How I Treat HR+/HER2- mBC

Atlanta Breast Cancer Conference

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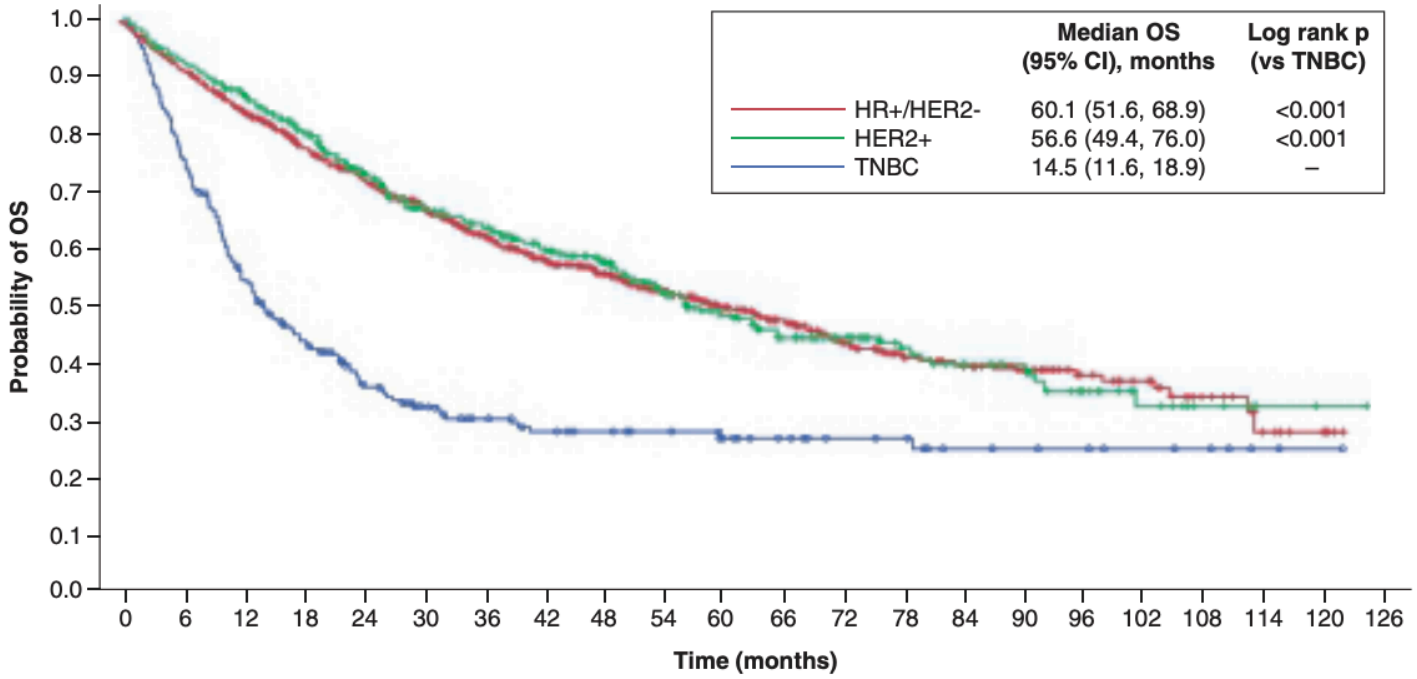
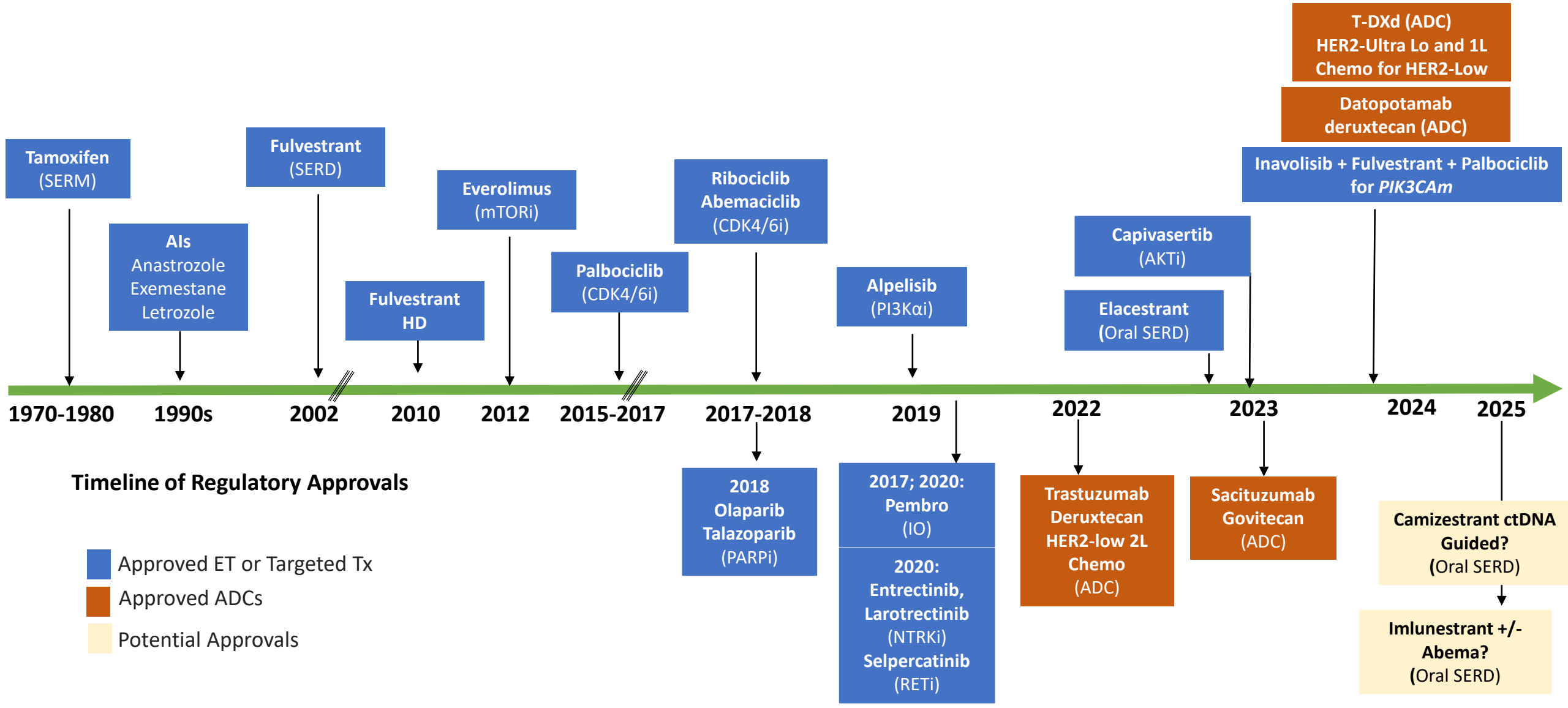


Figure 3. Kaplan–Meier analysis of overall survival: HR+/HER2- and HER2+ versus triple negative breast cancer in metastatic breast cancer patients diagnosed 2010+.
HR: Hormone receptor; OS: Overall survival; TNBC: Triple negative breast cancer.

DeClue et al. Future Oncol. (2023) 19(13)

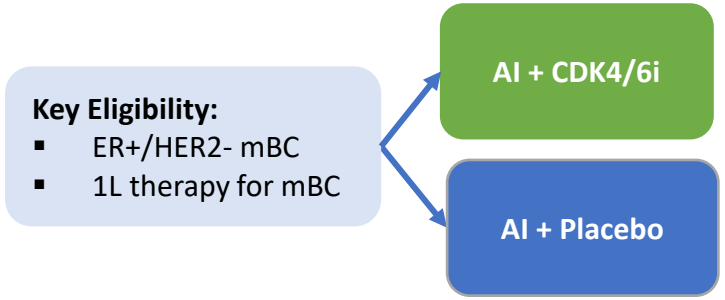
Evolving Treatment Landscape of HR+ Advanced MBC



Slide adapted from Komal Jhaveri

1L Setting

First Line Therapy P3 RCT
AI + CDK4/6 Inhibitors or Placebo



	PALOMA-2 N=666	MONALEESA-2 N=668	MONARCH-3 N=493
Endocrine Therapy	Letrozole	Letrozole	Letrozole or anastrozole
CDK4/i	Palbociclib	Ribociclib	Abemaciclib
Patients (n)	666	668	493
PFS Hazard Ratio	0.58**	0.56**	0.54**
PFS (months)	24.8 vs 14.5	25.3 vs 16	29 vs 14.8
OS Hazard Ratio	0.96	0.76**	0.80
OS (months)	53.9 vs 51.2	63.9 vs 51.4	66.8 vs 53.7

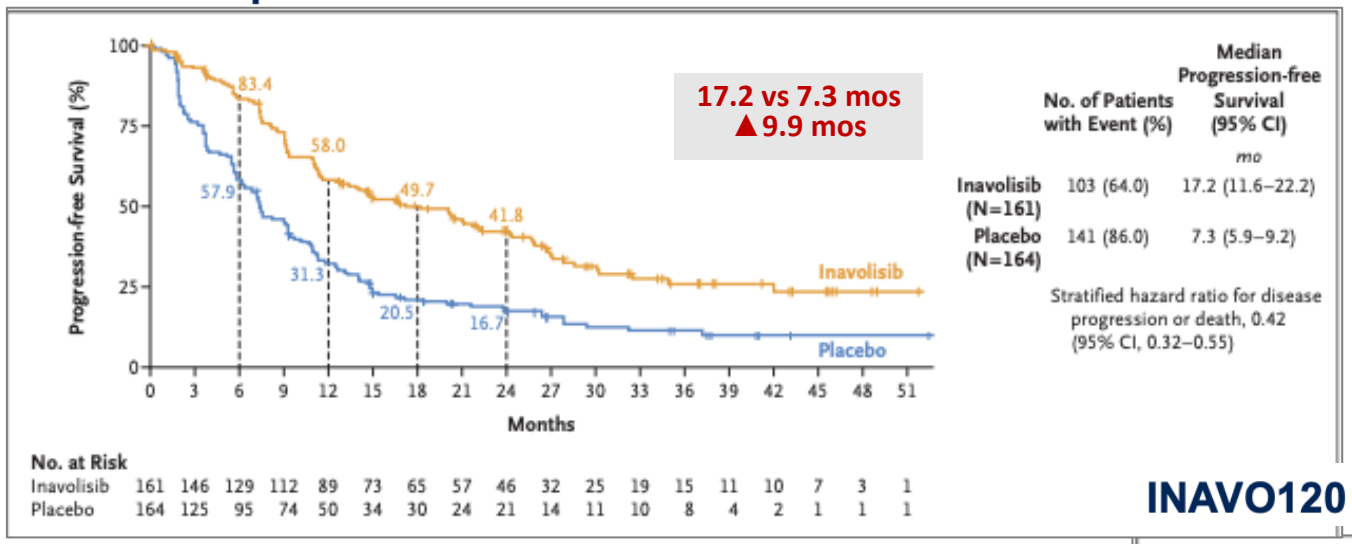
** statistically signficant

Finn *NEJM* 2016; Hortobagyi *NEJM* 2016; Goetz *J Clin Oncol* 2017; Finn, *ASCO* 2022; Hortobagyi *NEJM* 2022; Goetz SABCS 2023; GS01-12

INAVO120: 1L P3RCT Palbo + Fulvestrant + Inavolisib/Placebo

Pts with *PIK3CAm* progressing ≤ 12 mos of completing adj ET

INAVO120 updated PFS

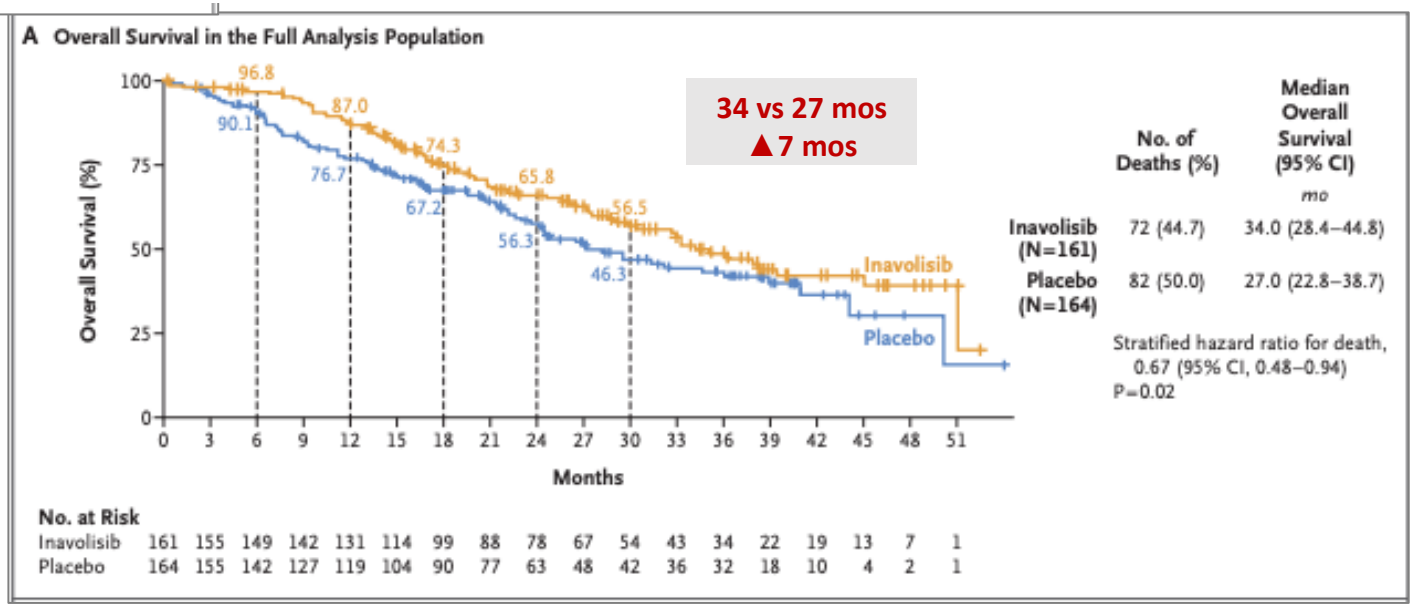


	No. of Patients with Event (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (N=164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio for disease progression or death, 0.42 (95% CI, 0.32–0.55)

