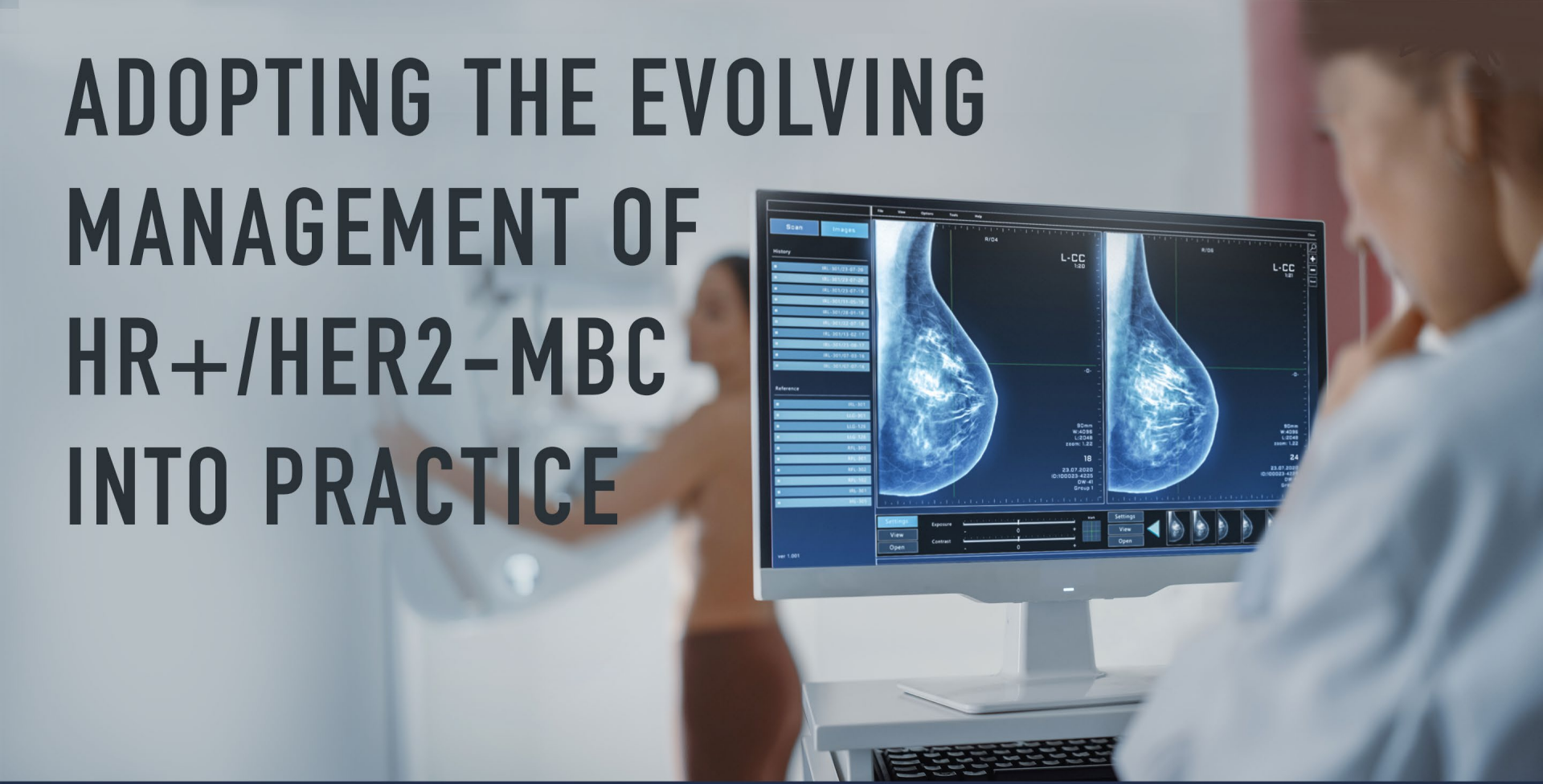
ADOPTING THE EVOLVING MANAGEMENT OF HR+/HER2- MBC INTO PRACTICE



ANNENBERG CENTER FOR HEALTH SCIENCES
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Imparting knowledge. Improving patient care.

This activity is supported by an independent educational grant from Lilly.

Background and Scope for Management of Patients With HR+/HER2- mBC

Module 1

Breast Cancer

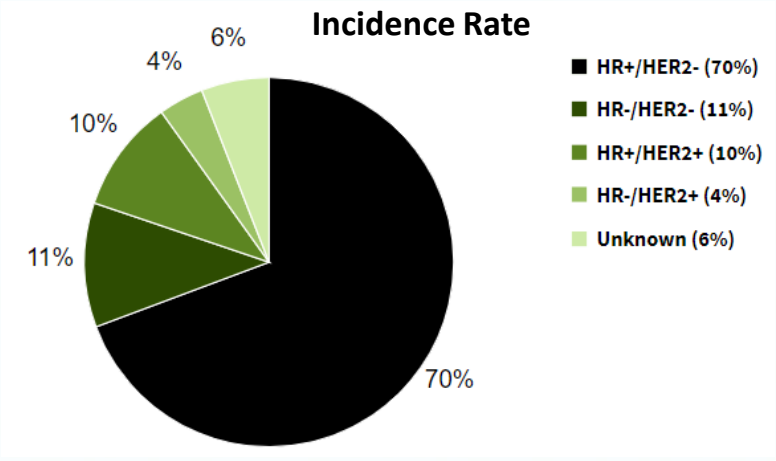
- Classified based on origin
  - Ductal or lobular
- Estrogen influences the growth/division of breast cells
- Most common sites of metastasis
  - Bone, soft tissue, lung, liver, brain
- Risk Factors
  - Advancing age, family history, increased breast density
  - Reproductive factors, genetic mutations (BRCA1/2)
    - Lifetime risk:
      - BRCA1= 55-65% and BRCA2= 55-65%

