Turner NC,et al. *N Engl J Med.* 2024 Oct 31;391(17):1584-1596

Resistance to ET in ER+/HER2− mBC can be classified by clinical and molecular variables[1–5]

Clinical definition	**Primary endocrine resistance**	**Secondary endocrine resistance**
	PD within first 6 months of 1L ET-based therapy, while on ET (regardless of CDK4/6i use)[1]	PD after ≥6 months of 1L ET[1] *or* PD after any duration of 2L+ ET-based therapy[1]
Molecular definition	**Intrinsic**	**Acquired**
	Alterations of the *PI3K/AKT/mTOR, RAS-MAPK, FGFR1* pathways, *BRCA1/2* mutations, *RB1* loss, *TP53* activation, etc.[2–4]	Mechanisms of resistance, such as *ESR1* mutations, occurring after prior endocrine therapy in mBC[3,5]

1L, first line; 2L+ second line and above; mBC, Metastatic breast cancer; ET, endocrine therapy; PD, progressive disease.

1. Cardoso F, et al. *The Breast.* 2024; [ePub ahead of print]; 2. Rani A, et al. *Front Endocrinol. (Lausanne)* 2019;10:245; 3. Xu P, et al. *Acta Pharmacol Sin.* 2021;42:171–178; 4. Karlsson E, et al. SABCS. 2023.PO5-13-02; 5. Brett JO, et al. *Breast Cancer Res*. 2021;23:85.

Sequential endocrine monotherapies or combination therapies are used in the second-line setting[1,2]

ET monotherapy

AIs, fulvestrant

mPFS
~2–3 months[3-6]

Fulvestrant

IM injection
Select AEs: injection site pain, musculoskeletal pain, back pain, peripheral neuropathy[7]

ET in combinations

CDK4/6i and PI3K/AKT/mTORi

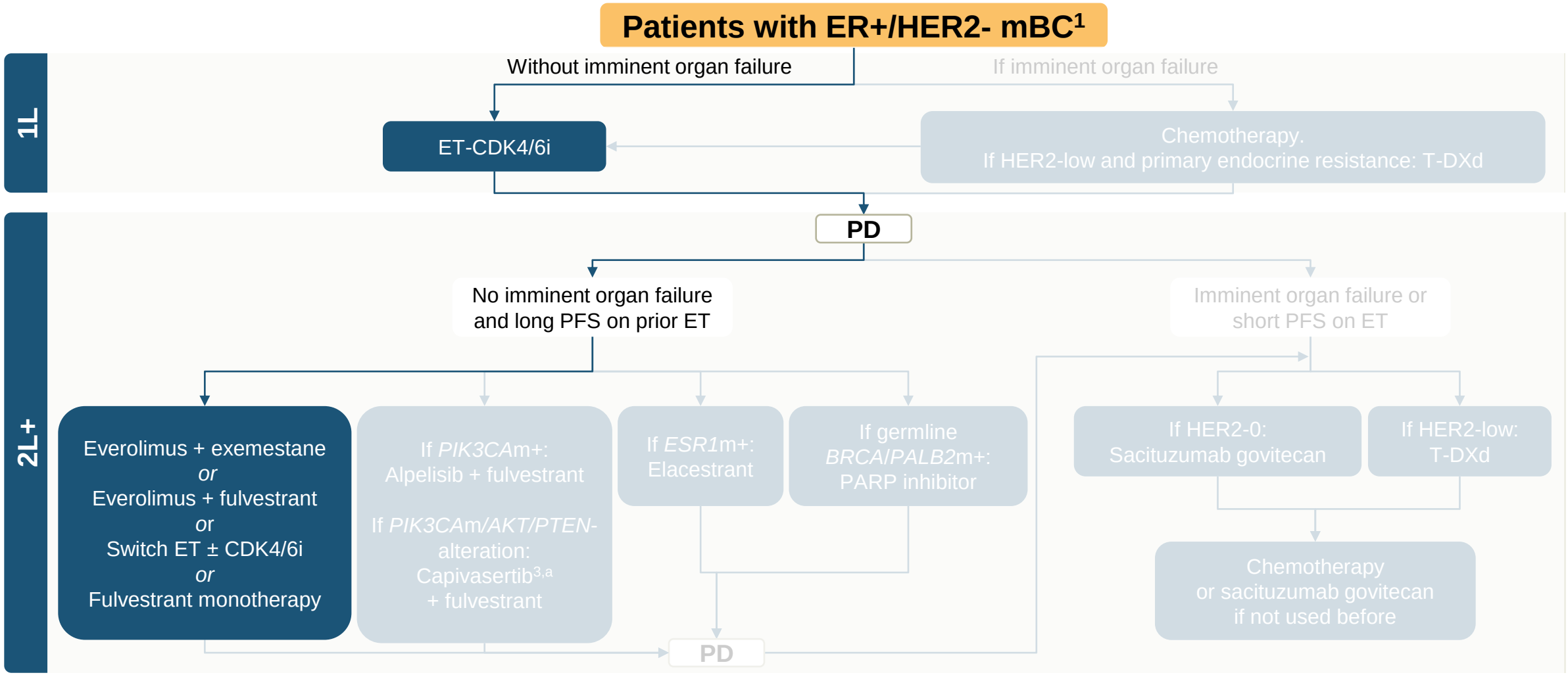
mPFS	Toxicity and discontinuation rates	IM injection
CDK4/6i ~5–6 months[8-11] **PI3K/AKT/mTORi** ~6–8 months[6,12-14]	**CDK4/6 inhibitors** • Neutropenia, leukopenia, and anemia[1,7,15-18] • Discontinuation due to AEs in up to 19% of pts[15,16,18] **PI3K/AKT/mTOR inhibitors** • Diarrhea, rash, and hyperglycemia[1, 6, 19–21] • Discontinuation due to AEs in up to 24% of pts[6,19, 20]	Combinations including fulvestrant require IM injection[7]

Guidelines recommend exhausting sequential endocrine therapy options after ET + CDK4/6i[1]

2L, second line; AE, adverse event; AI, aromatase inhibitor; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; IM, intramuscular; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

1.Burstein HJ, et al. *J Clin Oncol.* 2021;39:3959–3977; 2. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 3. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256; 4. Lindeman GJ, et al. *Clin Cancer Res.* 2022:28:3256–3267; 5. Oliveira M et al. SABCS. 2022. Abstract GS3-02; 6. Turner NC et al. *N Engl J Med.* 2023;388:2058–2070; 7. AstraZeneca. Faslodex (fulvestrant) Summary of Product Characteristics. 2024; 8.Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 9. Mayer EL, et al. *J Clin Oncol*. 2024.JCO2301940; 10. Llombart-Cussac A, et al. *J Clin Oncol*. 2023;41:S1001–S1001 oral presentation; 11. Kalinsky K, et al. J Clin Oncol. 2024:JCO2402086. Online ahead of print; 12. Yardley DA, et al. *Adv Ther*. 2013;30:870–884; 13. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-4185; 14. Chia S, et al. ASCO 2023. Abstract P10; 15. Pfizer. Ibrance (palbociclib) Summary of Product Characteristics. 2024; 16. Novartis. Kisqali (ribociclib) Summary of Product Characteristics. 2024; 17. Eli Lily and Company. Verzenio (abemaciclib) Summary of Product Characteristics. 2024; 18. Eli Lily and Company. Verzenio (abemaciclib) Prescribing Information. 2024; 19. Novartis. Afinitor (everolimus) Summary of Product Characteristics. 2024; 20. Novartis. Afinitor (everolimus) Prescribing Information. 2024; 21. Novartis. Piqray (alpelisib) Summary of Product Characteristics. 2024

Second-line treatment choices for patients with ER+/HER2- mBC are driven by biomarker status[1,2]



[a]Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

CDK4/6 inhibitor rechallenge

MAINTAIN and postMONARCH are the only positive trials in 100% prior CDK4/6i exposed patients, showing both ribociclib and abemaciclib deliver benefit mainly after palbociclib. Benefit has not been demonstrated in patients with *ESR1*-mut tumors

	MAINTAIN[1,5]	PACE[2,5]	PALMIRA[3,4,6]	postMONARCH[5,6]
Outcomes	**POSITIVE all comers** **NEGATIVE *ESR1*-mut**	**NEGATIVE**	**NEGATIVE**	**POSITIVE all comers**
Phase (n)	Ph2 (119)	Ph2 (220)	Ph2 (198)	Ph3 (368)
Experimental arm	Ribociclib + fulv or exemestane	Palbocilcib + fulv[a]	Palbociclib + fulv or letrozole	Abemaciclib + fulv
Prior CDK4/6i	Palboclicib 87% Ribociclib 10% Abemaciclib 3%	Palboclicib 92% Ribociclib 5% Abemaciclib 3%	Palboclicib 100%	Palboclicib 59% Ribociclib 33% Abemaciclib 8%
Control arm	Fulv or exemestane	Fulv	Fulv or letrozole	Fulv (+ PBO)
***ESR1*-mut (%)**	30%	50%	N/A	40%
mPFS all patients mPFS, months HR (95% CI)	**5.3 vs 2.8** 0.57 (95% CI 0.39-0.85)	**4.6 vs 4.8** 1.11 (90% CI 0.74-1.66)	**4.9 vs 3.6** 0.84 (95% CI 0.66-1.07)	**6.0 vs 5.3** 0.73 (95% CI 0.57-0.95)
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**3.0 vs 3.0** 1.22 (95% CI 0.59-2.49)	**5.2 vs 3.3** 0.68 (90% CI 0.42-1.09)	**Not reported**	**Not reported** 0.79 (95% CI 0.54-1.15)

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

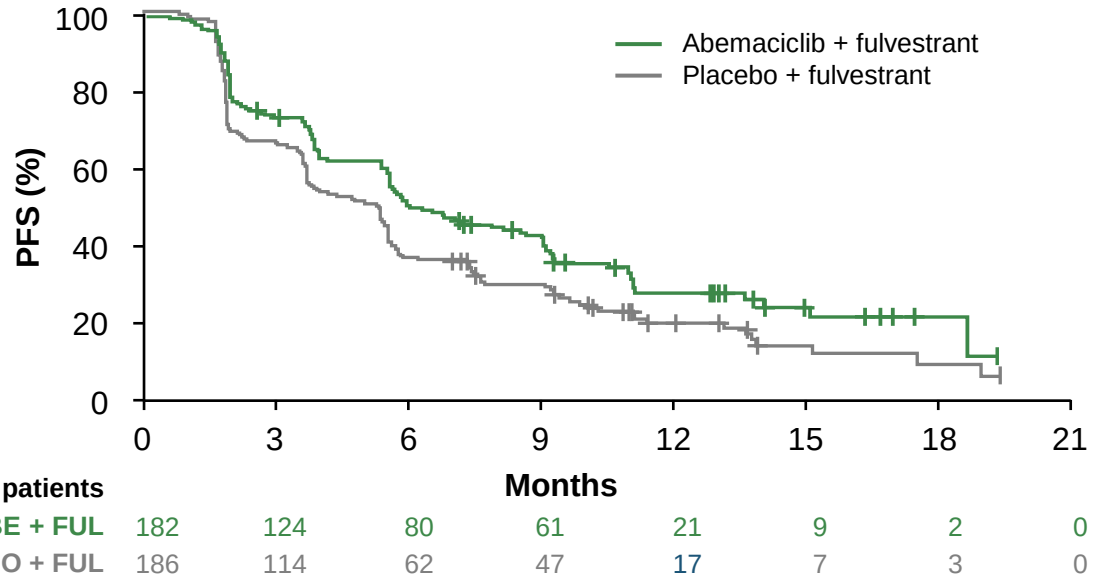
[a]Palbociclib + fulvestrant + avelumab arm not considered for this table

2L, second line; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; fulv, fulvestrant; HR, hazard ratio; (m)PFS, (median) progression-free survival; mut, mutation; NS, not significant; PBO, placebo; PFS, progression-free survival; N/A not available.

1. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 2. Mayer EL, et al. *J Clin Oncol*. 2024.JCO2301940; 3. Llombart-Cussac A, et al. *J Clin Oncol*. 2023;41:S1001–S1001 oral presentation; 4. PALMIRA. ClinicalTrials.gov identifier: NCT03809988. Accessed August 2024, https://clinicaltrials.gov/study/NCT03809988; 5. Kalinsky K, et al. *J Clin Oncol*. 2024;42. Abstract LBA1001. 6. Bardia, et al. *Clin Cancer Res.* 2024; Online ahead of print.

postMONARCH: CDK4/6 inhibitor rechallenge shows benefits, mainly after prior palbociclib, with negative outcomes after ribociclib

postMONARCH[a]



	ABE + FUL (N = 182)	PBO + FUL (N = 186)
mPFS, mo [95% CI]	**6.0** [5.6–8.6]	**5.3** [3.7–5.6]
HR [95% CI]	**0.73** [0.57–0.95]	
Nominal p-value	0.02	

postMONARCH: Subgroup analysis

Subgroup	N (%)	events	HR (95% CI)	Interaction p-value
Visceral Metastasis				*0.07*
Yes	221 (60)	173	0.87 (0.64-1.17)	
No	147 (40)	85	0.53 (0.34-0.83)	
Liver Metastasis				*0.40*
Yes	139 (38)	115	0.63 (0.44-0.91)	
No	229 (62)	143	0.78 (0.56-1.09)	
Prior CDK4/6 inhibitor				*0.19*
Palbociclib	217 (59)	145	0.62 (0.44-0.86)	
Ribociclib	122 (33)	94	1.01 (0.67-1.51)	
Abemaciclib	28 (8)	19	0.66 (0.27-1.84)	
ESR1				*0.98*
Detected	145 (45)	110	0.79 (0.54-1.15)	
Not detected	175 (55)	120	0.79 (0.55-1.13)	

Biomarker ctDNA by GuardantINFINITY assay.
[a]Investigator-assessed PFS.
ABE, abemaciclib; CI, confidence interval; ctDNA, circulating tumor DNA test; DNA, deoxyribonucleic acid; FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
Kalinsky K, et al. *ASCO*. 2024;42:LBA1001 oral presentation.

mTOR inhibitor plus ET has been associated with shorter mPFS in patients with prior CDK4/6i and *ESR1* mutation tumors

	BOLERO-2[1–3]	RWD Rozenblit et al.[4]	RWD Vasseur et al.[5]	TRINITI-1[6]
Phase (n)	Ph3 (724)	N/A (246)	N/A (57)	Ph1/2 (95)
Experimental arm	Everolimus + exemestane	Everolimus + ET	Everolimus + fulvestrant	Everolimus + exemestane + ribociclib
Control arm	Placebo + exemestane	N/A	N/A	N/A
Previous CDK4/6i Yes *No*	 - 100%	 22% 78%	 100% -	 100% -
***ESR1*-mut (%)**	30%	N/A	N/A	34%
mPFS all patients mPFS, months HR (95% CI)	**7.8 vs 3.2** 0.45 (0.38-0.54)	**mTTNT** *Prior CDK4/6i:* **4.3** *No prior CDK4/6i:* **6.2**	**6.8**	**5.7**
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**5.4 vs 2.8** 0.52 (0.36-0.75)	**N/A**	**N/A**	**3.5[a]**