- Time to 1st chemo: 35.6 vs 12.6 mo (HR 0.43, CI 0.3-0.6)
- Subsequent therapies (including 3L+)
  - Pbo arm: 15% PI3Ki 2L+
  - But, Pbo arm more ADC (T-DXd 29% vs 12% inavo)

INAVO120 key secondary endpoint: OS



	No. of Deaths (%)	Median Overall Survival (95% CI)
		mo
Inavolisib (N=161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (N=164)	82 (50.0)	27.0 (22.8–38.7)

Stratified hazard ratio for death, 0.67 (95% CI, 0.48–0.94)
P=0.02

Turner NC, *et al. NEJM* 2024; **391:**1584–1596;
Jhaveri KL et al. NEJM 2025; 393:151

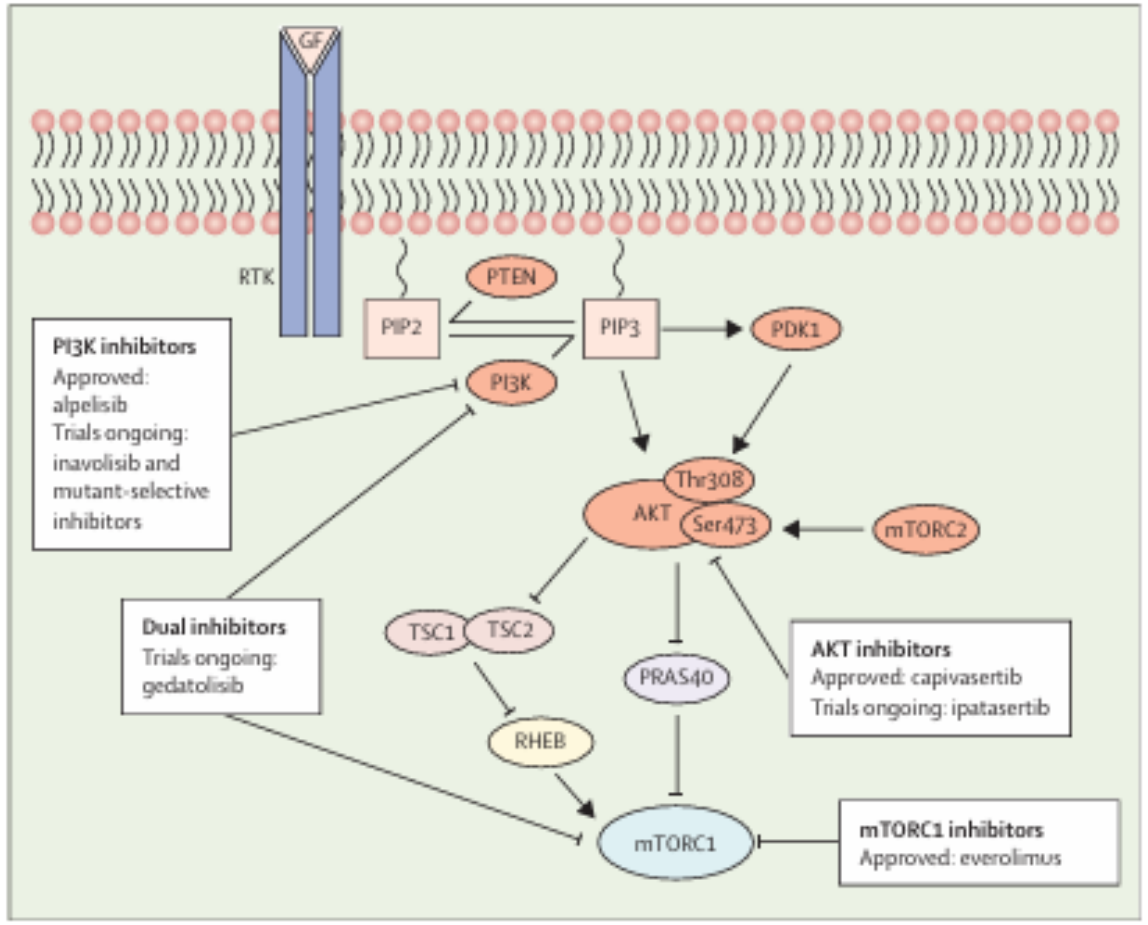
2L Therapy post PD

Molecularly Driven Recommendations

Targeted Therapies in 2L+ Setting

Agents targeting *PI3K* and *AKT* pathway

PI3K/AKT/mTOR Pathway

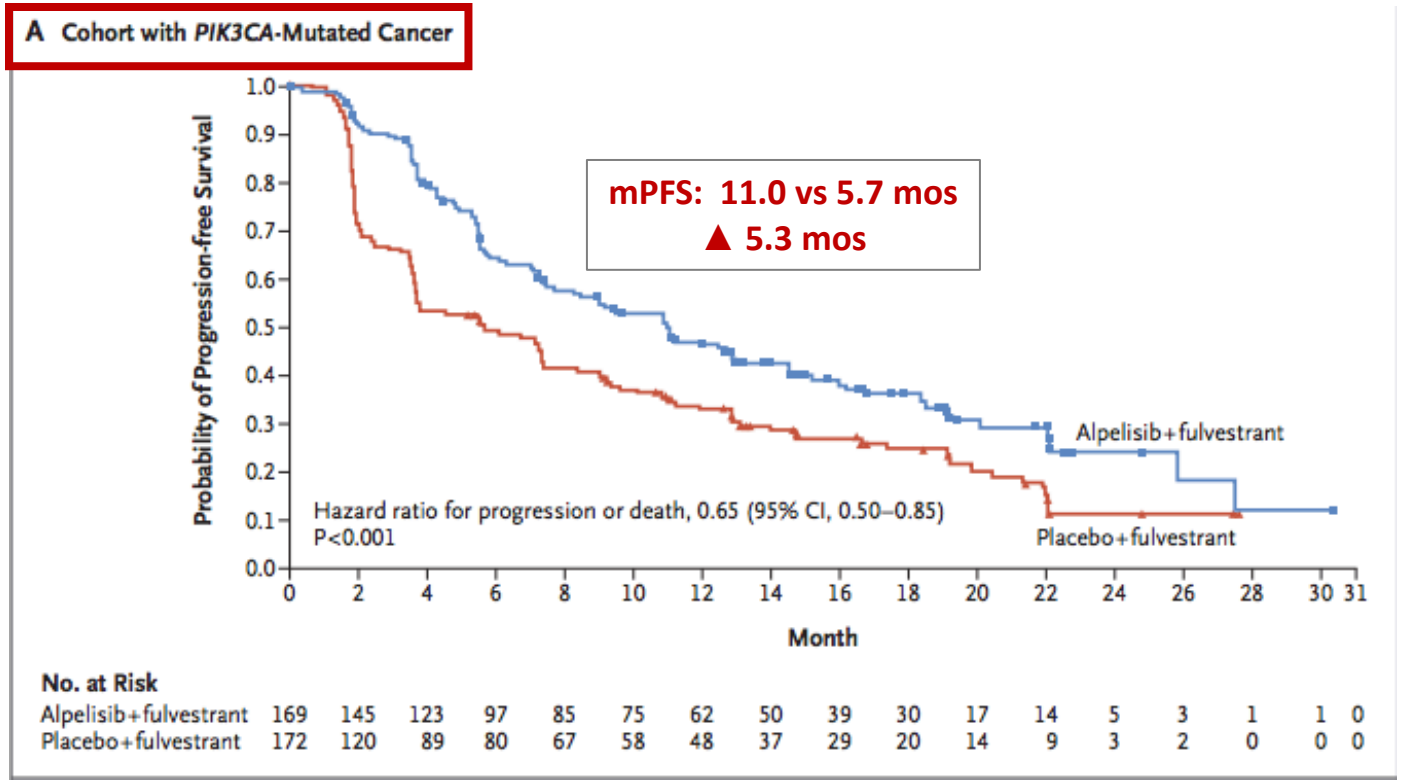


- PI3K-AKT-mTOR signaling promotes cell proliferation, anti-apoptotic signaling, and angiogenesis
- Activation of this pathway commonly occurs in breast cancer
- Mutations in *PIK3CA* seen in ~ 35–40% of ER+/HER2-neg breast cancer
- Most PI3K mutations are truncal -- present in the primary tumor and subsequent recurrence

Browne IM et al. Lancet Oncol 2024; 25:e139-51

SOLAR-1 Trial - *PIK3CA*-mutated HR+/HER2- mBC
Phase 3 RCT of Fulvestrant + Alpelisib/Placebo in unselected

***PIK3CA* mutations occur in about 40% HR+/HER2- breast cancers**
Alpelisib is α-selective PI3Ki



Key characteristics:
- HgbA1c < 6.4% allowed
- Lung or liver mets 50%
- 1st line 52%; 2nd line 46%
- Prior CDK4/6i 6%

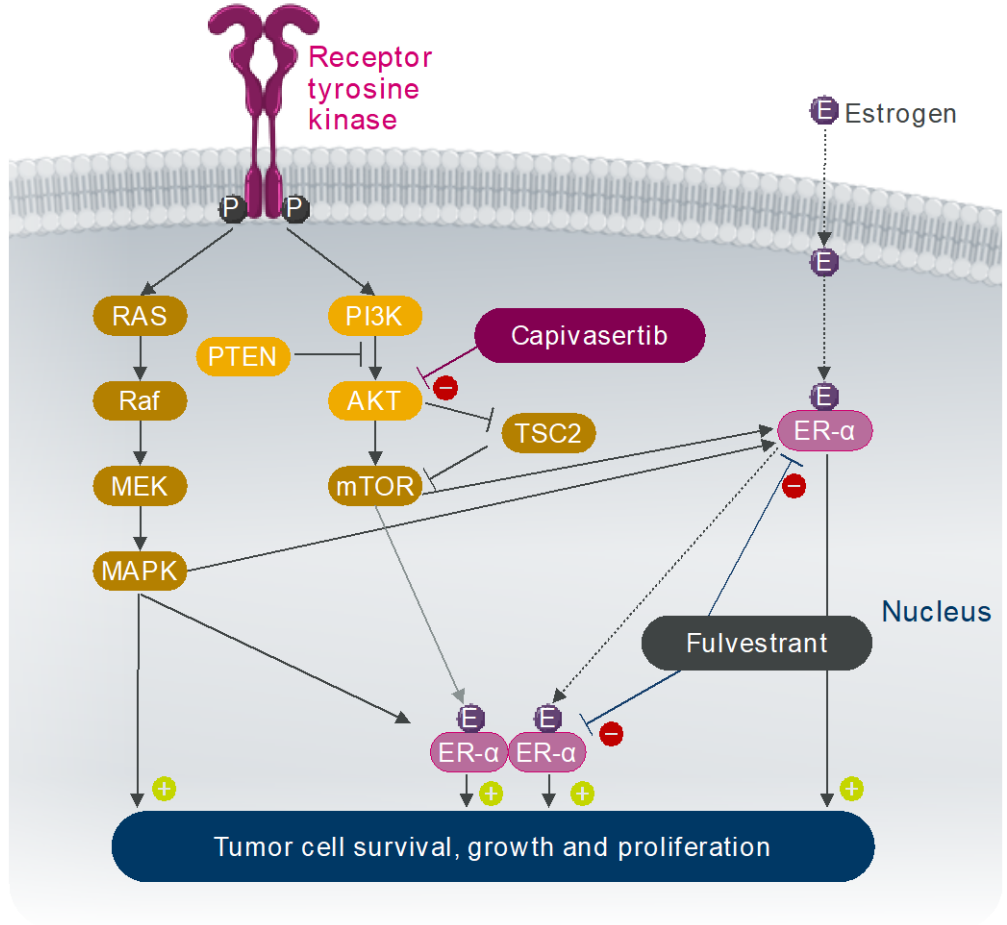
Key toxicities alpelisib:
- Hyperglycemia (G3/4 36%)
- Rash (G3/4 10%)
- Diarrhea (G3/4 7%)

