Sequencing Endocrine Therapy and Targeted Agents for the Treatment of Metastatic HR+/HER2- Breast Cancer

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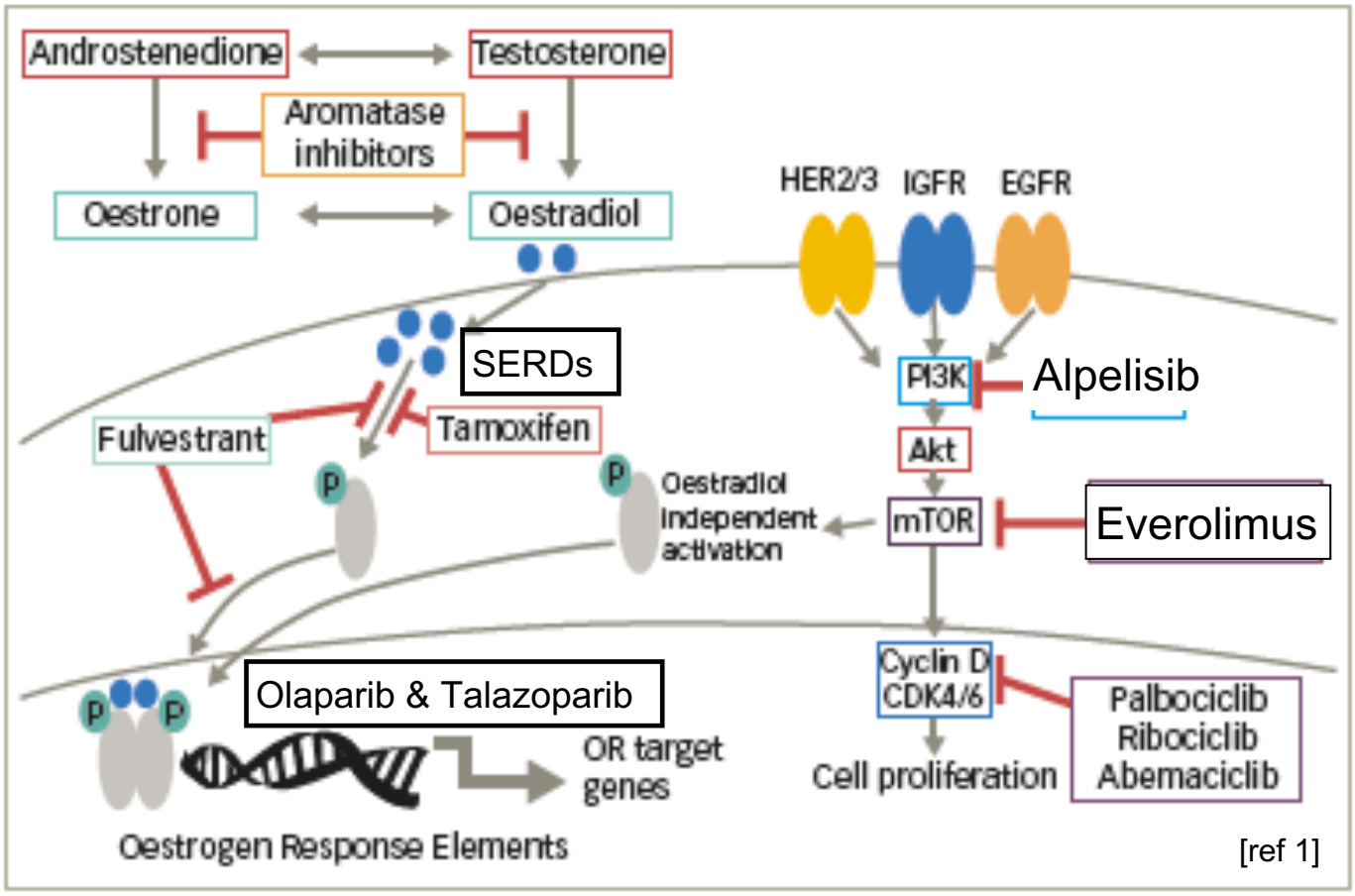
Targets in hormone receptor positive (HR+)/HER2- metastatic breast cancer (MBC)



- Activation of many growth factor receptor and estrogen receptor signaling pathways can promote growth of HR+/HER2- MBC.
- However, steps in these pathways can be inhibited by endocrine therapies and targeted agents.

[1]Image credit and reference: Adapted from Schmid, touchOncology, 2017.

Endocrine therapy with CDK 4/6 inhibitor as 1st line therapy for HR+/HER2- MBC

Study	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7
Design	Phase III First-line (Post-menopausal)	Phase III First-line (Post-menopausal)	Phase III First-line (Post-menopausal)	Phase III First-line (Premenopausal)
Therapies	Letrozole + Palbociclib vs. Letrozole	Letrozole + Ribociclib vs. Letrozole	Non steroidal AI + Abemaciclib vs. non steroidal AI	Endocrine therapy/LHRH agonist + Ribociclib vs. endocrine therapy/LHRH agonist
Median PFS	24.8 vs. 14.5 mo, HR 0.58	25.3 vs 16.0 mo, HR 0.57	28.1 vs 14.7 mo, HR 0.54	23.8 vs. 13.0 mo, HR 0.55
Median OS	53.9 vs 51.2 mo, HR 0.96 (NS)	63.9 vs 51.4 mo, HR 0.76 *	67.1 vs. 54.4 mo, HR 0.75 (interim analysis)	58.7 vs. 48 mo, HR 0.76 *

mo: months, HR: hazard ratio, *statistically significant. AI: aromatase inhibitor. NS: non-significant.

[1]Finn, NEJM, 2016. [2]Finn, JCO, 2022. [3]Hortobagyi, NEJM, 2016. [4]Hortobagyi, Ann Onc, 2018. [5]Hortobagyi, Ann Onc, 2021. [6]Goetz, JCO, 2017. [7]Goetz, Ann Onc, 2022. [8]Tripathy, Cancer, 2021.