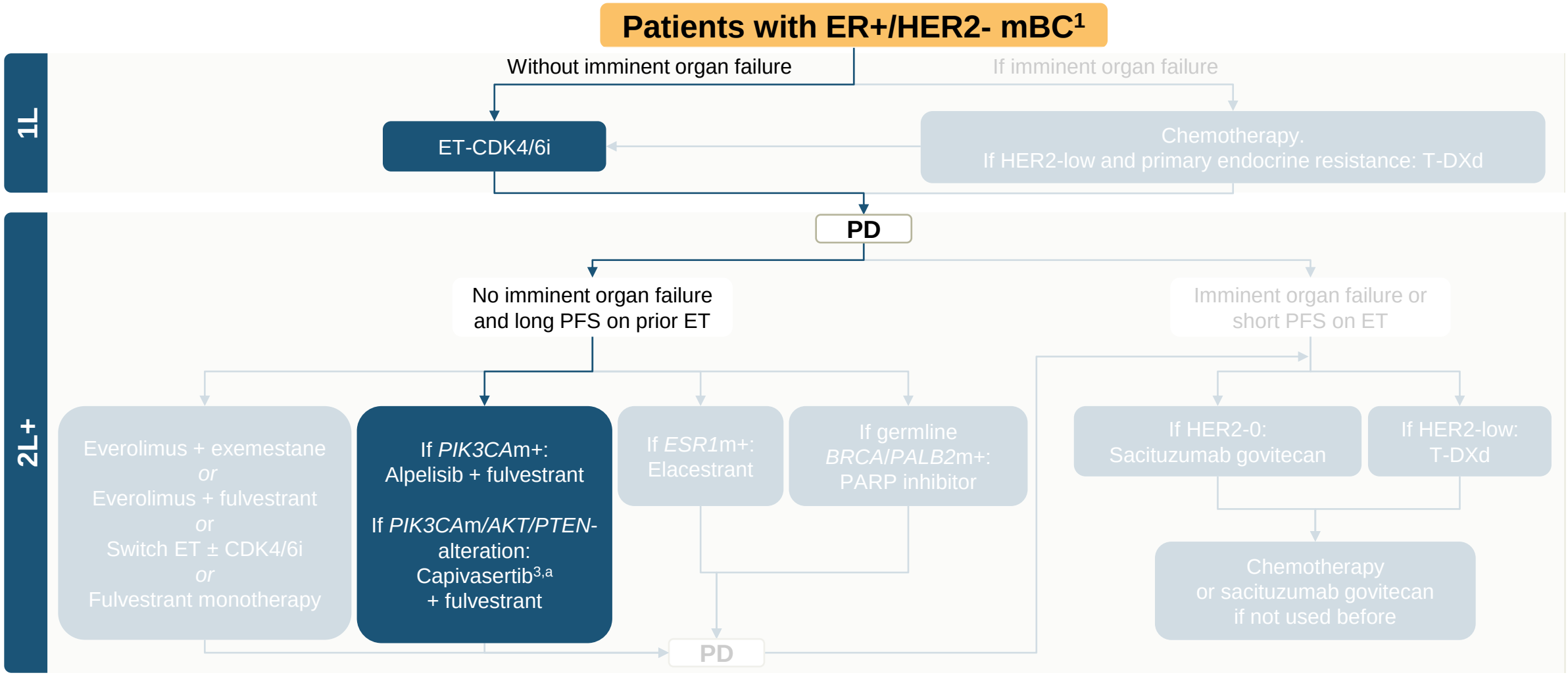
Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a] N = 89 patients had a baseline ctDNA biomarker assessment.

2L, second line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; mTOR, mammalian target of rapamycin; mTTNT, median time to next therapy; mut, mutation; N/A not available; NS, not significant; PBO, placebo; PFS, progression-free survival; RWD, real-world data.

1. Yardley DA, et al. *Adv Ther*. 2013;30:870–884; 2. Cook M, et al. *Oncologist*. 2021;26:101–106; 3. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2:1310–1315; 4. Rozenblit, et al. *Breast Cancer Res.* 2021;23:14; 5. Vasseur, et al. *Oncogene. 2024;*43:1214–1222, incl Suppl; 6. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-4185.

Second-line treatment choices for patients with ER+/HER2- mBC are driven by biomarker status[1,2]



[a] Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

PIK3CA/AKT-pathway inhibitors + ET show benefit in AKT-pathway altered tumors, but may be limited in endocrine sensitive tumors where ER is the driver

	SOLAR-1[1]	BYLieve[2,3]	Capitello 291[4]
Phase (n)	Ph3 (572)	Ph2 (336)	Ph3 (708)
Cohort (n)	*PIK3CA*-mutant (341)	Cohort A (127)	AKT pathway altered (289)
Experimental arm	Alpelisib + fulvestrant	Alpelisib + fulvestrant	Capivasertib + fulvestrant
Control arm	Placebo + fulvestrant	N/A	Placebo + fulvestrant
Previous CDK4/6i Yes *No*	 **6%** **94%**	 **100%** **-**	 **72%** **28%**
***ESR1*-mut (%)**	Data not available	21%	Data not available
mPFS all patients mPFS, months HR (95% CI)	**11 vs 5.7** 0.65 (0.50–0.85)	**8.0** (5.6-8.6)	**7.3 vs 3.1** 0.50 (0.38–0.65)
mPFS prior CDK4/6i mPFS, months HR (95% CI)i	**Data not available**	**8.0** (5.6-8.6)	**5.5 vs 2.0** 0.59 (0.48–0.72)
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**Data not available**	**5.6** (3.8–12.0)	**Data not available**

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

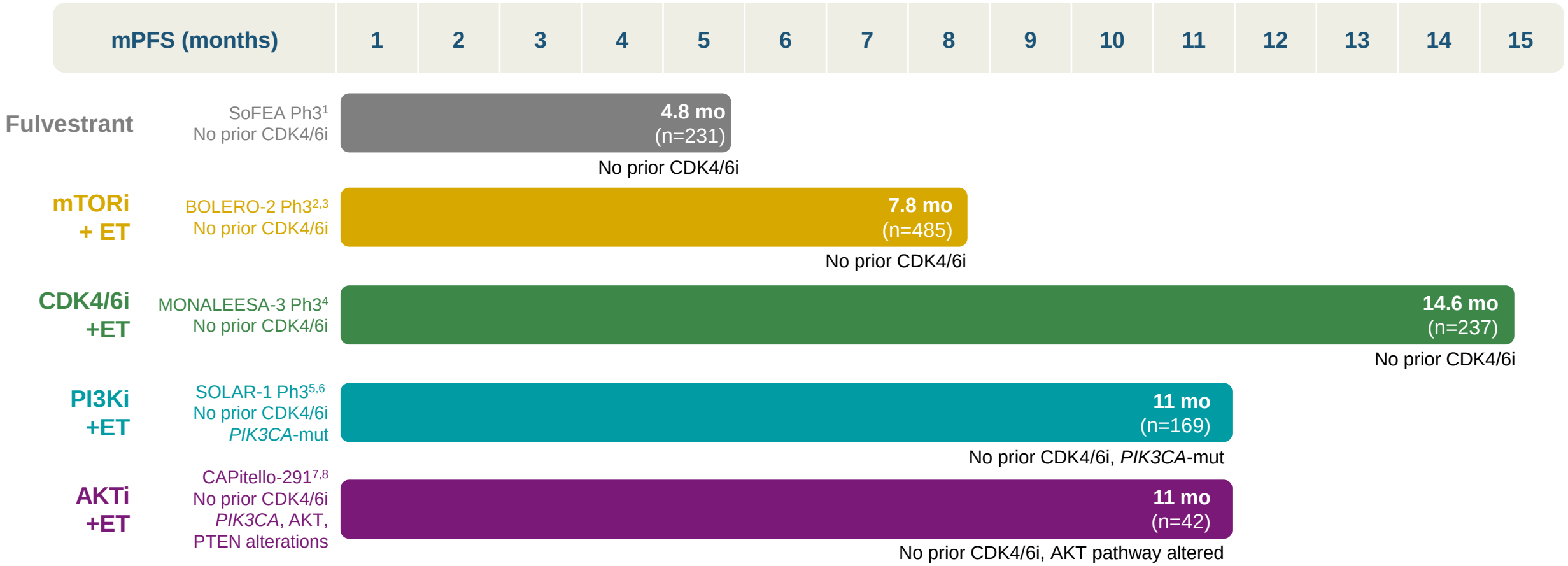
AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; HR, hazard ratio; N/A not available; mPFS, median PFS; mut, mutation; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TP53, tumor protein p53

1. André F, et al. *N Engl J Med*. 2019;380:1929–1940; 2. Chia S, et al. ASCO 2023. Abstract P1078; 3. Turner S, et al. SABCS 2021. PD15-01; 4 Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070

Summary - Efficacy of 2L+ ET regimens for ER+/HER2- mBC with no prior CDK4/6 inhibitor therapy

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

No prior CDK4/6i

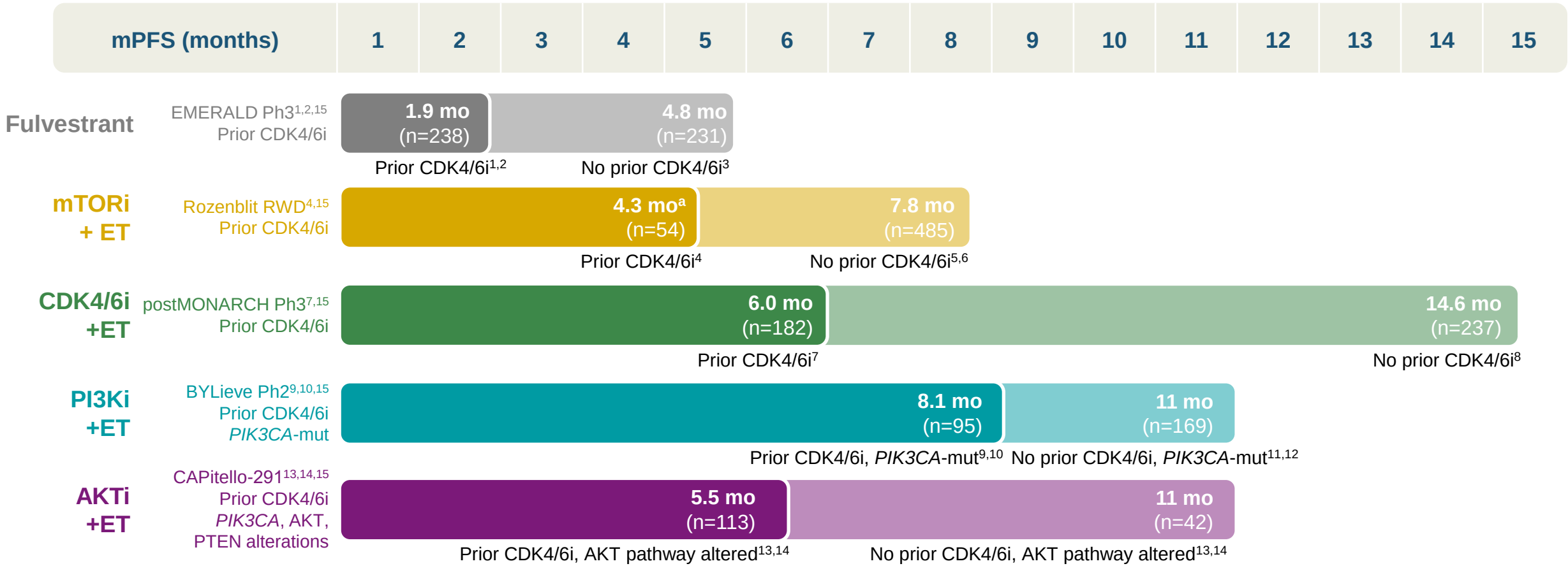


mPFS of studies represent n of intervention group.
2L, second line, ET, endocrine therapy; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*-mut, estrogen receptor 1 mutated; mPFS, median progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 2. Afinitor (everolimus). SmPC 2022; 3. Baselga J, et al. *N Engl J Med*. 2012;366:520–529; 4. Slamon DJ, et al. *N Engl J Med*. 2020; 382:514-524; 5. Piqray (alpelisib). SmPC 2023; 6. Andre F, et al. *N Engl J Med*. 2019; 380:1929-1940; 7. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O; 8. Turner NC, et al. *N Engl J Med.* 2023;388:2058–2070.

Summary - PFS duration is consistently lower in patients with prior CDK4/6 inhibitor therapy

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies



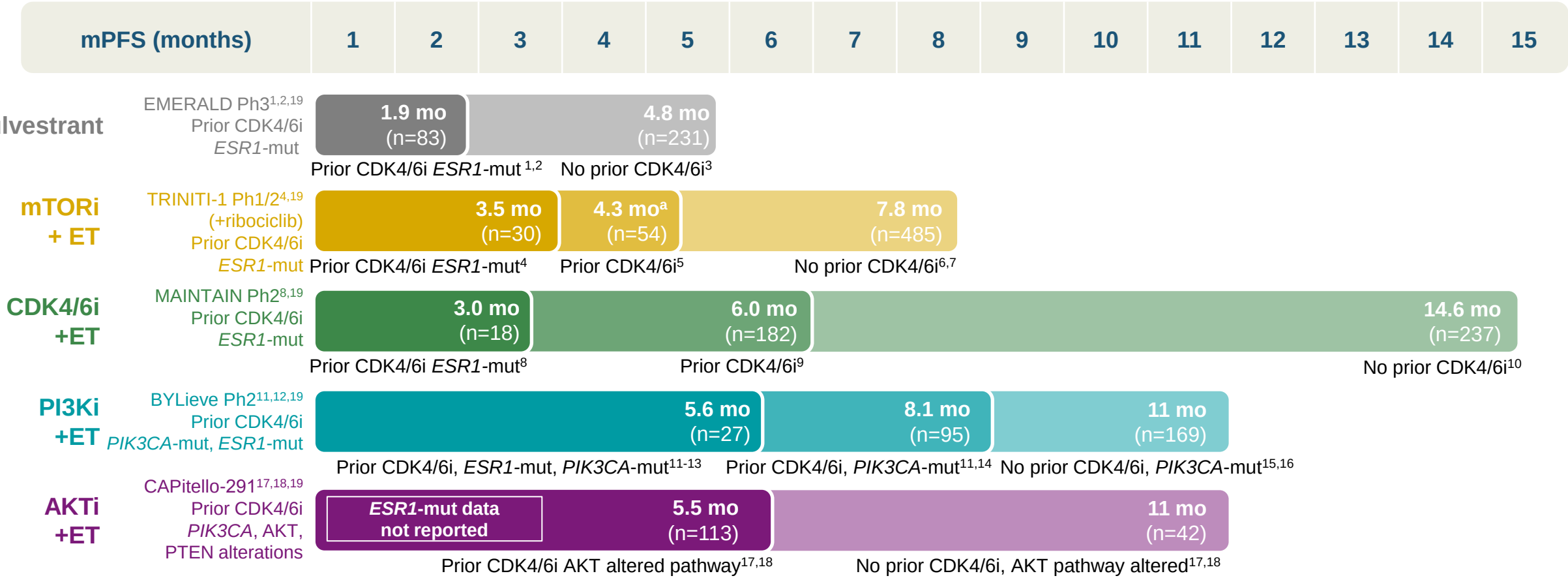
mPFS of studies represent n of intervention group; [a]Time to next treatment. 2L, second line, ET, endocrine therapy; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1; mut, mutated; mPFS, median progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWD, real-world data.