BYLieve P2 Trial (all had PD post CDK4/6i): Similar Activity

André F et al. *N Engl J Med*. 2019;380(20):1929-1940.
Ciruelos. SABCS 2020. Abstr PD2-06.
Rugo et al. ASCO 2020 and SABCS 2020

Capivasertib – *AKT* inhibitor

- AKT pathway activation in ~ 50% HR+/HER2- mBC
  - Alterations in *PIK3CA, AKT1*, and *PTEN*
- Capivasertib potent and selective inhibitor of all three *AKT* isoforms (*AKT1/2/3*)



CAPItello-291: P3 RCT Fulvestrant + Capivasertib/Placebo

Key Eligibility: **(N=708)**

- ER+/HER2- ABC (postmeno women)
- Recurrence on or < 12 mos from end of AI
- ≤ 2 lines prior ET for ABC
- ≤ 1 line of chemo for ABC
- Prior CDK4/6i allowed (≥ 51% required)
- No prior SERD or PI3K/AKT/mTORi
- HgbA1c < 8.0%

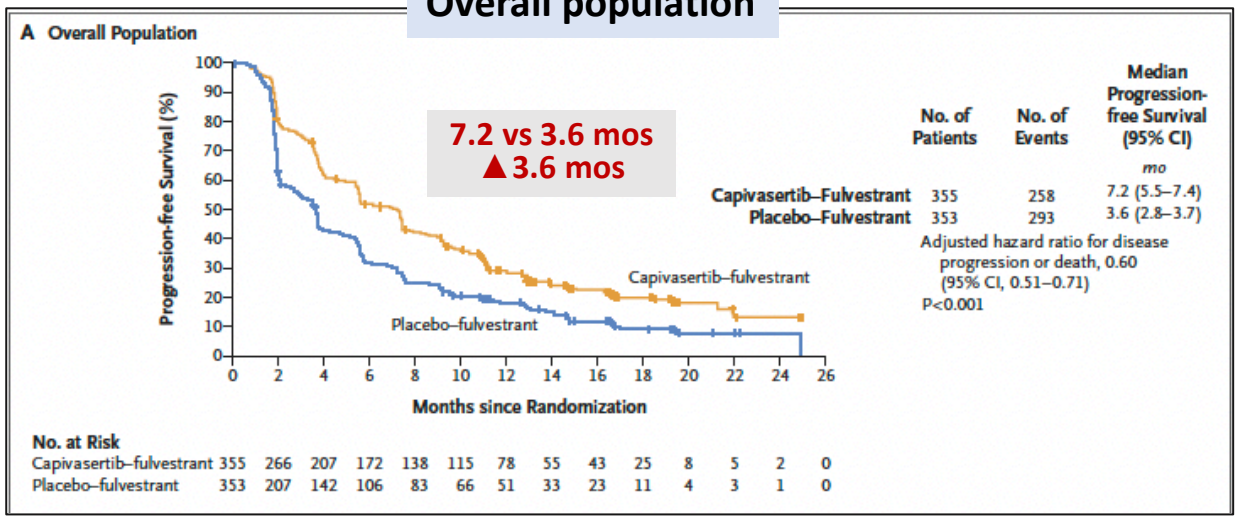
R → Fulvestrant + Capivasertib

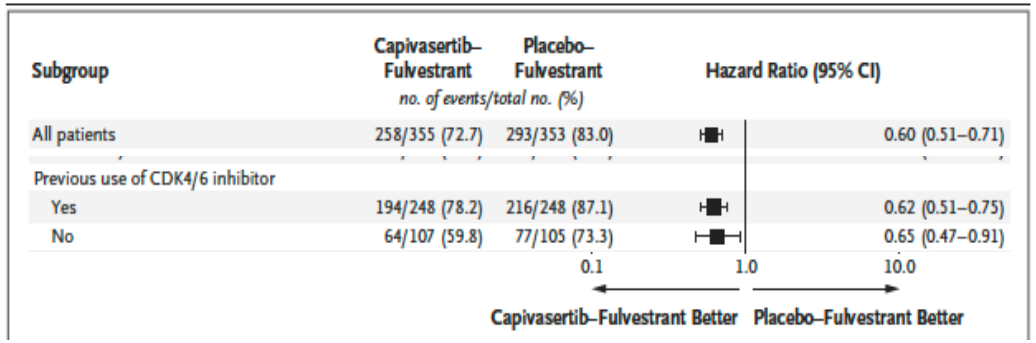
R → Fulvestrant + Placebo

Key Characteristics:

- Prior CDK4/6i: 69%
- Prior ET for ABC: 89%
- Prior chemo for ABC: 18%
- *AKT* pway alterations: ~41%
- HgbA1c < 8% allowed

Overall population





Similar benefit seen in those with alterations in *PIK3CA*, *AKT1*, or *PTEN*

Oliveira M et al. SABCS 2022; GS3-04; Turner et al NEJM 2023;388:2058

Summary of Trials with PIK3CAi or AKTi

	SOLAR-1[1]	Capitello-291[2]	Inavo-120[3]
Agent	Alpelisib (α-selective PI3Ki)	Capivasertib (*AKT1/2/3i)*	Inavolisib (α-selective PI3Ki)
Treatment Arms	Fulv + Alpelisib/Pbo; P3 RCT	Fulv + Capivasertib/Pbo; P3 RCT	Fulv + Palbo + Inavo/Pbo; P3 RCT
KEY PARTICIPANT CHARACTERISTICS			
Patient Population	Recurrence/PD post AI *PIK3CAm* (60%)	≤ 2L ET for ABC; ≤ 1L chemo *PIK3CAm/AKTm/mTORalt* (41%)	1L Relapsed < 12 adj ET *PIK3CAm* only (100%)
1L/2L/3L	52%/47%/0%	10%/66%/21%	100% 1L
HgA1c	< 6.4%	< 8%	< 6.0%
Prior CDK4/6i	6%	69%	1%
OUTCOME			
mPFS (for *PIK3CAm or AKT pway altered)*	**11 vs 5.7 mos** (HR 0.65, 0.50-0.85)	**7.3 vs 3.1 mos** (HR 0.50, 0.38–0.65)	**17.2 vs 7.3 mos** (HR 0.42, 0.32-0.55)
OS (for *PIK3CAm or AKT pway altered)*	39.3 vs 31.4 mos (HR 0.86, 0.64-1.15)	Not mature	34 vs 27 mos (HR 0.67, 0.48-0.94)
TOXICITIES			
Toxicities	Diarrhea 58% (G3+ 7%) ↑Glucose 64% (G3+ 37%) Rash 36% (G3+ 10%)	Diarrhea 72% (G3+ 9%) ↑Glucose 16% (G3+ 2%) Rash 38% (G3+ 12%)	Diarrhea 48% (G3+ 4%) ↑Glucose 59% (G3+ 6%) Rash 25% (G3+ 0%)
D/C rate due to TRAEs	25%	13%	7%

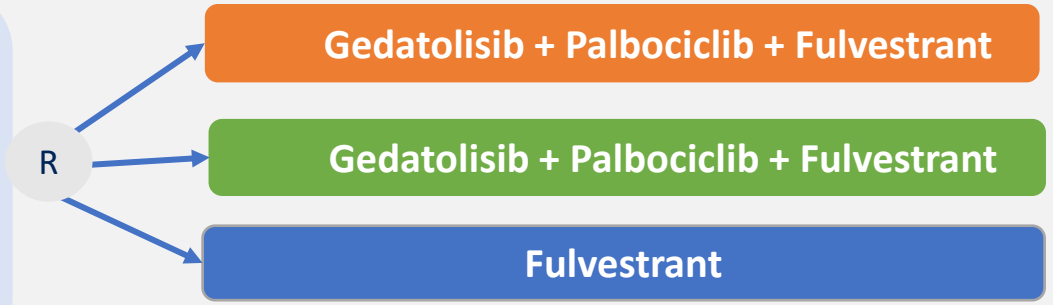
1. Andre F *Ann Oncol* 2021; 32:208; 2. Turner et al *NEJM* 2023;388:2058; 3. Jhaveri KL et al. *NEJM* 2025; 393:151

VICTORIA-1: P3 RCT Gedatolisib pan-PI3K and mTORC1/2i

PRESS RELEASE

Key Eligibility:

- ER+/HER2- ABC
- Confirmed PIK3CA mutation status
- ≤ 2 lines prior ET for ABC
- No chemo for ABC
- Prior CDK4/6i + AI
- No prior *AKT*, *PI3K*, *mTORi*



Two cohorts *PIK3CAwt* (n=351) and *PIK3CAm* (n=350)

- Gedatolisib triplet:
  - mPFS (BICR) 9.3 mo triplet vs 2.0 mo fulv alone (HR, 0.24; 95% CI, 0.17–0.35; *P* <.0001).
- Gedatolisib doublet:
  - mPFS (BICR) 7.4 mo doublet vs 2.0 mo fulv alone (HR, 0.33; 95% CI, 0.24–0.48; *P* <.0001).

Targeted Therapies in 2L+ Setting

Agents targeting *ESR1*

EMERALD Open Label P3RCT – Elacestrant vs SOC ET

- Postmeno women and men with ER+/HER2- ABC or mBC
- ≤1 lines prior chemo for mBC
- 1 to 2 lines of ET
- Documented PD on CDK4/6 inhibitor
- Measurable disease or bone-only disease eligible

Strat factors
- *ESR1* status (by ctDNA)
- Prior fulvestrant
- Visceral disease

N = 466

R

Elacestrant 400 mg PO QD

Endocrine therapy*

Key Characteristics:
- Visceral mets: ~ 70%
- Prior CDK4/6i: 100%
- Prior ET: 2 lines ~46%
- Prior chemo: 1 line 20%

* SOC ET: 69% received fulvestrant

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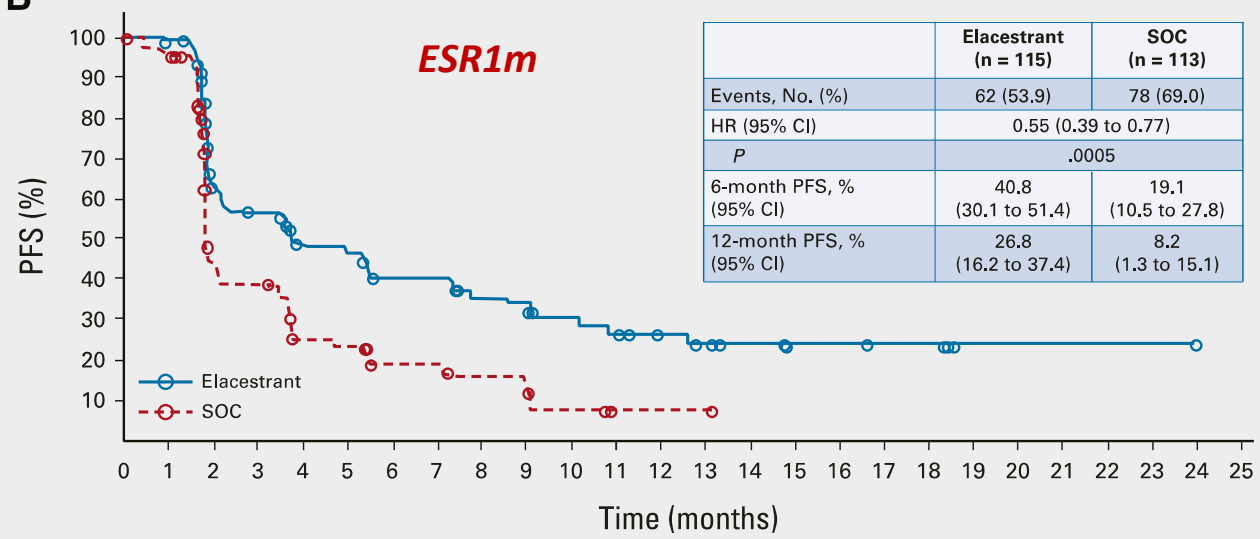


