Breakout session

LIVING BEYOND
BREAST CANCER®

Understanding the role of personalized medicine in your cancer journey

Speaker: Seth Wander, MD, PhD

Mass General Brigham
Mass General Cancer Center

Understanding the Role of Personalized Medicine in Your Cancer Journey

Evolving Biomarker-Based Treatment Options

Living Beyond Breast Cancer: 2026 Conference on Metastatic Breast Cancer
April 19th, 2026

Seth A. Wander, MD, PhD
Director of Precision Medicine, Termeer Center for Targeted Therapies
Director of Translational Research, Breast Oncology Program
Assistant Professor of Medicine, Harvard Medical School
Massachusetts General Hospital

swander@mgh.harvard.edu

Disclosures

Consulting/Advisory Board: Foundation Medicine, Veracyte, Hologic, Eli Lilly, Biovica, Pfizer, Arvinas, Puma Biotechnology, Novartis, AstraZeneca, Genentech, Regor Therapeutics, Stemline/Menarini, Gilead, Celcuity, Precede Biosciences, Halda Therapeutics, Boundless Bio

Education/Speaking: Eli Lilly, Guardant Health, 2ndMD

Institutional Research Support: Genentech, Eli Lilly, Pfizer, Arvinas, Nuvation Bio, Regor Therapeutics, Sermonix, Puma Biotechnology, Stemline/Menarini, Phoenix Molecular Designs

ASCO 2025:
“Optimizing Targeted Therapies with Molecular Markers”

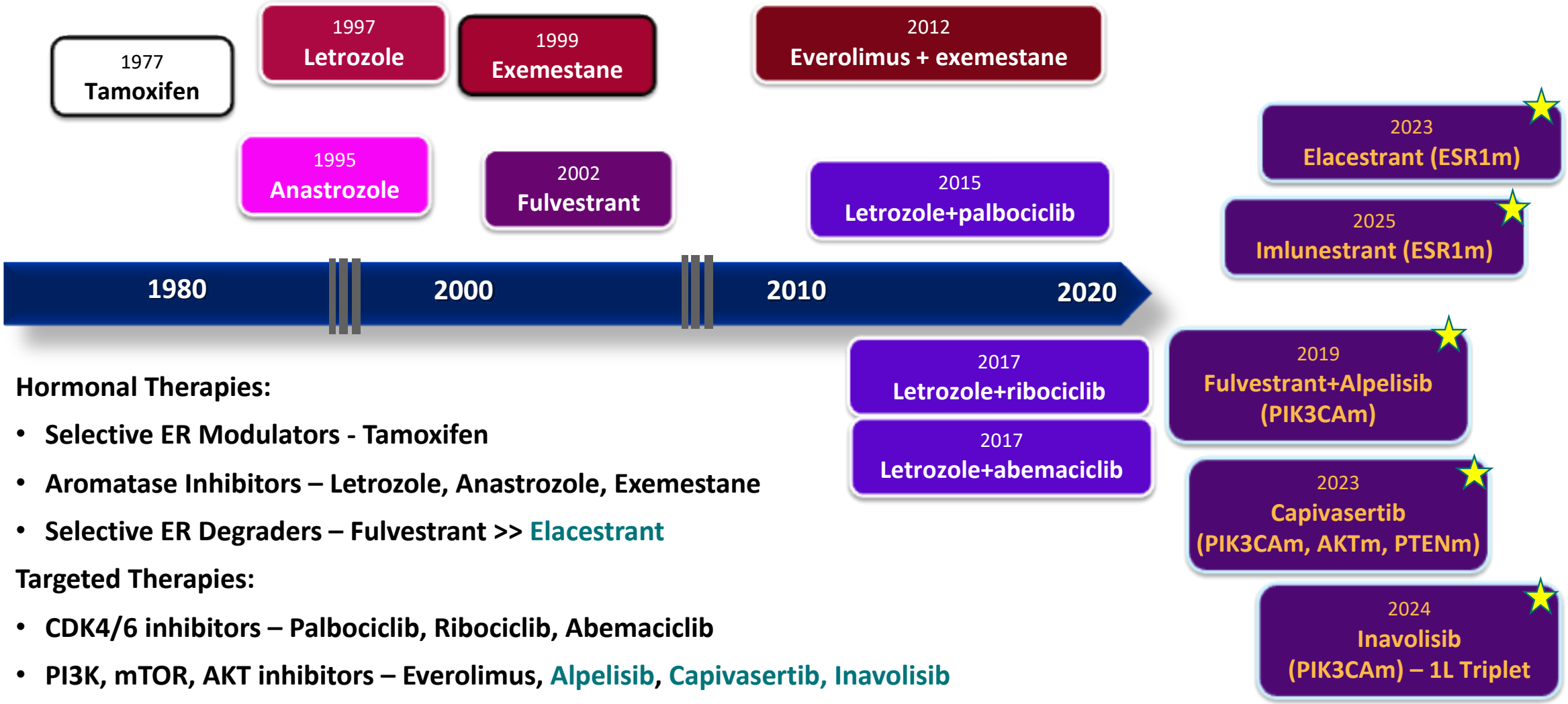
Delivering upon the promise of personalized medicine and precision oncology…

Finding the right drug, for the right patient, at the right time…

In 2014, for HR+/HER2- MBC….

Aromatase Inhibitor → **Fulvestrant (SERD)** → **Chemotherapy**

HR+/HER2- MBC: The Road to Personalized Therapy



Hormonal Therapies:

- **Selective ER Modulators - Tamoxifen**
- **Aromatase Inhibitors – Letrozole, Anastrozole, Exemestane**
- **Selective ER Degraders – Fulvestrant >> Elacestrant**

Targeted Therapies:

- **CDK4/6 inhibitors – Palbociclib, Ribociclib, Abemaciclib**
- **PI3K, mTOR, AKT inhibitors – Everolimus, Alpelisib, Capivasertib, Inavolisib**

Evolving Biomarkers for Precision Medicine in Metastatic Breast Cancer

- BRCA mutations and PARP inhibition
- Targeting endocrine resistance via ESR1 mutations (HR+/HER2-)
- Emerging strategies to target PI3K signaling
- HER2-low disease as a new dimension of therapy selection
- Summary, key questions, future directions

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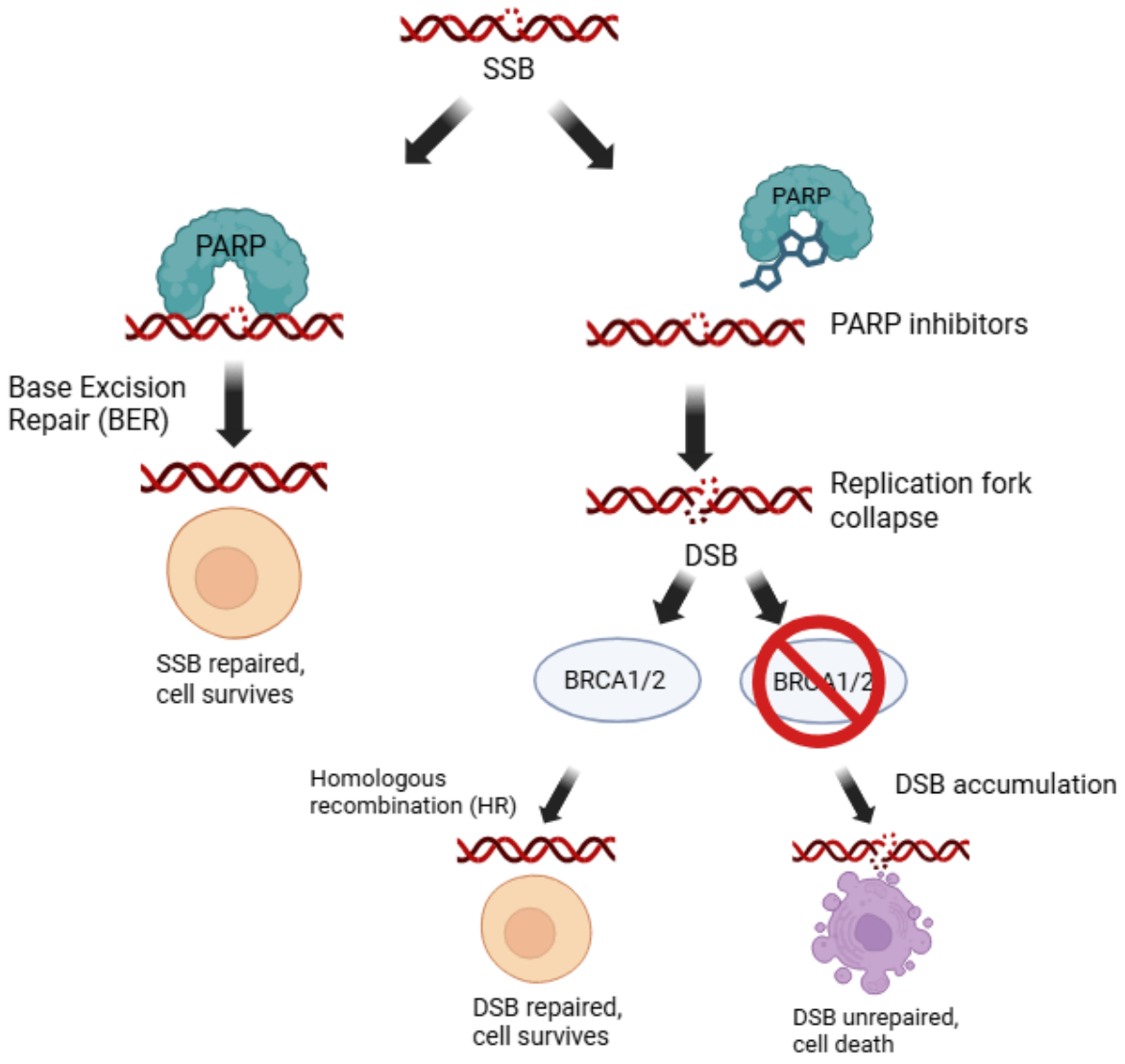
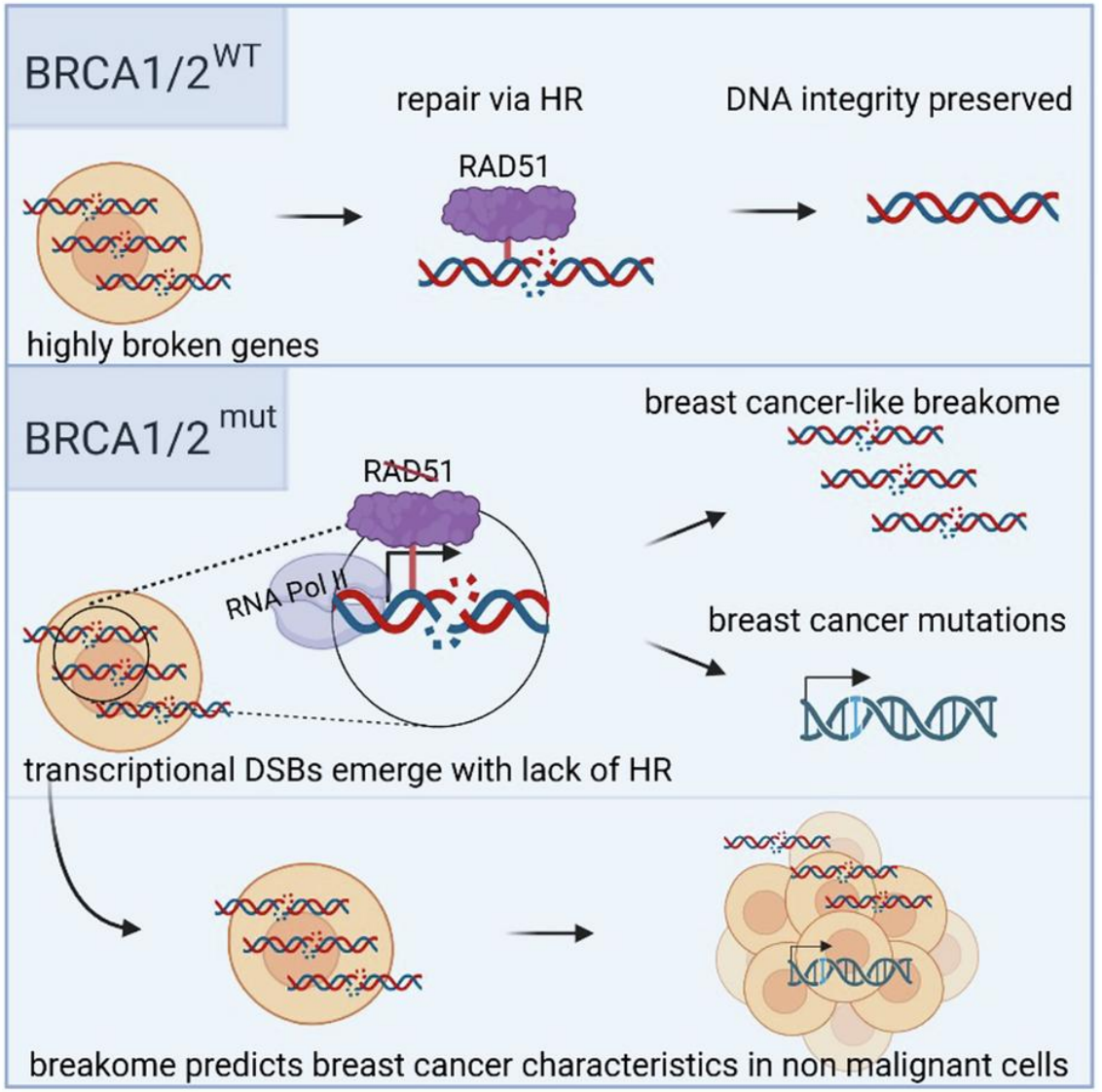
BRCA: Inherited Impact on DNA Damage Repair