Shah, R. *World J Clin Oncol*. 2014.10;5(3):283-298.
National Cancer Institute. Published 2024. https://www.cancer.gov/types/breast/hp
NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Breast Cancer

United States

- Most common type of cancer among females
- 13.1% of all women will be diagnosed with breast cancer at some point in their lifetime
- Median age of diagnosis is 63 y
- 5-y relative survival rate of 91.2%

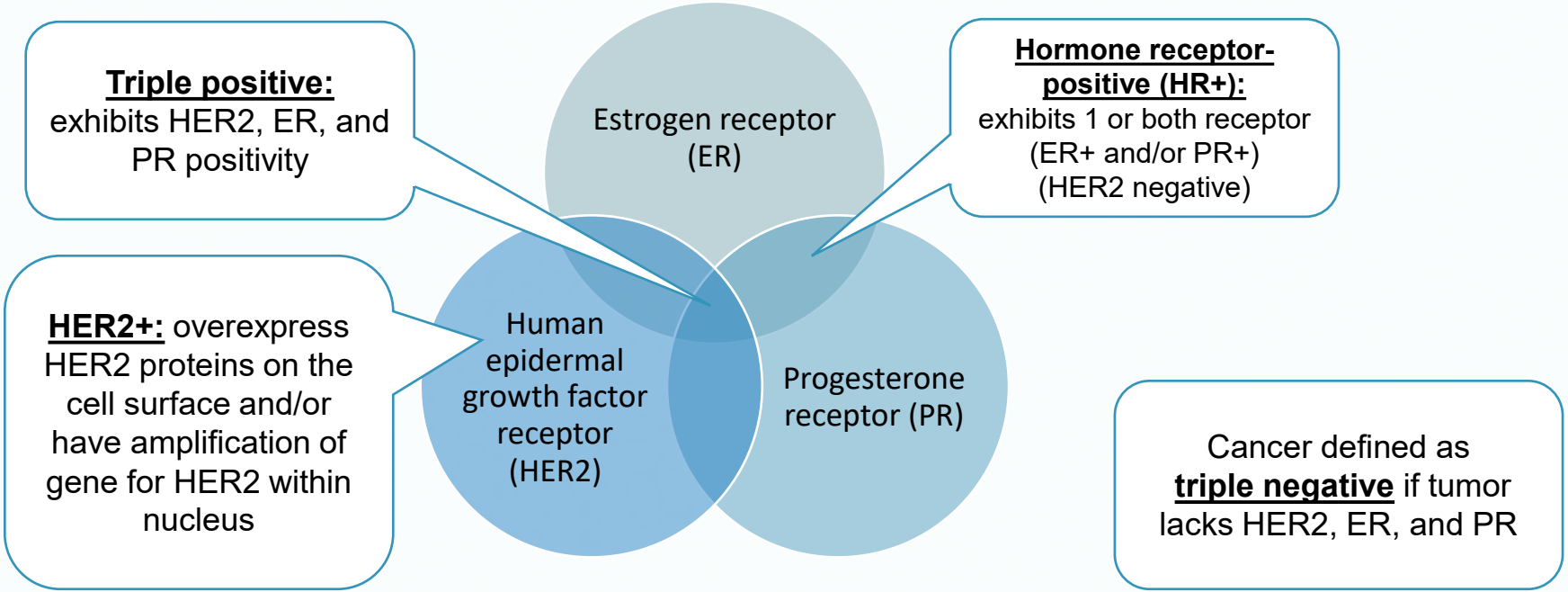


5-Year Relative Survival Percent

Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.5%	35.4%
HR-/HER2-	92.0%	66.8%	14.3%
HR+/HER2+	99.3%	90.4%	45.8%
HR-/HER2+	97.3%	84.2%	39.7%

SEER Cancer Stat Facts. September 2024. https://seer.cancer.gov/statfacts/html/breast.html
SEER Cancer Stat Facts. September 2024. https://seer.cancer.gov/statfacts/html/breast-subtypes.html

Breast Cancer Histology



Mitri Z, et al. *Chemother Res Pract*. 2012;743193.
NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Molecular and Tumor Profiling

Module 2

Patient Workup

- History and physical exam
- Imaging: CT, bone scan, MRI, US/mammography
- Laboratory results
- Diagnostic tissue
  - Pathology
  - Histology: HR/HER2 status
  - Biomarker testing
  - Germline genetic testing when appropriate

CT, computed tomography; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MRI, magnetic resonance imagine; US, ultrasound

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Definitions of HER2+ Disease

Score	Criteria	Classification	Reflex ISH	Result
IHC 0	• No membrane staining • Incomplete membrane staining that is faint/barely perceptible and in ≤10% of tumor cells	HER2 negative		IHC 0 HER2 – negative
IHC 1+	• Incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells	HER2 negative		IHC 1 HER2 – negative*
IHC 2+	• Weak to moderate complete membrane staining observed in >10% of tumor cells	HER2 equivocal	• Non-amplified	IHC 2+/ISH- HER2 – negative*
			• Amplified	IHC 2+/ISH+ HER2 – positive
IHC 3+	• Circumferential membrane staining that is complete, intense, and in >10% of tumor cells	HER2 positive		IHC 3+ HER2 – positive

ER, estrogen receptor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor

*HER2-low if IHC 1+ or 2+

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
Wolff AC, et al. *J Clin Oncol*. 2023;41(22):3867-3872.