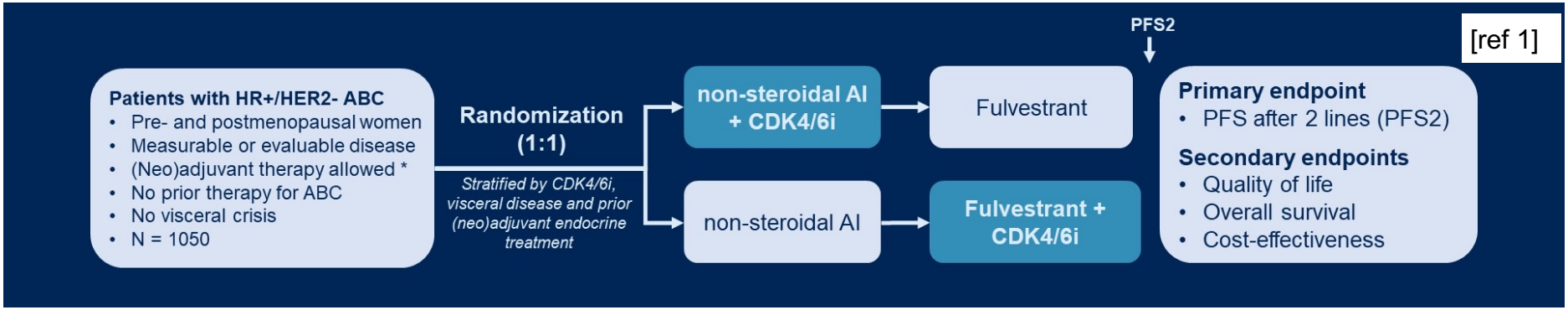
Endocrine therapy with CDK 4/6 inhibitor as 2nd line therapy for HR+/HER2- MBC

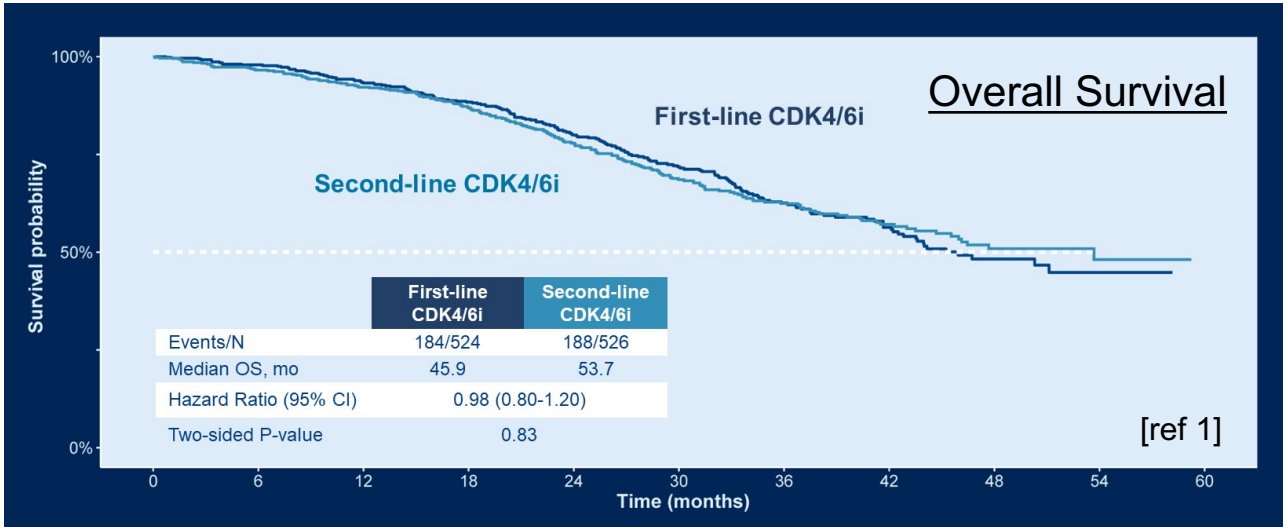
Study	**PALOMA-3**	**MONARCH-2**	**MONALEESA-3**
Design	Phase III Second-line (Pre & Post-menopausal)	Phase III Second-line (Pre- & Post-menopausal)	Phase III First and second-line (Post-menopausal)
Therapies	Fulvestrant + Palbociclib vs. Fulvestrant	Fulvestrant + Abemaciclib vs. Fulvestrant	Fulvestrant + Ribociclib vs. Fulvestrant
Median PFS	9.5 vs. 4.6 mo, HR 0.46	16.4 vs 9.3 mo, HR 0.55	20.5 vs 12.8 mo, HR 0.59
Median OS	34.8 vs. 28 mo, HR 0.81	46.7 vs 37.3 mo, HR 0.75	53.7 vs. 41.5 mo, HR 0.73

mo: months, HR: hazard ratio

[1]Cristofanalli, Lancet Oncology, 2016. [2]Sledge, Jama Oncol, 2020. [3]Slamon, NEJM, 2020. [4]Slamon, JCO, 2018.

Phase III study comparing CDK 4/6 inhibitor in 1st or 2nd line setting: SONIA trial





- PFS in first line setting (PFS1) longer with CDK 4/6 inhibitor (24.7 vs. 16.1 months)[1].
- No difference in PFS2 between arms (first line CDK 4/6 inhibitor 31 vs. second line CDK 4/6 inhibitor 26.8 months)[1].
- No difference in overall survival[1].

[1]Image credit and reference: Sonke, ASCO, 2023.

Potential role for CDK 4/6 inhibitor after CDK 4/6 inhibitor: MAINTAIN trial

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

[ref 1]

Arm 1
Ribociclib + Switch Endocrine Therapy*

1:1

N=120

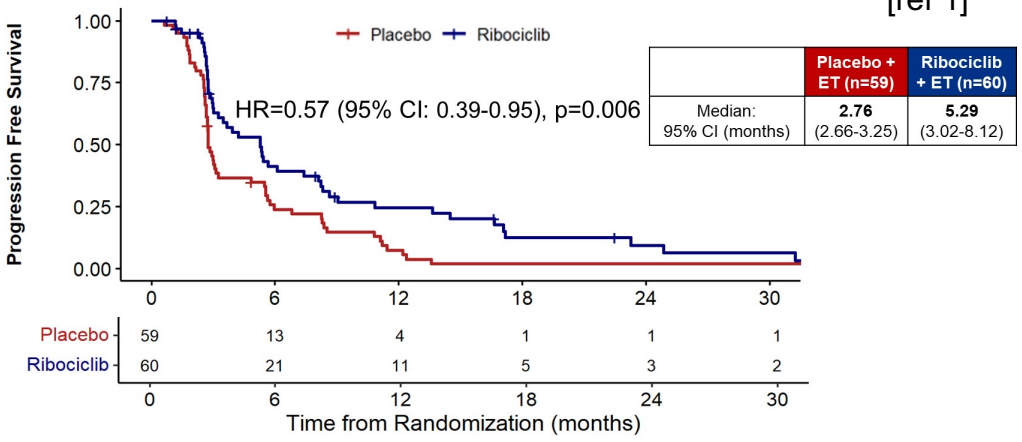
Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

Primary Endpoint: Progression Free Survival (PFS)

[ref 1]



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

- Phase II study noted improved PFS with switching to ribociclib based therapy[1].
- Notably patients had mainly received palbociclib as 1st CDK 4/6 inhibitor[1].