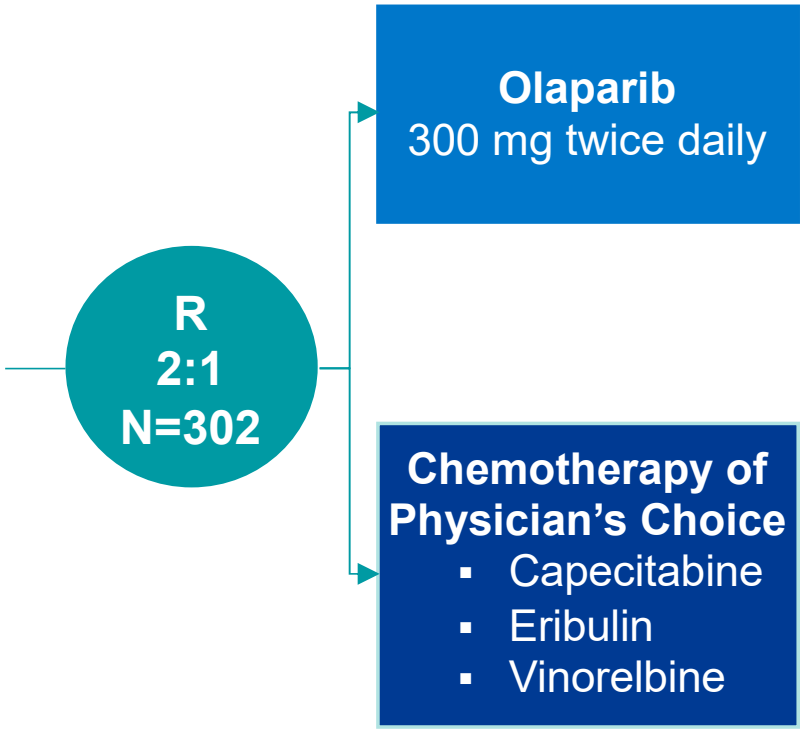




Zheng F et al Biomed and Pharm 2020; Flayshman SO et al Cell Death and Dis 2025

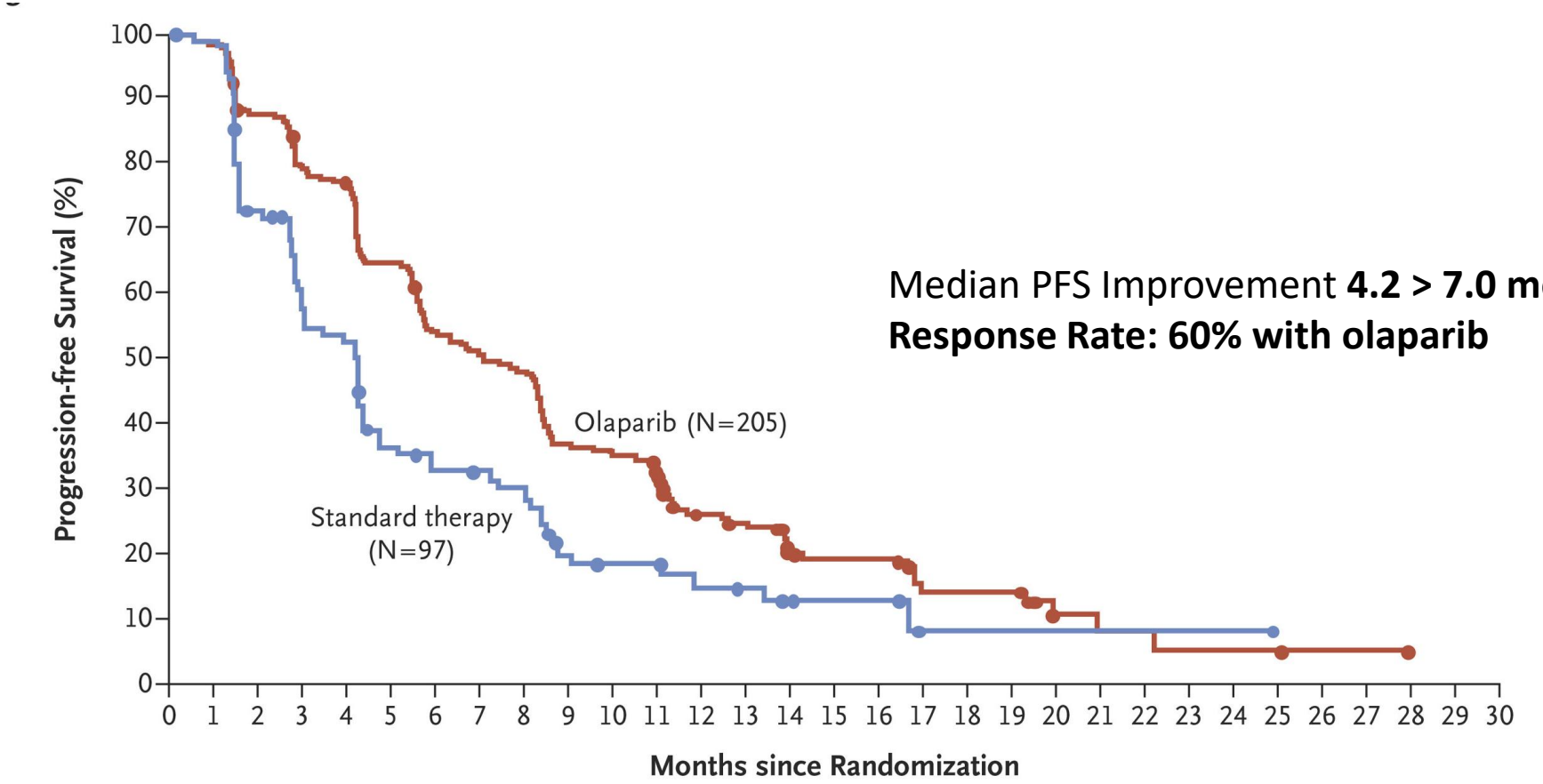
OlympiAD: PARP Inhibition Improves Outcomes for BRCAm MBC

- HER2– metastatic breast cancer (HR+ or TNBC[a])
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation[b]
- ≤2 prior lines of chemotherapy in the metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- Prior platinum use allowed if:
  - No evidence of progression during treatment in advanced setting
  - ≥12 months since (neo)adjuvant Tx



Robson M et al NEJM 2017

OlympiAD: PARP Inhibition Improves Outcomes for BRCAm MBC



Median PFS Improvement **4.2 > 7.0 months**
Response Rate: 60% with olaparib

No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Robson M et al NEJM 2017

OlympiAD: PARP Inhibition Improves Outcomes for BRCAm MBC

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N = 205)		Standard-Therapy Group (N = 91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

Robson M et al NEJM 2017

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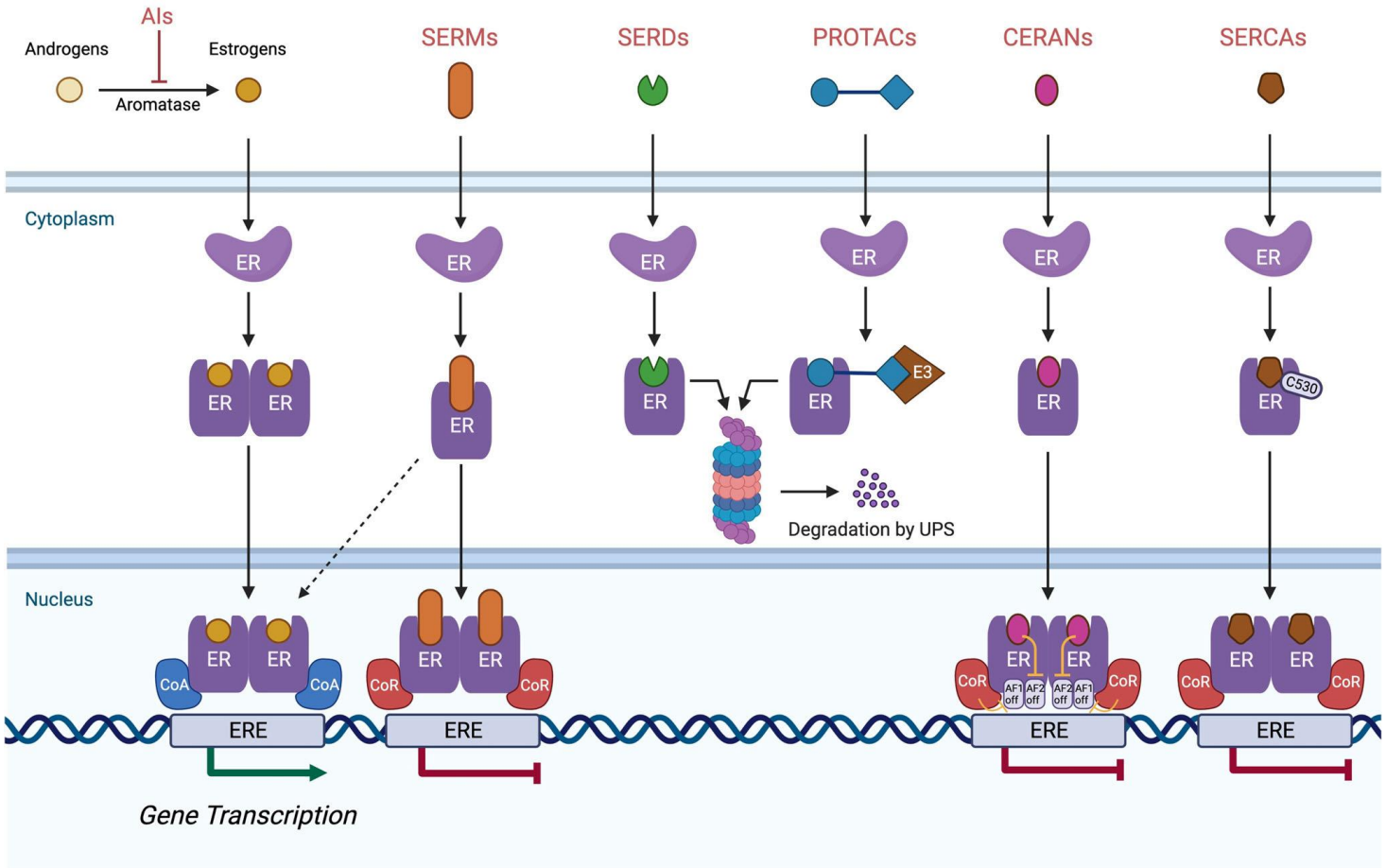
Emerging Antiestrogen Agents with Novel Mechanisms



AI: Aromatase Inhibitor

SERM: Selective ER Modulator

SERD: Selective ER Degrader

PROTAC: Proteolysis Targeting Chimeric

CERAN: Complete ER Antagonist

SERCA: Selective ER Covalent Antagonist

Patel R et al NPJ Breast Cancer 2023

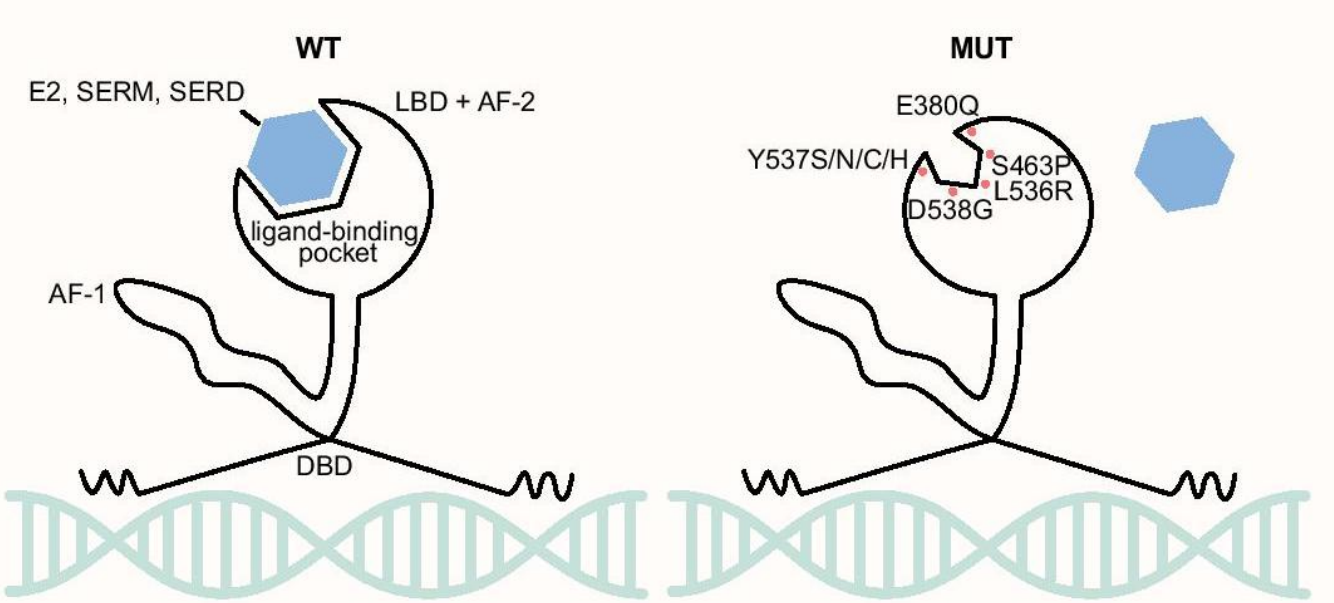
ESR1 Mutations Promote Ligand-Independent Signaling