Breast Cancer Molecular Subtype

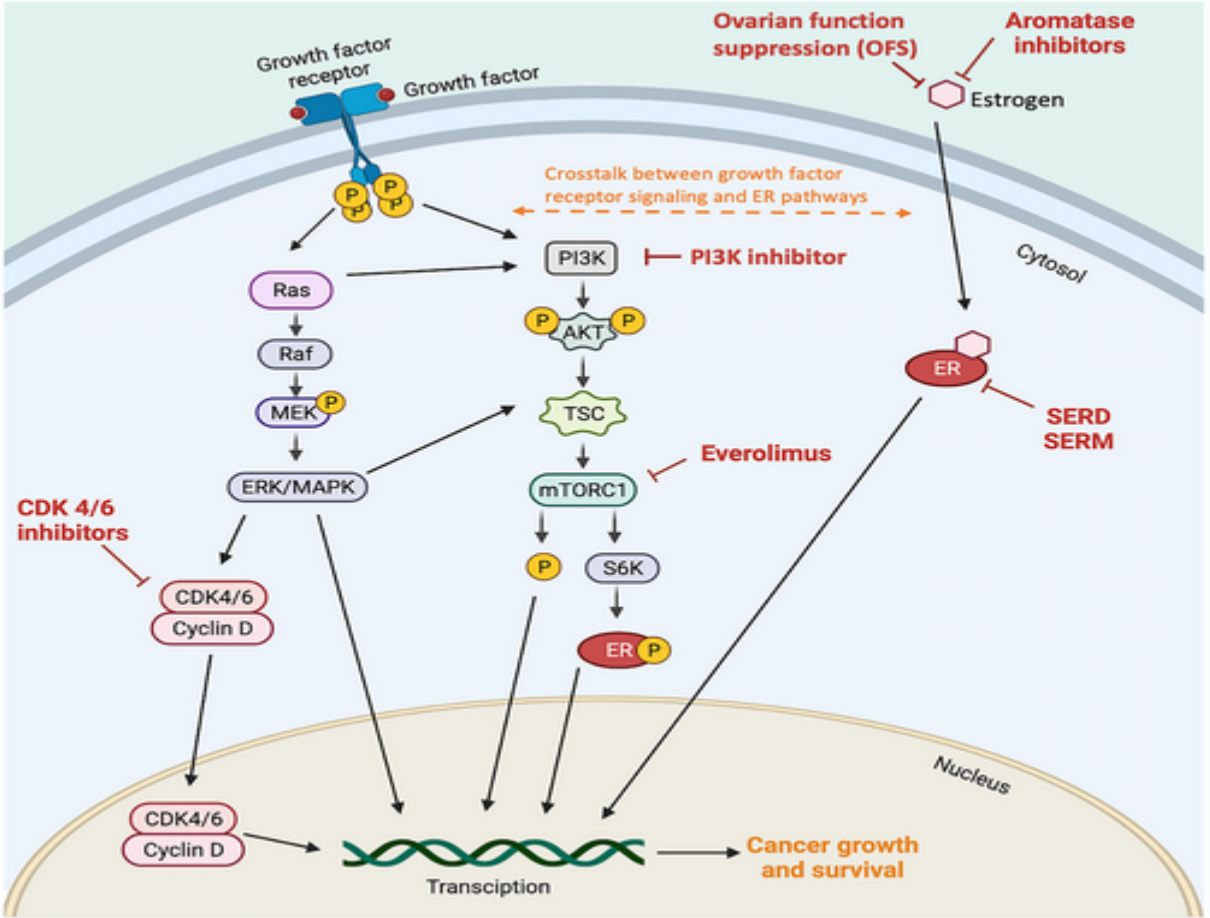
HR+/HER2-

- ~70% of patients with breast cancer
- Heterogeneous disease subset
  - Often low grade and low proliferation, endocrine sensitive, particularly in postmenopausal women
  - Subset are high grade, more proliferative and less endocrine sensitive
- Most common subtype

HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive

American Cancer Society. Published 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf
NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Treatment Pathway: HR+/HER2- Breast Cancer



CDK4/6 inhibitor, cyclin-dependent kinase 4 and 6 inhibitor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; SERD, selective estrogen receptor down regulator; SERM, selective estrogen receptor modulator

Detecting Targetable Mutations in HR+/HER2- mBC

De novo/recurrent diagnosis

- Tissue biopsy for comprehensive genomic paneling, confirm receptor status, and metastatic tumor of origin

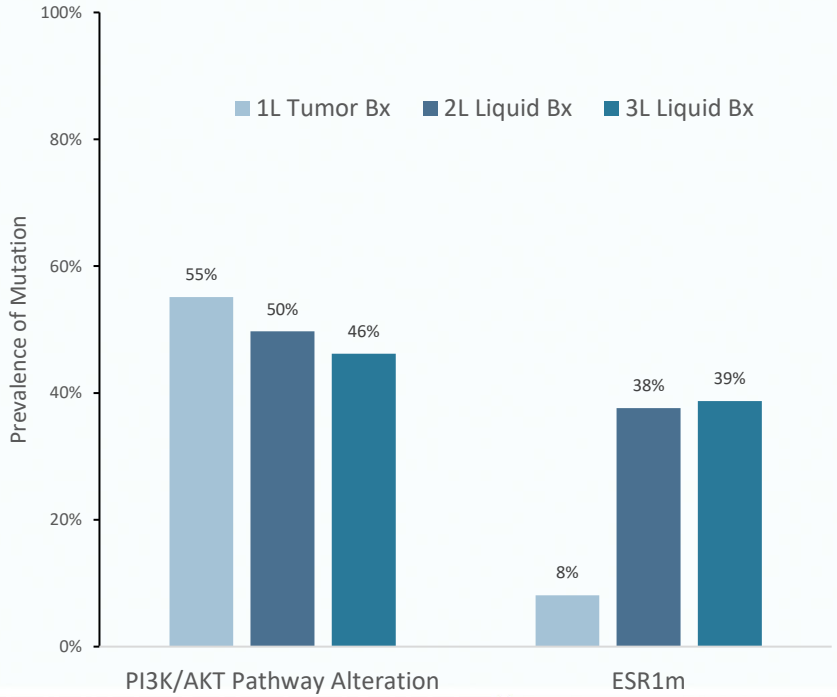
≥ 2nd Line

- Liquid biopsy for genomic alterations
- Consider reflex tissue biopsy if ctDNA tumor fraction **<1%**

ctDNA, circulating tumor DNA; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive

Bhave MA, et al. *Breast Cancer Res Treat*. 2024;207:599-609.