1. Orserdu (elacestrant) SmPC 2023; 2. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256; 3. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 4. Rozenblit M, et al. *Breast Cancer Res*. 2021;23:14; 5. Afinitor (everolimus). SmPC 2022; 6. Baselga J, et al. *N Engl J Med*. 2012;366:520–529; 7. Kalinsky K, et al. ASCO 2024. Abstract LBA1001; 8. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524; 9. Rugo HS, et al. *Lancet Oncol*. 2021;22:489-498; 10. Chia S, et al. *J Clin Oncol*. 2023;41(suppl 16; Abstract 1078; 11. Piqray (alpelisib). SmPC 2023; 12. Andre F, et al. *N Engl J Med*. 2019; 380:1929-1940; 13. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O; 14. Turner NC et al. *N Engl J Med*. 2023;388:2058–2070. 15. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print.

Summary - PFS duration is consistently lower in patients with prior CDK4/6 inhibitor therapy and *ESR1*-mut

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

Prior ET + CDK4/6i AND *ESR1*-mut



mPFS of studies represent n of intervention group; [a]Time to next treatment. 2L, second line, ET, endocrine therapy; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*-mut, estrogen receptor 1 mutated; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. 1. Orserdu (elacestrant) SmPC 2023; 2. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256; 3. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 4. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-4185; 5. Rozenblit M, et al. *Breast Cancer Res*. 2021;23:14; 6. Afinitor (everolimus). SmPC 2022; 7. Baselga J, et al. *N Engl J Med*. 2012;366:520–529; 8. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004-4013; 9. Kalinsky K, et al. ASCO 2024. Abstract LBA1001; 10. Slamon DJ, et al. *N Engl J Med*. 2020; 382:514-524; 11. Rugo HS, et al. *Lancet Oncol*. 2021;22:489-498; 12. Turner N, et al. SABCS. 2021; Abstract PD15-01; 13. Fillbrunn M, et al. *BMC*. 2022;22:1002. 14. Chia S, et al. *J Clin Oncol*. 2023;41(suppl 16; abstr 1078); 15. Piqray (alpelisib). SmPC 2023; 16. Andre F, et al. *N Engl J Med*. 2019; 380:1929-1940; 17. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O; 18. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070. 19. Bardia, et al. *Clin Cancer Res.* 2024; Online ahead of print.

Safety of ET combination regimens for second-line+, ER+/HER2− mBC

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	CDK4/6 inhibitors + ET		mTOR inhibitors + ET		*PIK3CA* inhibitors + ET		AKT-pathway[a] inhibitors + ET	
	Palbociclib,[1] ribociclib,[2] abemaciclib[3,4]		Everolimus[5]		Alpelisib[6]		Capivasertib[7]	
	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Adverse event incidence for combinations, %								
Neutropenia	**45–81**	**25–74**	–	–	–	–	–	–
Leukopenia	**26–45**	**9–31**	–	–	–	–	–	–
Anemia	**19–44**	**3–8**	16	6	–	–	10	2
Stomatitis	14–29	0–1	56	8	25	3	15	2
Rash	13–18	1–2	36	1	36	10	38	12
Diarrhea	**25–86**	**1–12**	30	2	58	7	72	9
Hyperglycemia	–	–	13	4	64	33	16	2
Fatigue	33–41	2–3	33	4	24	4	21	1
Nausea	34–49	0–2	29	0	45	3	35	1
Discontinuation rate, %	**2–15**		**19**		**25**		**13**	

CDK4/6 inhibitors are associated with myelosuppression (neutropenia, leukopenia, anemia) and diarrhea

[a]PIK3CA/AKT1/PTEN; 2L, second line; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Dieras V, et al. *J Natl Cancer Inst.* 2018;111:419–430; 2. Burris HA, et al. *Br J Cancer*. 2021;125:679–686; 3. Rugo HS, et al. *Oncologist*. 2021;26:e53–e65; 4. Jhavieri KL et al. *N Engl J Med* . 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print. 5. Baselga J, et al.*N Engl J Med*. 2012;366:520-529; 6. Andre F, et al. *N Engl J Med*. 2019;380:1929–1940; 7. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070.

Safety of ET combination regimens for second-line+, ER+/HER2− mBC

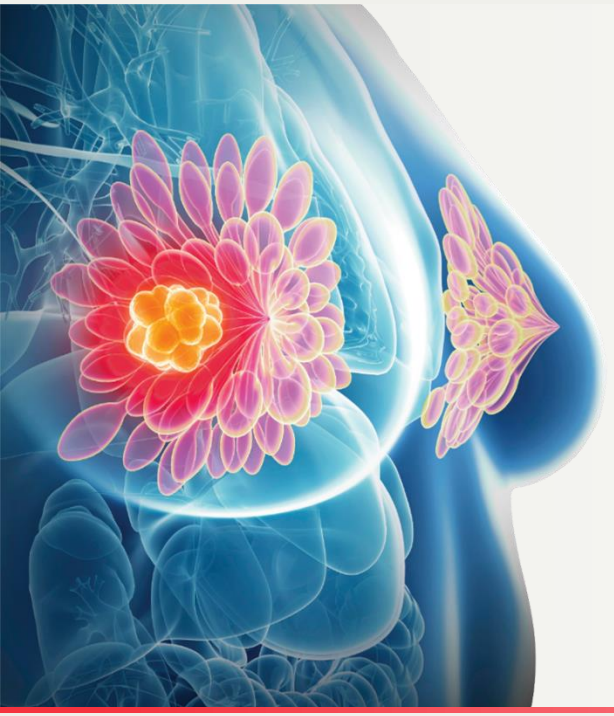
Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	CDK4/6 inhibitors + ET		mTOR inhibitors + ET		*PIK3CA* inhibitors + ET		AKT-pathway[a] inhibitors + ET	
	Palbociclib,[1] ribociclib,[2] abemaciclib[3,4]		Everolimus[5]		Alpelisib[6]		Capivasertib[7]	
	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Adverse event incidence for combinations, %								
Neutropenia	45–81	25–74	–	–	–	–	–	–
Leukopenia	26–45	9–31	–	–	–	–	–	–
Anemia	19–44	3–8	16	6	–	–	10	2
Stomatitis	14–29	0–1	**56**	**8**	**25**	**3**	**15**	**2**
Rash	13–18	1–2	**36**	**1**	**36**	**10**	**38**	**12**
Diarrhea	25–86	1–12	**30**	**2**	**58**	**7**	**72**	**9**
Hyperglycemia	–	–	**13**	**4**	**64**	**33**	**16**	**2**
Fatigue	33–41	2–3	33	4	24	4	21	1
Nausea	34–49	0–2	29	0	45	3	35	1
Discontinuation rate, %	2–15		19		25		13	

PI3K/AKT/mTOR pathway inhibitors are associated with Grade 3/4 diarrhea, rash, hyperglycemia and stomatitis

[a]*PIK3CA/AKT1/PTEN*; 2L, second line; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Dieras V, et al. *J Natl Cancer Inst.* 2018;111:419–430; 2. Burris HA, et al. *Br J Cancer*. 2021;125:679–686; 3. Rugo HS, et al. *Oncologist*. 2021;26:e53–e65; 4. Jhavieri KL et al. *N Engl J Med* . 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print. 5. Baselga J, et al.*N Engl J Med*. 2012;366:520-529; 6. Andre F, et al. *N Engl J Med*. 2019;380:1929–1940; 7. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070



Treatment Landscape for ER+/HER2- Metastatic Breast Cancer

Javier Cortés

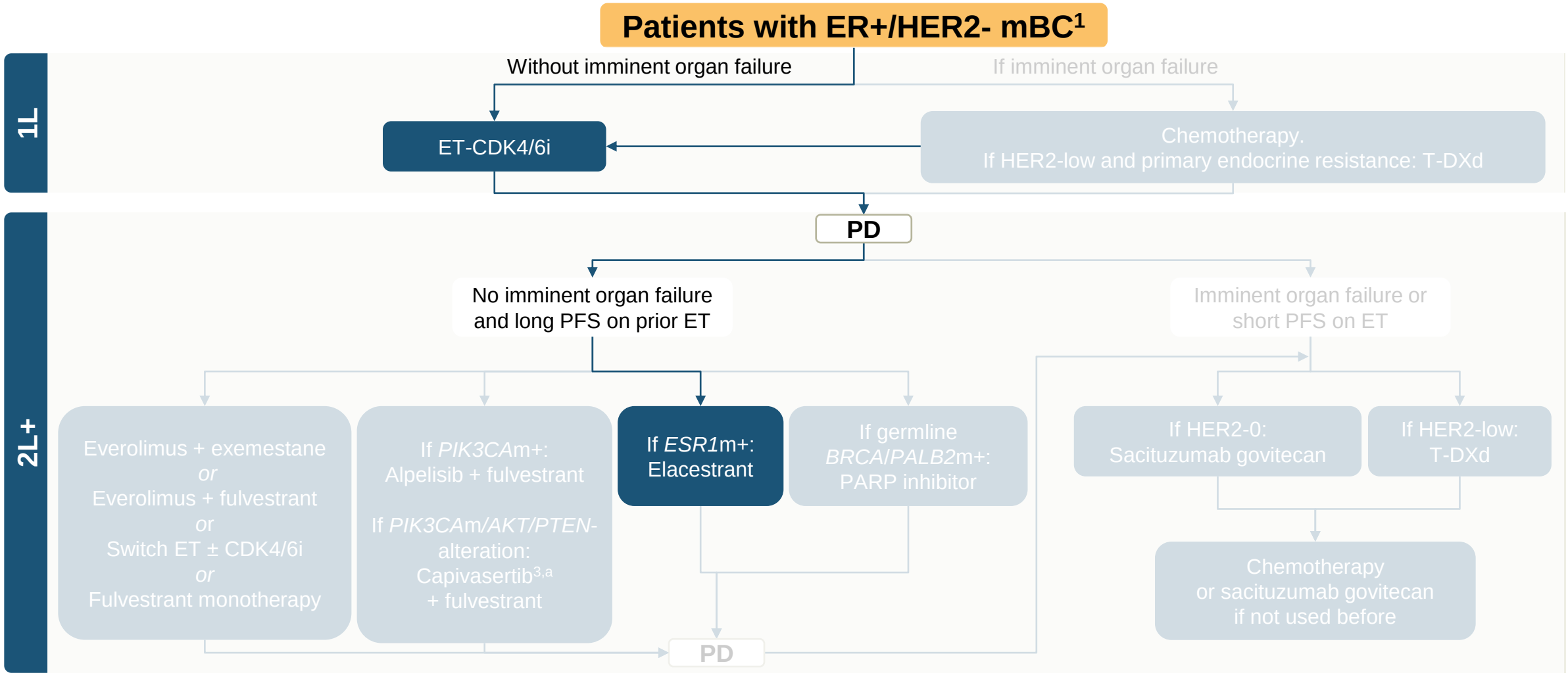
International Breast Cancer Center

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

MENARINI group

Stemline® A Menarini Group Company

Second-line treatment choices for patients with ER+/HER2- mBC are driven by biomarker status[1,2]



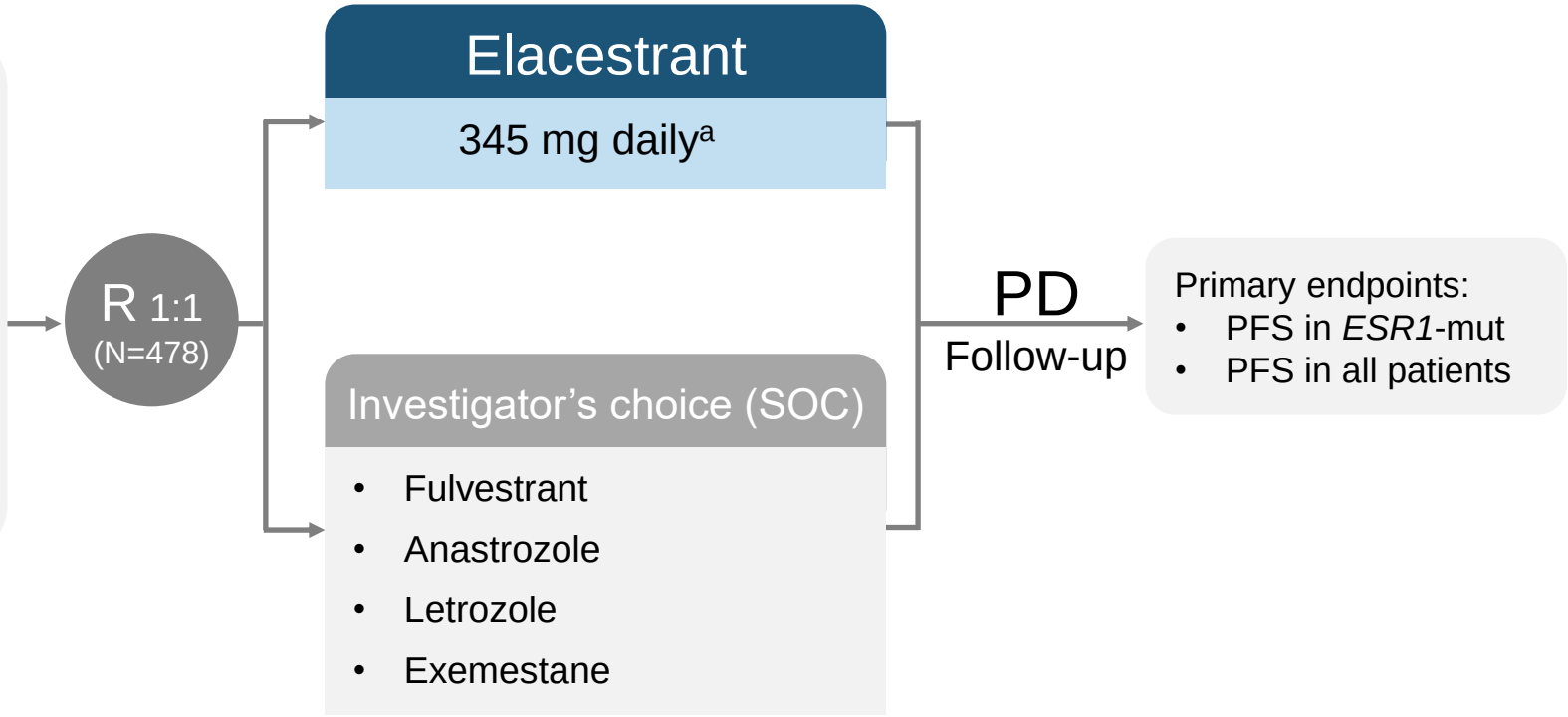
[a] Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

EMERALD: Phase 3 trial of elacestrant vs SOC endocrine therapy

100% of patients HAD received prior CDK4/6 inhibitor therapy

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER+/HER2-
- Progressed or relapsed on or after one or two lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for Metastatic disease
- ECOG PS 0 or 1

Stratification factors
- *ESR1*-mut status
- Presence of visceral metastases
- Prior treatment with fulvestrant



[a]345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride.
mBC, Metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1*, estrogen receptor 1 mutation; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PD, progressive disease; PFS, progression-free survival; R, randomization; SOC, standard of care.
Bidard FC, et al. *J Clin Oncol* 2022;40:3246–3256.