ESR1 = Estrogen receptor 1 (ERalpha)
Present in breast, ovary, uterus
Hormone-dependent transcription factor

After estrogen binding, complex genomic regulation of breast cell growth, survival, metabolism

Mutations tend to occur in the ligand binding domain

- Promote ligand (estrogen)-independent receptor activity and cell survival/growth

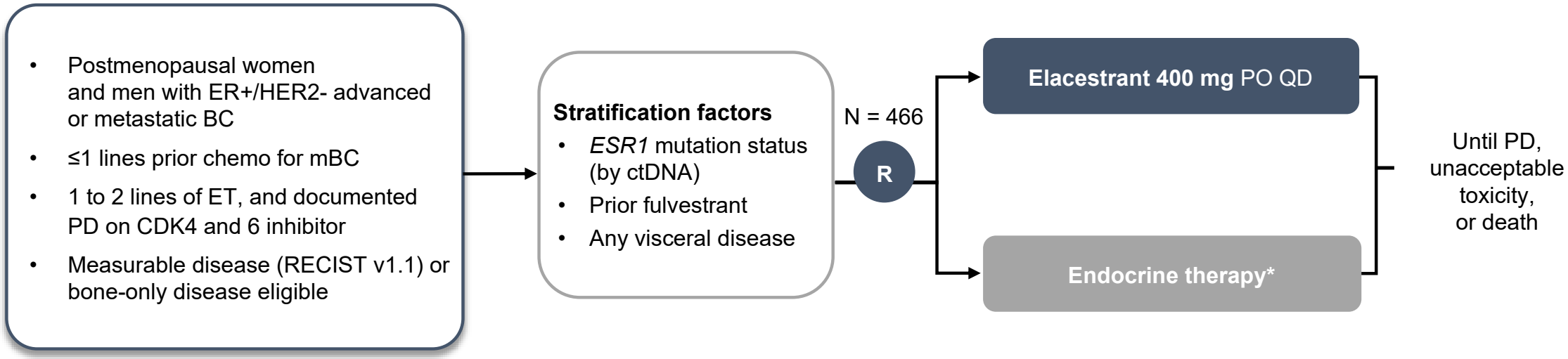


Jeselsohn R et al Nat Rev Clin Onc 2015
Brett JO et al Breast Cancer Res 2021

EMERALD: Elacestrant Phase III

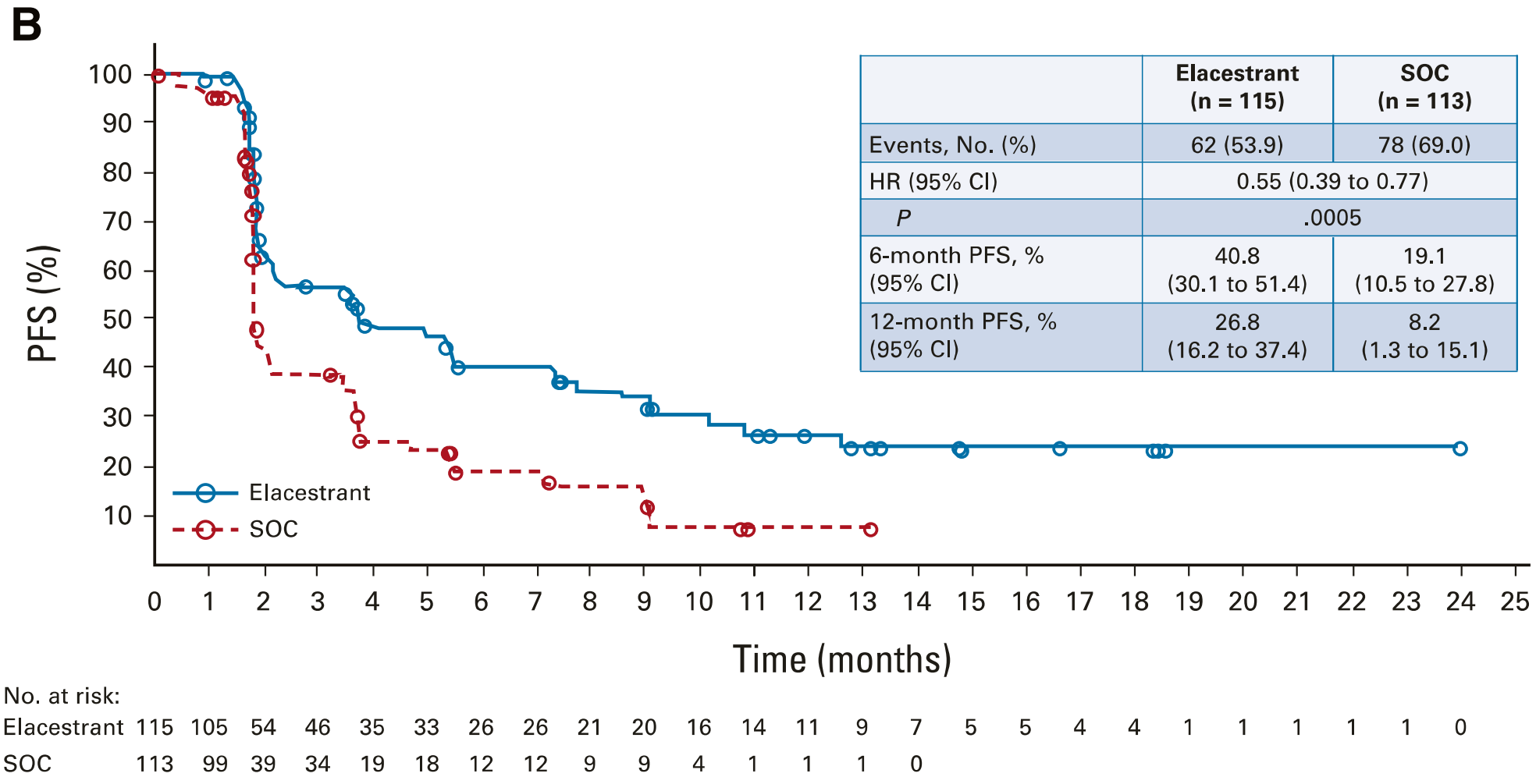
Patient Characteristics: Elacestrant vs. Control

- Prior Chemotherapy: 20% vs 24%
- ESR1m: 48% vs 47%
- Two prior lines of ET: 46% vs 41%



Bidard FC et al JCO 2022

EMERALD: Elacestrant Phase III

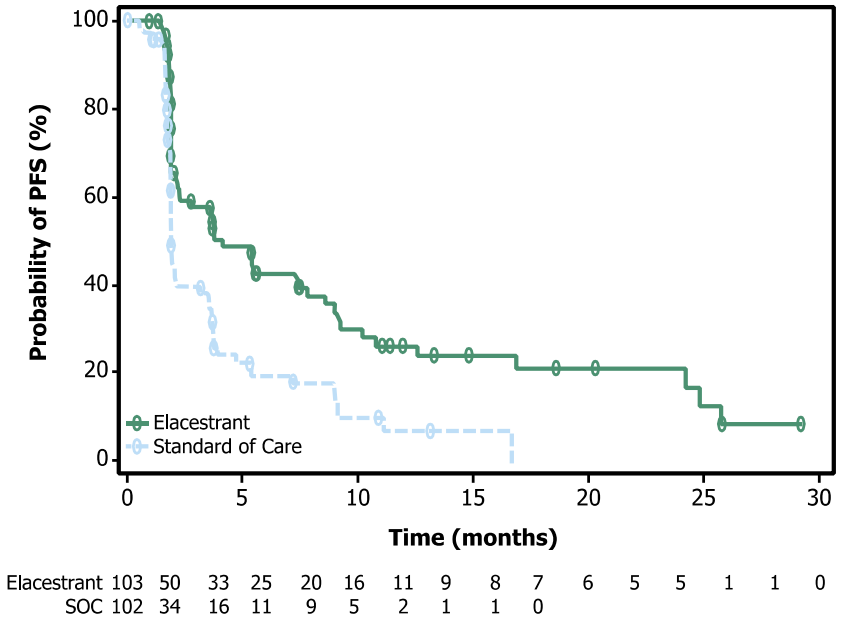


	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Bidard FC et al JCO 2022

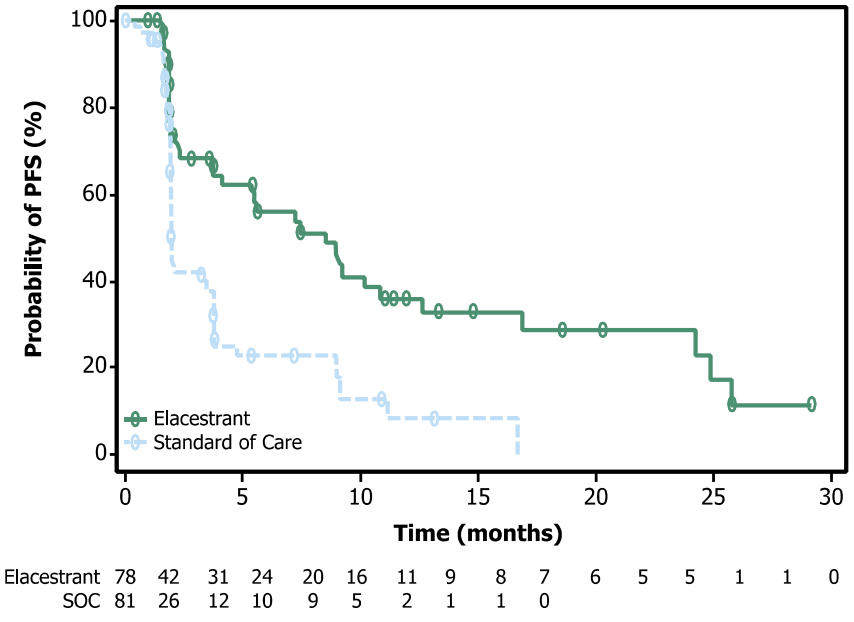
EMERALD: Efficacy Subgroups

At least 6 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

Bardia et al CCR 2024

Oral SERDs are Well Tolerated

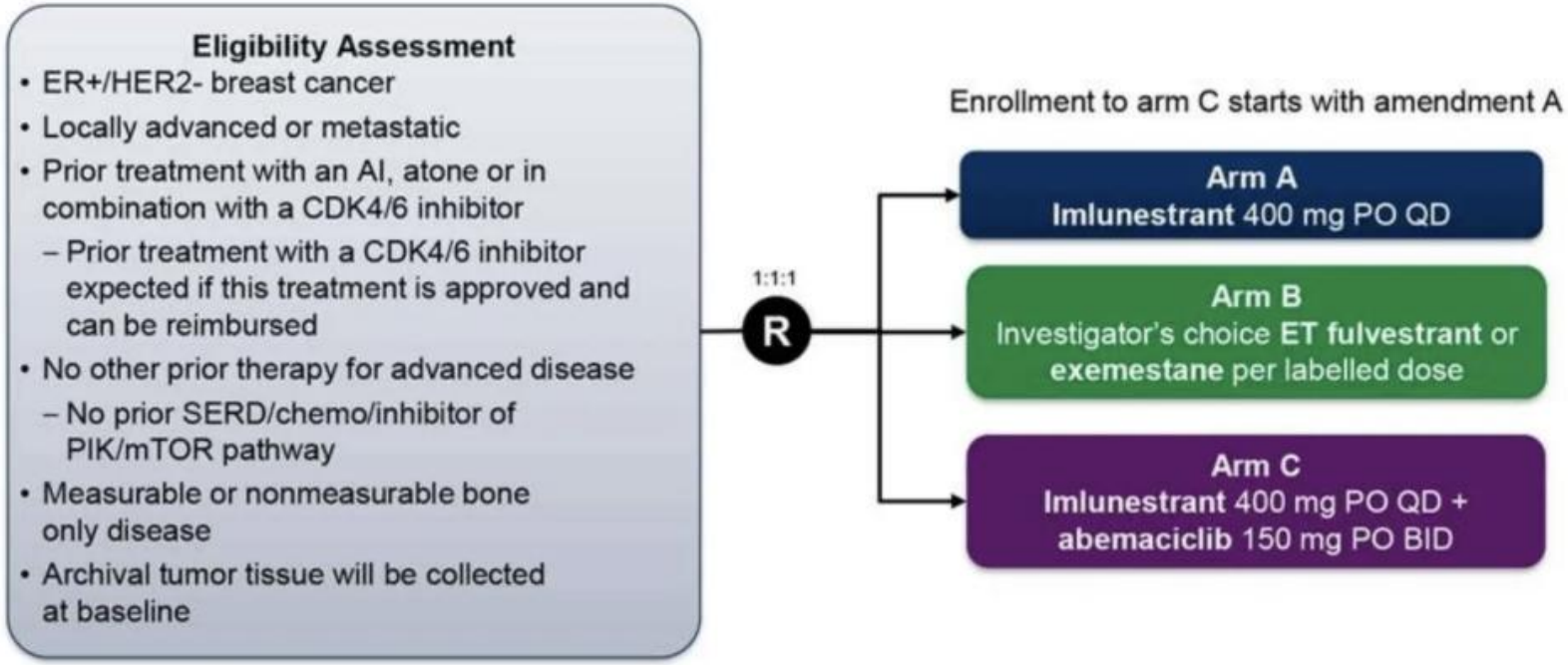
AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0
Constipation	29 (12.2)	0	15 (6.6)	0
Hot flush	27 (11.4)	0	19 (8.3)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