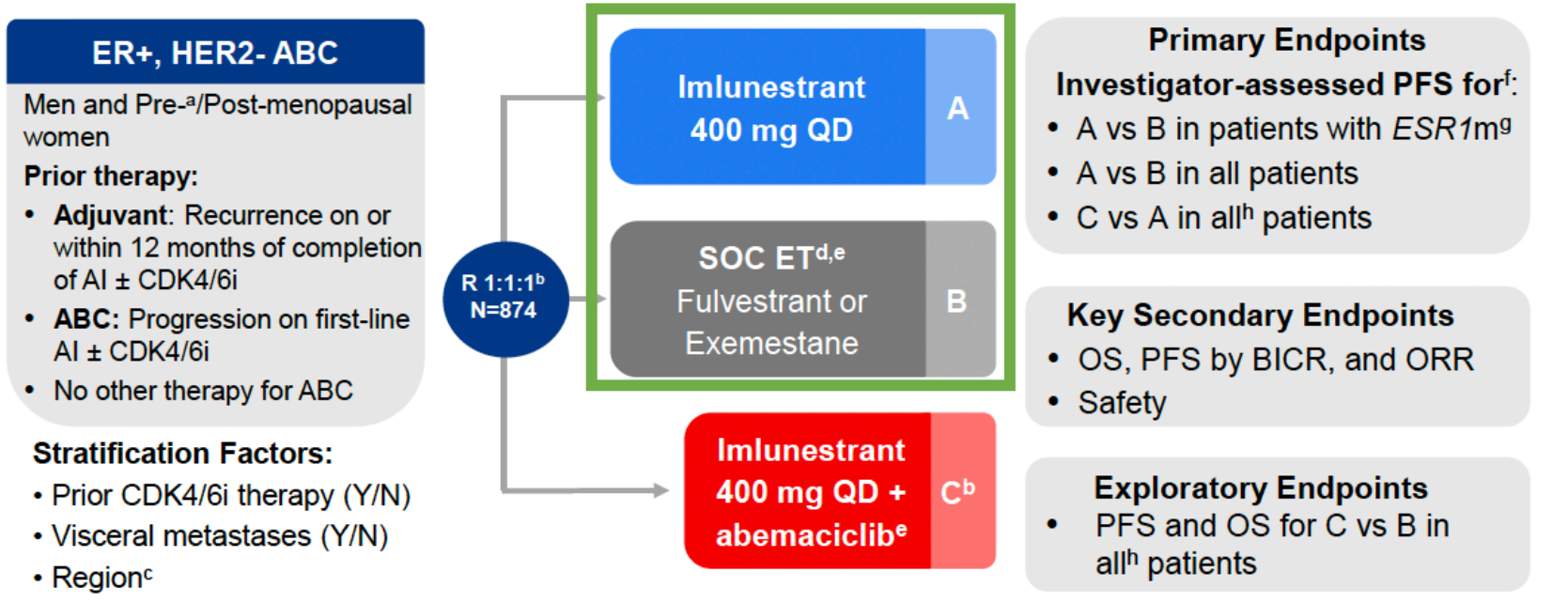
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

mPFS 3.78 vs 1.87 mos
HR 0.50 (95% CI 0.34-0.74), p=0.0005

Clinically significant benefit if ET sensitive disease, based on PFS duration on prior CDK4/6i:
- **≥ 6 mos: mPFS 4.1 vs 1.9 mos** (HR 0.52,.36-.74)
- **≥ 12 mos: mPFS 8.6 vs 1.9 mos** (HR 0.41,.26-.63)
- **≥ 18 mos: mPFS 8.6 vs 2.1 mos** (HR 0.47,.27-.79)

Bidard FC et al JCO 2022

EMBER-3 Trial: Open Label P3RCT



Key Characteristics

- SOC ET: 88% Fulvestrant; 10% Exemestane
- ~35% *ESR1m*
- 40% *PI3K* pathway alterations
- ~60% prior CDK4/6i

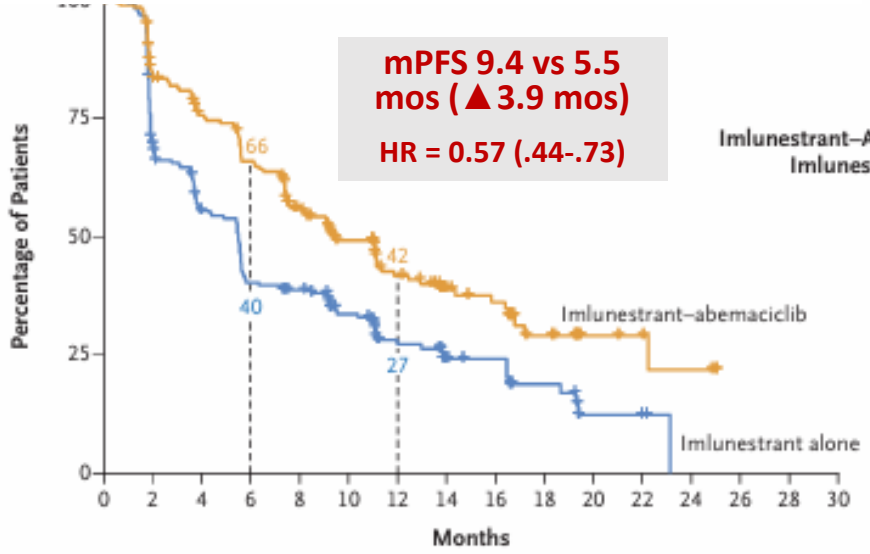
	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

FDA Approval 9/25/25

Jhaveri K, et al. *NEJM* 2025;392:12.

EMBER-3 Study
Imlunestrant + Abema vs Imlunestrant alone

A PFS Imlu + Abema vs Imlu Alone: **Overall population**



mPFS 9.4 vs 5.5 mos (▲3.9 mos)

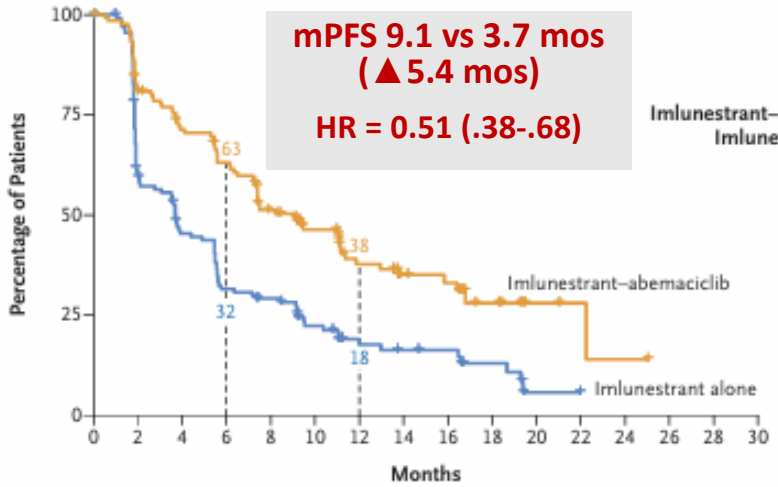
HR = 0.57 (.44-.73)

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

No. at Risk																
Imlunestrant–abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0
Imlunestrant alone	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0

B PFS Imlu + Abema vs Imlu Alone: **Prior CDK4/6i**



mPFS 9.1 vs 3.7 mos (▲5.4 mos)

HR = 0.51 (.38-.68)

-Abemaciclib vs. Imlunestrant Alone

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

No. at Risk																
Imlunestrant–abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0
Imlunestrant alone	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0

Consistent benefit of Imlu + Abema regardless of ESR1m status, PI3Km, and prior CDK4/6i use

Jhaveri K, et al. *NEJM* 2025;392:12.

Summary of Trials with Oral SERDs/PROTAC

	EMERALD[1]	EMBER-3[2]	VERITAC-2[3]
	Elacestrant (n = 239)	**Imlunestrant (n = 331)**	**Vepdegestrant (n=624)**
Lines of ET for mBC (0 / 1 / 2), %	NOT ALLOWED / 54 / 46	32 / 63 / NOT ALLOWED	NOT ALLOWED / 80 / 20
Prior mBC therapy			
CDK4/6i	100%	~60%	100%
Chemo	20%	NOT ALLOWED	NOT ALLOWED
FULV	30%	NOT ALLOWED	NOT ALLOWED
Population, %			
Primary resistance	24%	8%	NR (all > 6mos PFS prior ET)
Visceral mets	68%	57%	63%
Outcome			
mPFS (*ESR1m*)	**3.8 vs 1.9 mos (▲1.9 mos)** HR 0.50 (0.34-0.74), p=0.0005	**5.5 vs 3.8 mos (▲1.7 mos)** HR 0.62 (0.46-0.82), p<0.001	**5.0 vs 2.1 mos (▲2.9 mos)** HR 0.58 (0.43-0.78), p<0.001
mPFS (*ESR1m*) > 12 mos DOR CDK4/6i	**8.61 vs 1.91 mos** HR 0.41 (0.26-0.63)	NR	NR

1. Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256; 2. Jhaveri K, et al. *NEJM* 2025;392:12; 3. Campone M et al. NEJM 2025;393:556-68.

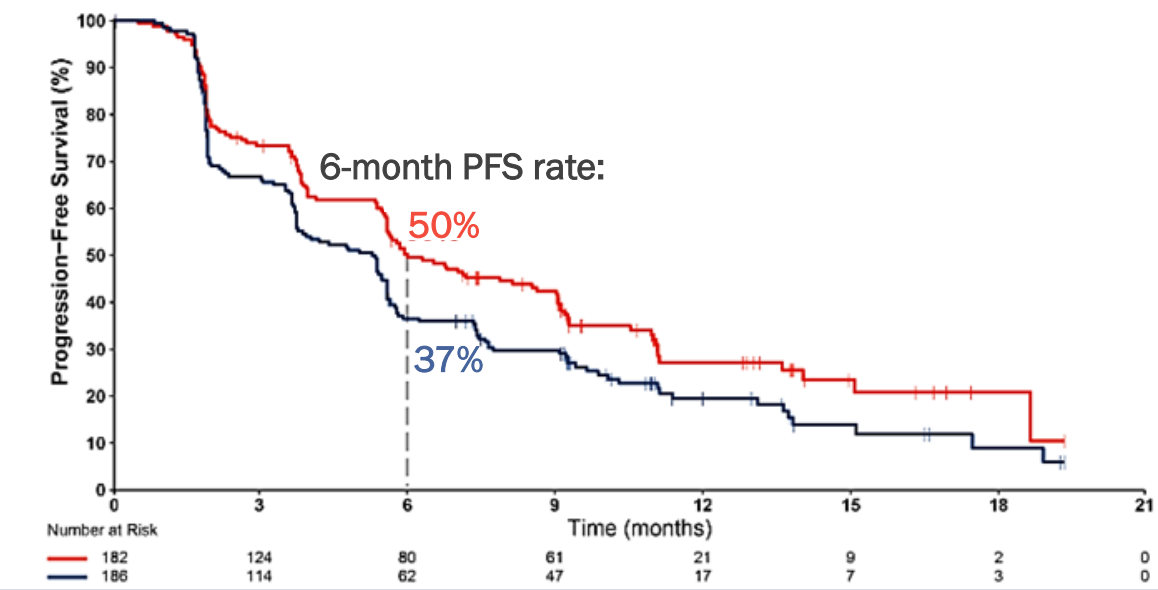
CDK4/6i post PD on CDK4/6i

postMONARCH P3 RCT: Fulvestrant + Abema/Pbo for HR+/HER2– mBC Post CDK4/6i + ET

Key Eligibility:
- ER+/HER2- aBC
- ABC: PD on 1L AI+CDK4/6i
- Adj: PD on/post ET+CDK4/6i
- No other Tx for ABC

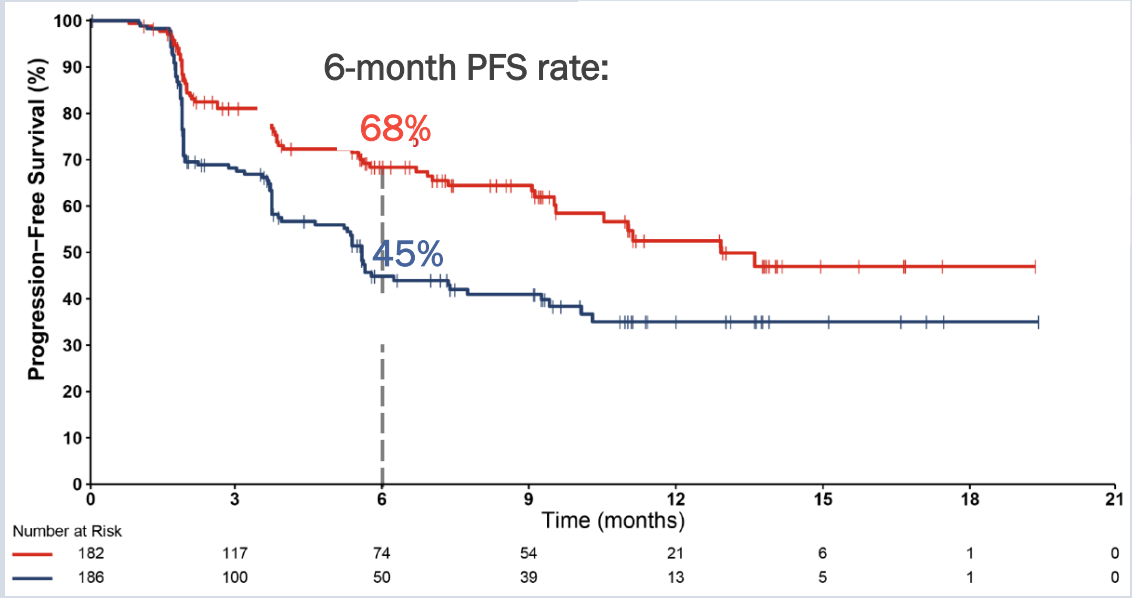
→ Abema + Fulv
→ Placebo + Fulv

Primary Analysis: PFS by INV



PFS by INV	Abemaciclib + Fulv (n=182)	Placebo + Fulv (n=186)
No. events	117	141
Median PFS (95% CI), months	6.0 (5.6-8.6)	5.3 (3.7-5.6)
HR (95% CI)	0.73 (0.57-0.95)	
P value	0.017	

Key Secondary Endpoint: PFS by BICR



PFS by BICR	Abemaciclib + Fulv (n=182)	Placebo + Fulv (n=186)
Events	60	92
Median PFS (95% CI), mo	12.9 (9.5-NR)	5.6 (3.9-7.7)
HR (95% CI)	0.55 (0.39-0.77)	
P value	< .001	

Kalinsky K, et al. ASCO 2024. Abstract LBA1001.