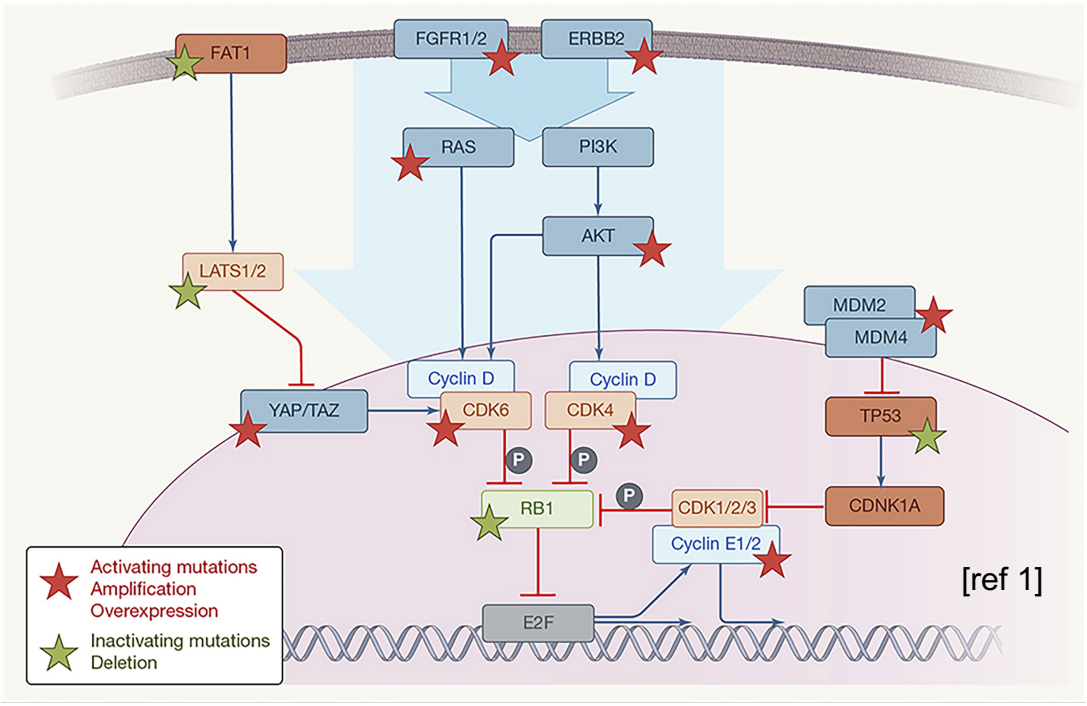
[1]Image credit and reference: Kalinsky, ASCO, 2022.

Additional studies investigating sequential CDK 4/6 inhibitor use

- **PACE study**[1]: randomized phase II study comparing fulvestrant, fulvestrant and palbociclib, and fulvestrant, palbociclib, and avelumab in patients with HR+/HER2- MBC who had prior AI + CDK 4/6 inhibitor.
  - PFS not improved with addition of palbociclib to fulvestrant[1].
    - PFS fulvestrant + palbociclib 4.6 mo vs. fulvestrant 4.8 mo, HR 1.11, p=0.62.
    - PFS fulvestrant + palbociclib + avelumab 8.1 mo.
- **postMONARCH study**[2]: phase III study of abemaciclib + fulvestrant vs. fulvestrant in HR+/HER2- MBC after progression on prior CDK 4/6 inhibitor and endocrine therapy.

[1]Mayer, SABCS, 2022. [2]NCT05169567.

Genotype directed therapy for HR+/HER2- MBC

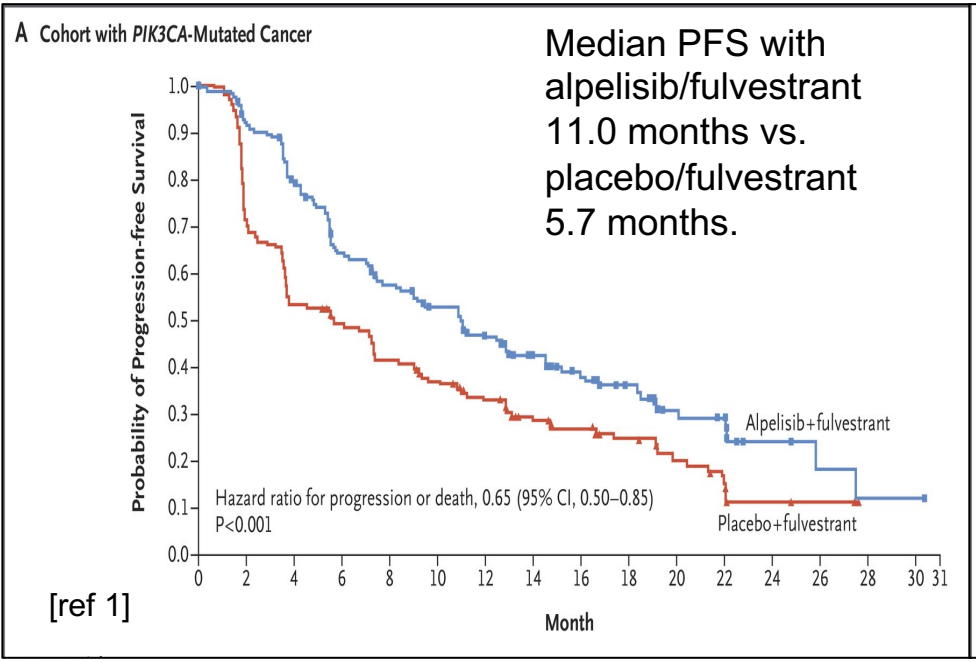


Major drivers of resistance to CDK 4/6 inhibitors[1].

- HR+/HER2- MBC is a heterogeneous disease entity with varying genomic alterations.
- New mutations may be acquired under the pressure of treatment.
  - *ESR1* mutations may be found in 20-40% of patients who received a prior aromatase inhibitor[2].
  - *PIK3CA/AKT/mTOR* mutations may be found in 40% of HR+/HER2- MBC[3].
- Cell-free DNA and/or tumor tissue genotyping can identify actionable mutations such as *PIK3CA* and *ESR1.*
- Germline genetic testing can identify actionable mutations such as *BRCA1/2.*

[1]Image credit and reference: Alvarez-Fernandez, Cancer Cell, 2020. [2]Brett, Breast Cancer Research, 2021. [3]Fusco, Frontiers Oncology, 2021.