Bidard FC et al JCO 2022

EMBER3: Imlunestrant Phase III

Patient Characteristics: Imlunestrant vs. Control

- No prior chemotherapy, 1 prior line of ET
- ~40% of patients were CDK4/6i-naive
- ESR1m: 41.7% vs 35.8

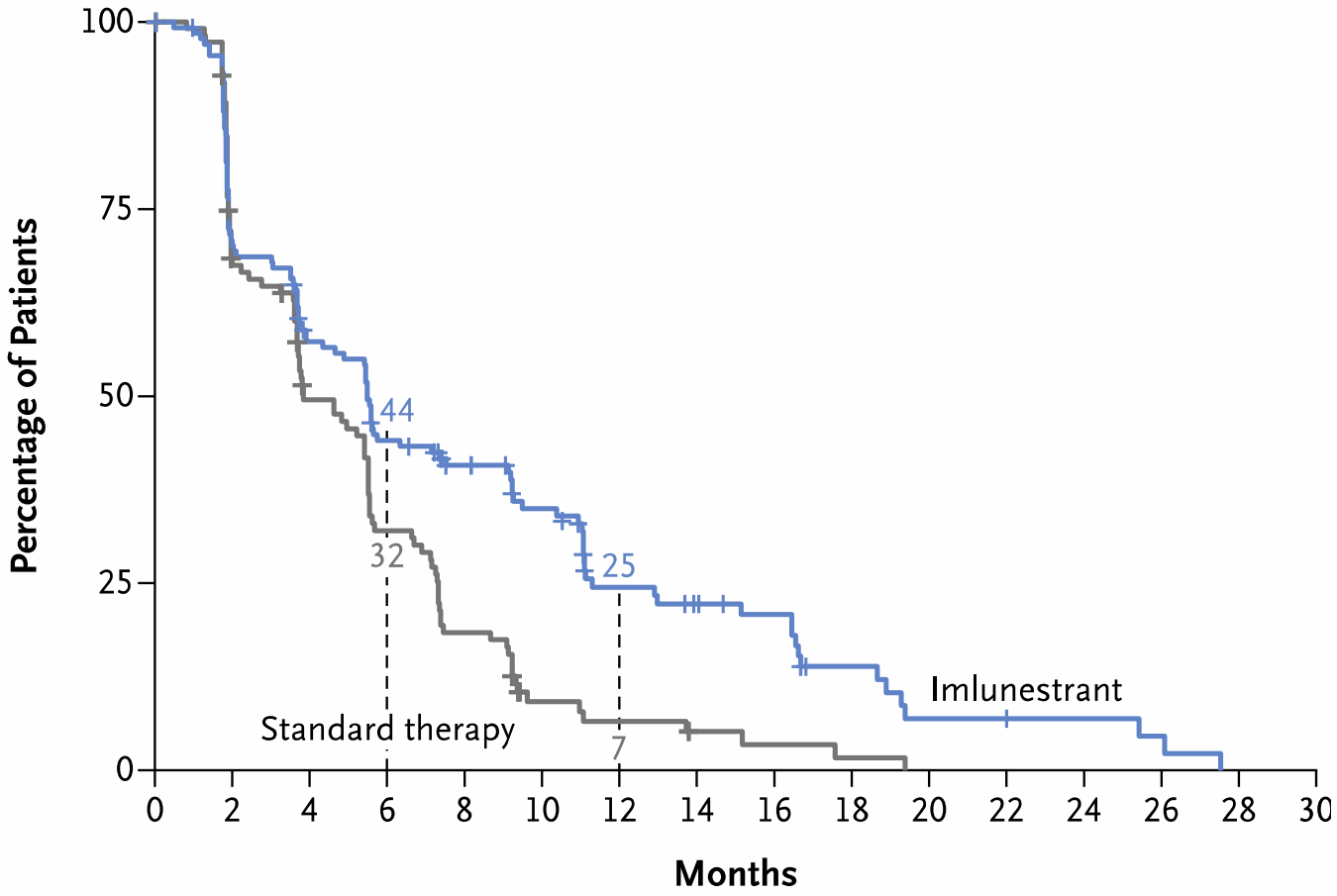


Jhaveri KL et al NEJM 2024

EMBER3: Imlunestrant Phase III

Median PFS Improvements:
ESR1m: 3.8 > 5.5 months

A Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard



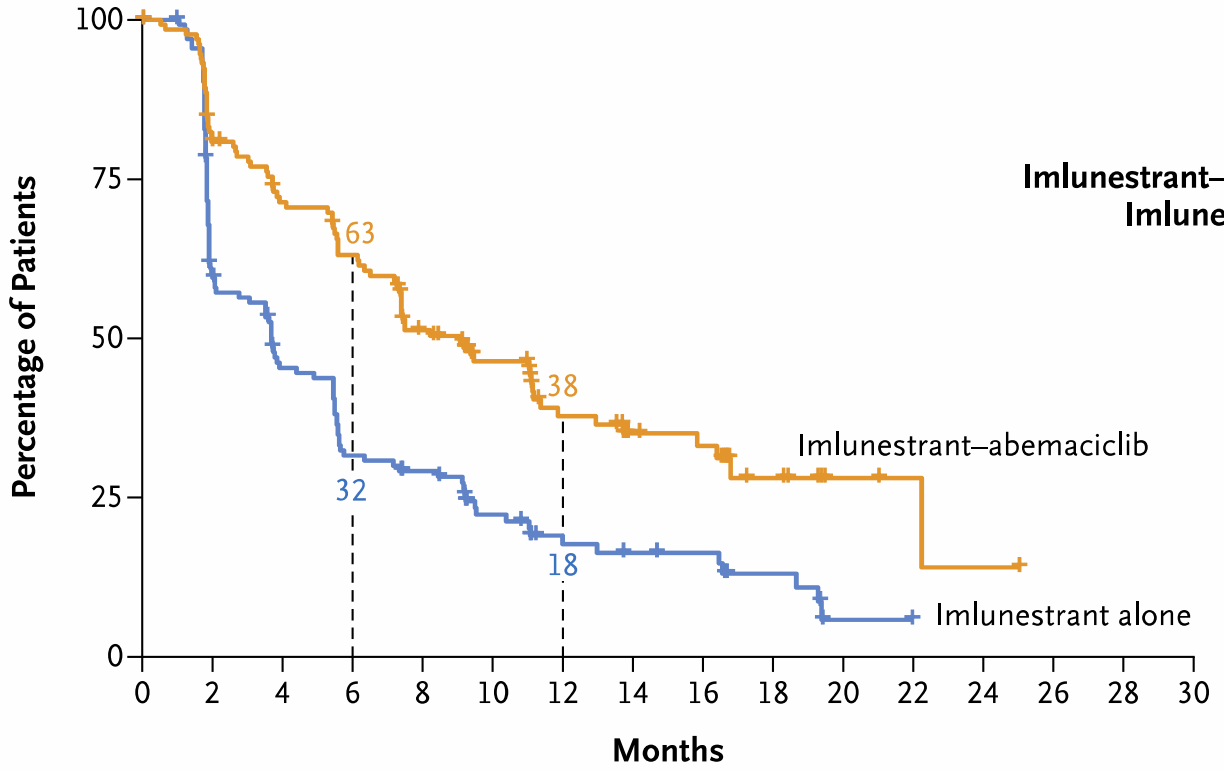
No. at Risk

Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

Jhaveri KL et al NEJM 2024

EMBER3: Imlunestrant + Abemaciclib Efficacy

B **Progression-free Survival among Patients with Previous CDK4/6 Inhibitor Treatment, Imlunestrant–Abemaciclib vs. Imlunestrant Alone**



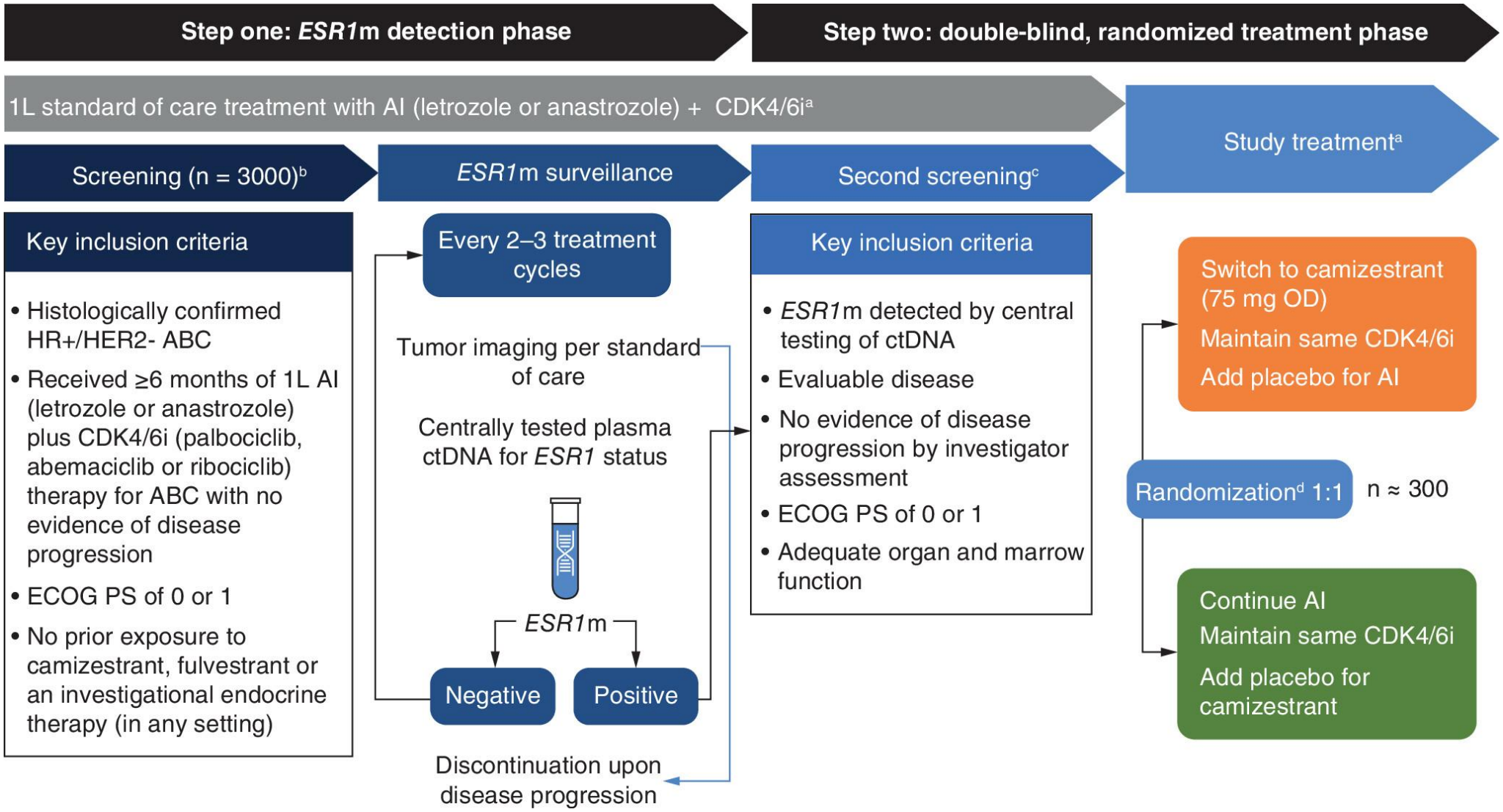
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