Second-Line CDK4/6i After Progression on First-Line CDK4/6i

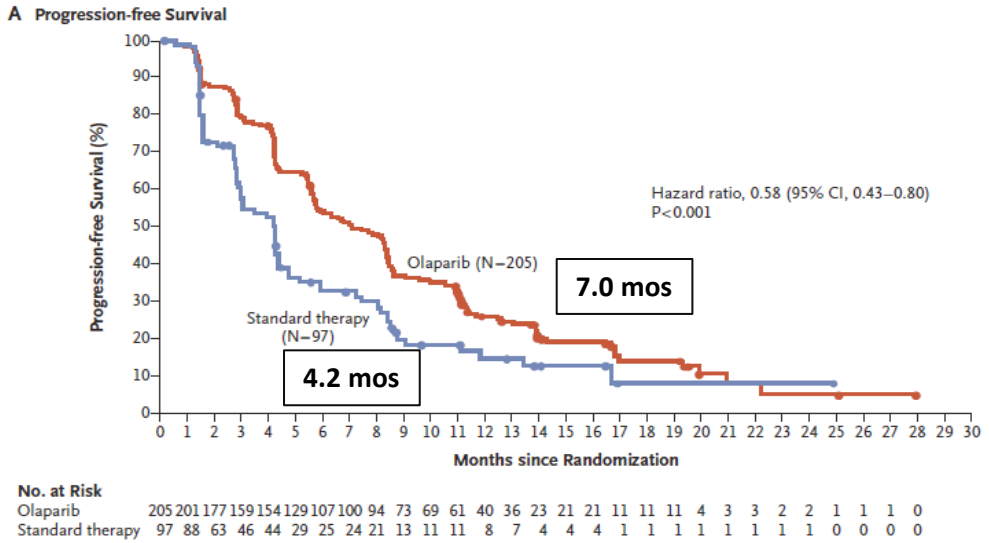
	POSTMONARCH[1]	MAINTAIN[2]	PACE[3]	PALMIRA[4]
Patients, n	368	120	166	198
1L CDK4/6i	Palbociclib (59%) Ribociclib (34%)	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
1L CDK4/6i >12 mo	~71%	67%	75%	86%
Endocrine therapy	Fulv (100%)	Fulv (83%) or Exem	Fulv (100%)	Fulv (90%) or Let
"Continuation" CDK4/6i	Abemaciclib	Ribociclib	Palbociclib	Palbociclib
PFS ET only, mo	5.3 (5.6 BICR*)	2.8	4.8	3.6
PFS fulvestrant + CDK4/6i, mo	6.0 INV (12.9 BICR*)	5.3	4.6	4.9

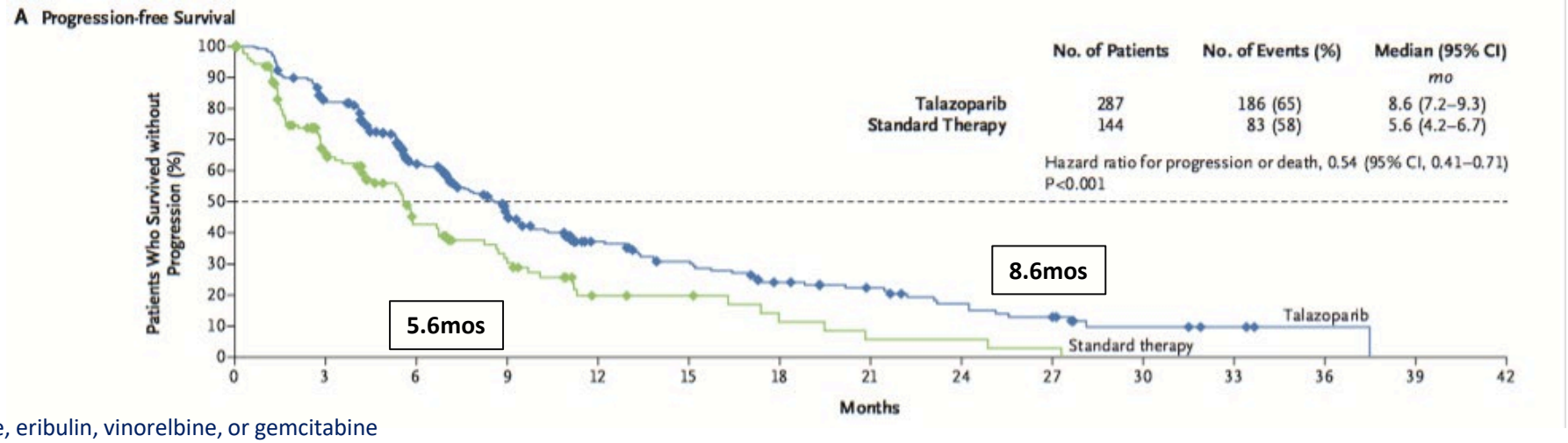
Caveats regarding cross-trial comparisons: different studies, designs, populations, prior therapy, and subgroup definitions

* secondary endpoint

1. Kalinsky K, et al. ASCO 2024. LBA1001. 2. Kalinsky K et al. *J Clin Oncol*. 2023;41:4004-4013. 3. Mayer EL et al. SABCS 2022. Abstract GS3-06. 4. Llombart-Cussac A et al. ASCO 2023. Abstract 1001.

RCT of PARP Inhibitors in g*BRCA1/2* Carriers with HER2-neg mBC



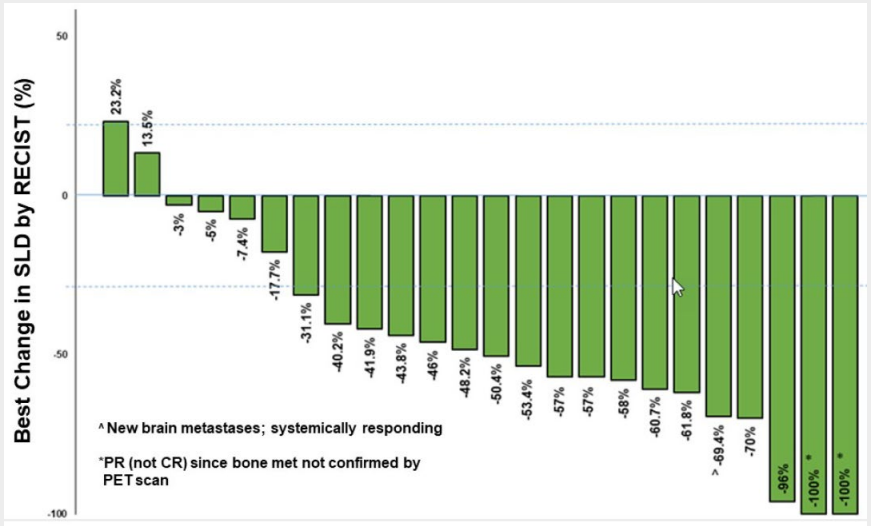


TPC: Capecitabine, eribulin, vinorelbine, or gemcitabine

Litton JK et al. N Engl J Med. 2018;379(8):753-763.
Robson M et al. N Engl J Med. 2017;377(6):523-533.

Expansion Cohorts of TBCRC 048 Phase 2 Study of Olaparib in MBC With g*PALB2*mut or *sBRCA1/2*mut: Efficacy in g*PALB2*mut and in *sBRCA1/2*

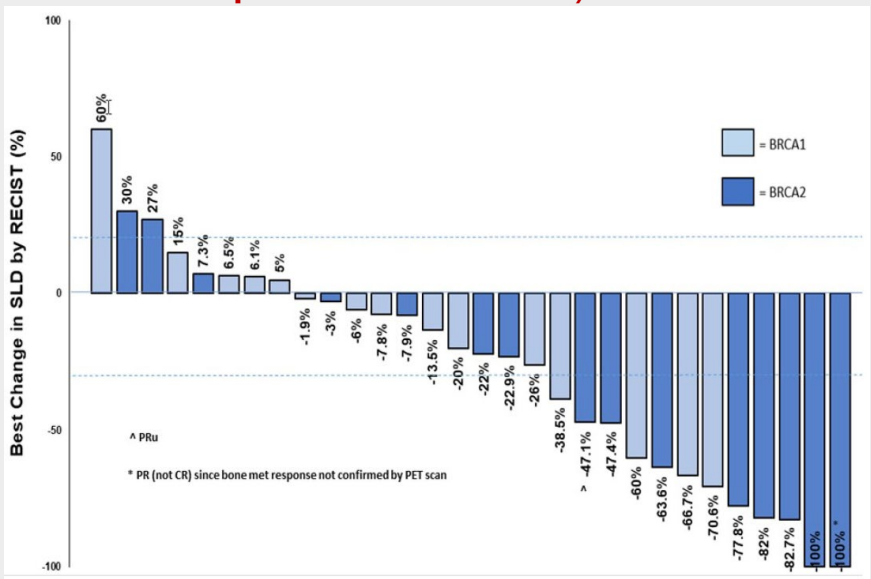
Responses for g*PALB2*mut



gPALB2mut (n=24)	
Best Response	**Response Rate, n (%)**
ORR, n (%)	**75%** (80% CI:60-86%)
CR	1 (4%)
PR	17 (71%)
SD	5 (21%)
PD	1 (4%)
CBR (18 weeks), n (%)	**83%** (90% CI: 66-94%)

mPFS = 9.6 months (90% CI: 8.3-12.4)
mDOR = 7.1 months (90% CI: 5.5-11.0)

Responses for s*BRCA1/2*mut

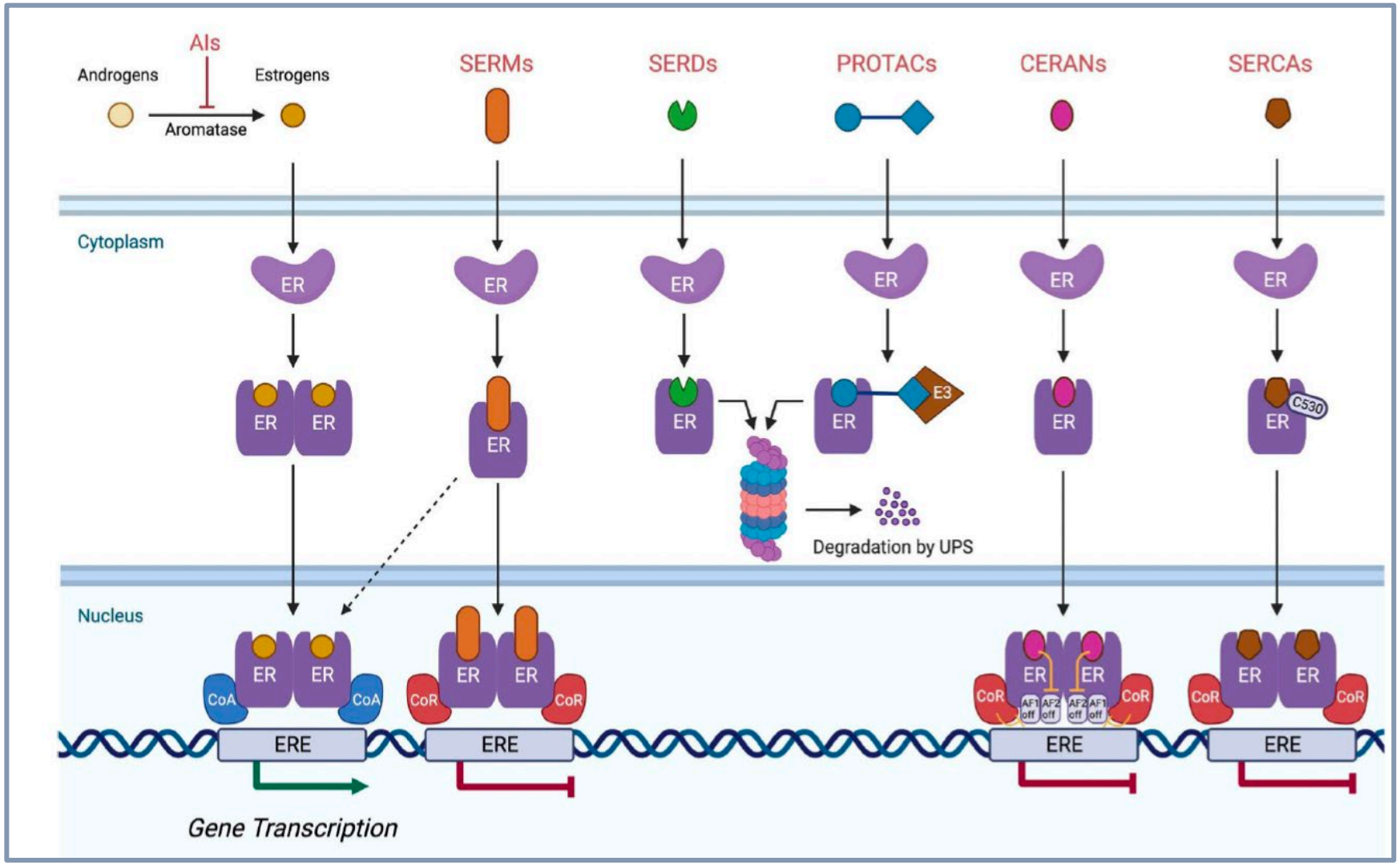


sBRCA1/2mut (n=30)	
Best Response	**Response Rate, n (%)**
ORR, n (%)	**37%** (80% CI: 25-50%)
CR	1 (3)
PR	10 (33)
SD	13 (43)
PD	6 (20)
CBR (18 weeks), n (%)	**53%** (90% CI: 37-69%)

mPFS = 7.2 months (90% CI: 3.9-13.6)
mDOR = 12.4 months (90% CI: 4.3-NR)

Tung N, et al. ASCO 2024. Abstract 1021.