EMERALD trial baseline characteristics[1,2]

	Elacestrant (N=115)		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63 (24-89)	64 (28-89)	63 (32-83)	63 (32-83)
Female, n (%)	233 (97.5)	115 (100)	238 (99.6)	113 (100)
ECOG PS, n (%)				
0	143 (59.8)	67 (58.3)	135 (56.5)	62 (54.9)
1	96 (40.2)	48 (41.7)	103 (43.1)	51 (45.1)
Visceral metastasis[a], n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6 inhibitor, n %)	239 (100)	115 (100)	239 (100)	113 (100)
No. of prior lines of endocrine therapy in the advanced or metastatic setting, n (%)				
1	129 (54.0)	73 (63.5)	142 (59.4)	69 (61.1)
2	110 (46.0)	42 (36.5)	97 (40.6)	44 (38.9)
Prior therapies for advanced or metastatic disease, n (%)				
Fulvestrant	70 (29.3)	27 (23.5)	75 (31.4)	28 (24,8)
Aromatase inhibitor	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)				
0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
1	26 (20.1)	26 (22.6)	59 (24.7)	32 (28.3)

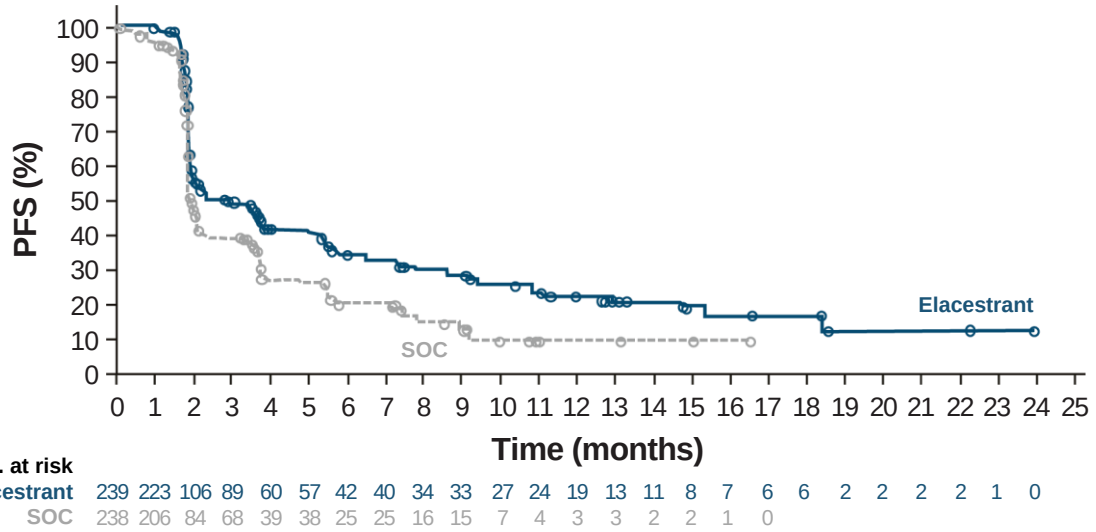
[a]Includes lung, liver, brain, pleural, and peritoneal involvement.

mBC, Metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1*, estrogen receptor 1 mutation; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PD, progressive disease; PFS, progression-free survival; R, randomization; SOC, standard of care.

1. Orserdu (elacestrant) SmPC 2023; 2023; 2. Bardia A, et al. SABCS 2022. Abstract GS3–01.

EMERALD: Elacestrant demonstrated PFS improvement versus SOC both in the overall population and in patients with *ESR1* mutations

mPFS in all patients

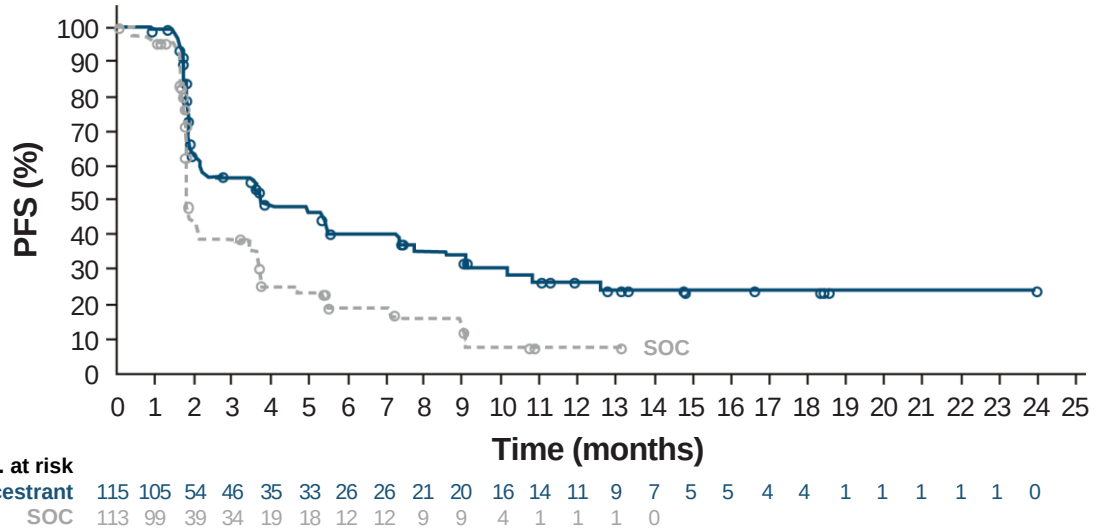


No. at risk

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

	Elacestrant (n=239)	SOC (n=238)
6-mo PFS, % [95% CI]	**34.3** [27.2-41.5]	**20.4** [14.1-26.7]
12-mo PFS,% [95% CI]	**22.3** [15.2-29.4]	**9.4** [4.0-14.8]
HR [95% CI]	**0.70** [0.55–0.88]	
p-value	0.0018	

mPFS in patients with *ESR1*-mut



No. at risk

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

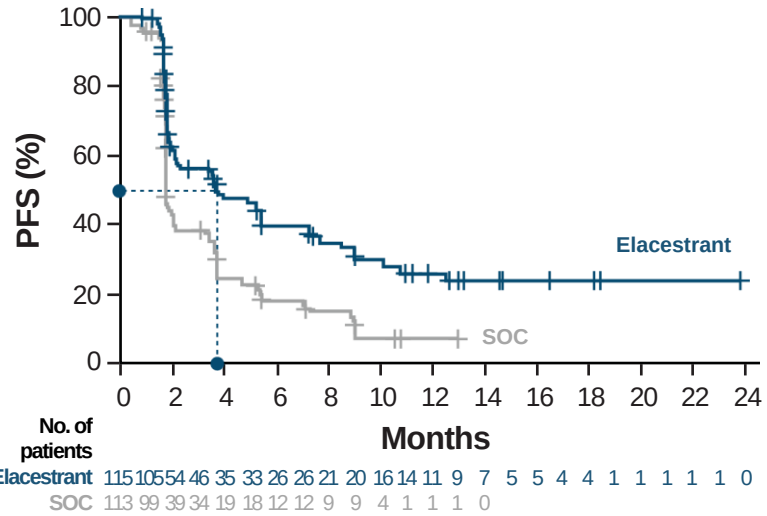
	Elacestrant (n=115)	SOC (n=113)
6-mo PFS, % [95% CI]	**40.8** [30.1-51.4]	**19.1** [10.5-15.1]
12-mo PFS,% [95% CI]	**26.8** [16.2-37.4]	**8.2** [1.3-15.1]
HR [95% CI]	**0.55** [0.39–0.77]	
p-value	0.0005	

CI,confidence interval; ESR1,estrogen receptor 1; HR,hazard ratio; ITT,intent-to-treat; mo,months; mPFS,median progression-free survival; mut,mutated; PFS,progression-free survival.

Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256

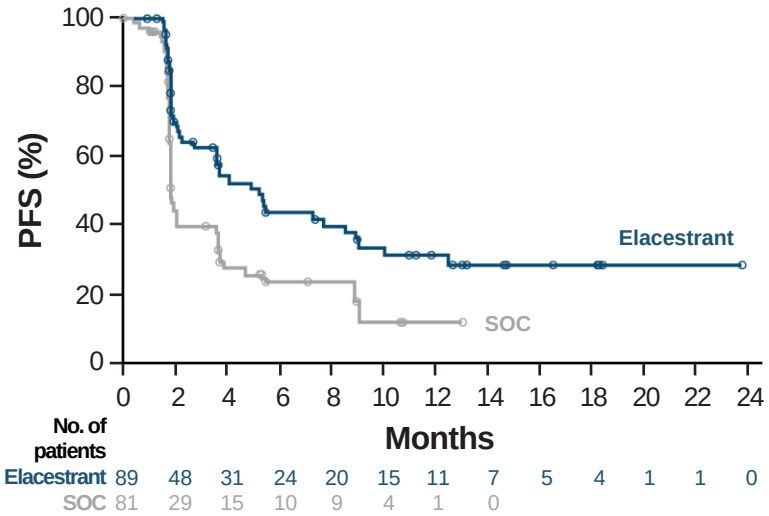
EMERALD: Elacestrant provides improved PFS results vs SOC in patients with *ESR1* mutations

45% reduction in risk of progression or death



	Elacestrant (n=115)	SOC (n=113)
mPFS, mo	**3.8**	**1.9**
HR [95% CI]	**0.55** [0.39–0.77]	
p-value	0.0005	

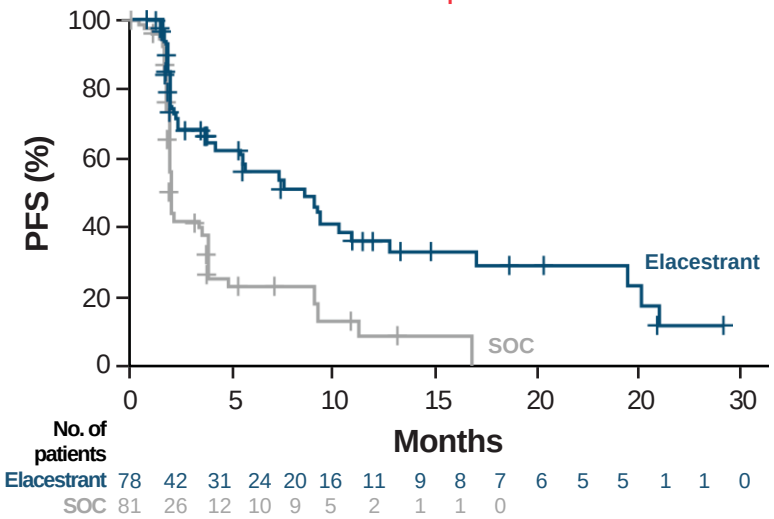
Significant PFS improved in patients who did not receive prior chemotherapy



	Elacestrant (n=89)	SOC (n=81)
mPFS, mo [range]	**5.3** [3.7–9.0]	**1.9** [1.9–3.7]
HR [95% CI]	**0.54** [0.36–0.80]	
p-value	0.00235	

Duration of prior ET + CDK4/6 inhibitor therapy is positively associated with mPFS

≥12 months of prior ET + CDK4/6i[b]



	Elacestrant (n=78)	SOC (n=81)
mPFS, mo [95% CI]	**8.6** [4.1–10.8]	**1.9** [1.9–3.7]
12-mo PFS, % [95% CI]	**35.8** [21.8–49.8]	**8.39** [0.0–17.7]
HR [95% CI]	**0.41** [0.26–0.63]	

[a]Calculated with covariates; [b]Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

CI, confidence interval; HR, hazard ratio;*ESR1*, estrogen receptor 1; mo, months; mPFS, median progression-free survival; mut, mutated; No, number; PFS, progression-free survival; SOC, standard of care.

Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; Kaklamani V, et al. *J Clin Oncol.* 2022;40(16_suppl):Abstract 1100; Bardia A, et al. SABCS 2022. Abstract GS3–01.

In tumors with retained endocrine-sensitivity (longer exposure to prior ET + CDK4/6i), *ESR1* mutations are a main driver of disease

Patients with ≥12 months of prior ET + CDK4/6i	% (n)	Elacestrant mPFS, months	SOC mPFS, months	HR [95% CI]
All *ESR1*-mut patients	**100** (159)	**8.6**	**1.9**	**0.41** [0.26–0.63]
PIK3CA-mut[a]	**39** (62)	**5.5**	**1.9**	**0.42** [0.18–0.94]
Bone metastases[b]	**86** (136)	**9.1**	**1.9**	**0.38** [0.23–0.62]
Liver and/or lung metastases[c]	**71** (113)	**7.3**	**1.9**	**0.35** [0.21–0.59]
TP53-mut	**38** (61)	**8.6**	**1.9**	**0.30** [0.13–0.64]
HER2-low expression[d]	**48** (77)	**9.0**	**1.9**	**0.30** [0.14–0.60]
High *ESR1* VAF	**50** (79)	**9.1**	**1.9**	**0.36** [0.19–0.69]
Low *ESR1* VAF	**50** (79)	**8.6**	**1.9**	**0.51** [0.26–0.99]

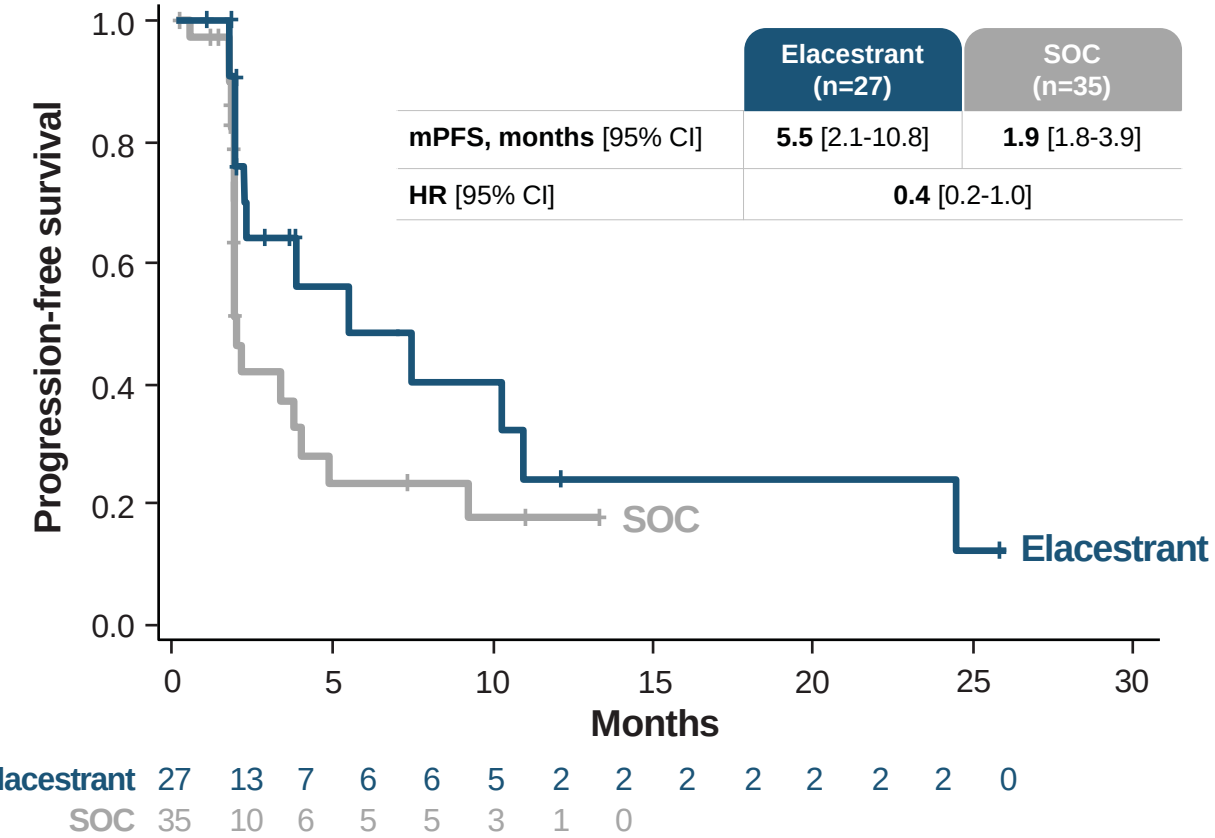
This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

[a] Includes E545K, H1047R, E542K, and others; [b] 85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [c] 55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement); [d] Locally assessed HER2 immunohistochemistry 1+, and 2+ with no *in situ* hybridization amplification; Data not available for all patients. CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1,* estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mut, mutation; PIK3CA , phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care; TP53, tumor protein p53.