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

Jhaveri KL et al NEJM 2024

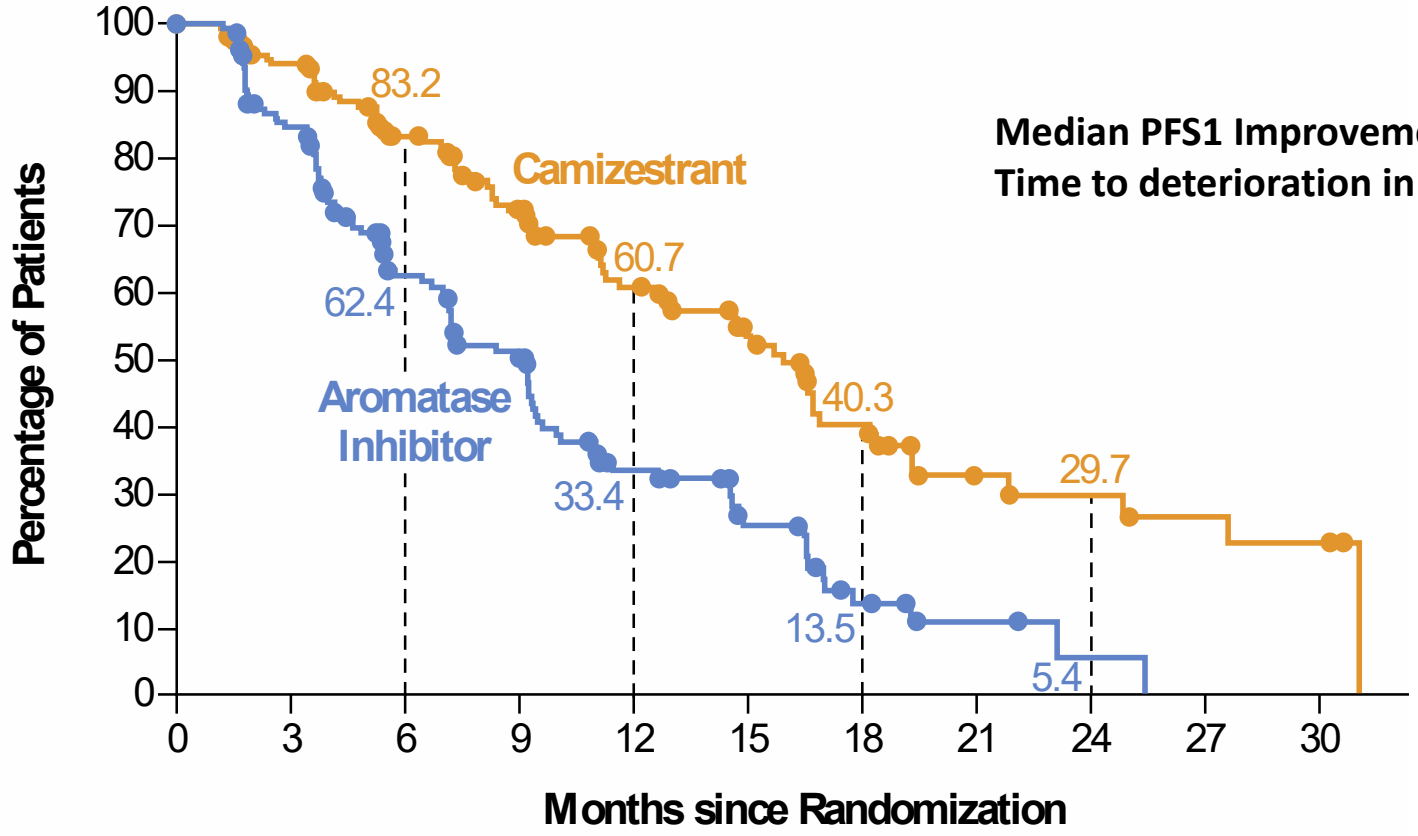
SERENA-6: Phase III, Camizestrant via ctDNA ESR1 Dynamics



Turner NC et al Future Onc 2023; NCT04964934

SERENA-6: Dynamic ctDNA Switch Outcomes

A Progression-free Survival among All Patients



Median PFS1 Improvement: 9.2 > 16.0 months
Time to deterioration in quality of life: 6.4 > 23.0 months

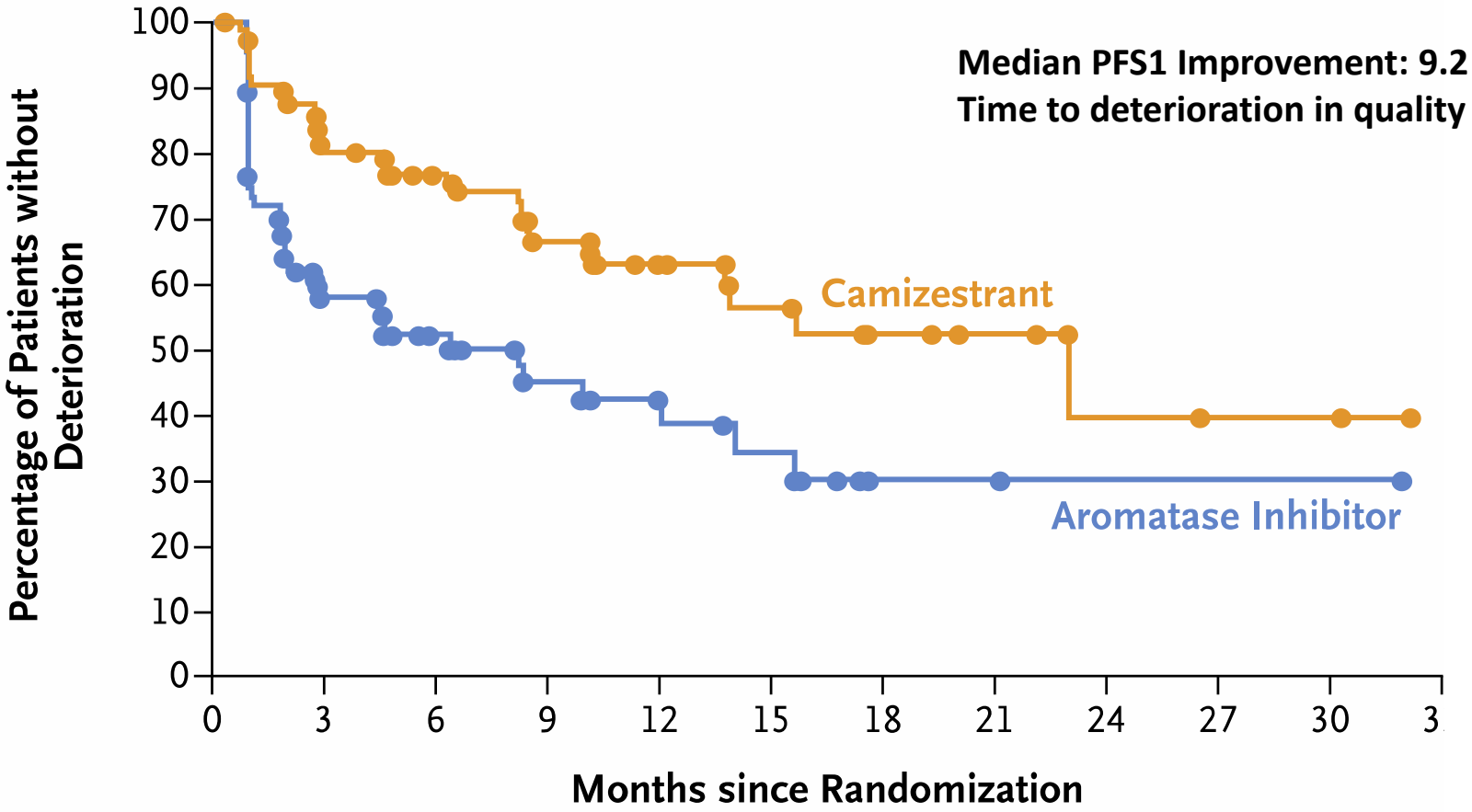
No. at Risk

Camizestrant	157	138	105	82	55	41	26	11	9	7	6
Aromatase inhibitor	158	124	73	55	29	17	7	3	1	0	0

Bidard FC et al NEJM 2025

SERENA-6: Dynamic ctDNA Switch Outcomes

Median PFS1 Improvement: 9.2 > 16.0 months
Time to deterioration in quality of life: 6.4 > 23.0 months



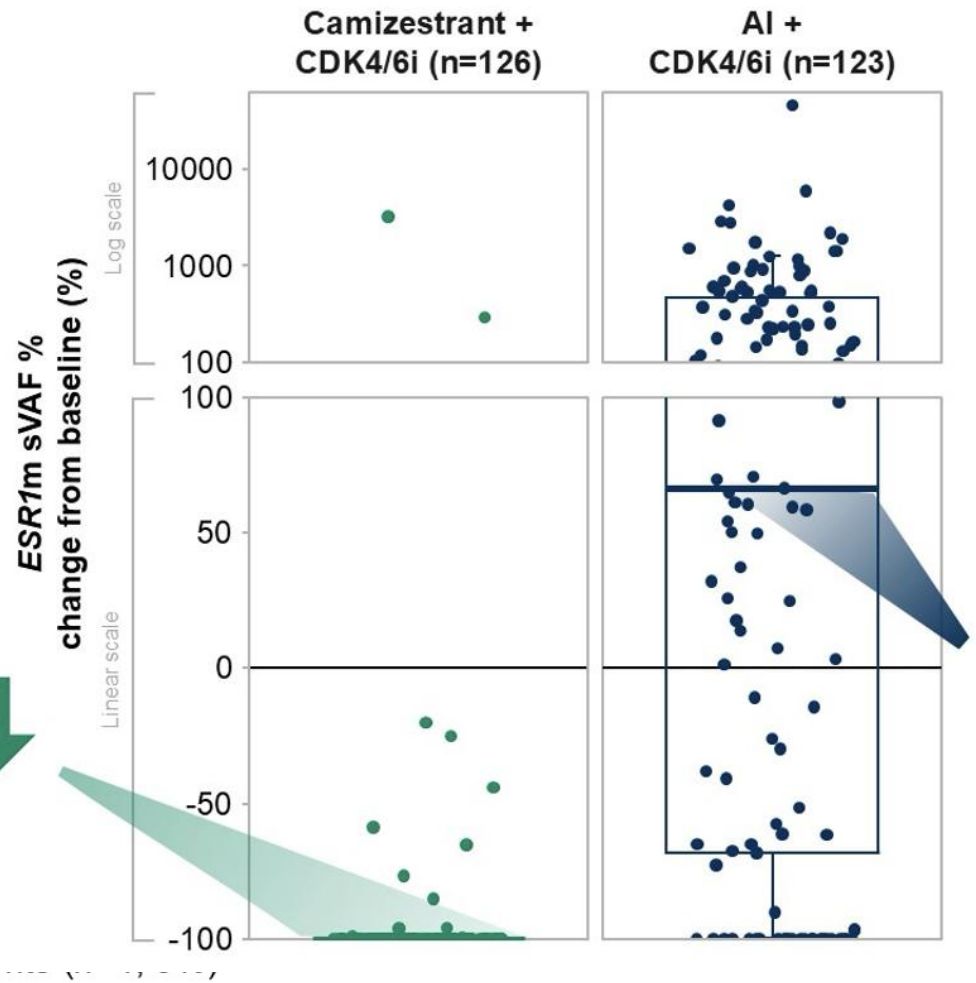
No. at Risk

Camizestrant	107	72	59	40	24	16	9	6	3	2	2	0
Aromatase inhibitor	95	42	26	16	11	8	2	2	1	1	1	0

Bidard FC et al NEJM 2025

SERENA-6: Dynamic ESR1 VAF on Treatment

*ESR1*m allele frequency was **profoundly reduced** in the camizestrant + CDK4/6i arm vs the AI + CDK4/6i arm (Wilcoxon nominal P<0.00001)



In the AI + CDK4/6i arm, *ESR1*m allele frequency increased >500% from baseline in **24.4%** of patients vs **0.8%** of patients in the camizestrant + CDK4/6i arm

Median change from baseline at C3D1 (8 weeks):

−100% (IQR: −100 to −100)

Median change from baseline at C3D1 (8 weeks):

+66.7% (IQR: −67.9 to +465.0)