Other Emerging ER-Targeting Agents



SERM: Selective ER modulator
eg: Lasofoxifene, Bazedoxifene

SERD: Selective ER degrader
eg: Elacestrant, Imnulestrant

PROTAC: Proteolysis-targeting chimera
eg: Vepdegestrant

CERAN: Complete ER antagonist
eg: Palazestrant

SERCA: Selective ER covalent antagonist
eg: H3B-6545

Patel R et al. NPJ Breast Cancer 2023

Other Emerging Therapies

- Mutant selective PI3Ki
- Novel CDKi
- Triplets
- KAT6i
- Radioligand options

- Novel ADCs for endocrine refractory

ADCs

DESTINY Breast-04: P3 RCT T-DXd vs TPC in HER2-low mBC after 1-2 prior L Chemo for mBC

Key Eligibility:
- HER2- mBC
- 1-2L prior chemo for mBC

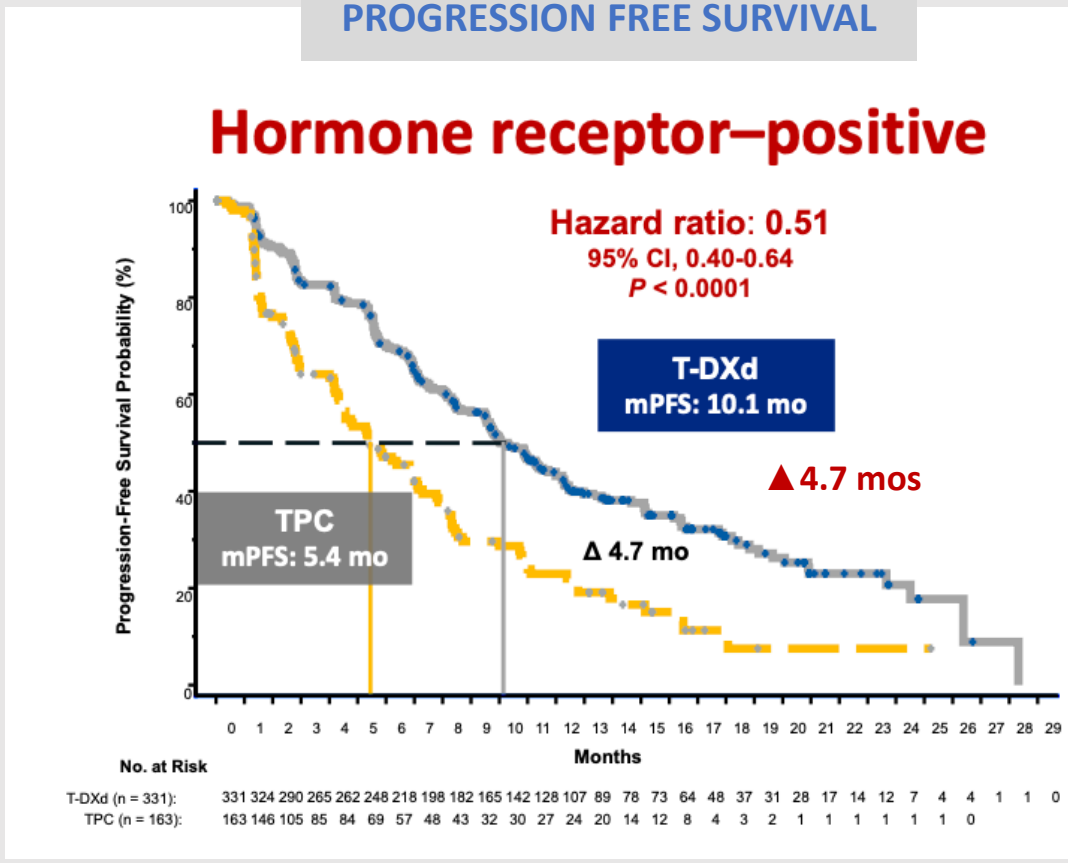
T-DXd

TPC

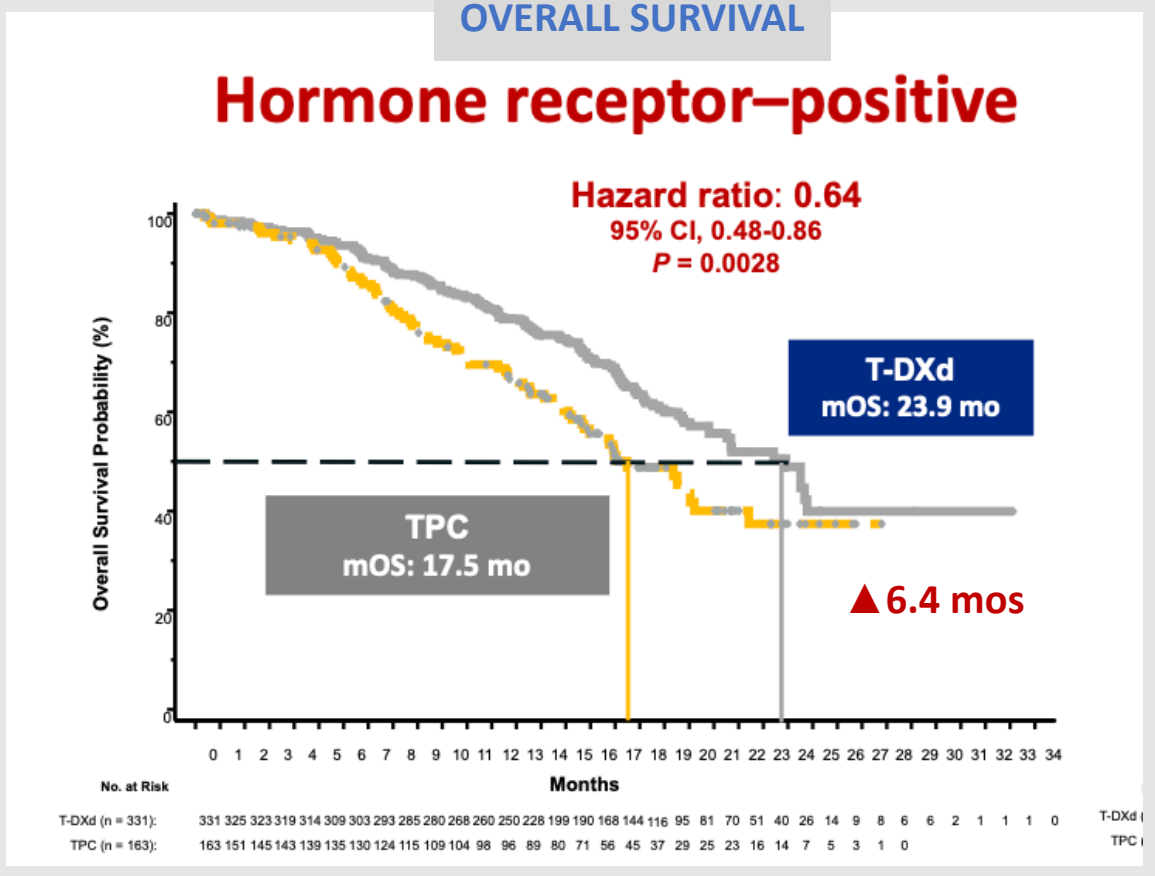
N=540 (HR+ 480)

TPC: cape, eribulin, gem, paclitaxel, or nab-pac

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



Modi S, et al. ASCO 2022. Abstract LBA3, Modi et al. NEJM 2022.

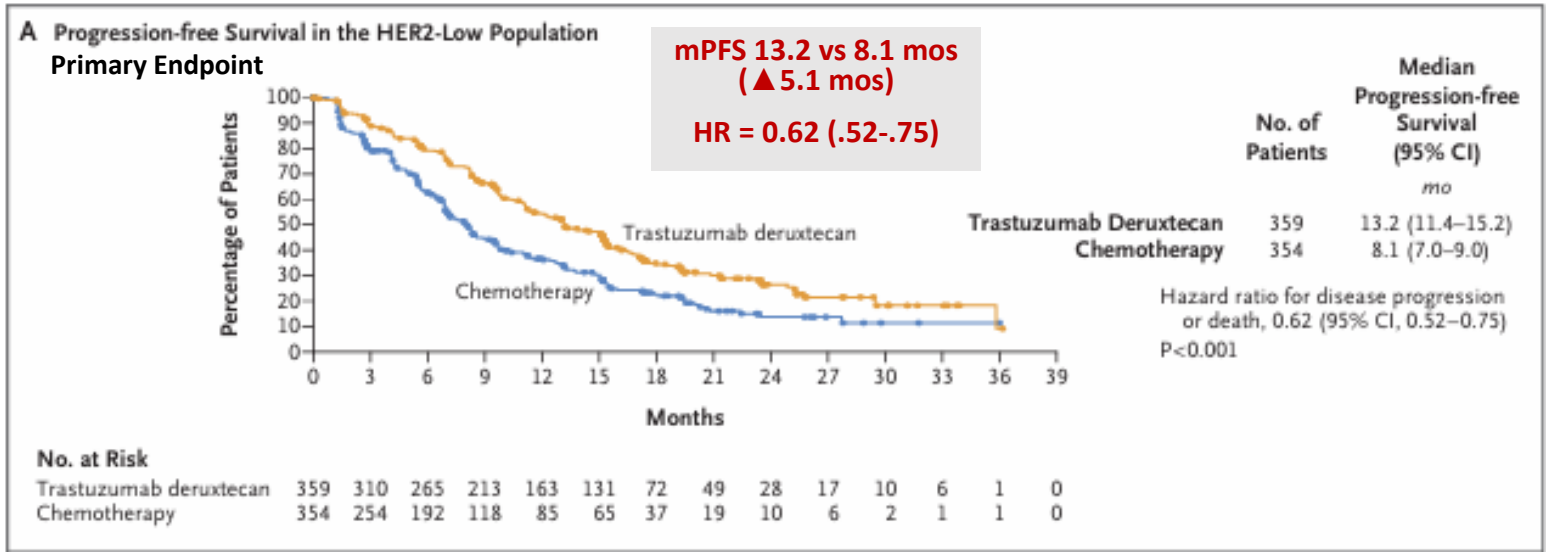
DESTINY Breast-06: P3 RCT T-DXd vs TPC in HER2-low/ultralow mBC in Chemo-naïve

Key Eligibility:
- HR+/HER2 lo/ultralo* mBC
- Chemo naïve for mBC
- > 2L ET for mBC or 1L ET if endo-resistant

N=866

→ T-DXd
→ TPC

TPC: cape, paclitaxel, or nab-pac



Key Characteristics:
- HER2-low 82%
- De-novo mBC ~31%
- Visceral ~ 85%
- 1º ET resistance ~31%

Similar PFS benefit seen in HER2 ultralow
OS data immature – 12 mos OS in HER2-low 87.6% vs 81.7% (NS)

*HER2 low: IHC 1+, 2+ (ISH neg); HER2 ultralow: IHC 0 with any membrane staining

Bardia et al. *NEJM* 2024;2110-22

DESTINY Breast-06: P3 RCT T-DXd vs TPC in HER2-low/ultralow mBC in Chemo-naïve

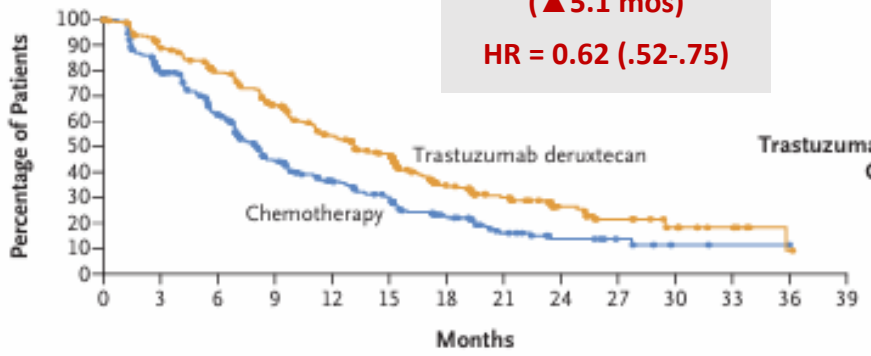
Key Eligibility:
- HR+/HER2 lo/ultralo* mBC
- Chemo naïve for mBC
- > 2L ET for mBC or 1L ET if endo-resistant