Bardia A, et al. *Clin Cancer Res.* 2024; Online ahead of print.; Bardia et al SABCS 2024. P1-01-25

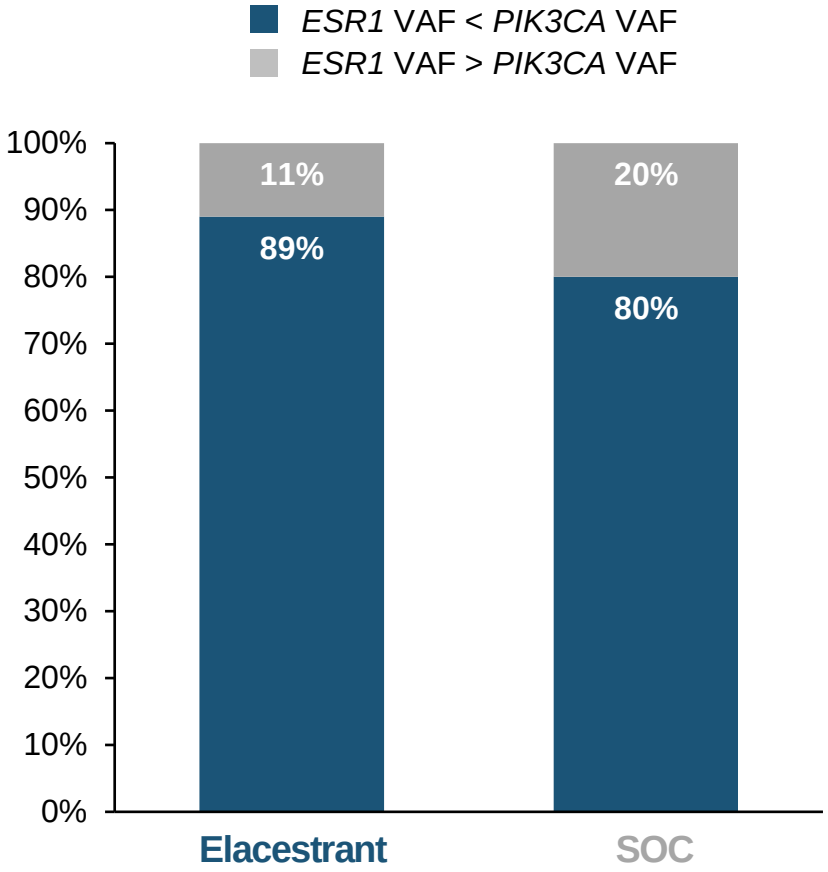
Elacestrant was associated with a longer PFS compared with SOC even though 89% of *ESR1* mutations were characterized by having a lower VAF compared to *PIK3CA* VAF

Prior ET + CDK4/6i ≥12 months with the coexistence of *ESR1*-mutated and *PIK3CA*-mutated tumors



	Elacestrant (n=27)	SOC (n=35)
mPFS, months [95% CI]	**5.5** [2.1-10.8]	**1.9** [1.8-3.9]
HR [95% CI]	**0.4** [0.2-1.0]	

Elacestrant	27	13	7	6	6	5	2	2	2	2	2	2	2	0
SOC	35	10	6	5	5	3	1	0						



This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error. [a] Includes E545K, H1047R, E542K, and others
CDK4/6, cyclin dependent kinase 4/6; *ESR1*-mut, estrogen receptor 1 mutation; ET, endocrine therapy; PFS, progression-free survival; PIK3CA , phosphatidylinositol-4,5-bisphosphate 3-kinase; SOC, standard of care
Bardia et al SABCS 2024. P1-01-25

EMERALD: Safety

Most common adverse events ≥ 10% in either arm in the overall population[1]

	Elacestrant (n=237)		SOC (n=230)	
Adverse events[1,a]	**All grades (%)**	**Grade ≥ 3 (%)**	**All grades (%)**	**Grade ≥ 3 (%)**
Nausea	35	2.5	19	0.9
Vomiting[b]	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain[b]	11	1	10	0.9
Dyspepsia	10	0	2.6	0
Fatigue[b]	26	2	27	1
Decreased appetite	15	0.8	10	0.4
Headache	12	2	12	0
Hot flush	11	0	8	0

Nausea summary[1]	**Elacestrant (n=237)**	**SOC (n=230)**
Grade 3 nausea, %	2.5	0.9
Dose-reduction rate due to nausea, %	1.3	N/A
Discontinuation rate due to nausea, %	1.3	0
Antiemetic use*, %	8.0	10.3 (AI) 3.7 (fulvestrant)

Nausea was generally reported early, with a median time to first onset of 14 days.[2]
*Patients may have been on antiemetics prior to enrollment.[1]

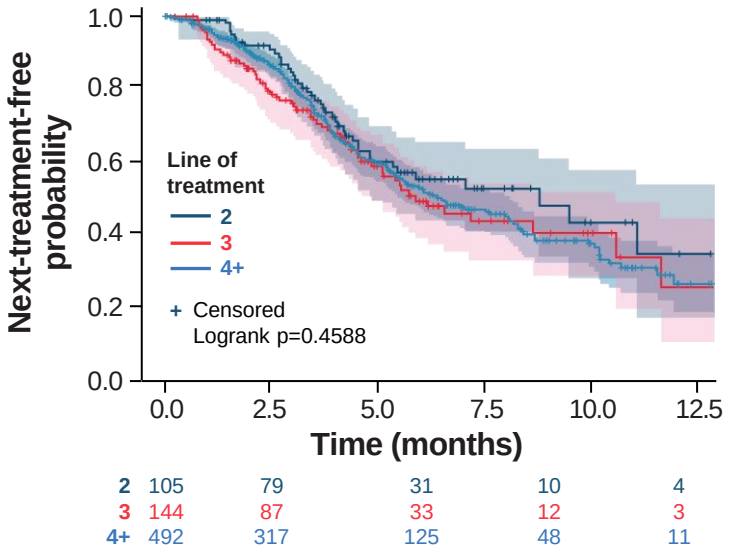
- No grade 4 treatment-related AEs were reported[1]
- Treatment-related AEs leading to discontinuation were 3.4% and 0.9% in the elacestrant and SOC arms, respectively[1]
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia[1]

[a]Adverse events were graded using NCI CTCAE version 5.0; [b]Includes other related terms.
AI, aromatase inhibitor; AE, adverse event;; ER, estrogen receptor; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SOC, standard of care (fulvestrant or aromatase inhibitor).

1. Bardia A et al. *Clin Cancer Res.* 2024; Online ahead of print; 2. Stemline. ORSERDU (elacestrant) Summary of Product Characteristics. 2024.

Elacestrant showed consistent real-world TTNT and PFS benefit among clinically relevant subgroups

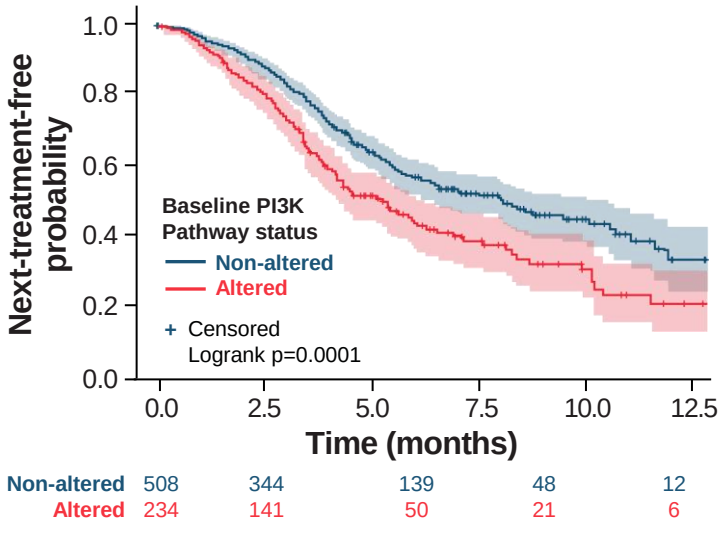
rwTTNT since elacestrant initiation by line of treatment



2	105	79	31	10	4
3	144	87	33	12	3
4+	492	317	125	48	11

	2	3	4+
Subjects	104	144	492
Event	42	62	208
Censored	62	82	284
Median survival	8.8	5.9	6.4
95% CI	4.8-	4.6-10.6	5.5-8.1

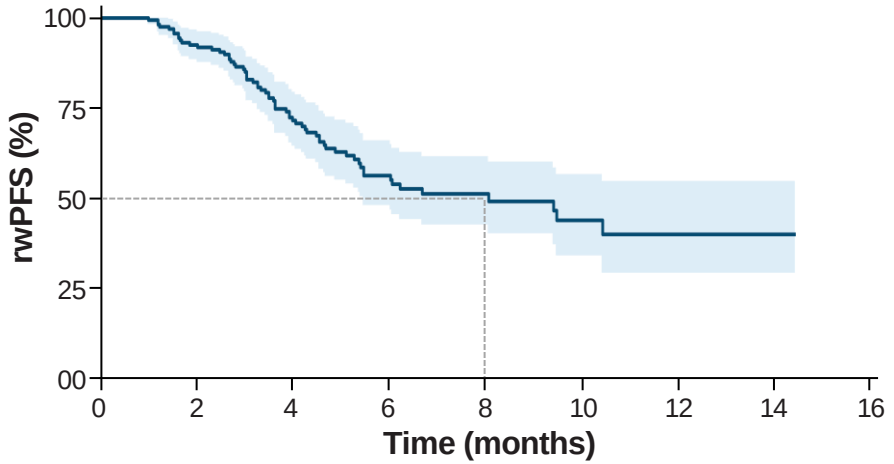
rwTTNT since elacestrant initiation by baseline PI3K* pathway status



Non-altered	508	344	139	48	12
Altered	234	141	50	21	6

	Non-altered	Altered
Subjects	508	234
Event	191	121
Censored	317	113
Median survival	8.0	5.2
95% CI	6.2–10.1	4.2–6.0

1–2 prior lines of ET



Events	0	12	41	57	61	64	65	65	65

	Elacestrant (n=166)
Events, n (%)	**65 (39)**
Median rwPFS, mo [95% CI]	**8.0** [5.5-NR]
12 mo rwPFS, % [95% CI]	**40** [29-54]

* Oncogenic alterations in *AKT1*, *PTEN*, and *PIK3CA* with an FDA approved targeted therapeutic indication were included as PI3K pathway alterations: *PIK3CA* (n=197), *AKT1* (n=30), and/or *PTEN* (n=15).
2L,second line; 3L,third line; 4L,fourth line; AKT, protein kinase B; CI,confidence interval; CL, confidence limits; HR, hazard ratio; mo, months, PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog rw,real-world; TTNT,time to next treatment

1. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 2.Swallow et al. SABCS 2024. Abstract P3 10-08

Elacestrant shows consistent ~8-9 months benefit in nearly 1200 patients with prior exposure to CDK4/6i, as demonstrated by EMERALD and RWE analyses

	Bardia et al, EMERALD CCR (n=159)[1]	**Lloyd et al, Guardant** Inform (n=742)[2]	**Swallow et al, Komodo** Calims (n=276)[3]
Baseline Characteristics			
Prior CDK4/6i mBC	100%	83%	90%
Prior CDK4/6i >12 mo	100%	-	88%
Prior fulvestrant in mBC	23%	53%	61%
Prior chemo in mBC	20%	41%	33%
mPFS / rwPFS / TTNT			
2L	-	8.8	-
2-3L	8.6	-	8.0

[a]Palbociclib + fulvestrant + avelumab arm not considered for this table

1.Mayer EL et al. *J Clin Oncol.* 202. JCO2301940;2. Llombart-Cussac A, et al. J Clin Oncol. 2023;41:S1001-S1001 oral presentation; 3.Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004-4013; 4. Kalinsky K, et al. *J Clin Oncol*. 2024;42.Abstract LBA1001; 4.PALMIRA. ClinicalTrials.gov identifier: NCT03809988. Accessed August 2024, https://clinicaltrials.gov/study/NCT03809988; 5.Kalinsky K, et al. *J Clin Oncol*. 2024;42.Abstract LBA1001; 6.Bardia, et al. *Clin Cancer Res; Onlin ahead of print.*

1. Bardia A et al. *Clin Cancer Res.* 2024; Online ahead of print; 2.Llyod, SABCS 2024. Abstract PS7-05; 3.Swallow et al, SABCS 2024. Abstract P3 10-08