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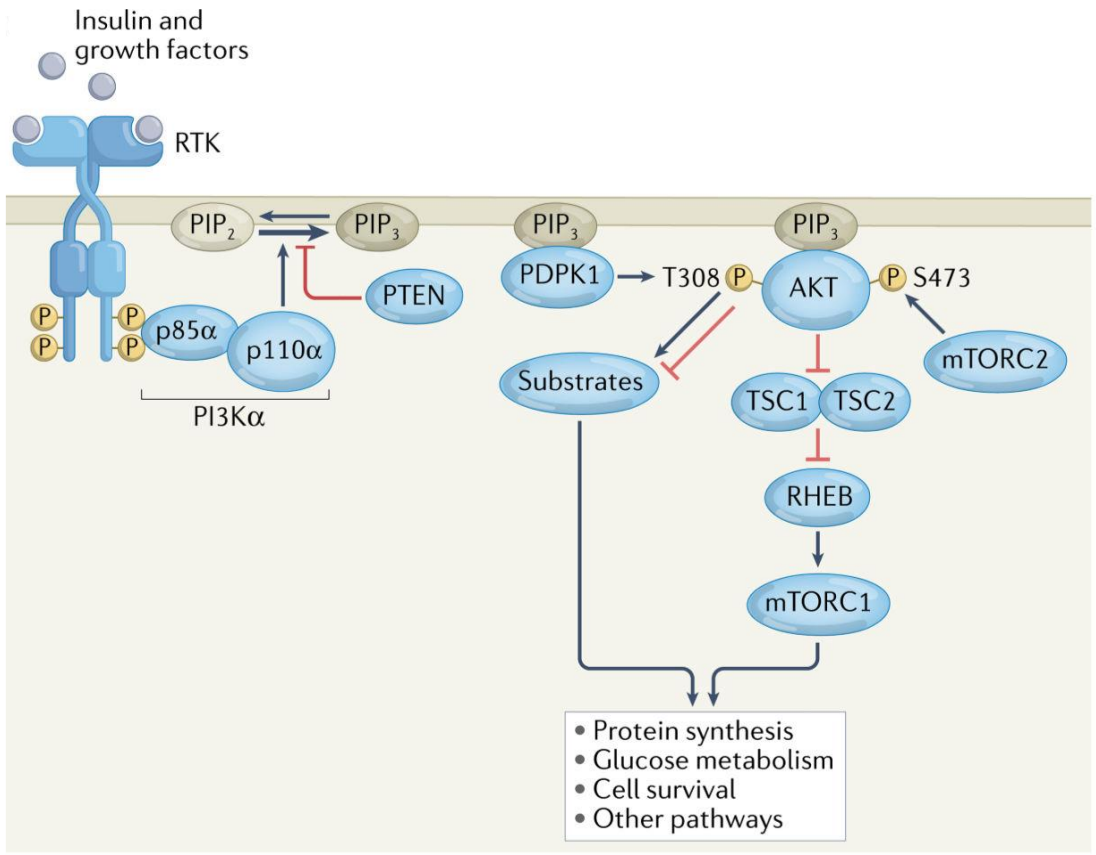
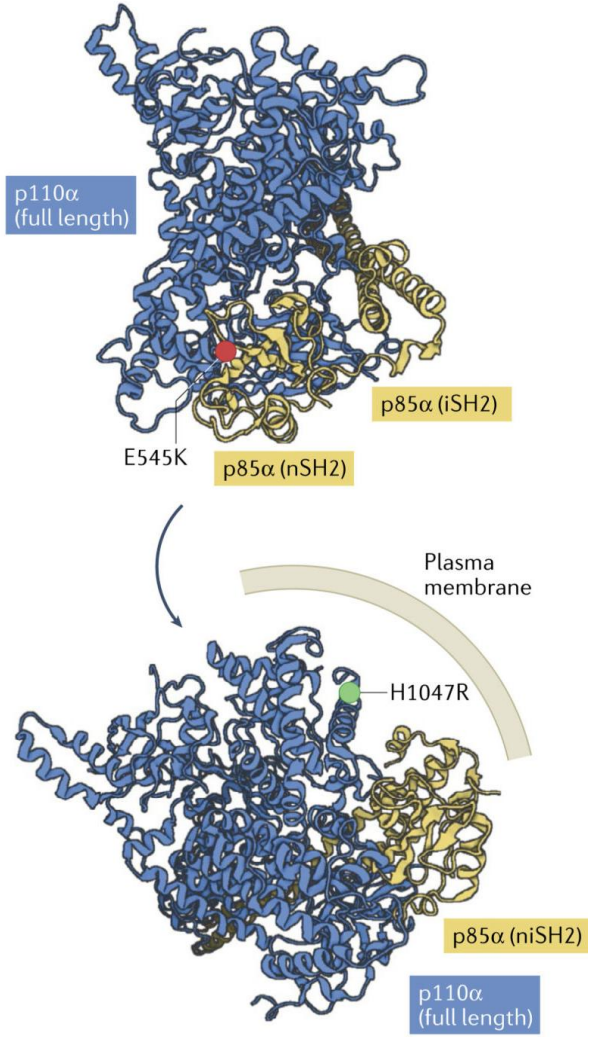
Oncogenic PI3K Signaling and Structure





PI3K = Phosphoinositide 3-kinase
PIK3CA = p110a, key catalytic subunit of PI3K

Key cancer progression driver

Translates signals outside the cell to nucleus, impacts:

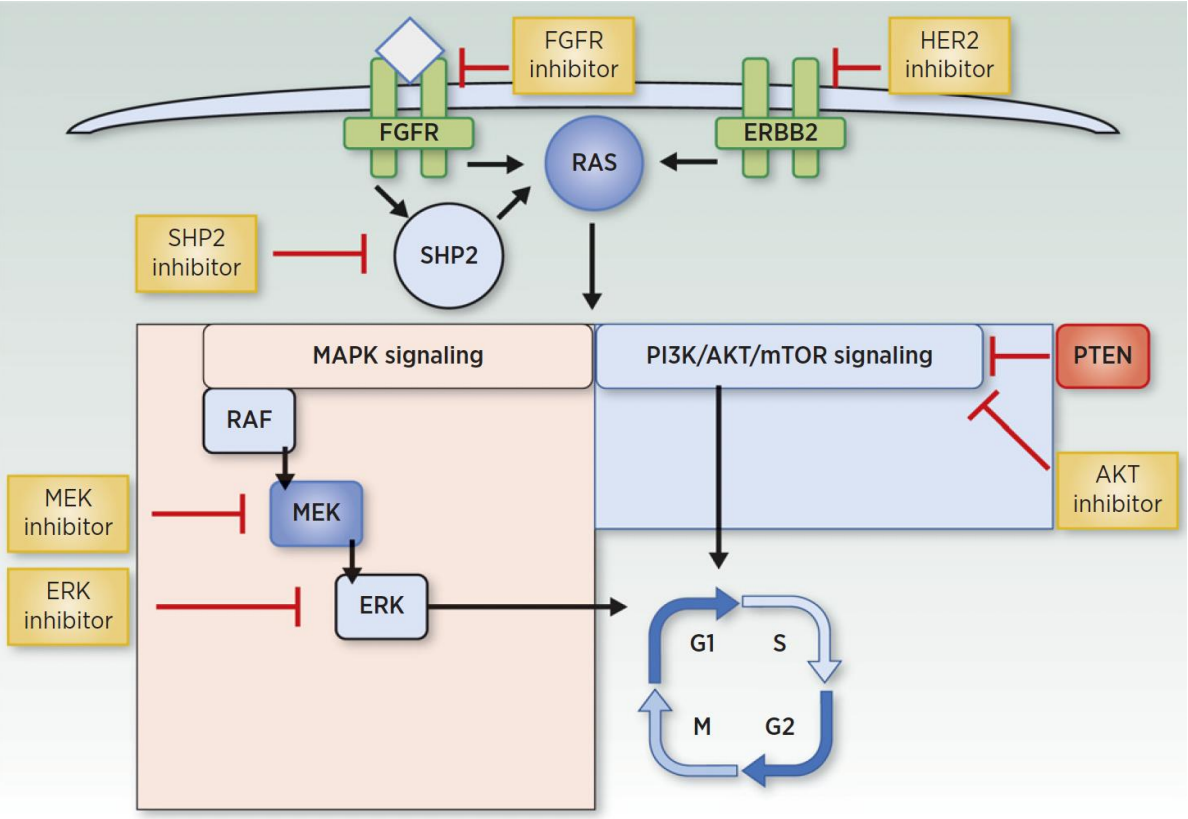
- Cell survival
- Cell growth
- Metabolism
- Motility and metastasis

Vasan N and Cantley LC Nat Rev Clin Onc 2022

Resistance Drivers Define New Therapeutic Targets

Oncogenic growth signaling mediators

Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway



RTKs @ cell surface + external ligands

PI3K >>>>>> Activated PI3K

Alpelisib
Inavolisib

Gedatolisib

AKT

Capivasertib

Everolimus

mTOR::

Cellular Growth
Survival + Division
Motility + Metastasis

Lloyd MR et al CCR 2022

INAVO123: Triplet Therapy in the 1L Metastatic Setting

Phase 3 Study of 1L Inavolisib or Placebo + CDK4/6 inhibitor + Letrozole in endocrine-sensitive, HR+/HER2–, *PIK3CA*-mut Advanced BC

INAVO123 STUDY DESIGN

Key Inclusion Criteria
- Endocrine-sensitive,* HR+/HER2-, LA/mBC
- *PIK3CA* mutation (by central ctDNA or pre-existing local tissue or ctDNA test)
- Fasting blood glucose <126 mg/dl and HbA1c <6.5%

Key Exclusion Criteria
- Any prior systemic therapy for LA/mBC
- Pts with aBC who progressed while on/within 12 months of ending adjuvant therapy
- Known and untreated, or active CNS metastases

N ≈ 450

R 1:1

- Inavolisib 9 mg PO QD + CDK4/6i† PO on D1–21 + LET PO QD of each 28-day cycle‡
- Placebo PO QD + CDK4/6i† PO on D1–21 + LET PO QD of each 28-day cycle‡

Until disease progression, unacceptable toxicity, patient withdrawal of consent, death, or study termination

Follow-up
- Safety: 30 ± 7 days after last study drug dose (or until initiation of another systemic cancer therapy, whichever occurs first)
- Hyperglycemia: 90 days
- Tumor assessments: until disease progression per RECIST v1.1
- Patient-reported outcomes

Primary endpoint
- PFS

Key Secondary endpoints
- OS
- Safety and tolerability
- ORR
- DOR
- CBR
- PROs

Stratification factors
- De novo HR+ advanced BC (yes vs. no)
- Visceral metastases (yes vs. no)

* De novo or relapsed after at least 2 years of standard neoadjuvant/adjuvant endocrine therapy. † Palbociclib is the only option currently. Additional CDK4/6i options may be available in the future. ‡ Pre- and perimenopausal women, and men will receive an LHRH agonist for the duration of the study treatment.

aBC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; D, day; DOR, duration of response; HR, hormone receptor; IM, intramuscularly; LA, locally advanced; LET, letrozole; mBC, metastatic breast cancer; mut, mutated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PRO, patient-reported outcome; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; RECIST v1.1. 1. Cortés J et al. Presented at the European Society for Medical Oncology (ESMO) Breast Cancer Annual Congress. Munich, Germany. May 14-17, 2025. #408TiP. 2. NIH. Available at: NCT06790693. Accessed on August 28, 2025.