N=866

→ T-DXd
→ TPC

TPC: cape, paclitaxel, or nab-pac

A Progression-free Survival in the HER2-Low Population
Primary Endpoint



mPFS 13.2 vs 8.1 mos (▲5.1 mos)

HR = 0.62 (.52-.75)

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	359	13.2 (11.4–15.2)
Chemotherapy	354	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, P<0.001

No. at Risk

Trastuzumab deruxtecan	359	310	265	213	163	131	72	49	28	17	10	6	1	0
Chemotherapy	354	254	192	118	85	65	37	19	10	6	2	1	1	0

Key Characteristics:
- HER2-low 82%
- De-novo mBC ~31%
- Visceral ~ 85%
- 1º ET resistance ~31%

Similar PFS benefit seen in HER2 ultra
OS data immature – 12 mos OS in HER2-low 87.6%

Table 3. Most Common Drug-Related Adverse Events (Safety Population).*

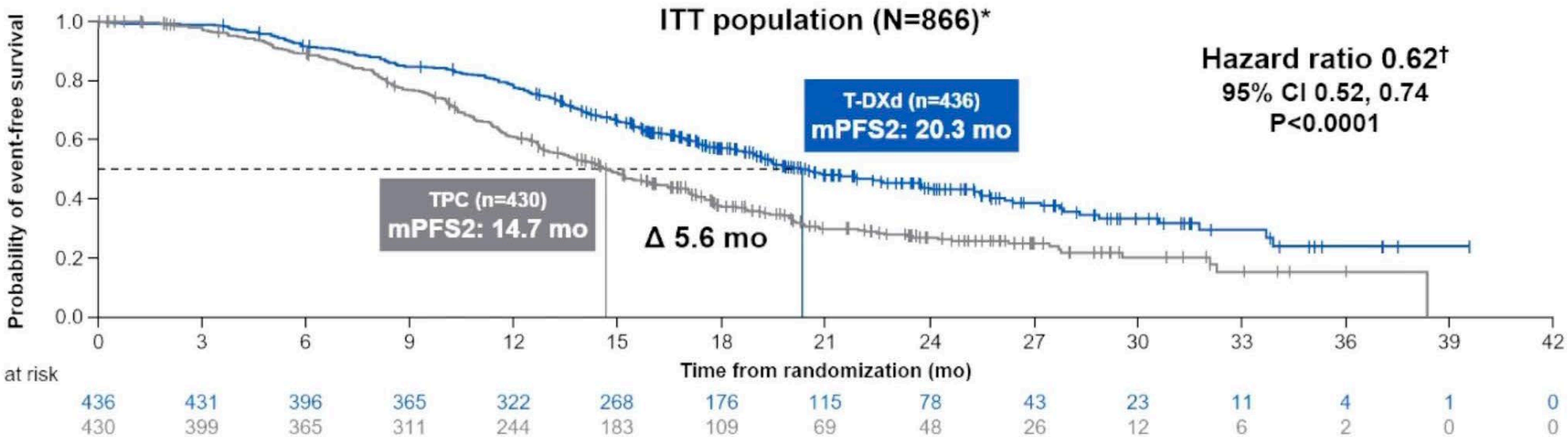
ILD all grade 11.3%
G3/4: 0.7% (n=3)
G5: 0.7% (n=3)

Event	Trastuzumab Deruxtecan (N=434)		Chemotherapy (N=417)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Nausea	286 (65.9)	7 (1.6)	98 (23.5)	1 (0.2)
Fatigue†	203 (46.8)	16 (3.7)	143 (34.3)	6 (1.4)
Alopecia‡	197 (45.4)	0	81 (19.4)	1 (0.2)
Neutropenia§	163 (37.6)	90 (20.7)	115 (27.6)	69 (16.5)
Transaminase increased¶	128 (29.5)	10 (2.3)	49 (11.8)	0
Anemia‖	122 (28.1)	25 (5.8)	81 (19.4)	10 (2.4)
Vomiting	118 (27.2)	6 (1.4)	39 (9.4)	0
Diarrhea	103 (23.7)	8 (1.8)	94 (22.5)	10 (2.4)
Decreased appetite	102 (23.5)	6 (1.4)	39 (9.4)	2 (0.5)
Leukopenia**	101 (23.3)	30 (6.9)	61 (14.6)	23 (5.5)
Palmar–plantar erythrodysesthesia syndrome	2 (0.5)	0	135 (32.4)	28 (6.7)

*HER2 low: IHC 1+, 2+ (ISH neg); HER2 ultralow: IHC 0 with any membrane staining

Bardia et al. *NEJM* 2024;2110-22

PFS2 in the overall ITT population and time-to-progression subgroups



	<6-mo 1L TTP		6–12-mo 1L TTP		>12-mo 1L TTP	
	T-DXd (n=65)	TPC (n=59)	T-DXd (n=60)	TPC (n=52)	T-DXd (n=168)	TPC (n=166)
mPFS2, mo (95% CI)	18.9 (14.4, 24.0)	15.2 (10.9, 17.5)	17.1 (13.9, 31.8)	13.7 (10.3, 17.1)	20.0 (18.6, 25.3)	14.3 (12.6, 15.9)
PFS2 hazard ratio (95% CI)	0.73 (0.46, 1.14)†		0.59 (0.37, 0.94)†		0.57 (0.43, 0.75)†	

Delay in PFS2‡ was clinically meaningful in favor of T-DXd in the ITT population and TTP subgroups

DB-06 Implications

- T-DXd is highly effective drug in HR+/HER2 low/ultralow
- In order to meaningfully assess PFS2 (and OS), need to know % patients who received T-DXd in 2L (or subsequent line)
  - In US, question is **when to use T-DXd not whether to use it**
  - In DB-04 (T-DXd given as 2-3L chemo) PFS▲ 4.7 mos, OS▲ 6.4 mos (vs DB-06 with PFS ▲ **5.1 mos**)
  - Based on data from ASCO 2024, only 20% pts in TPC arm in DB-06 got subsequent T-DXd

TROPICS-02: P3 RCT Sacituzumab Govitecan vs TPC in HR+/HER2- mBC

Key Eligibility:
- HER2- mBC
- **2-4L prior chemo for mBC**

N=543

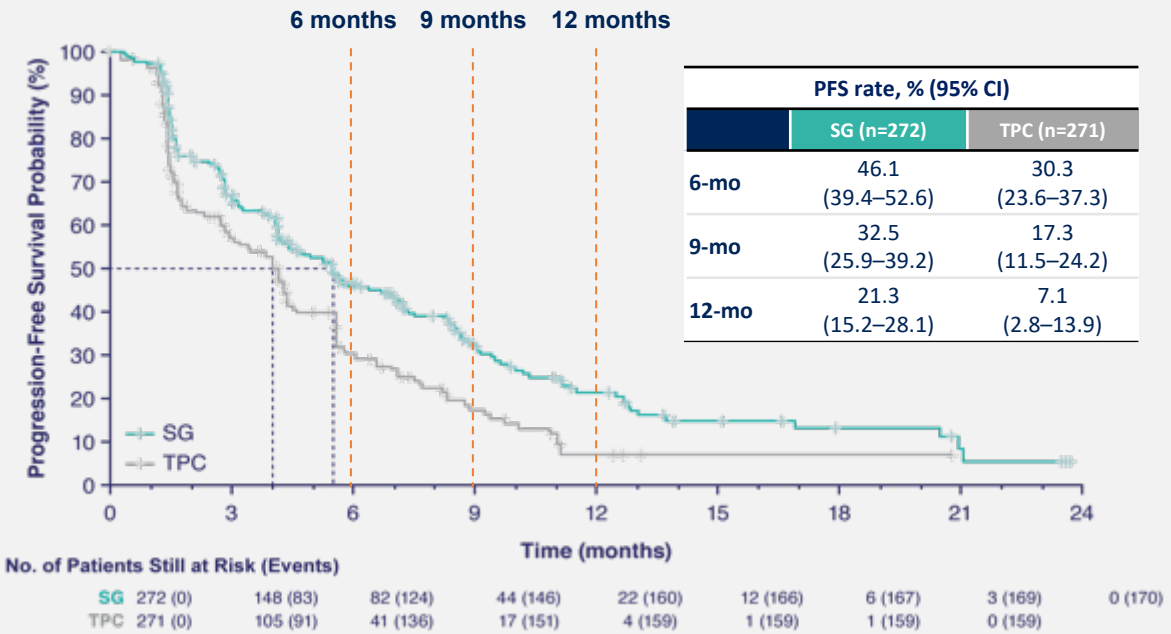
→ Sacituzumab Govitecan

→ TPC

PFS[1] Median F/U: 10.2 mos

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	

▲1.5 mos

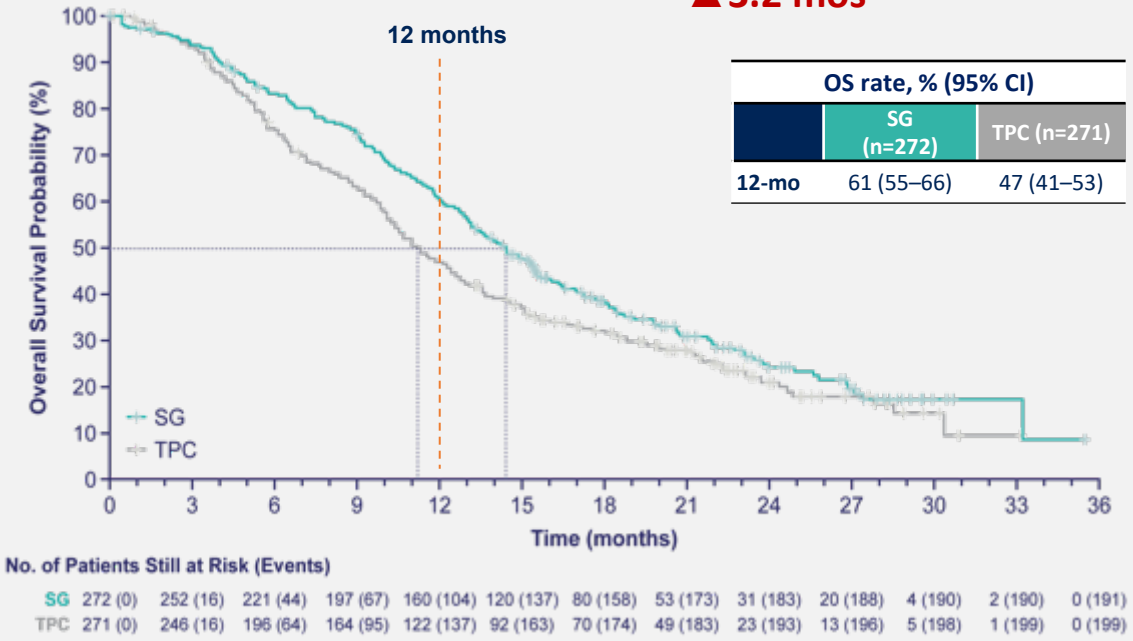


PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2] Median F/U: 12.5 mos

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	

▲3.2 mos



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376; 2. Rugo H, et al. ESMO 2022. Oral LBA76.