Detecting Targetable Mutations in HR+/HER2- mBC



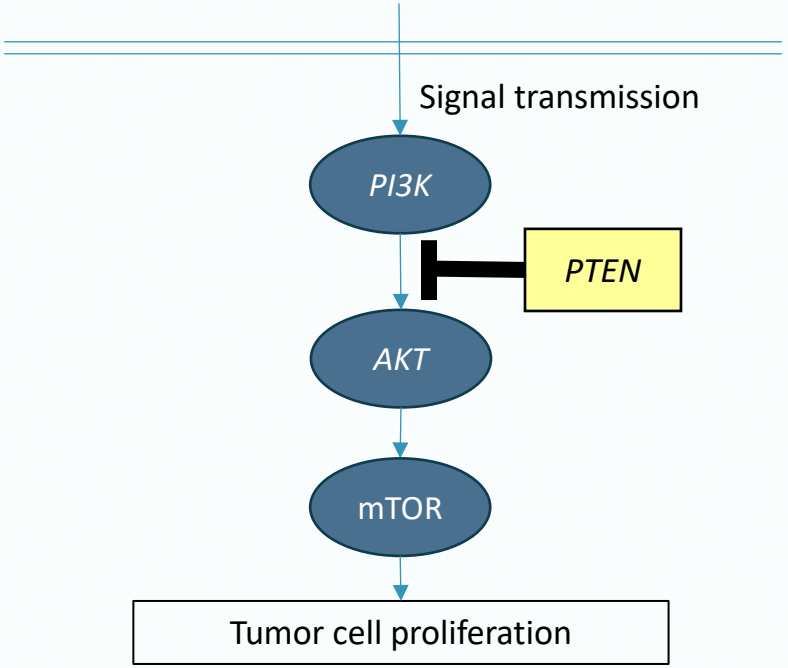
- Genomic alterations (GAs) commonly identified in first line (1L) setting
  - Tissue biopsy: 58.8%
  - Liquid biopsy: 42.7%
- Increases in GAs in later lines of therapy detected at 62%-71% incidences, mainly due to acquisition of *ESR1* mutation
- Tissue biopsy > Liquid biopsy for detection of *PTEN* loss

Bx, biopsy; ctDNA, circulating tumor DNA; ESR1m, estrogen receptor 1 mutation; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive

Bhave MA, et al. *Breast Cancer Res Treat*. 2024;207:599-609.

Alterations in *PI3K/AKT/PTEN* Pathway

- Occurs in ~40% of patients with HR+ breast cancer
- Majority of mutations in *PIK3CA*
- *PIK3CA* mutations do NOT predict response to CDK4/6 inhibitors
- Less common mutations
  - *AKT1* (2%-3%)
  - *PI3K* regulatory subunit alpha (1%-2%)
  - Loss-of-function mutations in *PTEN* (2%-4%)

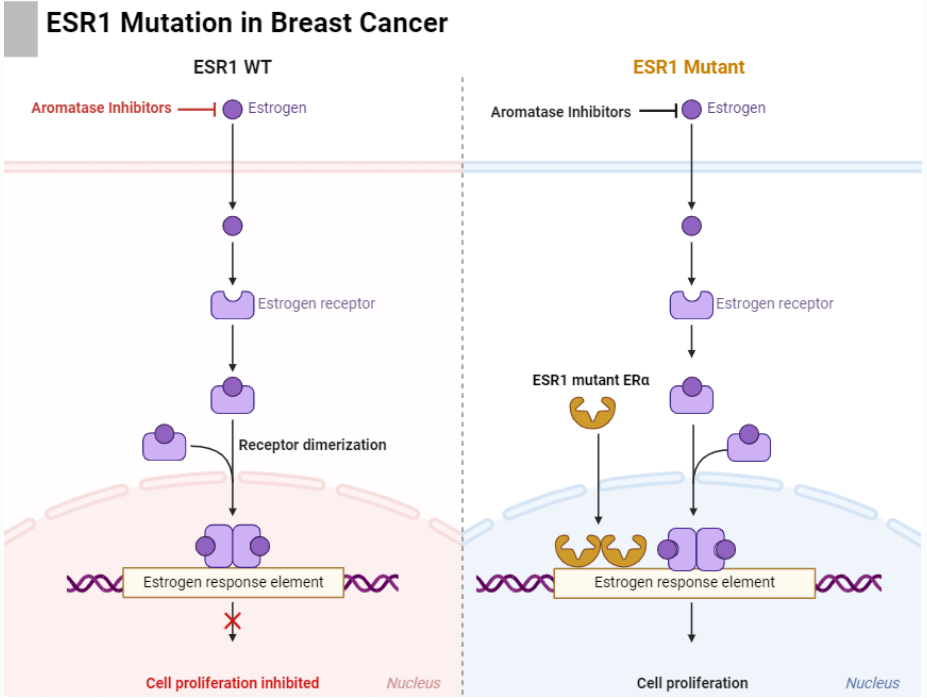


CDK4/6, cyclin-dependent kinase 4 and 6; HR+, hormone receptor-positive

Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85.

Estrogen-Receptor 1 (*ESR1*) Mutations

- Mechanism
  - *ESR1* is a transcription factor coding for estrogen receptor (ER) alpha protein
  - After exposure to ET, *ESR1* mutation may develop leading to constitutive activation of ER pathway
- Prevalence
  - Dependent on time of testing
  - Occurs in 40%-50% of patients who have been previously exposed to an AI
    - < 1% of patients who have treatment-naive BC
    - 4%-5% of patients who receive adjuvant AI
    - 50% of patients after 1 year of first-line CDK4/6 inhibitor + AI
  - Tend to develop 3 to 6 mos before radiologic progression on AI
- Consequences
  - Associated with poor response to AI with shorter PFS and 1-year OS



AI, aromatase inhibitor; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4 and 6; ESR1, estrogen receptor 1; ET, endocrine therapy; HR+, hormone receptor-positive, PFS, progression free survival; OS, overall survival