Alpelisib for *PIK3CA* Mutated HR+/HER2- MBC: SOLAR-1 trial



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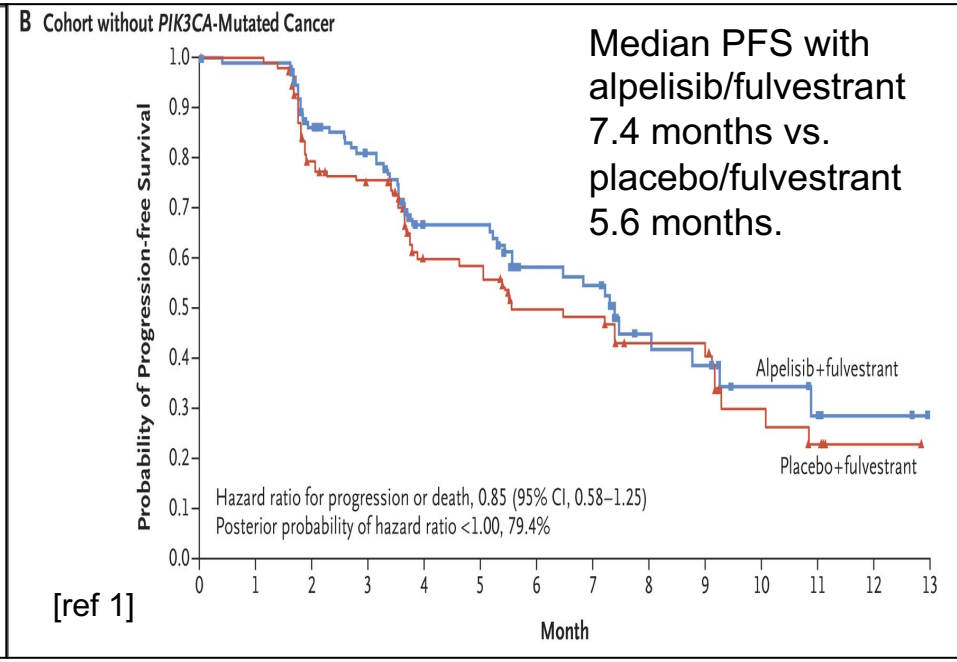
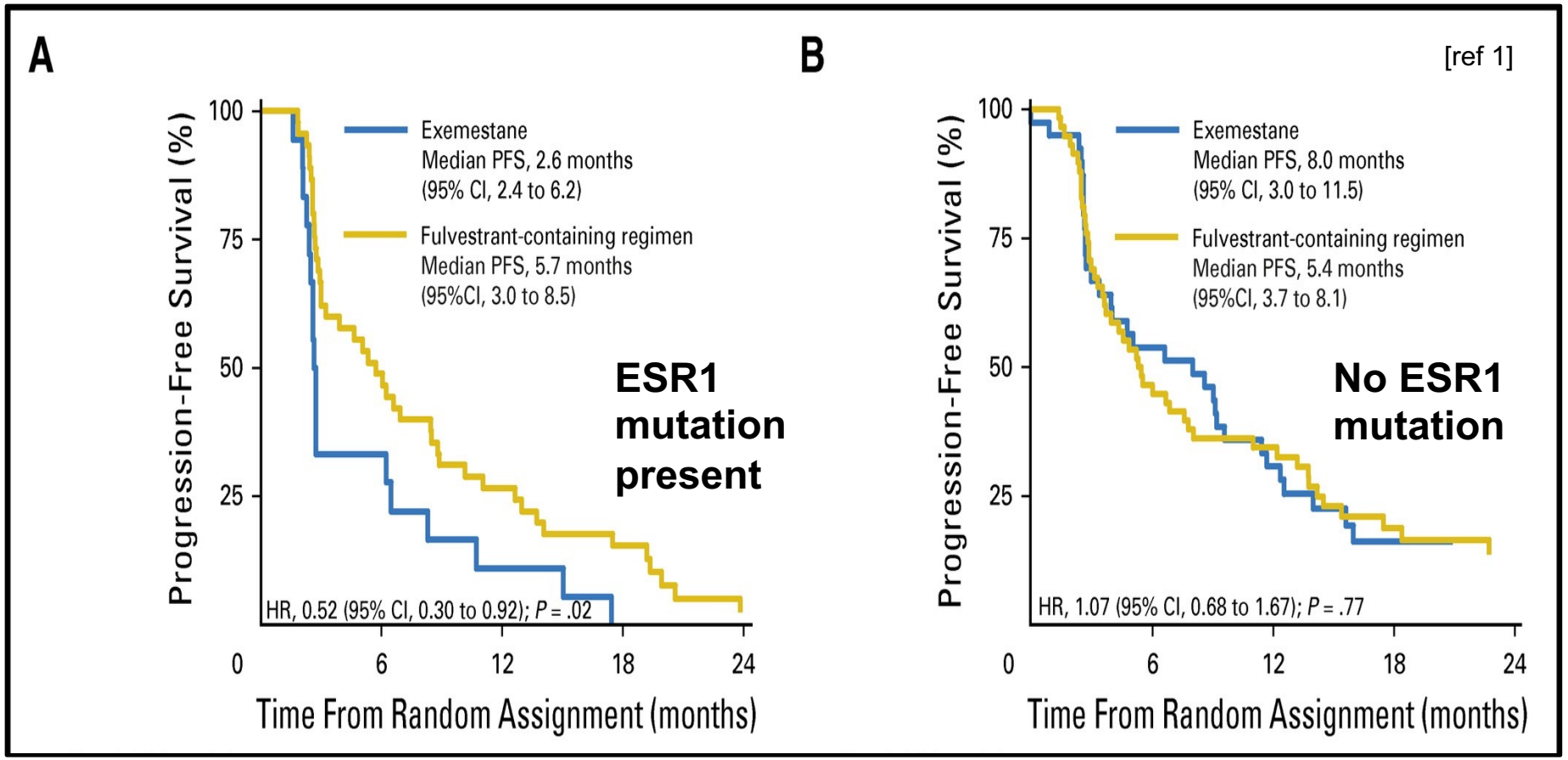


[ref 1]

- Current clinical SOC to evaluate for *PIK3CA* mutations for HR+/HER2- MBC.
- BYLeive study: alpelisib and fulvestrant in *PIK3CA* HR+/HER2- MBC after CDK 4/6 inhibitor with 50% of patients alive without progressive disease at 6 months[2].