TROPION-Breast01: P3 RCT Dato-DXd vs Chemo in HR+/HER2– MBC

Key Eligibility Criteria

- HR+/HER2– MBC (HER2 IHC 0/1+/2+; ISH–)
- Progressed on and not suitable for ET
- **1-2 prior lines** of Chemo in inoperable/metastatic setting
- ECOG PS 0-1

N=732

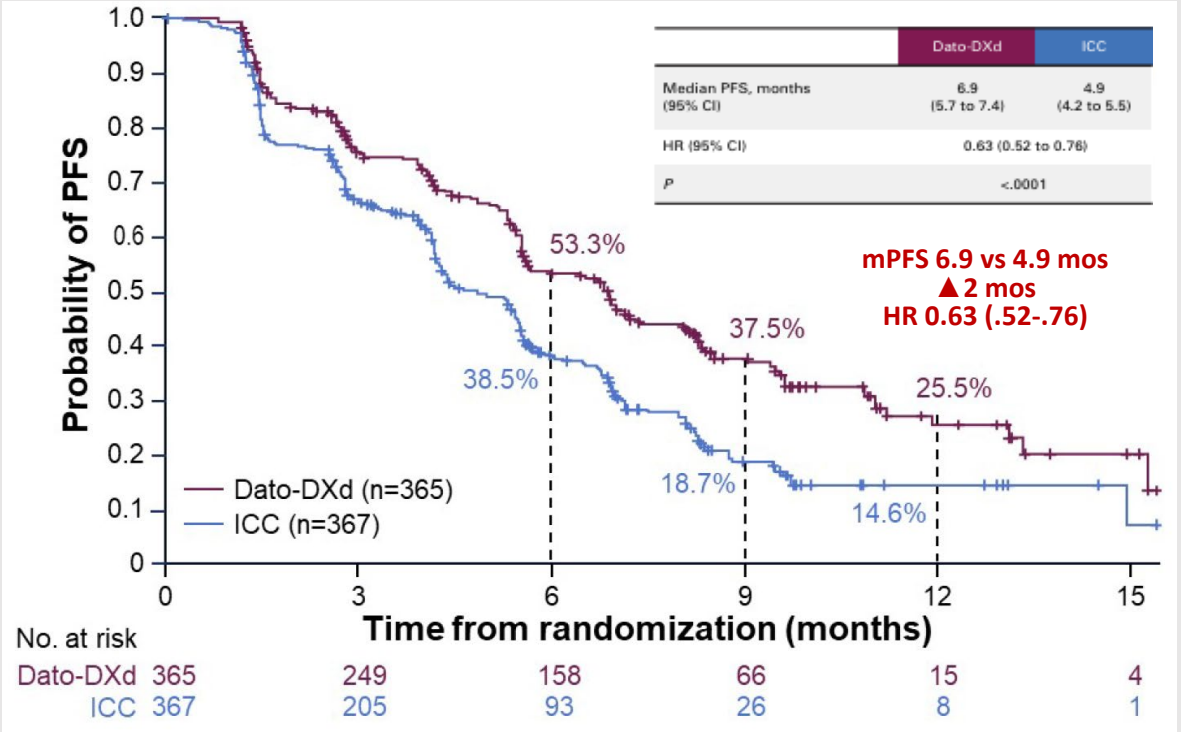
RANDOMIZED

1:1

Dato-DXd
6 mg/kg IV day 1 q3w
n=365

ICC[a]
Eribulin D1, 8 q3w; vinorelbine D1, 8 q3w;
gemcitabine D1, 8 q3w; capecitabine D1-14 q3w
n=367

Dual primary endpoints: PFS by BICR per RECIST v1.1, OS
Secondary endpoints: ORR, PFS by investigator, TFST, safety, PROs



- Similar findings in those with prior CDK4/6i ≤ 12 mos vs > 12 mos
- Any grade stomatitis seen in 50% on Dato-DXd (6% G3) – 0.3% D/C rate due to stomatitis

[a] Investigator's choice of Chemo (ICC): eribulin, 1.4 mg/kg IV on D1, 8, q3w; vinorelbine, 25 mg/m^2 IV on D1, 8, q3w; gemcitabine 1000 mg/m^2 IV on D1, 8, q3w; capecitabine 1000 or 1250 mg/m^2 (dose per standard institutional practice BID D1-14, q3w.

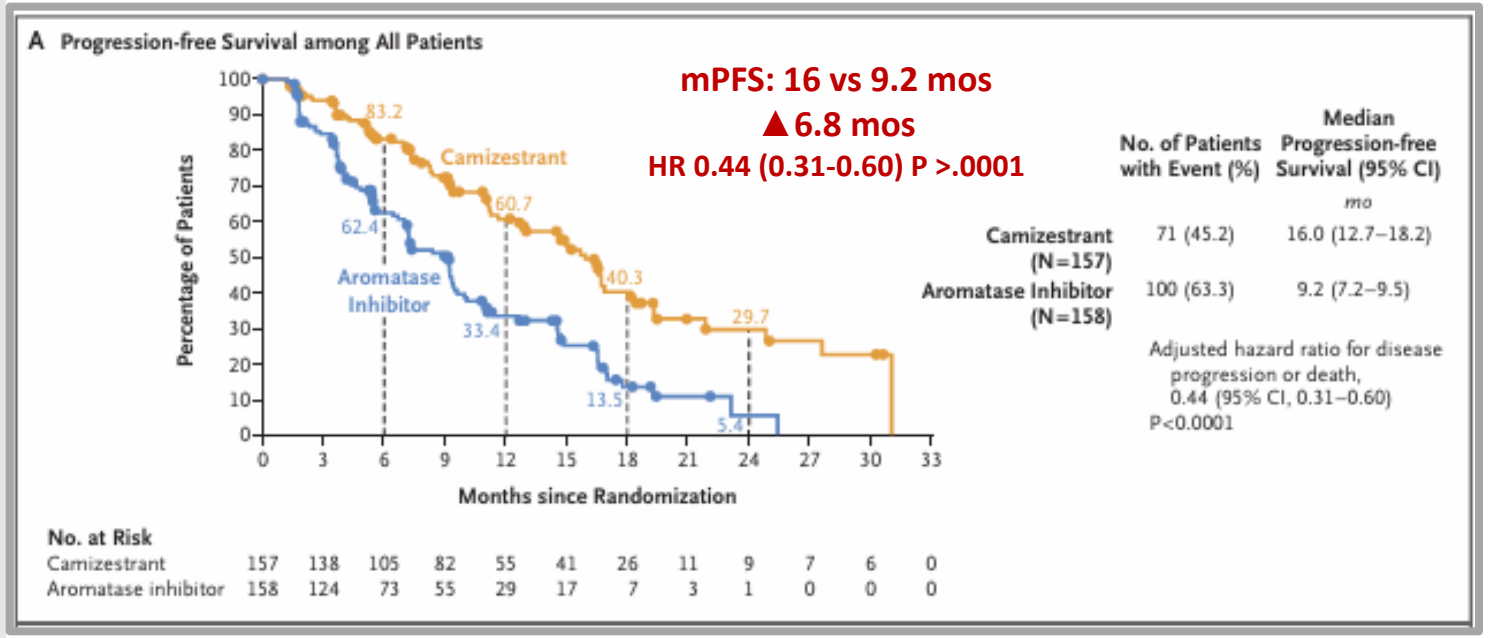
Pernas S, et al. ASCO 2024. Abstract 1006
Bardia A et al. JCO 2024;43:285-96.

SERENA-6 P3 Pbo Controlled RCT: Role of Switching 1L ET at time of Molecular Progression

Key Eligibility Criteria
- HR+/HER2- aBC
- On AI + CDK4/6i as 1L ET for at least 6 mos
- **ESR1m detected in ctDNA with no radiographic PD**

N=315 → RANDOMIZED (1:1)
- **Camizestrant (75 mg qd) + AI Pbo + continuing CDK4/6i**
- **Continuing AI + Camizestrant Pbo + continuing CDK4/6i**

Primary endpt: PFS
Key secondary endpts: PFS2, OS



<u>*ESR1m* surveillance during 1L AI + CDK4/6i</u>:
- **3256** pts tested for *ESR1m* in ctDNA every 2-3 mos at time of scans
- **548 (17%)** found to have *ESR1m* (median time: 22 mos)
  - 51% at 1st test; 38% after 2- 5 tests; 11% after > 5 tests
  - **53 (10%)** concurrent PD on scan
- **1949** still in screening when enrollment closed (estimated emergence *ESR1m* 42%)

Bidard FC et al NEJM 2025;393:569-80

SERENA-6: PFS2

Second progression-free survival (PFS2)

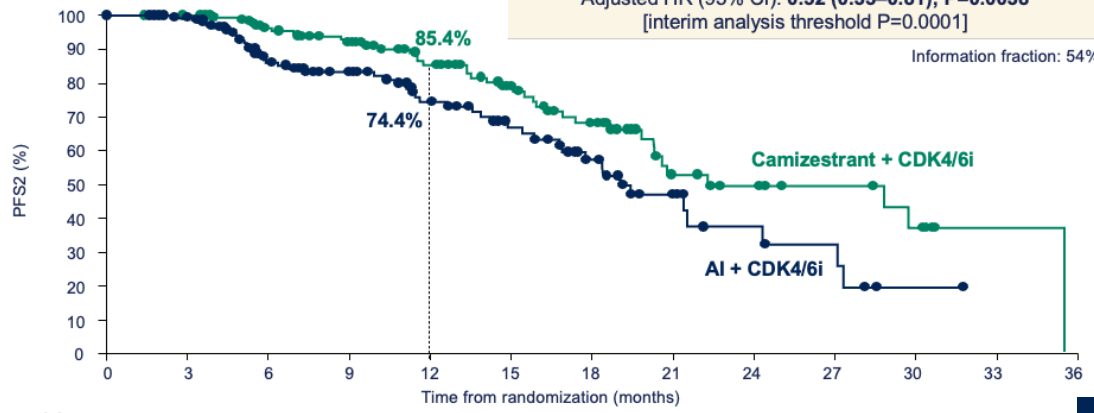
Key secondary endpoint

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47

Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038**
[interim analysis threshold P=0.0001]

Information fraction: 54%

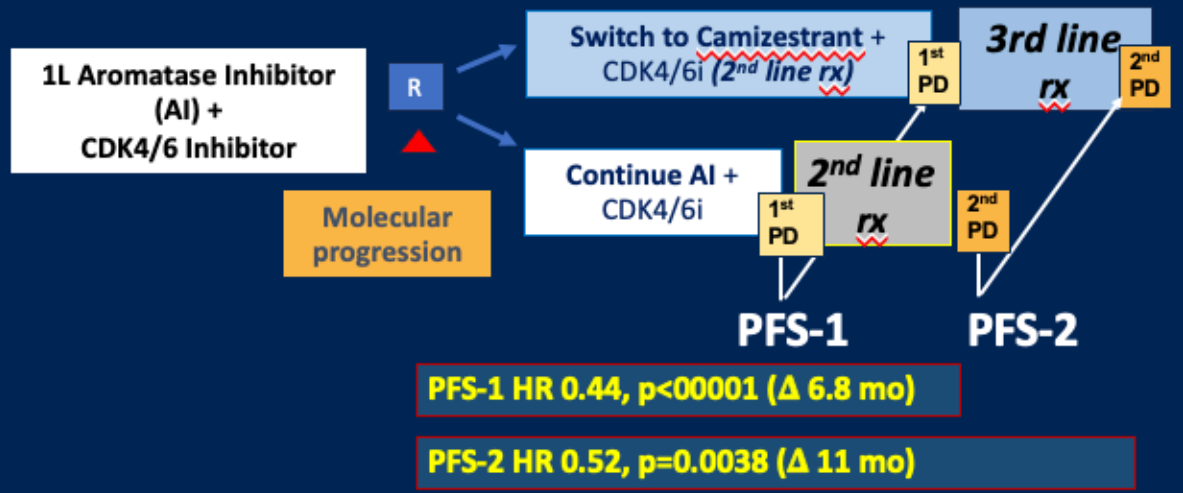


Number of patients at risk

Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0

HR was estimated using the Cox proportional hazard model adjusted for stratification factors. Final PFS2 analysis will occur at 158 PFS2 events.

PFS-2 in SERENA-6



Limitations:

- Design issues
- Only 10% oral SERD in control after PD
- Impact of ctDNA screening
- Interesting that mPFS of control group 9 mos

Turner N et al. ASCO 2025; LBA4; DeMichele A. ASCO 2025 Plenary Discussion

Current Approach for HR+/HER2 Negative mBC (September 2025)

1L

- AI/OS + CDK4/6i
- Fulv + Palbo + Inavolisib (*PIK3CAm* and ET refractory)

▲ NGS

Biopsy/ctDNA at diagnosis and ctDNA at PD

2L

Actionable mutation

- Fulv + Alpelisib (*PIK3CAm*)
- Fulv + Capivasertib (*PIK3CAm/PTENm/AKTm*)
- Elacestrant (*ESR1m*)
- PARPi (*g/tBRCA* or *gPALB2*)

No actionable mutation

- ET + Everolimus OR
- Switch CDK4/6i + ET

- Cape OR
- T-DXd (if aggressive disease and HER2low/ultralow)

Other Agents:

- Imlunestrant +/- Abema??
- Vepdegestrant??
- Camizestrant (ctDNA guided)??

3L and beyond

- ET + Capivasertib
- ET + Everolimus
- Switch CDK4/6i + ET
- T-DXd (if not given 2L)
- Sacituzumab
- Dato-DXd
- Chemo many options

Other Key Points:

- If visceral crisis: go to chemo/ADCs
- *NTRKm,* MSI-H; TMB; RETm

Ongoing clinical trials exploring:

- New antiestrogens
- New CDK inhibitors (4/2; 4; 2; 7 …)
- New targeted agents (PI3K, RAS pathway)
- New ADCs


Thank you.....

Summary of Trials with Oral SERDs

	EMERALD[1]	EMBER-3[2]
	Elacestrant (n = 239)	**Imlunestrant (n = 331)**
Lines of ET for mBC (0 / 1 / 2), %	NOT ALLOWED / 54 / 46	32 / 63 / NOT ALLOWED
Prior mBC therapy		
CDK4/6i	100%	~60%
Chemo	20%	NOT ALLOWED
FULV	30%	NOT ALLOWED
Population, %		
Primary resistance	24%	8%
Visceral mets	68%	57%
Outcome		
mPFS (*ESR1m*)	**3.78 vs 1.87 mos** HR 0.50 (95% CI 0.34-0.74), p=0.0005	**5.5 vs 3.8 mos** HR 0.62 (95% CI 0.46-0.82), p<0.001
mPFS (*ESR1m*) if > 12 mos DOR prior CDK4/6i	**8.61 vs 1.91 mos** HR 0.41 (95% CI 0.26-0.63)	NR

1. Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256; 2. Jhaveri K, et al. *NEJM* 2025;392:12.