Created in BioRender.com

Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85.
Chaudhary N, et al. *NPJ Breast Cancer*. 2024;10(1):15.
Andujar JMC, et al. *Cancer Drug Resist*. 2025;8:5.
Reprinted from "ESR1 Mutation", by BioRender.com (2025). Retrieved from https://app.biorender.com/biorender-templates

EMERALD Trial
ctDNA monitoring for acquired *ESR1* mutations

- First study to lead to an approved SERD for *ESR1* mutated breast cancer
- Oral elacestrant vs standard-of-care
  - Fulvestrant (n=166); AI (n=73)
- Postmenopausal breast cancer patients in the second or subsequent line for HR+/HER2- metastatic or advanced BC

Results:

- ESR1 mutation rate = 47.8%
- PFS (± ESR1 mutated breast cancer) (Elacestrant vs standard-of-care)
  - All patients: 2.8 mos vs 1.9 mos
    - (HR 0.70; 95% CI 0.55-0.88; *P*=0.0018)
  - *ESR1* mutated cancer: 3.8 mos vs 1.9 mos
    - (HR 0.55; 95% CI 0.39-0.77; *P*=0.0005)
- Impact of duration of prior ET + CDK4/6 inhibitor on PFS
  - Those with at least 1 year as a surrogate marker for endocrine sensitivity had a marked improvement in PFS

AI, aromatase inhibitor; BC, breast cancer; CDK4/6; cyclin-dependent kinase 4 and 6; ctDNA, circulating tumor DNA; ESR1, estrogen receptor 1; SERD, selective estrogen receptor down regulator

Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256.
Bidard FC, et al. *Lancet Oncol*. 2022;23(11):1367-1377.

PADA-1 Trial
ctDNA monitoring for acquired *ESR1* mutations

- AI + palbociclib vs fulvestrant + palbociclib
- Tested clinical utility of real time *ESR1* mutation detection at baseline, 1 mo, then every 2 mos
- Patients with a rising *ESR1* mutation (no radiographic progression) via ctDNA with first-line AI + palbociclib were randomized in a second step to stay on AI + palbociclib or switch to fulvestrant + palbociclib

Results:

- N=172
- *ESR1* mutation rate at baseline = 2.1%
- *ESR1* mutation related to prior AI exposure, adjuvant setting = 4.9%
- Patients with a *ESR1* mutation had a benefit in median PFS when switched to fulvestrant/palbociclib
  - PFS: 11.9 vs 5.7 mos
    - HR 0.61; 95% CI 0.43–0.86; *P*=0.004
  - Improved PFS2 but no control of subsequent therapy
- No OS results

AI, aromatase inhibitor; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4 and 6; ctDNA, circulating tumor DNA; ESR1, estrogen receptor 1; SERD, selective estrogen receptor down regulator

Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256.
Bidard FC, et al. *Lancet Oncol*. 2022;23(11):1367-1377.

SERENA-6 Trial
oral SERD + CDK4/6 inhibitor vs. AI + CDK4/6 inhibitor

- Goal = detect molecular marker of treatment resistance
- Patients with HR+/HER2- advanced BC to utilize real-time prospective liquid biopsy monitoring (ctDNA)
  - ctDNA screened for ESR1 mutation every 2-3 treatment cycles
- Switch patients to a next-generation SERD that targets the resistance mechanism at the time of detection
- Assess efficacy and safety of switching patients who have acquired *ESR1* mutation and WITHOUT clinical disease progression to:
  - Camizestrant + CDK4/6 inhibitor vs
  - Continuing AI + CDK4/6 inhibitor

Results:

- Improved PFS when switching to camizestrant + CDK4/6 inhibitor
- No new safety concerns identified
- Discontinuations were low and similar in both arms
- Final results pending

AI, aromatase inhibitor; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4 and 6; ctDNA: circulating tumor DNA; ESR1, estrogen receptor 1; SERD, selective estrogen receptor down regulator

Turner N, et al. *Future Oncol.* 2023;19(8):559-573.
AstraZeneca. Published February 26, 2025. https://www.astrazeneca.com/media-centre/press-releases/2025/camizestrant-improved-pfs-in-1l-hr-breast-cancer.html

Actionable Biomarkers

HR+/HER2- mBC

Biomarker	Detection	FDA-Approved Agents
PIK3CA activating mutation	NGS, PCR	• Inavolisib + palbociclib + fulvestrant • Alpelisib + fulvestrant
PIK3CA or *AKT1* activating mutations or *PTEN* alterations	NGS, PCR	• Capivasertib + fulvestrant
ESR1 mutation	NGS, PCR (ctDNA preferred)	• Elacestrant

ctDNA, circulating DNA; ESR1, estrogen receptor 1; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mBC, metastatic breast cancer; NGS, next generation sequencing; PCR, polymerase chain reaction