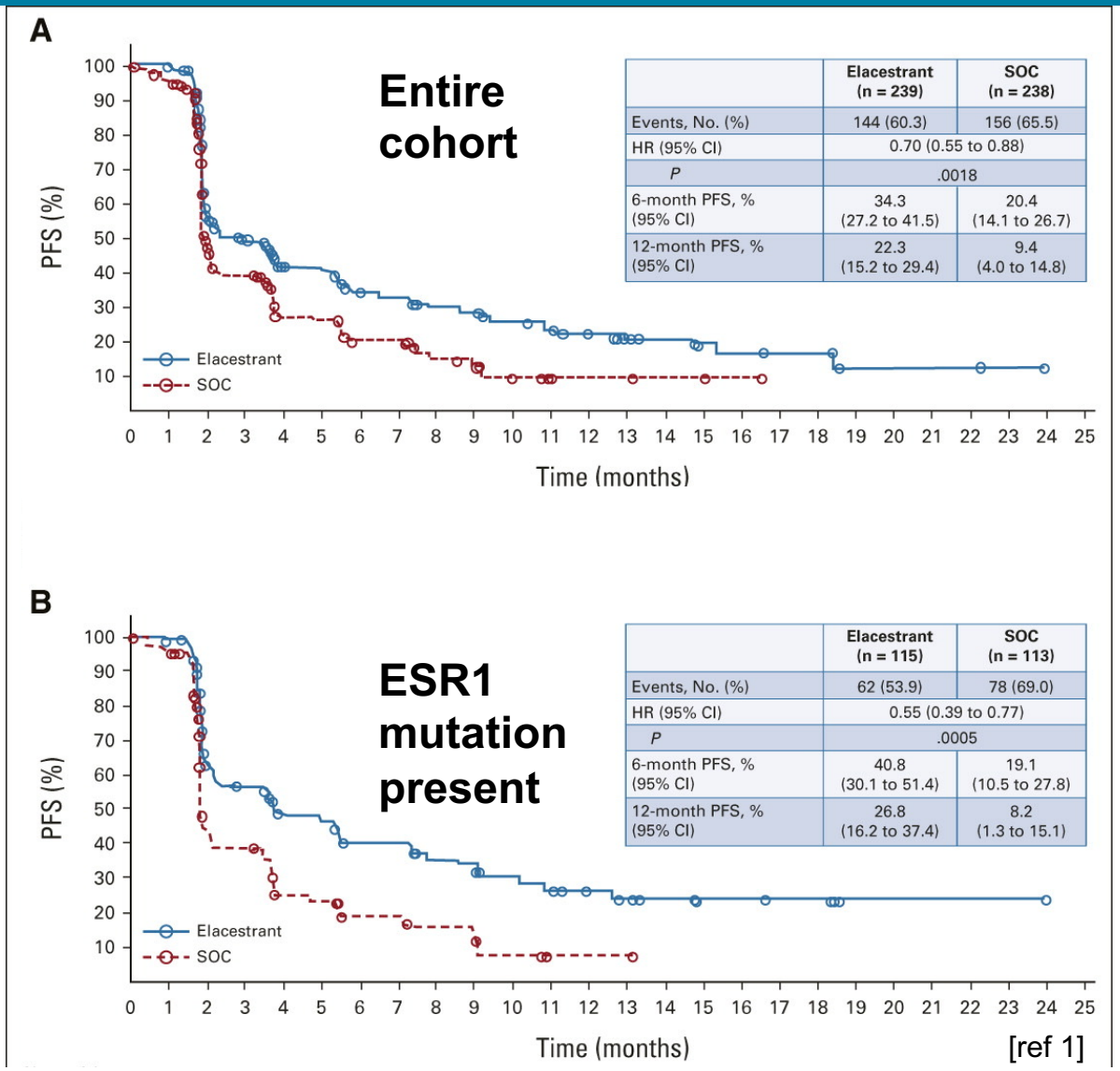
[1]Image credit and reference: Andre, NEJM, 2019. [2]Rugo, Lancet Oncology, 2021.

Fulvestrant for *ESR1* Mutant HR+/HER2- MBC: SoFEA study



[1]Image credit and reference: Fribbens. J Clin Oncol, 2016.

Elacestrant (oral SERD) for *ESR1* Mutant HR+/HER2- MBC: EMERALD study



	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)

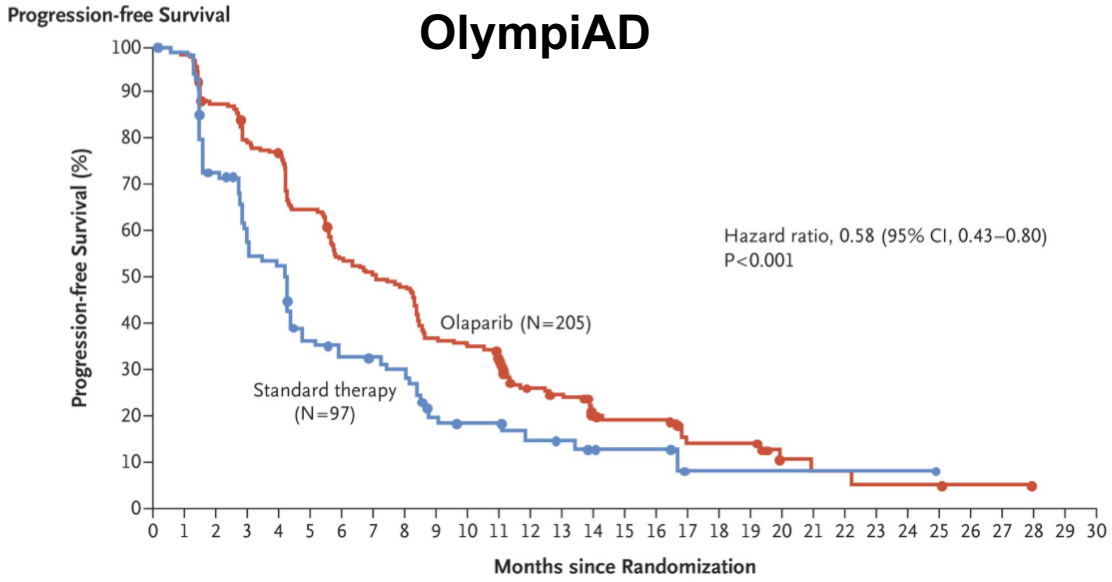
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

[ref 1]