EMBER-3: Study design and baseline demographics

Study design

ER+, HER2- ABC

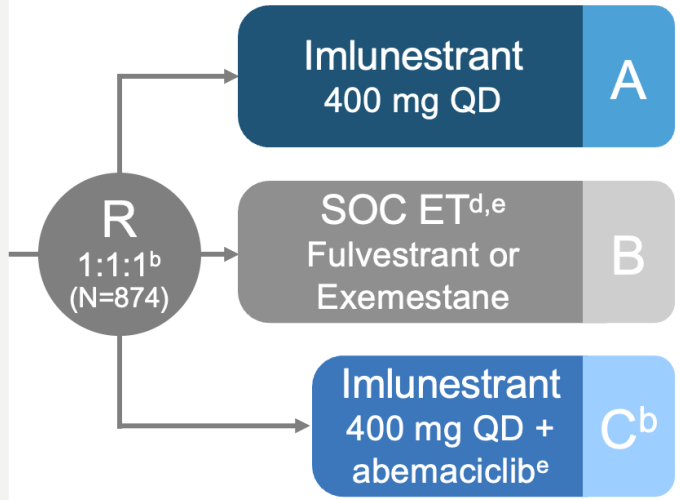
Men and pre-[a]/post-menopausal women

Prior therapy:

- **Adjuvant:** Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary endpoints

Investigator-assessed PFS for:

- A vs B in patients with *ESR1*-mut
- A vs B in all patients
- C vs A in all patients

Key secondary endpoints:

- OS, PFS by BICR, and ORR
- Safety

Baseline demographics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Post-menopausal, %		84	86	86
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41
Prior chemotherapy, %	Yes	0	0	0
	No	100	100	100
Prior fulvestrant, %	Yes	0	0	0
	No	100	100	100
Most recent ET,%				
As (neo) adjuvant therapy		32	34	30
For aBC		63	63	68
Prior CDK4/6i, %	Overall	59	57	65
As adjuvant therapy		4	4	3
For aBC		55	53	62

Table adapted from Jhaveri KL et al, 2024

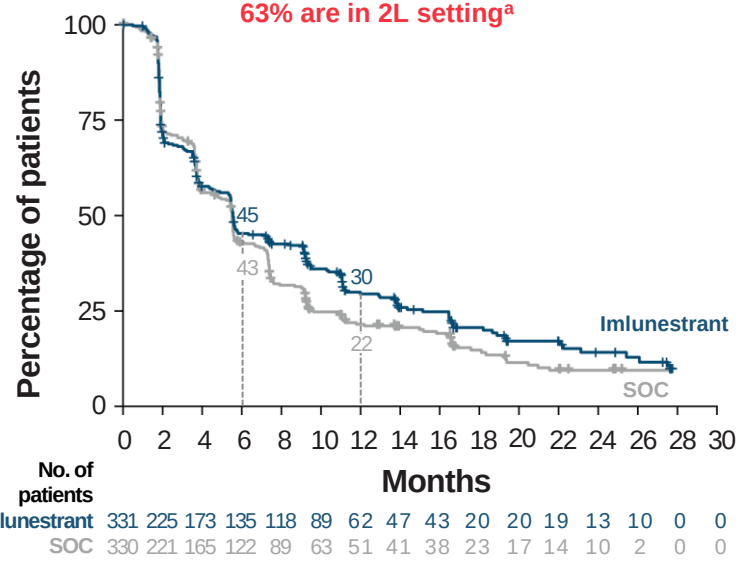
[a] A GRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B), [c] East Asia vs United States/European Union vs others, • Investigator's choice; • Labeled dose, "Scans every 8 weeks for the first 12 months, then every 12 weeks; [d] *ESR1*-mut status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; "Analysis conducted in all concurrently randomized patients. ABC, advanced breast cancer, AI, aromatase inhibitor, BICR, blinded independent central review; CDK4/6 CDK4/6 inhibitor, ER, estrogen receptor, ESR1-mut, ESR1 mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 lo November 2023 across 195 sites in 22 countries.

Jhaveri KL et al. *N Engl J Med* . 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print

Imlunestrant monotherapy provided PFS benefit over standard therapy among patients with *ESR1* mutations. Imlunestrant did not show benefit in the all-patient population

mPFS in all patients

59% HAD prior CDK4/6i therapy[a]
32% are in 1L setting[a]
63% are in 2L setting[a]

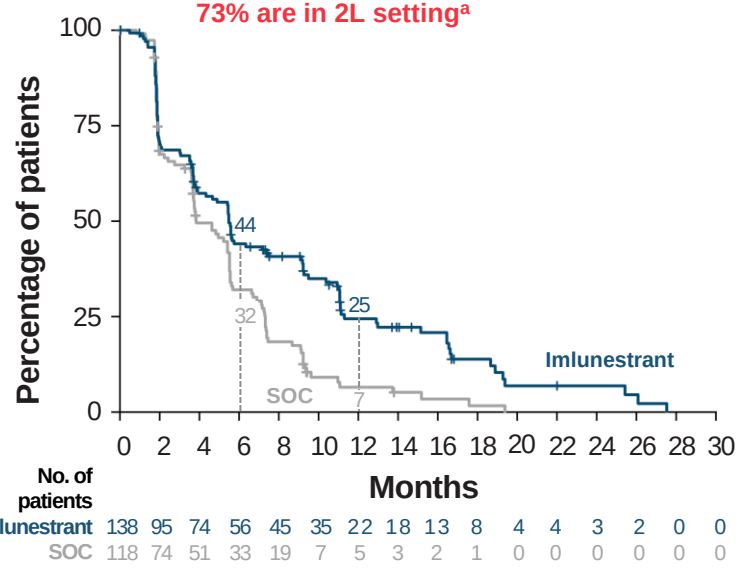


No. of patients																
Imlunestrant	331	225	173	135	118	89	62	47	43	20	20	19	13	10	0	0
SOC	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

	Imlunestrant (n=331)	SOC (n=330)
mPFS, mo	**5.6**	**5.5**
HR [95% CI]	**0.87** [0.72–1.04]	
p-value	0.12	

mPFS in patients with *ESR1*-mut

67% HAD prior CDK4/6i therapy[a]
21% are in 1L setting[a]
73% are in 2L setting[a]



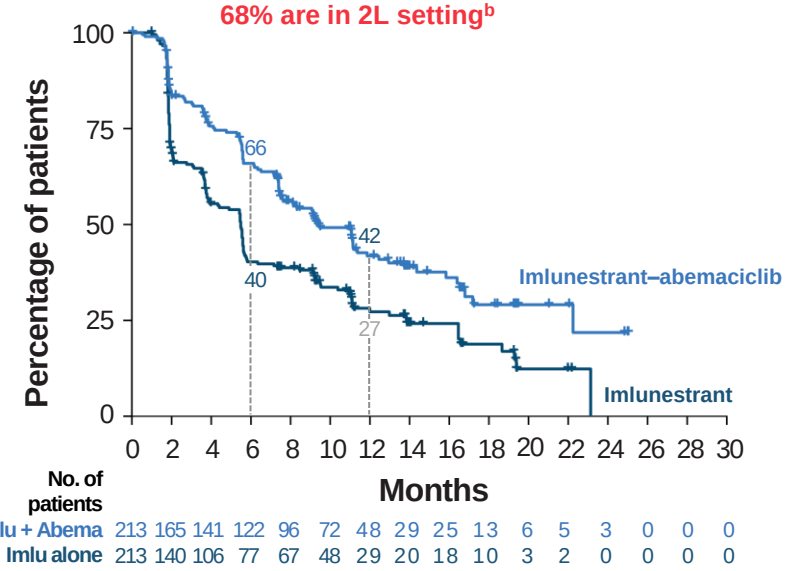
No. of patients																
Imlunestrant	138	95	74	56	45	35	22	18	13	8	4	4	3	2	0	0
SOC	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

	Imlunestrant (n=138)	SOC (n=118)
mPFS, mo	**5.5**	**3.8**
HR [95% CI]	**0.62** [0.46–0.82]	
p-value	< 0.001	

Imlunestrant + abemaciclib combination provided PFS benefit vs imlunestrant alone in all comers

mPFS in all patients

65% HAD prior CDK4/6i therapy[b]
30% are in 1L setting[b]
68% are in 2L setting[b]



No. of patients																
Imlu + Abema	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0
Imlu alone	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0

	Imlu + abema (n=213)	Imlu alone (n=213)
mPFS, mo	**9.4**	**5.5**
HR [95% CI]	**0.57** [0.44–0.73]	
p-value	< 0.001	

[a]Baseline characteristic for patients in the imlunestrant arm only: [b]Baseline characteristic for patients in the imlunestrant-abemaciclib arm only
CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ESR1, estrogen receptor 1; PFS, progression free survival
Jhaveri KL et al. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print

EMBER-3: The safety profiles of imlunestrant and imlunestrant–abemaciclib were consistent with previous findings

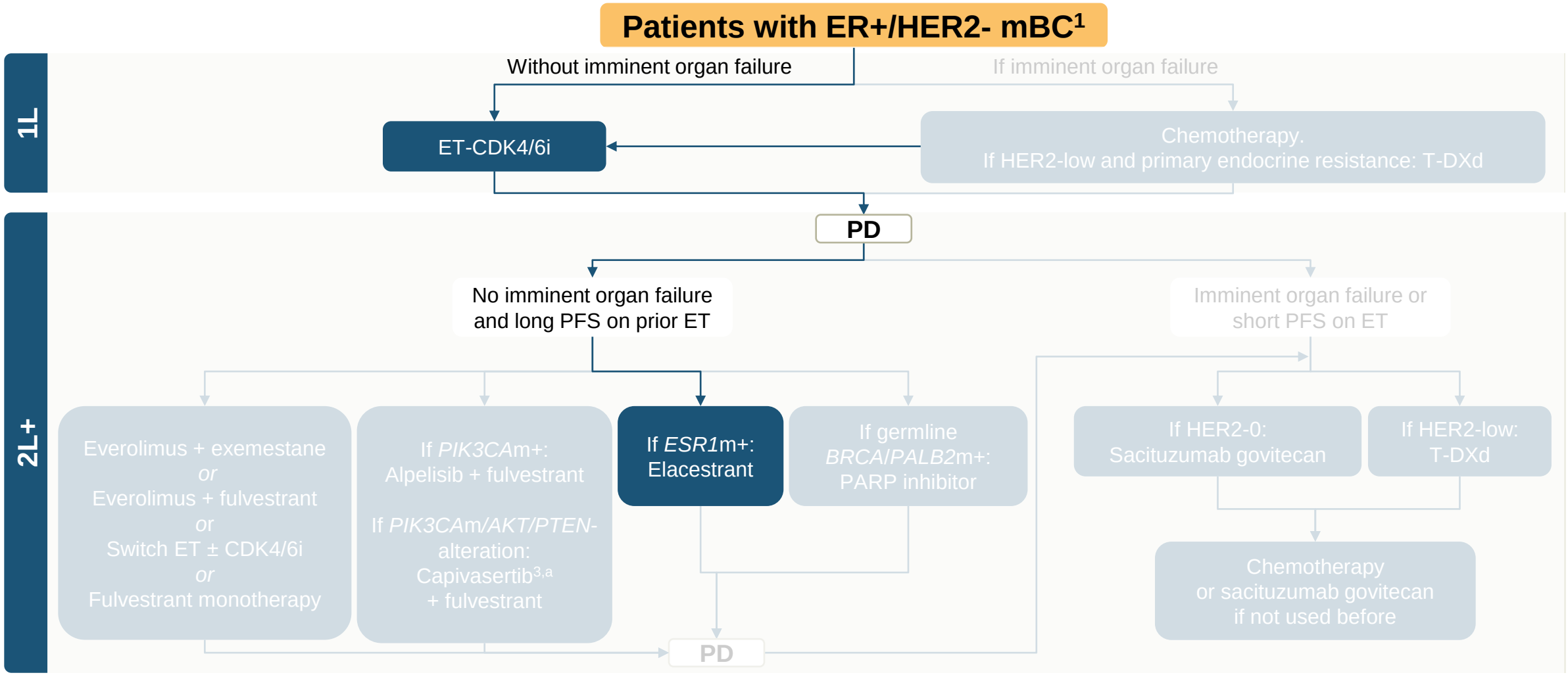
TEAEs in ≥10% of patients, %	Imlunestrant (n=327)		SOC ET (n=324)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Patients with ≥1 TEAE	83	17	84	21
Fatigue	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia	10	2	13	3
Constipation	10	0	6	<1
Patients with ≥1 SAE, %		10	12	
Dose reductions due to AE, %		2	0	
Discontinuations due to AE, %		4	1	
Deaths due to AE on study, %		2	1	
Injection site reaction. TEAE, n/N (%)		NA	27/292 (9%)	
Injection site reaction. PRO-CTCAE, n/N (%)		NA	201/278 (72%)	

TEAEs in ≥20% of patients, %	Imlunestrant + abemaciclib (n=208)	
	All grades	Grade ≥ 3
Patients with ≥1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia	48	20
Anemia	44	8
Fatigue	39	5
Vomiting	31	1
Leukopenia	26	4
Hypercreatinemia	22	1
Abdominal pain	20	2
Decreased appetite	20	1
Patients with ≥1 SAE, %	17	
Dose reductions due to AE, %	39	
Discontinuations due to AE, %	6	
Deaths due to AE on study, %	1	

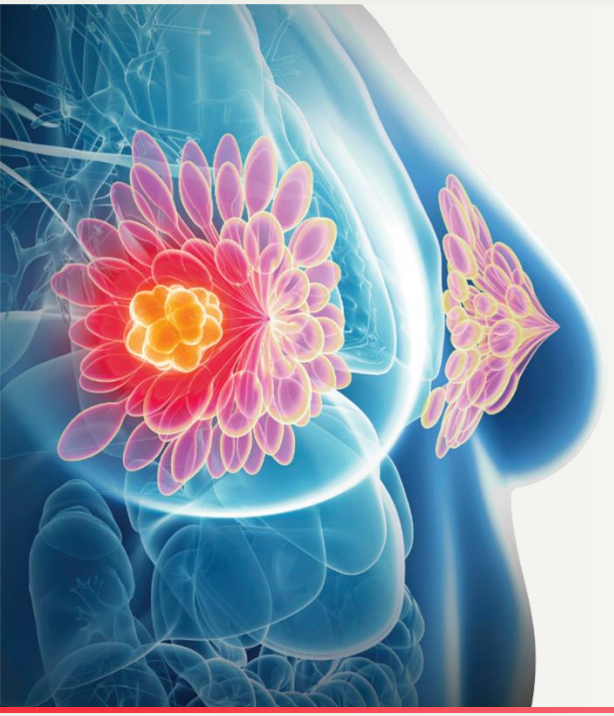
AE, adverse event; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Jhaveri KL, et al. *N Engl J Med.* 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print

Second-line treatment choices for patients with ER+/HER2- mBC are driven by biomarker status[1,2]



[a]Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.



Emerging Biomarkers in Metastatic BC

Frédérique Penault-Llorca

University of Clermont-Ferrand, France

MENARINI group

Stemline® A Menarini Group Company

Breast cancer is a dynamic disease where mutations may emerge over the course of first-line mBC treatment

***ESR1* mutations:**

… are acquired

Breast cancer is a dynamic disease: new mutations develop over the course of treatment[1,2]

… are subclonal

Molecular profile can vary between and within tumor sites, with a heterogeneous distribution in tissue[2,3]

… drive treatment decisions

Biomarker profile influences choice of therapy in 2L+[1]

2L, second line; *ESR1*, estrogen receptor 1; mBC, metastatic breast cancer.