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

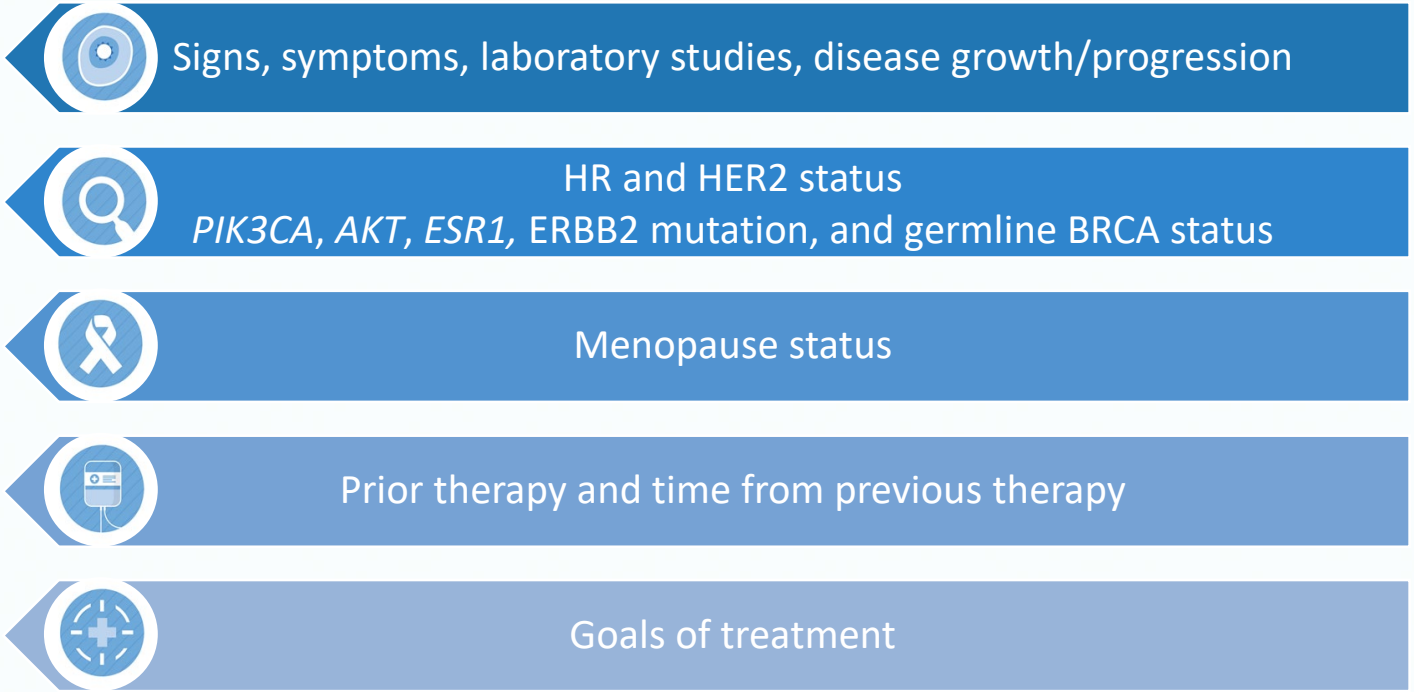
Key Concepts

- Latest evidence and clinical implications of biomarkers
- Biomarker testing recommendations
  - Utilize liquid biopsy techniques
- Optimizing early detection and treatment planning
  - Guide therapy for ET resistance
- Personalized treatments tailored to individual patient profiles and biomarker results
  - Enhance patient care and outcomes

Navigating Through the Current Treatment of Patients With HR+/HER2- mBC

Module 3

Treatment: Patient Factors



HER2-, human epidermal growth factor receptor 2; HR, hormone receptor

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Ovarian Ablation and Suppression

Targeted to stop or lower the amount of estrogen made by the ovaries

- Ablation
  - Oophorectomy
  - Ovarian irradiation
- Suppression
  - LHRH agonists (Goserelin, Leuprolide)

Premenopausal patients not highly represented in many HR+ trials. NCCN recommends to treat the same as postmenopausal patients.

HR+, hormone receptor-positive; LHRH, luteinizing hormone-releasing hormone; NCCN, National Comprehensive Cancer Network

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Treatment Options

HR+/HER2- mBC

Class	Agents
Aromatase inhibitors	Anastrozole, letrozole, exemestane
SERD	Elacestrant, fulvestrant
SERM	Tamoxifen
CDK4/6 inhibitors	Abemaciclib, palbociclib, ribociclib
PI3K inhibitor	Alpelisib, inavolisib
AKT inhibitor	Capivasertib
mTOR	Everolimus

CDK4/6 inhibitor, Cyclin-dependent kinase 4 and 6 inhibitor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mBC, metastatic breast cancer; SERD, selective estrogen receptor down regulator; SERM, selective estrogen receptor modulator

NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Treatment Recommendations

HR+/HER2- mBC

First line

- CDK4/6 inhibitor + ET
- Inavolisib/palbociclib/fulvestrant*

*if recurrence on/within 12 months of adjuvant aromatase inhibitor treatment

Subsequent Lines

- Endocrine-targeted therapies
  - CDK4/6 inhibitor + fulvestrant (if not used first-line)
  - Everolimus + ET
  - Targeted therapy (*PI3K*/*AKT1*/mTOR, *PTEN*, *ESR1*, etc)
  - Endocrine monotherapy (fulvestrant, aromatase inhibitor, or tamoxifen)

CDK4/6 inhibitor, cyclin-dependent kinase 4 and 6 inhibitor; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2; HR, hormone receptor;

Burstein HJ, et al. *J Clin Oncol*. 2024;42(12):1450-1453.
NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Key Concept

- Since our understanding of mutations is rapidly evolving and advancements in targeted therapies continue to be made, it is important to implement treatment based on evidence-based guidelines and recommendations to help mitigate the risk of endocrine therapy resistance.

Therapeutic Approaches for the Treatment of Patients With HR+/HER2- mBC

Module 4

CDK4/6i Efficacy in Combination With AI

1L HR+/HER2- mBC

	PALOMA-2		MONARCH-3		MONALEESA-2		MONALEESA-7	
	Palbociclib + Letrozole	Placebo + Letrozole	Abemaciclib + NSAI	Placebo + NSAI	Ribocicilb + Letrozole	Placebo + Letrozole	Ribocicilb + Goserelin/NSAI or Tamoxifen	Placebo + Goserelin/ NSAI or Tamoxifen
No. of patients	444	222	328	165	334	334	335	337
mPFS – mos	27.6	14.5	NR	14.7	25.3	16	23.8	13
HR for disease progression/ death	0.56 (0.46-0.68)		0.54 (0.41-0.72)		0.56 (0.43-0.72)		0.55 (0.44-0.69)	
P value	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
mOS – mos	53.9	51.2	67.1	54.5	63.9	51.4	58.7	48
HR for disease progression/ death	0.95 (0.77-1.77)		0.75 (0.58-0.97)		0.76 (0.63-0.93)		0.76 (0.61-0.96)	
P value	**NOT significant**		**NOT significant**		**0.008**		**Not reached**	

AI, aromatase inhibitor; HER2-, human epidermal growth factor receptor 2; HR, hormone receptor; mOS, median overall survival; mPFS, median progression free survival; NSAI, nonsteroidal aromatase inhibitor

Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174(3):719-729. Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646.
Hortobagyi GN, et al. *N Engl J Med*. 2016;375(18):1738-1748. Tripathy D, et al. *Lancet Oncol*. 2018;19(7):904-915.
Lu YS, et al. *Clin Cancer Res*. 2022;28(5):851-859.