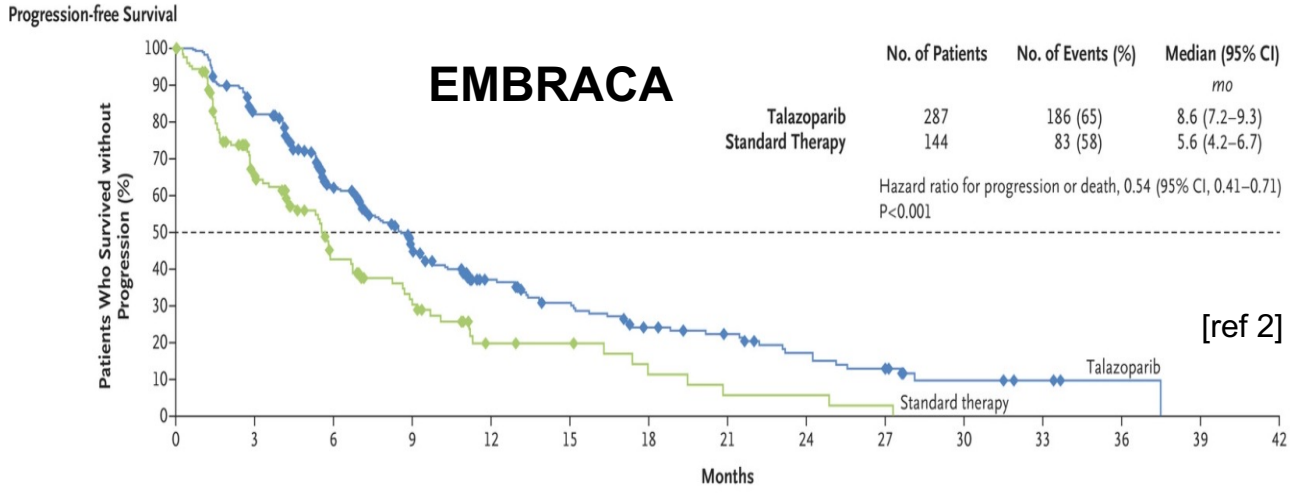
- Phase III study comparing elacestrant vs. standard endocrine therapy[1].
- *ESR1* mutations present in 47.8% of patients[1].
- Improved PFS with elacestrant in *ESR1* mutant MBC[1].
- Elacestrant vs. fulvestrant in *ESR1* mutant MBC PFS: 3.8 vs 1.9 months[1].

[1]Image credit and reference: Bidard, JCO, 2022.

PARP inhibitors for germline *BRCA1/2* mutant HR+/HER2- MBC



[ref 1]



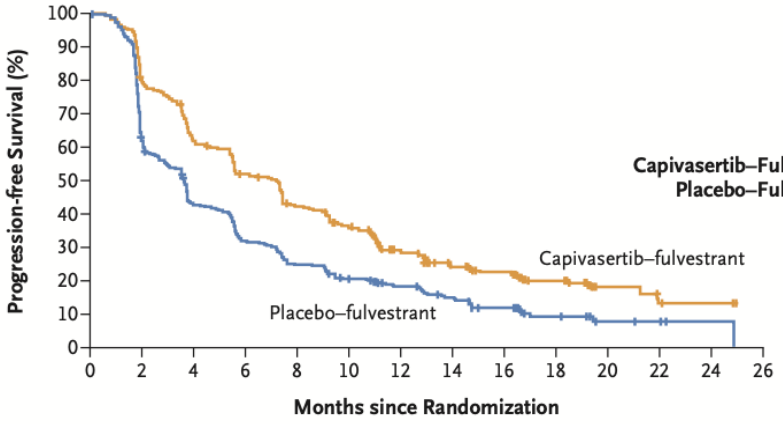
[ref 2]

- **OlympiAD study:** 2:1 randomization to olaparib vs. treatment of physician's choice [TPC] (capecitabine, vinorelbine, eribulin)[1].
- **EMBRACA study:** 2:1 randomization to talazoparib vs. TPC (eribulin, vinorelbine, gemcitabine, capecitabine)[2].
- PARP inhibitors are also being evaluated in somatic *BRCA1/2* mutant metastatic breast cancer[3,4].

[1]Image credit and reference: Robson, NEJM, 2017. [2]Image credit and reference: Litton, NEJM, 2018. [3]Tung, NCT03344965. [4]Vidula, NCT03990896.

Capivasertib for HR+/HER2- advanced breast cancer: CAPItello-291 trial

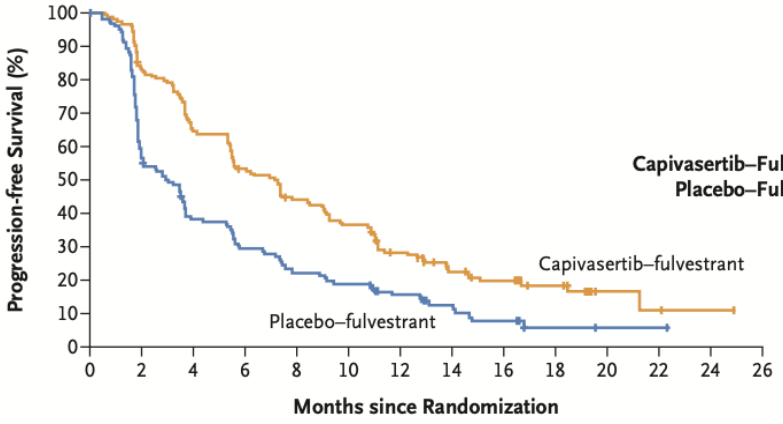
A Overall Population



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Capivasertib–Fulvestrant	355	258	7.2 (5.5–7.4)
Placebo–Fulvestrant	353	293	3.6 (2.8–3.7)

Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51–0.71)
P<0.001

B Patients with AKT Pathway–Altered Tumors



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Capivasertib–Fulvestrant	155	121	7.3 (5.5–9.0)
Placebo–Fulvestrant	134	115	3.1 (2.0–3.7)

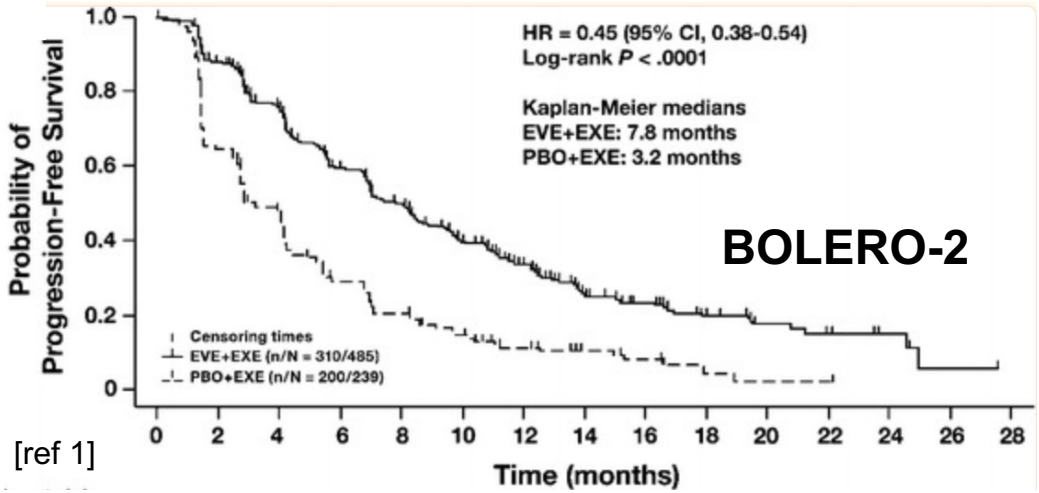
Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65)
P<0.001

[ref 1]

- Capivasertib is an AKT inhibitor[1].
- Phase III study comparing capivasertib and fulvestrant vs. fulvestrant in patients who had received prior AI +/- CDK 4/6 inhibitor[1].
- 40.8% of patients had AKT pathway alterations[1].
- 69.1% had received prior CDK 4/6 inhibitor[1].
- Improved PFS with addition of capivasertib[1].
- Undergoing FDA review.