1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Hartkopf A, et al. *Breast Care (Basel).* 2020;15:347-354. 3. Bennett C, et al. *Cancers* (Basel). 2022;14:3046.

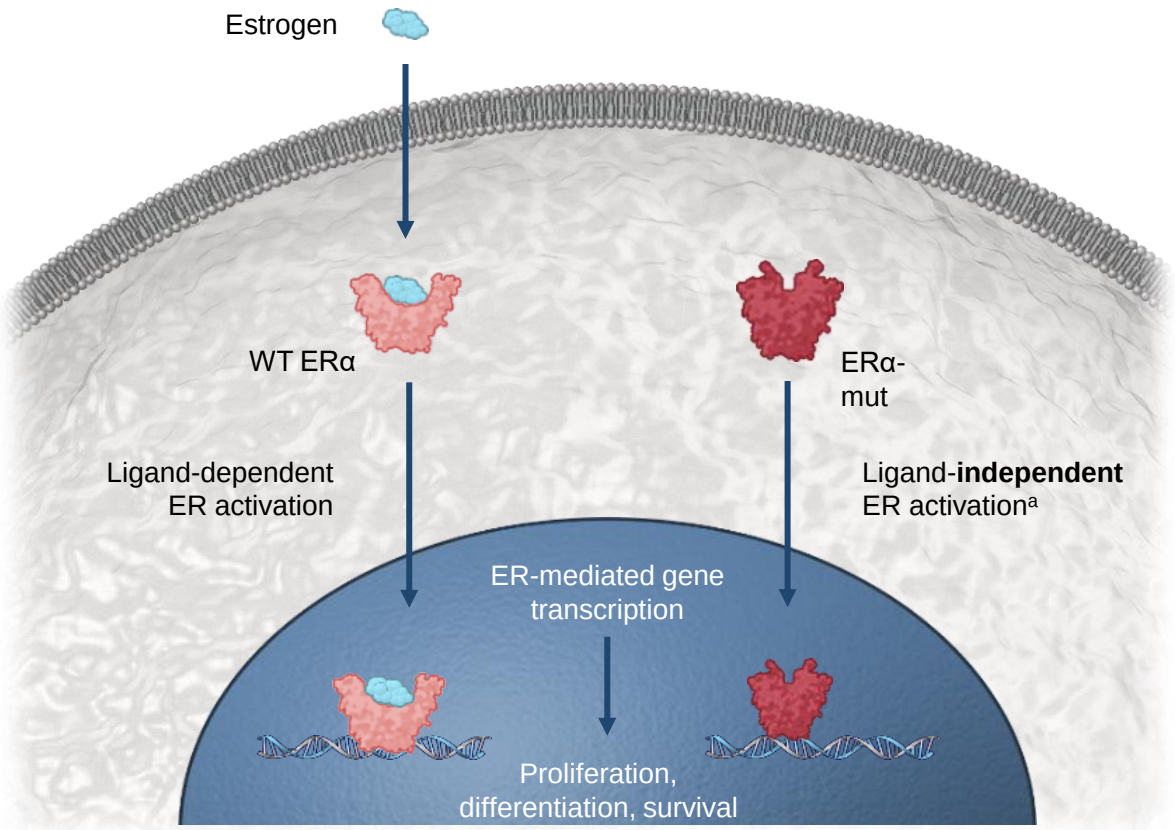
Endocrine resistance has a significant impact on prognosis[1]

Clinical definition	**Primary endocrine resistance** PD within first 6 months of 1L ET-based therapy for mBC, while on ET (regardless of CDK4/6i use)[2]	**Secondary endocrine resistance** PD after ≥6 months of 1L ET for mBC[2] *or* PD after any duration of 2L+ ET-based therapy for mBC[2]
Molecular definition	**Intrinsic** Alterations of the *PI3K/AKT/mTOR*, *RAS-MAPK, FGFR1* pathways, *BRCA1/2* mutations, *RB1* loss, *TP53* activation, etc.[2–4]	**Acquired** Mechanisms of resistance, such as *ESR1* mutations, occurring after prior endocrine therapy in mBC[3,5]

1L, first line; 2L+ second line and above; mBC, Metastatic breast cancer; ET, endocrine therapy; PD, progressive disease.

1. Cardoso F, et al. *The Breast*. 2024; Online ahead of print; 2. Rani A, et al. *Front Endocrinol (Lausanne).* 2019;10:245; 3. Xu P, et al. *Acta Pharmacol Sin.* 2021;42:171–178; 4.Karlsson E, et al. SABCS. 2023.PO5-13-02; 5. Brett JO, et al. *Breast Cancer Res.*. 2021;23:85.

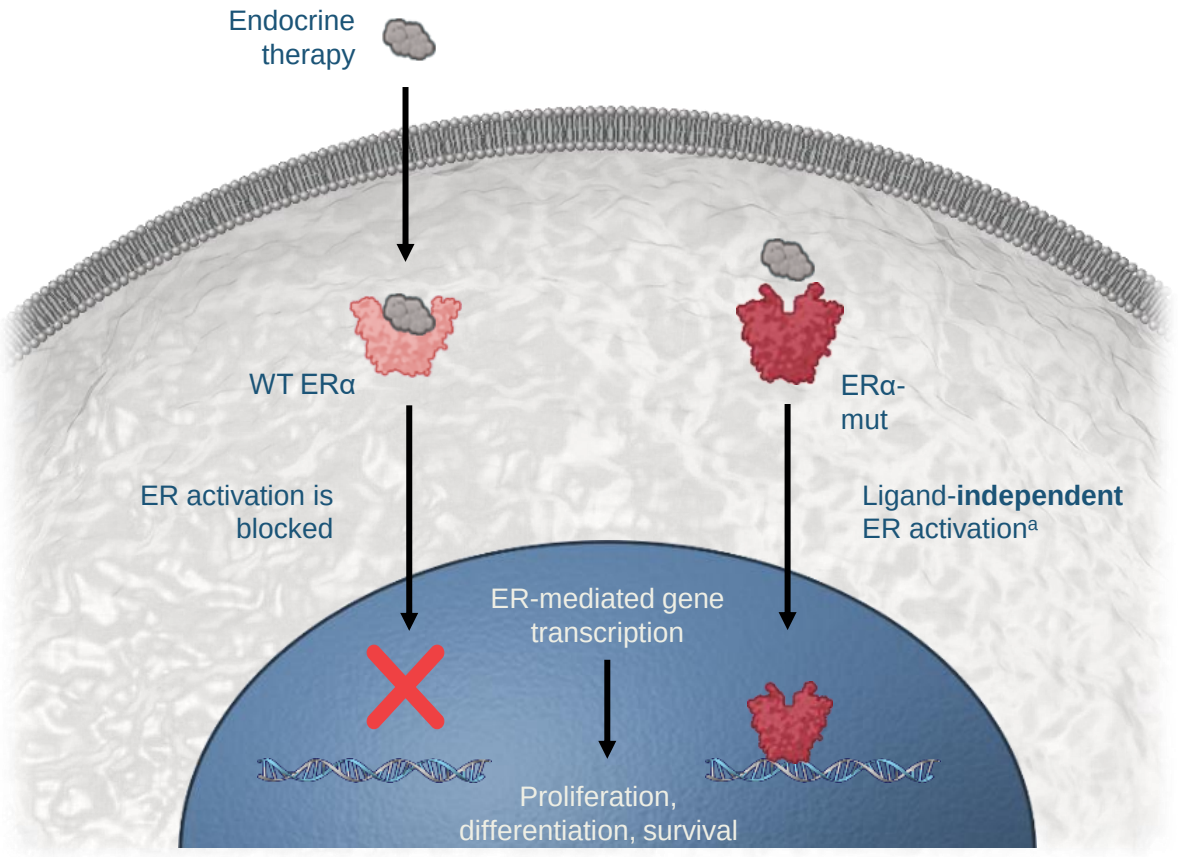
ESR1 mutations lead to ligand independent estrogen receptor activation and constitutive ER signaling, driving tumor growth[1]



- *ESR1* mutations result in constitutive ER signaling and altered ERα function, leading to increased proliferation, differentiation and survival[1–3]
- *ESR1* mutations have been associated with endocrine resistance, visceral metastases and poorer outcomes[1–5]
- *ESR1* mutations predominantly occur after ET in the metastatic setting, leading to resistance to AIs or fulvestrant[1]

[a] Without the need for estrogen binding.
AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; LBD, ligand-binding domain; mut, mutant; NGS, next-generation sequencing; NR, nuclear receptor C-terminal domain; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; WT, wild-type.
Figure adapted from: 1. Bardia A, et al. *N Engl J Med.* 2018;379:1946–53; 2. Williams MM, et al. *Cancer Res*. 2021 81:732–746; 3. Jeselsohn R, et al. *Nat Rev Clin Oncol*. 2015;12:573–583; 4. Brett JO, et al. *Breast Cancer Res*. 2021;23:85; 5. Jeselsohn R, et al. *Cancer Cell*. 2018;33:173–186.

ESR1 mutations are key drivers of resistance to established endocrine therapies



- ETs exert their anti-tumor activity by binding to the ligand-binding pocket of the ER and inhibiting the activation of downstream targets[1,2]
- By altering the ligand-binding domain, *ESR1* mutations can also cause endocrine resistance to ETs[1,2]

[a] Without the need for estrogen binding.
AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; LBD, ligand-binding domain; mut, mutant; NGS, next-generation sequencing; NR, nuclear receptor C-terminal domain; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; WT, wild-type.
Figure adapted from: 1. Bardia A, et al. *N Engl J Med.* 2018;379:1946–53; 2. Brett JO, et al. *Breast Cancer Res.* 2021;23:85.

Longer exposure to ET in mBC increases the chance of developing *ESR1*-mut during treatment, emerging in up to 40% of patients[1–10]

Early breast cancer[1–3,5,7] — **Advanced / metastatic breast cancer[2–9]**

Adjuvant Tx

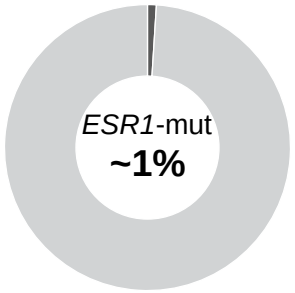
First progression during / after adjuvant therapy

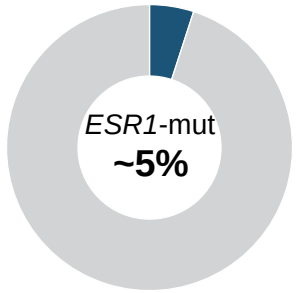
1L mBC Tx AI + CDK4/6i

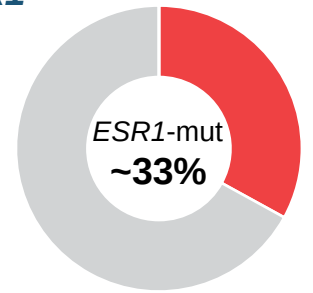
Progression

Tissue biopsy to confirm breast cancer and testing for **intrinsic mutations**
- ***PIK3CA/AKT/PTEN***
- ***BRCA1/2, PALB2***

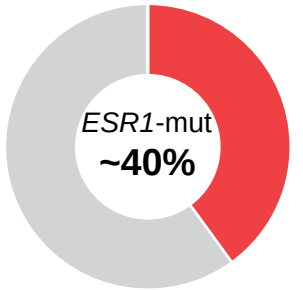
Liquid biopsy
Testing for **acquired mutations**
- ***ESR1***







2L

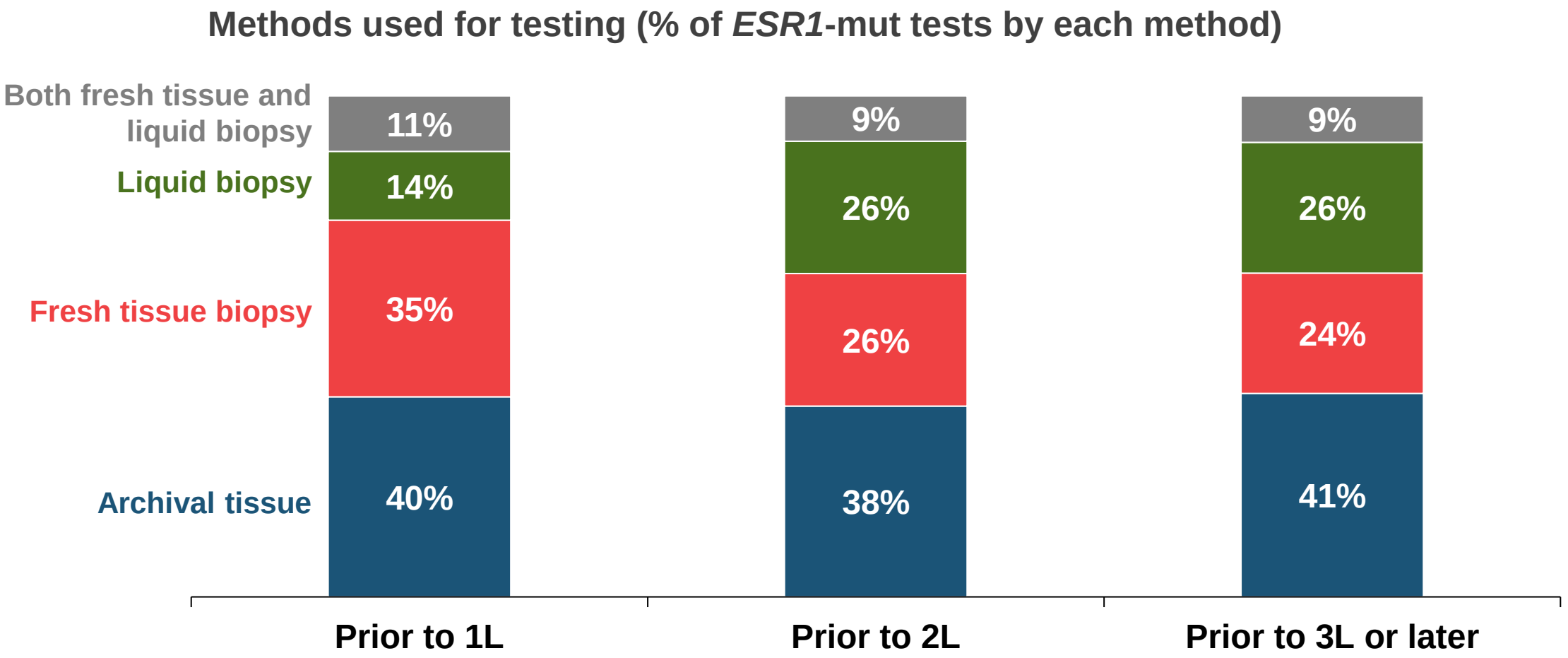


3L

As *ESR1* mutations occur almost exclusively after ET in the mBC setting,[5] testing for *ESR1*-mut should occur at each progression if not detected previously[10–12]

1L, first line; 2L, second line; 3L, third line; *ESR1*, estrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer; mut, mutation; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Modified from: 1. Jeselsohn R, et al. *Clin Cancer Res*. 2014;20:1757-1767; 2. Allouchery V, et al. *Breast Cancer Res*. 2018;20:40; 3. Schiavon G, et al. *Sci Transl Med*. 2015;7:313ra182; 4. Brett JO, et al. *Breast Cancer Res*. 2021;23:85; 5. Toy W, et al. *Nat Genet*. 2013;45:1439-1445; 6. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256; 7. Jhaveri et al, *Annals of Oncology.* 2023;34(suppl_2):S334-S390; 8. Lin, et al, *Annals of Oncology.* 2023;34(suppl_2):S334-S390; 9. Bhave, et al, SmBCS 2023.Abstract PO2-1605; 10. Lee N, et al *Int J Mol Sci*. 2020;21:8807; 11. Gennari A, et al. *Ann Oncol*. 2021;32:1475-1495; 12. Burstein HJ, et al *J Clin Oncol*. 2023;41:3423-3425.