CDK4/6i Efficacy in Combination With Fulvestrant
HR+/HER2- mBC

	PALOMA-3		MONARCH-2		MONALEESA-3	
	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Ribocicilb + Fulvestrant	Placebo + Fulvestrant
No. of patients	347	174	446	223	484	242
mPFS – mos	11.2	4.6	16.4	9.3	20.6	12.8
HR for disease progression/ death	0.50 (0.40-0.62)		0.55 (0.45-0.68)		0.59 (0.49-0.71)	
P value	**<0.000001**		**<0.001**		**<0.001**	
mOS – mos	34.9	28.0	46.7	37.3	NR	40.0
HR for disease progression/ death	0.81 (0.64-1.03)		0.76 (0.61-0.95)		0.72 (0.57-0.92)	
P value	**NOT significant**		**0.01**		**0.00455**	

HER2-, human epidermal growth factor receptor 2; HR, hormone receptor; mPFS, median progression free survival; mOS, median overall survival; NSAI, nonsteroidal aromatase inhibitor

Cristofanilli M, et al. *Clin Cancer Res*. 2022;258(16):3433-3442.
Sledge GW, et al. *J Clin Oncol.* 2017;35(25):2875-2884.
Sledge GW, et al. *JAMA Oncol*. 2020;6(1):116-124.
Slamon DJ, et al. *N Engl J Med*. 2020;382(6):514-524.

Optimizing Treatment Approaches
HR+/HER2- mBC

- Recommendations at disease progression on CDK4/5 inhibitor
  - *PIK3CA* mutations: alpelisib, inavolisib
  - AKT: capivasertib
  - *ESR1*: elacestrant
  - Lack of *PIK3CA* and *ESR1* mutations: Switching CDK4/6i; ET + everolimus
  - NGS with extensive gene panels: Recommended in the context of clinical trials

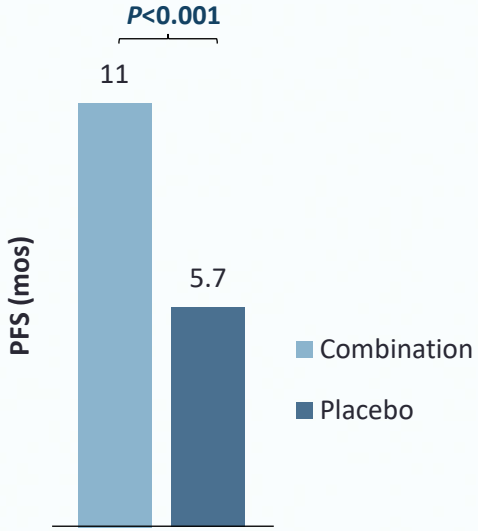
CDK4/6i, cyclin-dependent kinase inhibitors; ERS1, estrogen receptor 1; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mBC, metastatic breast cancer; NGS, next-generation sequencing

Andujar JMC, et al. *Cancer Drug Resist*. 2025;8:5.
NCCN. Published 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

SOLAR-1 Trial

PIK3CA inhibitor + SERD

- Postmenopausal women with *PIK3CA mutation* who previously received endocrine therapy (N=572)
- Treatment
  - Alpelisib 300 mg PO daily + fulvestrant 500 mg IM every 28 d
  - Placebo + fulvestrant
- Results
  - Overall response 26.6% vs 12.8%
  - Grade ≥3 AEs (alpelisib)
    - Hyperglycemia 36.6%
    - Rash 10%
    - Diarrhea 6.7%



PFS, progression free survival

André F, et al. *N Engl J Med.* 2019;380(20):1929-1940.
André F, et al. *Ann Oncol.* 2021;32(2):208-217.

INAVO120 Trial

CDK4/6 inhibitor + SERD + *PIK3CA* inhibitor

- Patients receiving 1st-line therapy in ET-resistant, *PIK3CA* mutated, HR+/HER2- locally advanced or mBC (N=325)
  - Included patients with progression during/within 12 mos of adjuvant ET completion
  - Strict glucose requirements at enrollment (A1c <6%, FPG < 126 mg/dL)
- Treatment
  - Inavolisib 9 mg PO daily + palbociclib 125 mg PO daily on D1-21 + fulvestrant 500 mg IM every 28 d
  - Placebo + palbociclib + fulvestrant

- Results
  - mPFS: 15 vs 7.3 mos
    - (HR 0.43; 95% CI 0.43-0.97, *P*<0.0001)
  - OS positive trend
    - (stratified HR=0.64; 95% CI 0.43-0.97, *P*=0.0338)
  - ORR 58.4% vs 25%
  - DOR 18.4 mos

FDA approved October 2024

- For patients with endocrine-resistant, *PIK3CA* mutated, HR+/HER2- metastatic or locally advanced breast cancer following adjuvant endocrine therapy

DOR, duration of response; FPG, fast plasma glucose; mPFS, median progression free survival; ORR, objective response rate

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

CAPItello-291 Trial

AKT inhibitor + SERD

- Patients who previously received AI ± CDK4/6 inhibitor for their HR+/HER2- mBC (N=708)
  - Stratified based on presence or absence of *AKT*-pathway alterations
  - Prior CDK4/6 inhibitor use noted in 69.1% of patients
- Treatment
  - Capivasertib PO 400 mg BID x 4 d followed by 3 d off + fulvestrant 500 mg IM every 28 d
  - Placebo + fulvestrant
- Results