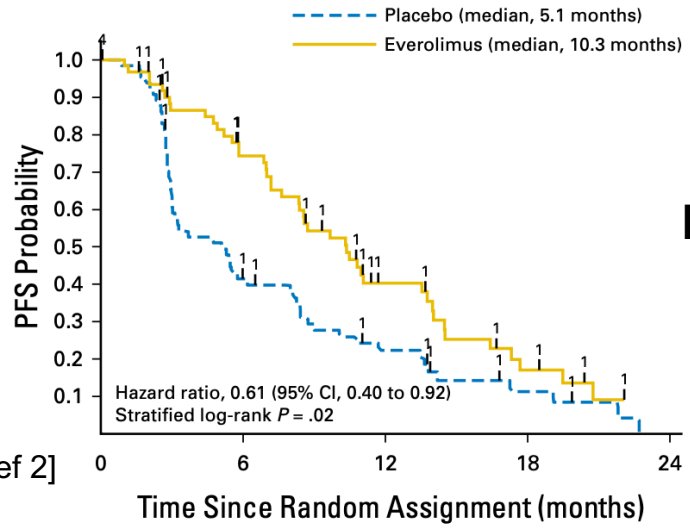
[1]Image credit and reference: Turner, NEJM, 2023.

Everolimus combinations in HR+/HER2- MBC



BOLERO-2

[ref 1]



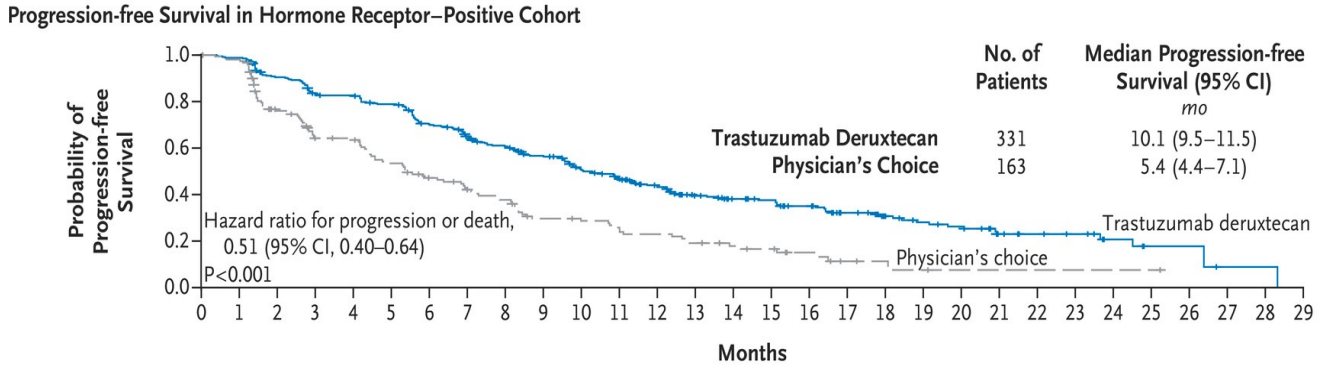
PrE0102

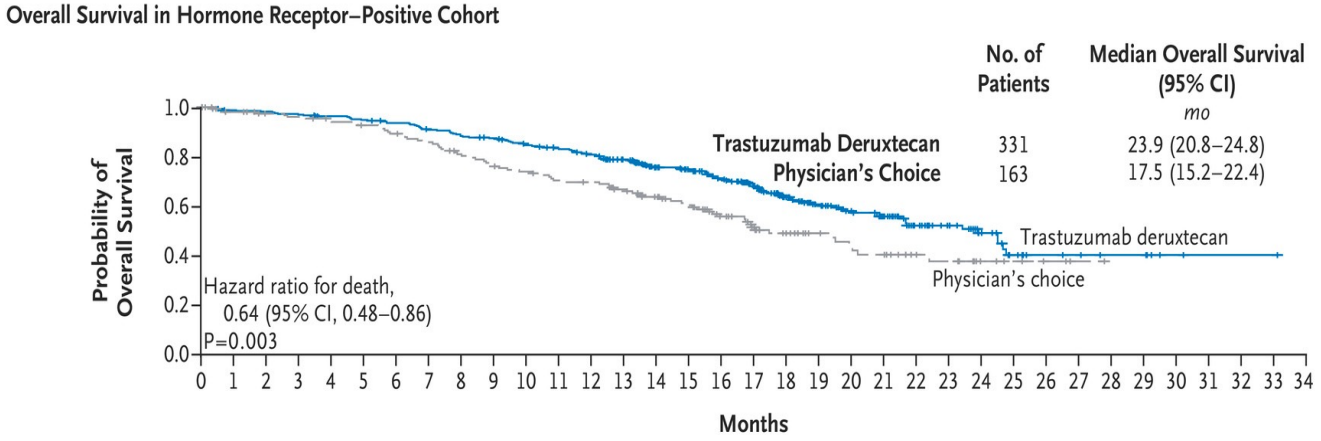
[ref 2]

- Everolimus is an mTOR inhibitor.
- **BOLERO-2** Phase III study compared everolimus and exemestane vs. exemestane in patients who received a prior non-steroidal AI, demonstrating improvement in PFS with addition of everolimus[1].
- **PrE0102** Phase II study compared everolimus and fulvestrant vs. fulvestrant in patients who received prior AI, demonstrating improved PFS with addition of everolimus[2].

[1]Image credit and reference: Yardley, Adv Therapy, 2013. [2]Image credit and reference: Kornblum, JCO, 2018.

Trastuzumab Deruxtecan (T-DXd) for HER2-low advanced breast cancer: DESTINY-Breast04 HR+ cohort