ESR1 mutation testing in the US

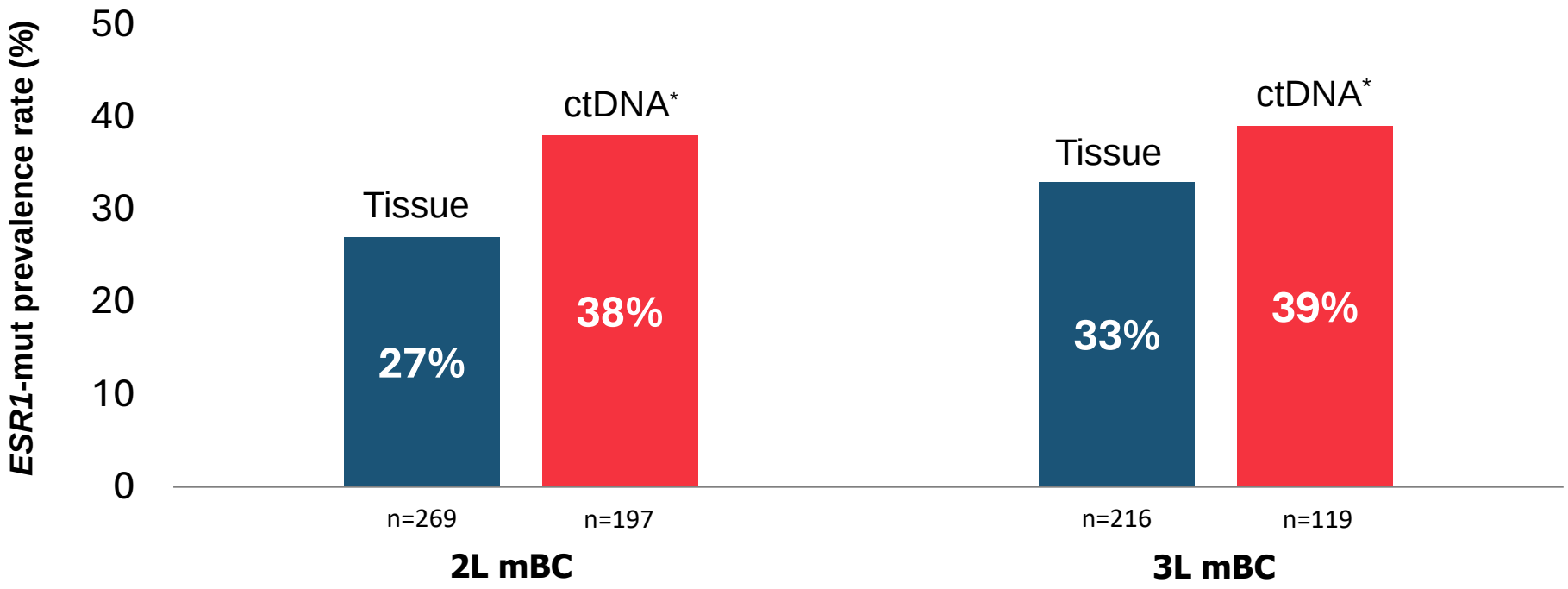


BASE: Total respondents (n=112 HCPs) May 2024.
ESR1, estrogen receptor 1; HCP, healthcare professional; L, line.
IPSOS - Menarini Stemline internal data. IPSOS research is sponsored by Menarini Stemline.

ESR1 mutations are subclonal and heterogenous within the tumor

Not all *ESR1* mutations will be detected in a tissue biopsy; therefore, blood-based ctDNA is considered the preferred testing methodology due to greater sensitivity.[1,2] If *ESR1* mutations are not found when testing on tissue biopsy, ctDNA in liquid biopsy is recommended.[2]

ESR1-mut prevalence rate by line in tissue and liquid biopsy[3]



***ctDNA (TF≥1%) showed a markedly higher prevalence of any of the genomic alterations assessed[3]**

2L, second line; 3L, third line; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1; mBC, metastatic breast cancer; mut, mutation; TF,tumor fraction.

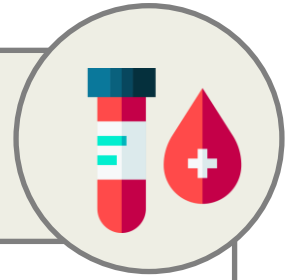
1. Dustin D, et al. *Cancer*. 2019.1;125(21):3714-3728. 2. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423-3425. 3. Adapted from: Bhave MA, et al. *Breast Cancer Res Treat.* 2024;207:599-609.

Liquid biopsy is less invasive and more sensitive in identifying *ESR1* mutations

Tissue biopsy

- Invasive and associated with unnecessary risks[1,2]
- Impractical to repeat regularly[1–3]
- Lower sensitivity for *ESR1*-mut[1,3]

Liquid biopsy



- ✓ Minimally invasive[1–3]
- ✓ Can be repeated regularly at any time following 1L therapy[1–3]
- ✓ Higher sensitivity for *ESR1*-mut[1,3]

1L, first line; AE, adverse event; ASCO, American Society of Clinical Oncology; ctDNA, circulating tumor DNA; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

1. Lone SN et al. *Mol Cancer.* 2022;21:79; 2. Rodríguez J, et al. *Onco Ther.* 2021;9:89–110; 3. Pascual J et al. *Ann Oncol*. 2022;33:750–768.

ESMO, NCCN and ASCO recommend testing for *ESR1* mutations at each progression, preferably in ctDNA, if not detected previously[1-5]

ESMO[1]

Blood ctDNA or Tissue[1]

- NGS plasma or tissue biopsy

NCCN[3,4]

Blood ctDNA *or* Tissue[3,4]

- NCCN recommends evaluating *ESR1* mutation status using NGS or PCR blood or tissue biopsy[3]
- **NCCN does not recommend testing with primary archived tissue given the acquired nature of *ESR1* mutations during mBC treatment[4]**

ASCO[5]

Blood ctDNA (preferred) or Tissue[5]

- **Testing with a certified assay should be performed at each progression**, on blood or tissue
- **Blood-based ctDNA is preferred** owing to greater sensitivity
- ***ESR1* mutations** develop in response to selection pressure during treatment and are **typically undetectable in the primary tumor**
- Patients whose tumor or ctDNA tests remain ***ESR1* wild-type may warrant retesting at subsequent progression(s)** to determine if an *ESR1* mutation has arisen

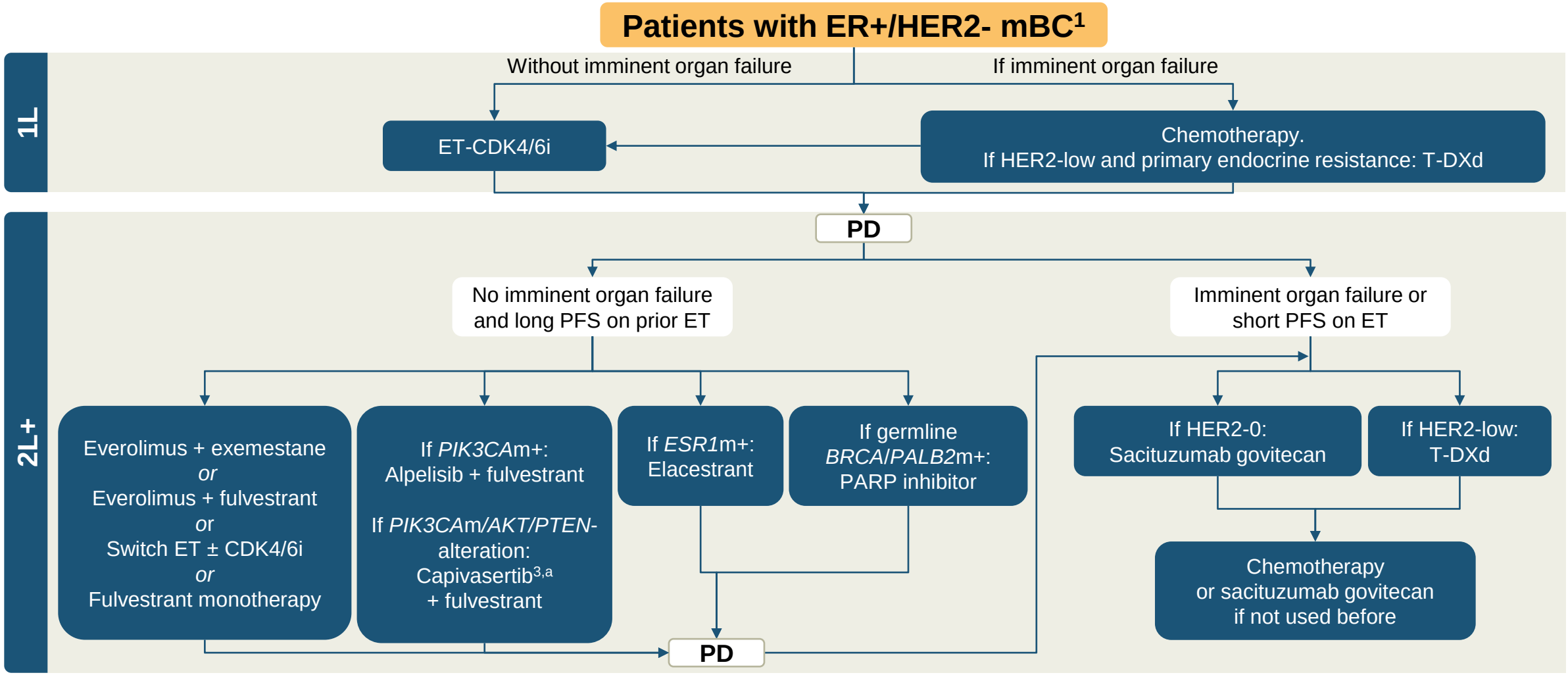
ASCO, American Society of Clinical Oncology; ctDNA, circular tumor DNA; ESMO, European Society for Medical Oncology; *ESR1*, estrogen receptor 1; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction.

1. Mosele MF, et al. *Ann Oncol*. 2024;35:588-606; 2. Pascual J, et al. *Ann Oncol*. 2022;33:750-768; 3. National Comprehensive Cancer Network. Breast Cancer (Version 4.2024); 4. Gradishar WJ, et al. J *Natl Compr Canc Netw*. 2023;21:594-608; 5. Burstein HJ, et al. *J Clin Oncol*. 2023;41:3423-3425.

Key Takeaways

Shaheenah Dawood
Mediclinic City Hospital Dubai

At first-line progression, patients should be tested for genomic alterations to define the optimal treatment[1–3]



[a] Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; T-DXd, trastuzumab deruxtecan. Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024.

Key takeaways 1/2

- ET + CDK4/6 inhibitors is the SOC for 1L treatment in ER+/HER2- mBC[1–3]
- Guidelines recommend exhausting sequential ET-based regimens in the 2L setting (as monotherapy or combinations)[1-4]
- A biomarker-driven treatment algorithm is needed to ensure optimal treatment selection for patients[3-7]
- Elacestrant is indicated for patients with *ESR1*-mut tumors based on its efficacy and safety profiles[3,8]
- Longer duration of prior ET + CDK4/6i is a surrogate for endocrine sensitivity to elacestrant in *ESR1*-mutated tumors[3,9,10]
- Elacestrant real world data shows consistent results in patient exposed to prior ET + CDK4/6i and ESR1-mut tumors[11,12]
- In tumors retaining endocrine-sensitivity and coexisting *PIK3CA* and *ESR1* mutations, elacestrant monotherapy can be a good option before PI3K/AKT inhibitors, as data suggest the ER pathway may drive disease progression[10]

mBC, Metastatic breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy;HER2, human epidermal growth factor receptor 2; mut, mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care.

1. Burstein HJ, et al *J Clin Oncol*. 2023;41:3423–3425; 2. Gennari A, et al. *Ann Oncol*. 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 3. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 4. Burstein HJ, et al. *J Clin Oncol*. 2021;39:3959–3977; 5.Turner S, et al. SABCS 2021. Abstract PD15-01; 6. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 7. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070. 8. Orserdu (elacestrant) SmPC 2023. 9. Bardia A, et al. SABCS 2022. Abstract GS3–01; 10. Bardia, et al. *Clin Cancer Res* 2024; Online ahead of print.; 11. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 12. Swallow et al. SABCS 2024. Abstract P3 10-08

Key takeaways 2/2

- Intrinsic alterations like *BRCA* and *PIK3CA* mutations can be detected at the moment of disease diagnosis in tissue samples[1,2]
- *ESR1* mutations emerge over time in up to 40% of patients after initial endocrine therapy in mBC[3-7]
- Testing for *ESR1* mutations should occur at each progression on ET if not detected previously, due to increasing chances of finding it[8-11]
- *ESR1* mutations are subclonal; therefore, not always detected with tissue biopsy. Blood-based ctDNA is considered the preferred testing methodology for *ESR1* mutations[11,12]
- Archival tissue from primary tumor should NOT be used to identify *ESR1* mutations, as *ESR1* mutations develop mainly during 1L metastatic treatment[13]

mBC, Metastatic breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy;HER2, human epidermal growth factor receptor 2; mut, mutation; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care.

1. Mosele MF, et al. *Ann Oncol*. 2024;35:588-606. 2. National Comprehensive Cancer Network. Breast Cancer (Version 4.2024). 3. Brett JO, et al. *Breast Cancer Res*. 2021;23:85; 4. Bidard et al. *Lancet Oncol*. 2022;23:1367–1377; 5. Santiago Novello RG, et al. *ESMO Open*. 2023;8(suppl 4):104409. Abstract 220P; 6. Lin et al. *Annals of Oncology*. 2023;34 (suppl_2): S334–S390; 7. Bhave MA, et al. *Breast Cancer Res Treat*. Published online: 14 June 2024; 8. Jeselsohn R, et al. *Clin Cancer Res*. 2014;20:1757–1767; 9. Jeselsohn R, et al. *Cancer Cell*. 2018;33:173–186; 10. Allouchery V et al. *Breast Cancer Res*. 2018;20:40. 11. Burstein HJ, et al *J Clin Oncol*. 2023;41:3423–3425; 12. Turner NC, et al. Lancet Oncol. 2020;21:1296–1308; 13. Gradishar WJ, et al. NCCN Guidelines® Insights: *Breast Cancer*, Version 4.2023. *J Natl Compr Canc Netw*. 2023;21:594–608.