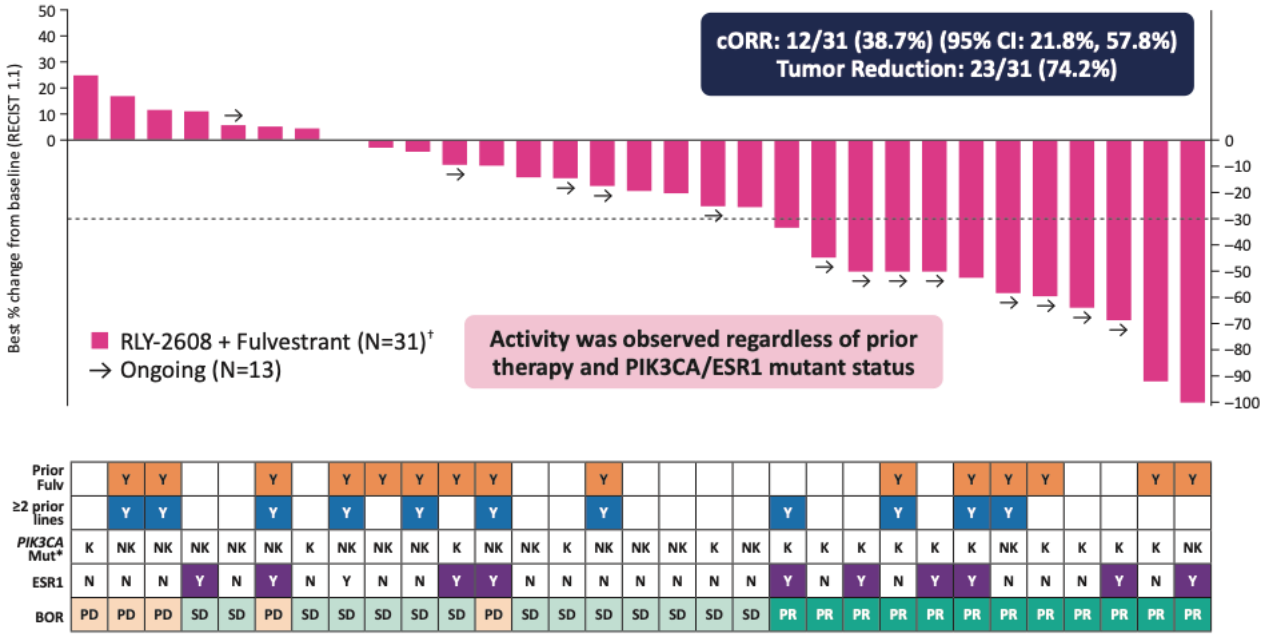
NCT06790693

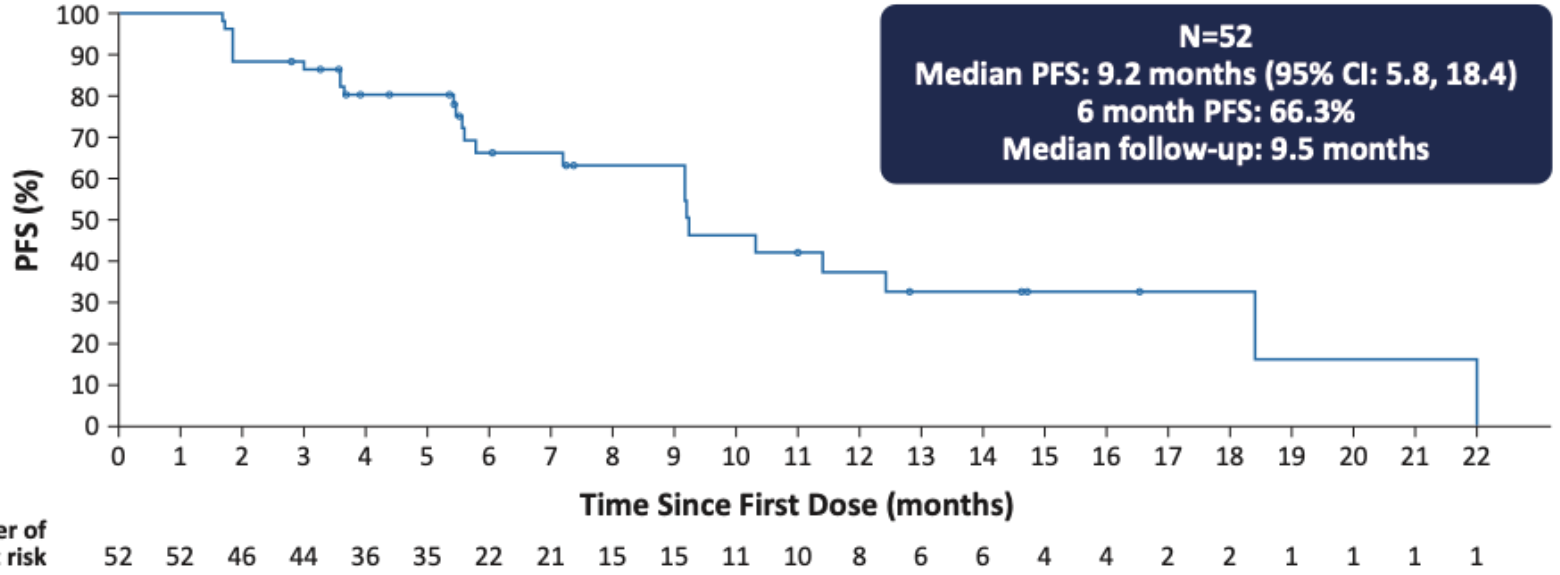
Pan-Mutant Selective, Next-Generation PI3Ki: RLY-2608

ReDiscover: phase I

- RLY-2608 selectively targets mutant PI3K
- n=118 patients, n=64 at phase 2 dose

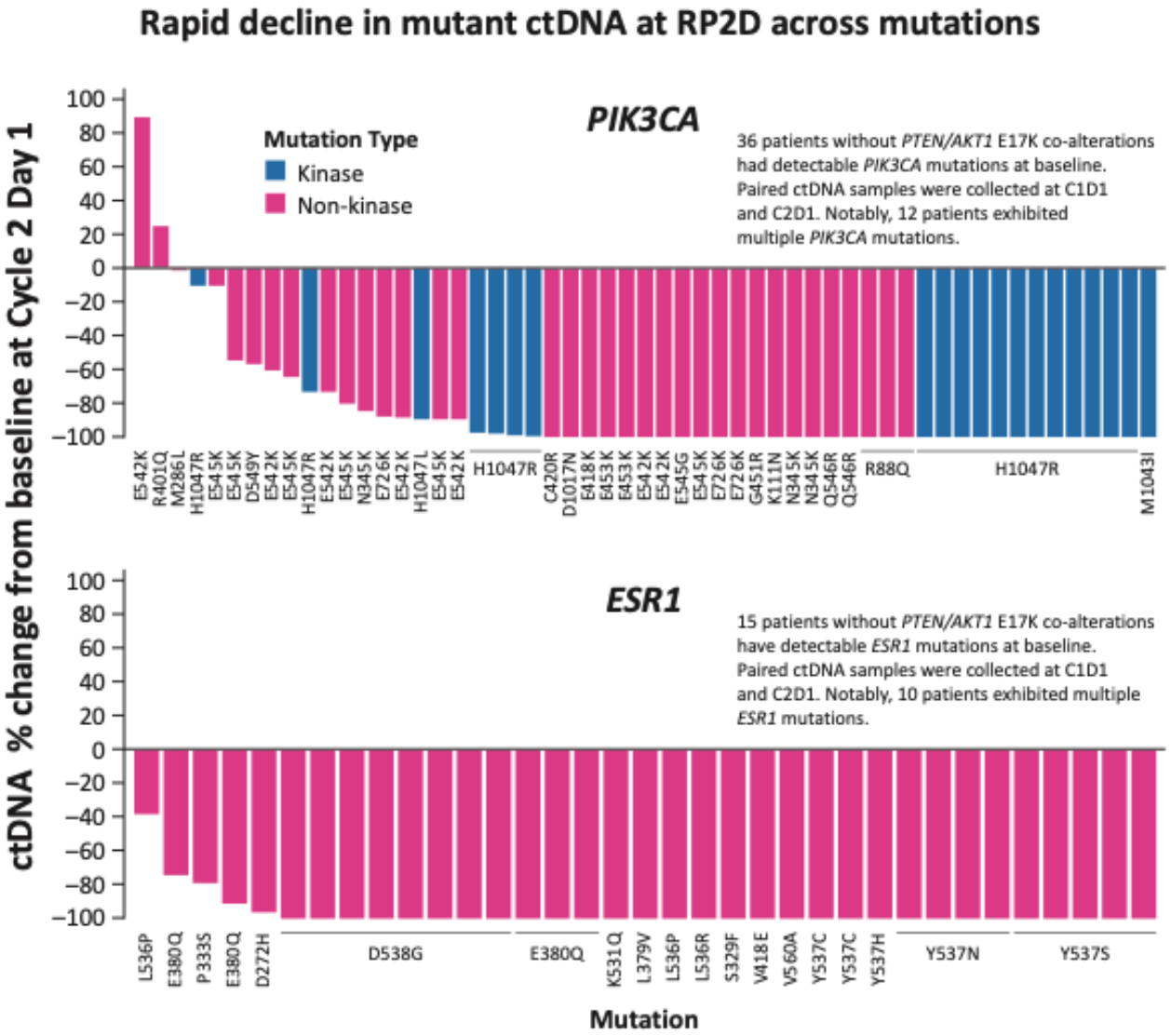
- ~50% 2nd line metastatic
- ~33% with concurrent ESR1m
  - 100% with prior CDK4/6i
  - ~50% prior fulvestrant
  - ~25% prior chemotherapy





Saura C et al SABCS 2024
NCT05216432

Pan-Mutant Selective, Next-Generation PI3Ki: RLY-2608



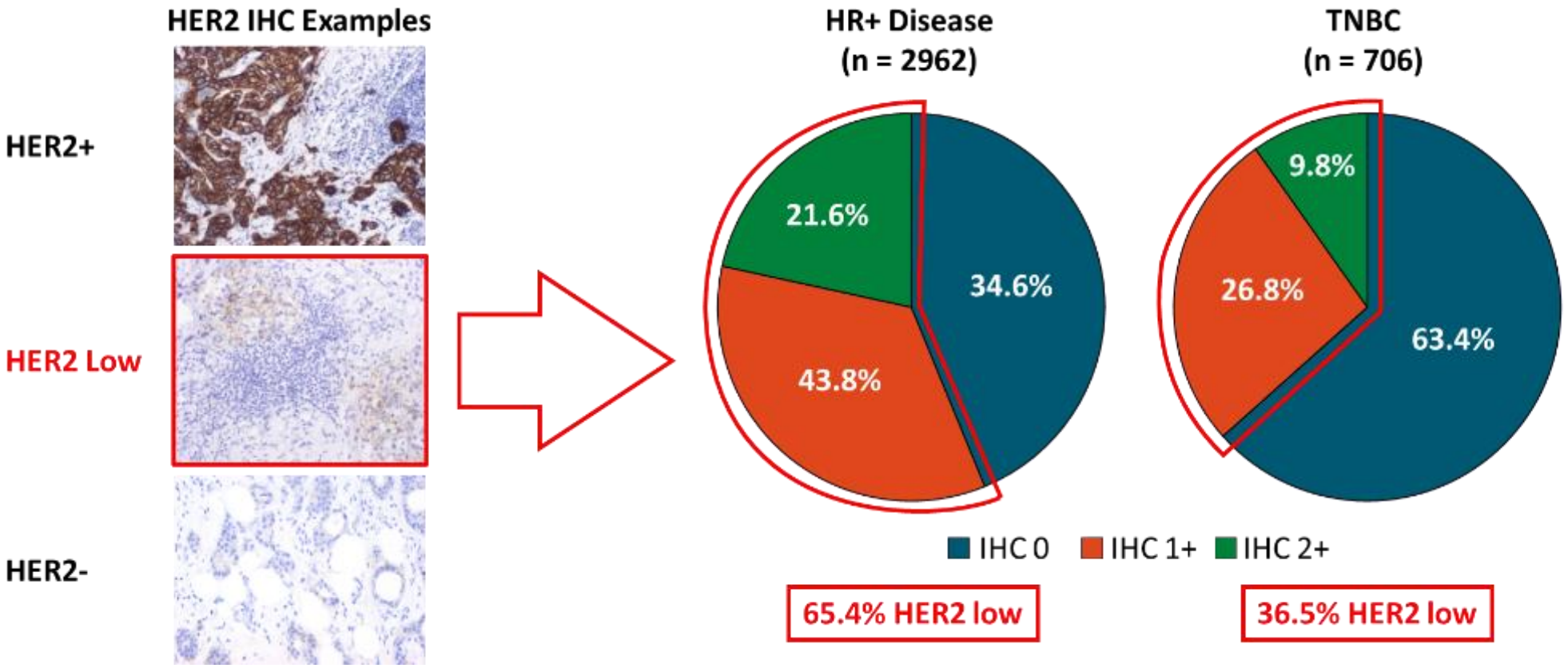
- Next generation PI3K inhibitor with on-target reductions in PIK3CA mutation load
- ESR1 reductions also noted in patients with dual-mutant disease