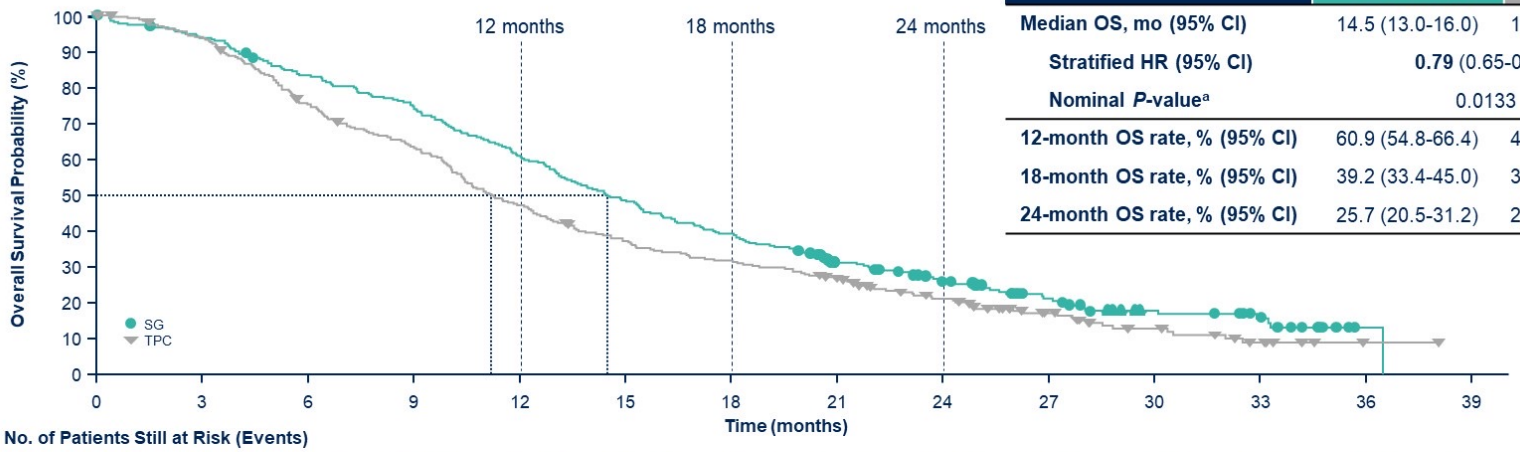
[ref 1]

- Randomized phase III study of T-DXd vs. TPC in HER2- low advanced breast cancer including HR+ after 1-2 prior lines of chemotherapy[1].
- Improvement in PFS and OS were seen across all cohorts with T-DXd vs. TPC, and in HR+ breast cancer[1].
- FDA approved T-DXd for HER2 low, HR+ advanced breast cancer after 1 prior chemotherapy.

[1]Image credit and reference: Modi, NEJM. 2022.

Sacituzumab Govitecan for HR+/HER2- advanced breast cancer: TROPiCS-02 study

Overall Survival



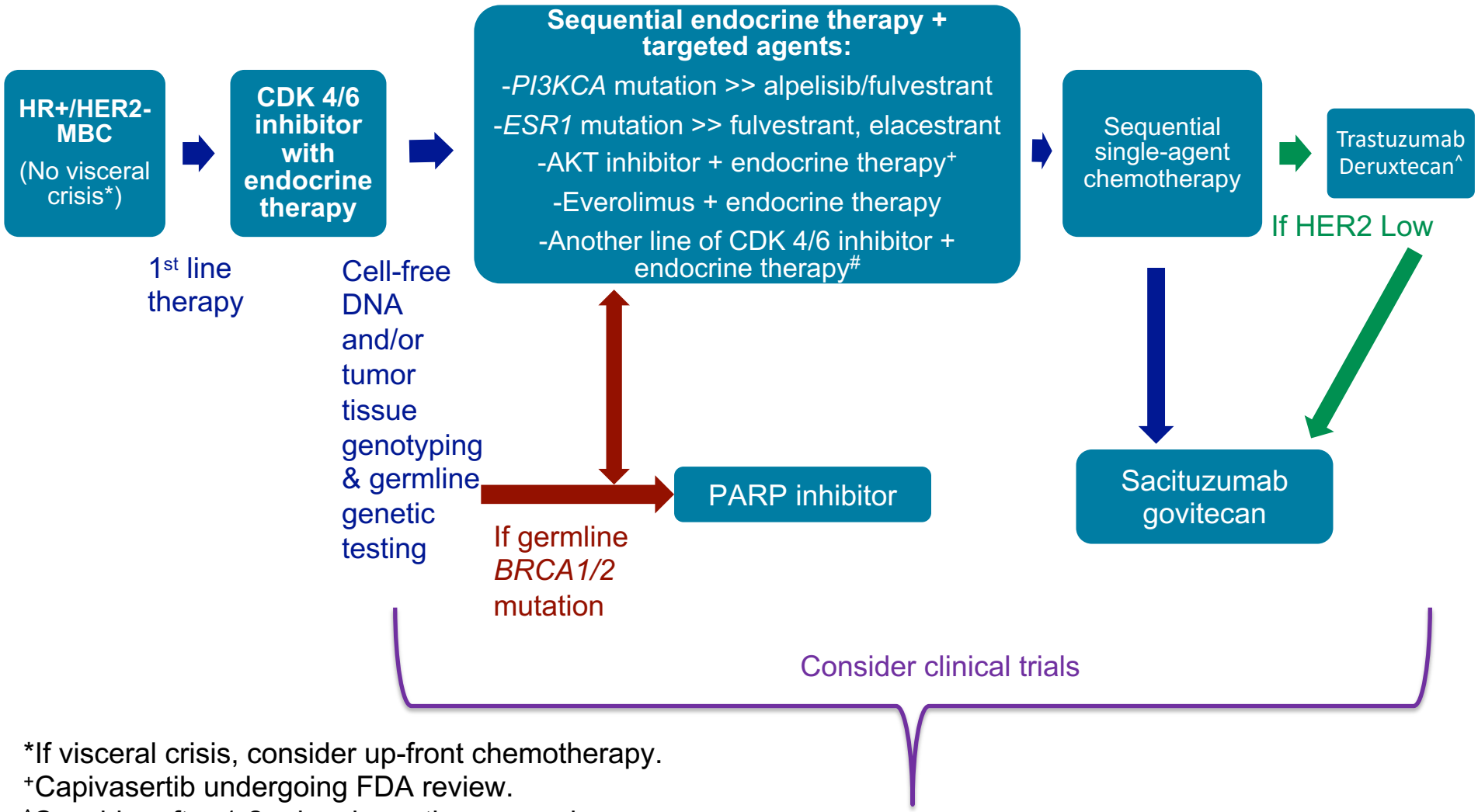
	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate,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

[ref 1]

- Randomized phase III study of sacituzumab govitecan vs. TPC (capecitabine, vinorelbine, gemcitabine, or eribulin) in advanced HR+/HER2- breast cancer after 2-4 prior lines of chemotherapy and at least 1 prior endocrine therapy, taxane, and CDK 4/6 inhibitor[1].
- Significant improvement in PFS (SG: 5.5 months vs. TPC: 4.0 months)[1,2] and OS with sacituzumab govitecan vs. TPC[1].
- Now FDA approved for HR+/HER2- advanced breast cancer.

[1]Image credit and reference: Tolaney, ASCO, 2023. [2]Rugo, JCO, 2022.

Sequencing endocrine and targeted therapies for HR+/HER2- MBC



*If visceral crisis, consider up-front chemotherapy.
+Capivasertib undergoing FDA review.
^Consider after 1-2 prior chemotherapy regimens.
#Phase III post-MONARCH study ongoing.

Thank you!

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