Saura C et al SABCS 2024; NCT05216432

Evolving Biomarkers for Precision Medicine in Metastatic Breast Cancer

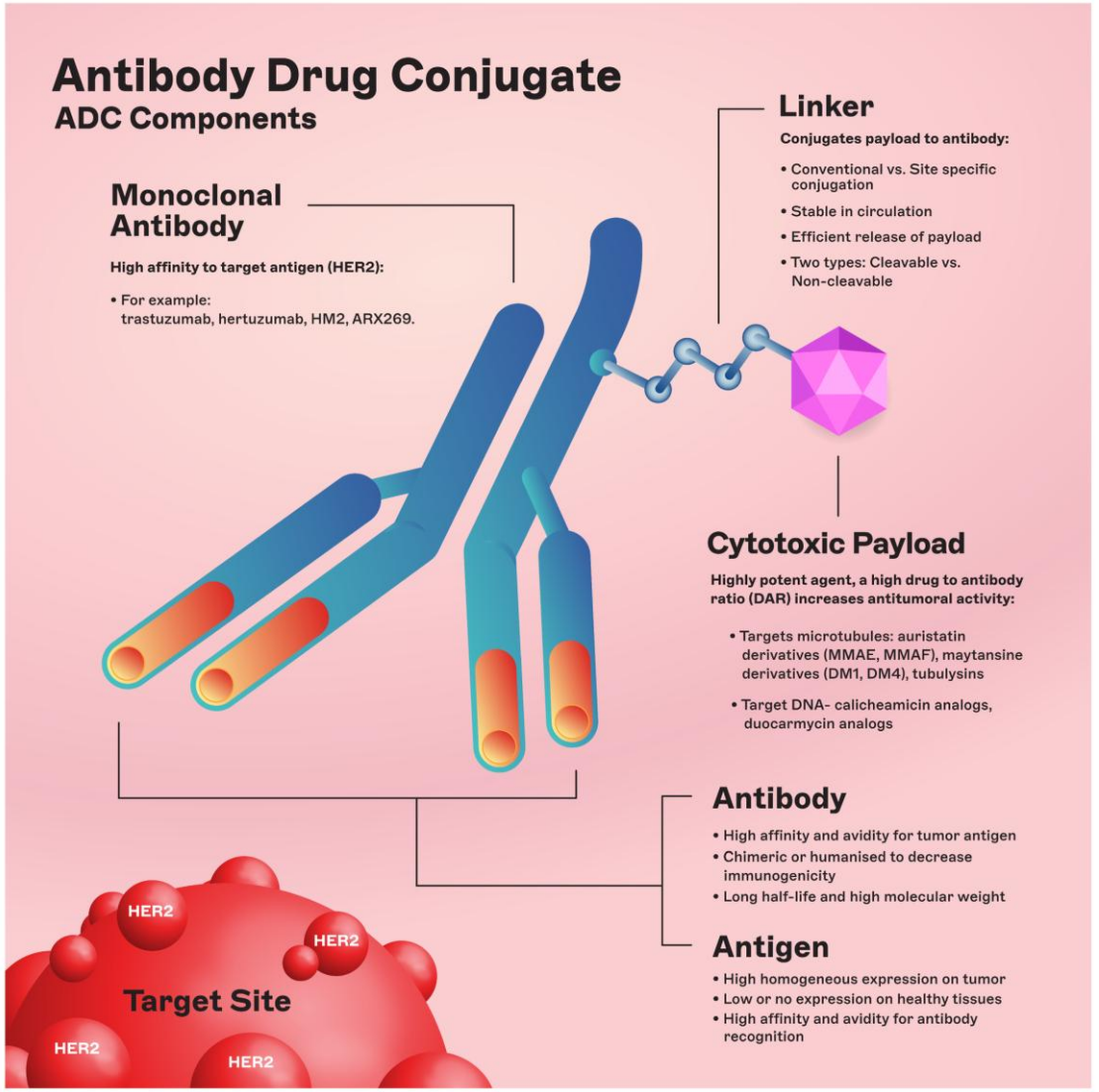
- BRCA mutations and PARP inhibition
- Targeting endocrine resistance via ESR1 mutations (HR+/HER2-)
- Emerging strategies to target PI3K signaling
- HER2-low disease as a new dimension of therapy selection
- Summary, key questions, future directions

High Prevalence of HER2-Low by HR Status



Schettini et al NPJ Breast Cancer 2021; Schettini et al Breast 2021

Trastuzumab Deruxtecan: Antibody Drug Conjugate Biology



Zimmerman BS et al Cancers 2024

Destiny-Breast06: Trastuzumab Deruxtecan for Chemo-Naïve HR+/HER2- Breast Cancer

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

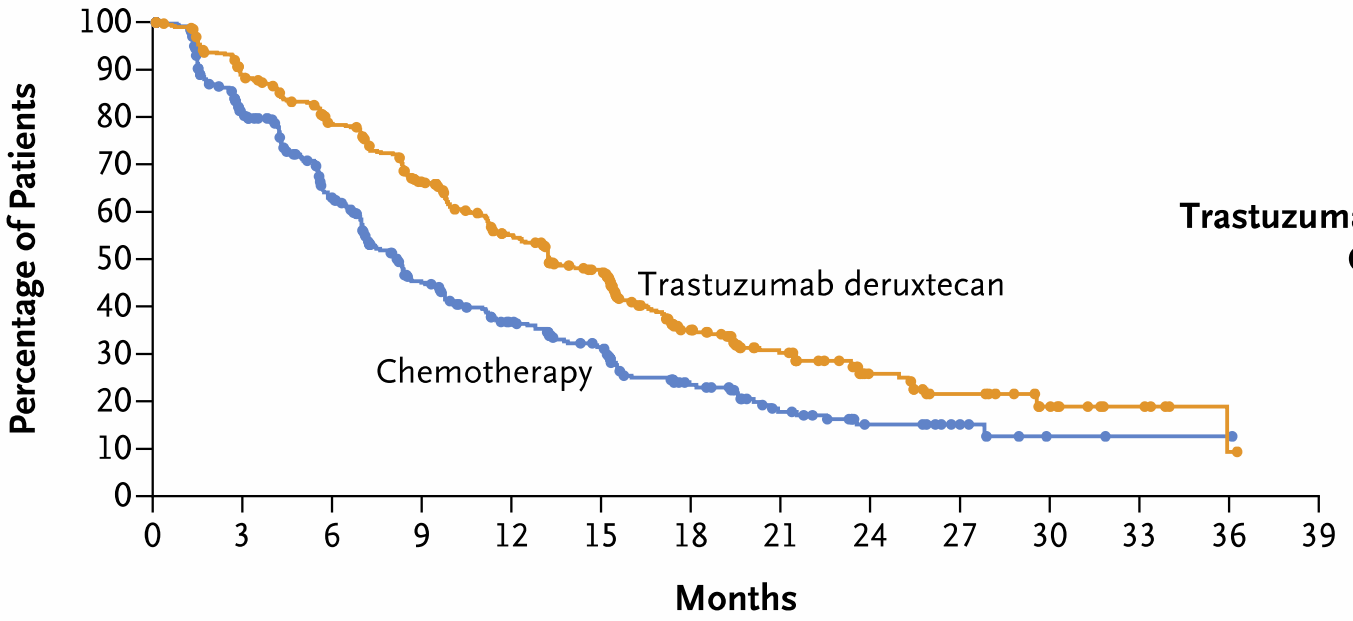
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Destiny-Breast06: TDxD for Chemo-Naïve HR+/HER2- Breast Cancer

B **Progression-free Survival in the Intention-to-Treat Population**



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	436	13.2 (12.0–15.2)
Chemotherapy	430	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, 0.64 (95% CI, 0.54–0.76)
P<0.001

No. at Risk

Trastuzumab deruxtecan	436	375	319	258	199	156	82	56	32	21	11	6	1	0
Chemotherapy	430	306	224	142	103	79	44	25	13	7	2	1	1	0

Destiny-Breast06: TDxD for Chemo-Naïve HR+/HER2- Breast Cancer, Toxicity

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)

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Current and Evolving Therapeutic Landscape: ER+ MBC

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(*PIK3CAm*,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

Current and Evolving Therapeutic Landscape: ER+ MBC

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(*PIK3CAm*,
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NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib
Antiestrogen + Everolimus
(*NGS Negative*)

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant or Imlunestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

Current and Evolving Therapeutic Landscape: ER+ MBC

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Olaparib
(*BRCAm*)

3rd Line (and beyond)::
Trastuzumab Deruxtecan (ADC, HER2-low)
Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

Current and Evolving Therapeutic Landscape: ER+ MBC

(+) Phase III Data (not yet approved)
Camizestrant Switch via ESR1 ctDNA?

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(Ribociclib)

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Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

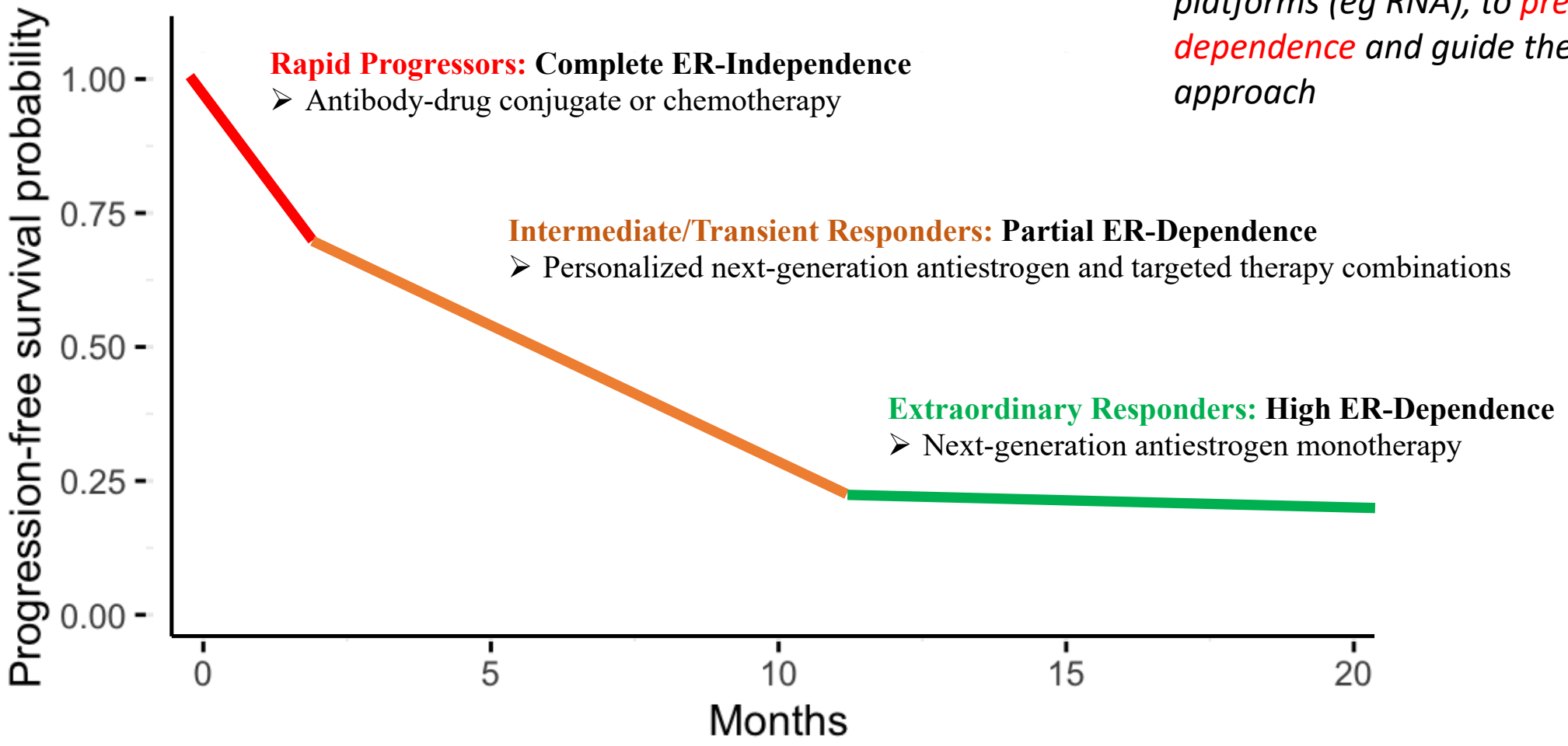
**Ongoing clinical trials exploring:
New antiestrogens (KAT6i) and doublets/triplets
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

(+) Phase III Data (not yet approved)
Single Agent: Vepdegestrant? ESR1m?

Doublet/Triplet:
Imlunestrant + Abemaciclib? NGS agnostic?
Giredestrant + Everolimus? ESR1m?
Gedatolisib + Fulvestrant +/- Palbociclib? NGS agnostic?

Defining Relevant Patient Populations for Precision Therapeutics

Utilize multi-gene signatures, and new platforms (eg RNA), to predict ER-dependence and guide therapeutic approach



Rapid Progressors: **Complete ER-Independence**
- Antibody-drug conjugate or chemotherapy

Intermediate/Transient Responders: **Partial ER-Dependence**
- Personalized next-generation antiestrogen and targeted therapy combinations

Extraordinary Responders: **High ER-Dependence**
- Next-generation antiestrogen monotherapy

Teysir J et al ASCO Ed Book 2025

Summary, Key Questions, Future Directions

- BRCA mutations impact DNA repair and convey sensitivity to well-tolerated PARP inhibitor therapy

- PI3K pathway elements drive cell growth, survival, motility/metastasis: PIK3CA alterations often present at baseline/truncal
- ESR1 mutations are rate in untreated disease, acquired after AI therapy

- Next-generation antiestrogen agents are well tolerated, active in patients with ESR1 mutations, and under development in new combinations
  - *Should we be testing ctDNA on 1st line treatment for emergence of ESR1? Will this approach be more broadly deployed for other targetable alterations in the future?*
  - *What causes resistance to next-generation antiestrogen therapy?*

- PI3K pathway inhibitors are widely utilized in clinic with well-established activity and toxicity risks
  - *What are the resistance mechanisms to PI3K/AKT inhibitors? How will emerging agents be integrated into clinical practice?*

- *How do we personalize therapy and use dynamic blood-based monitoring in this rapidly evolving landscape of treatment options?*

Thank You!