AKT Pathway alterations include: *PIK3CA*, *AKT*, and *PTEN* loss

	***AKT*-pathway altered population**		**Overall population**	
	Capivasertib + Fulvestrant	Placebo + Fulvestrant	Capivasertib + Fulvestrant	Placebo + Fulvestrant
mPFS, mos	7.3	3.1	7.2	3.6
HR for disease progression/ death	0.50 (0.38-0.65)		0.60 (0.51-0.71)	
P value	<0.001		<0.001	

mPFS, median progression free survival

FDA approved November 2023

- For patients with HR+/HER2- mBC with ≥ 1 *PIK3CA*/*AKT1*/*PTEN*-alterations

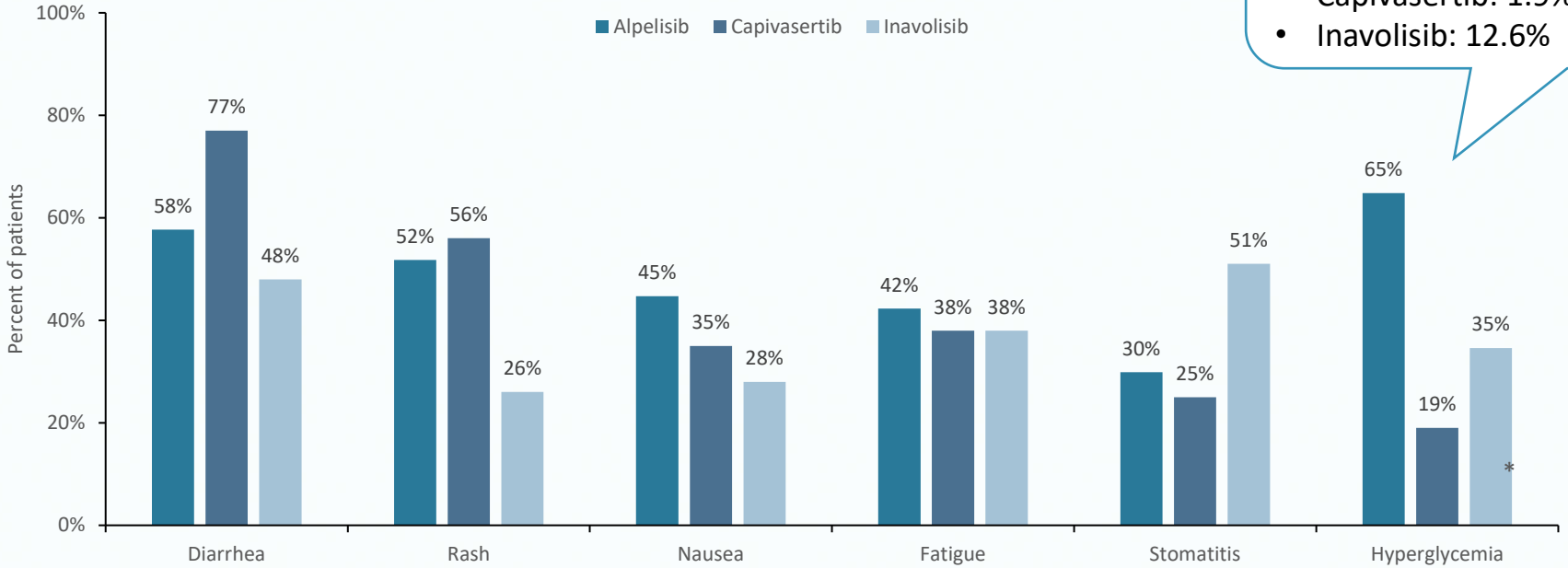
Turner NC, et al. *N Engl J Med*. 2023;388(22):2058-2070.

PI3K/AKT/mTOR Targeted Agents

Safety and Tolerability Profiles

Grade ≥ 3 hyperglycemia:

- Alpelisib: 37%
- Capivasertib: 1.9%
- Inavolisib: 12.6%



*different A1c eligibility between trials

Itovebi. Prescribing information. October 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s000lbl.pdf
Piqray . Prescribing information. January 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf
Truqap. Prescribing information. February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf

Fulvestrant Activity and *ESR1* Mutations

- Two phase 3, randomized, placebo-controlled trials in patients with baseline *ESR1* mutated HR+/HER2- advanced BC (N=383)
  - Fulvestrant vs exemestane
- *ESR1* mutations detected in 30% of samples at baseline
- PFS compared between endocrine therapies (*ESR1* mutated and *ESR1* wild-type)
- Results

mPFS and *ESR1* Mutation Status	Fulvestrant (n=220)	Exemestane (n=163)	Statistical Analysis
ESR1 mutant (n=115)	3.9 mos	2.4 mos	HR 0.59; 95% CI 0.39-0.89; *P*=0.01
ESR1 wild-type (n=268)	4.1 mos	4.8 mos	HR 1.05; 95% CI 0.81-1.37; *P*=0.69

- Fulvestrant RETAINS activity in *ESR1* mutated population
- Fulvestrant exhibits superior survival advantage over exemestane in patients with baseline *ESR1* mutation

ESR1, estrogen receptor 1; mPFS, median progression free survival

Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177.

EMERALD Trial
oral SERD

- Postmenopausal women and men receiving second- or subsequent-line therapy for HR+/HER2- mBC (N=477)
  - International, multicenter, randomized, open-label phase 3 trial
  - Stratified based on *ESR1* mutation status and prior fulvestrant use
- Treatment
  - Elacestrant 345 mg PO daily
  - Standard-of-care [Fulvestrant (n=166); AI (n=73)]
- Results (mPFS)
  - All patients: 2.8 mos vs. 1.9 mos
    - (HR 0.70; 95% CI 0.55-0.88; *P*=0.0018)
  - Patients with *ESR1* mutation: 3.8 mos vs 1.9 mos
    - (HR 0.55; 95% CI 0.39-0.77; *P*=0.0005)

Exploratory analysis of PFS in non-*ESR1* mutated population showed HR 0.86; 95% CI 0.36-1.19

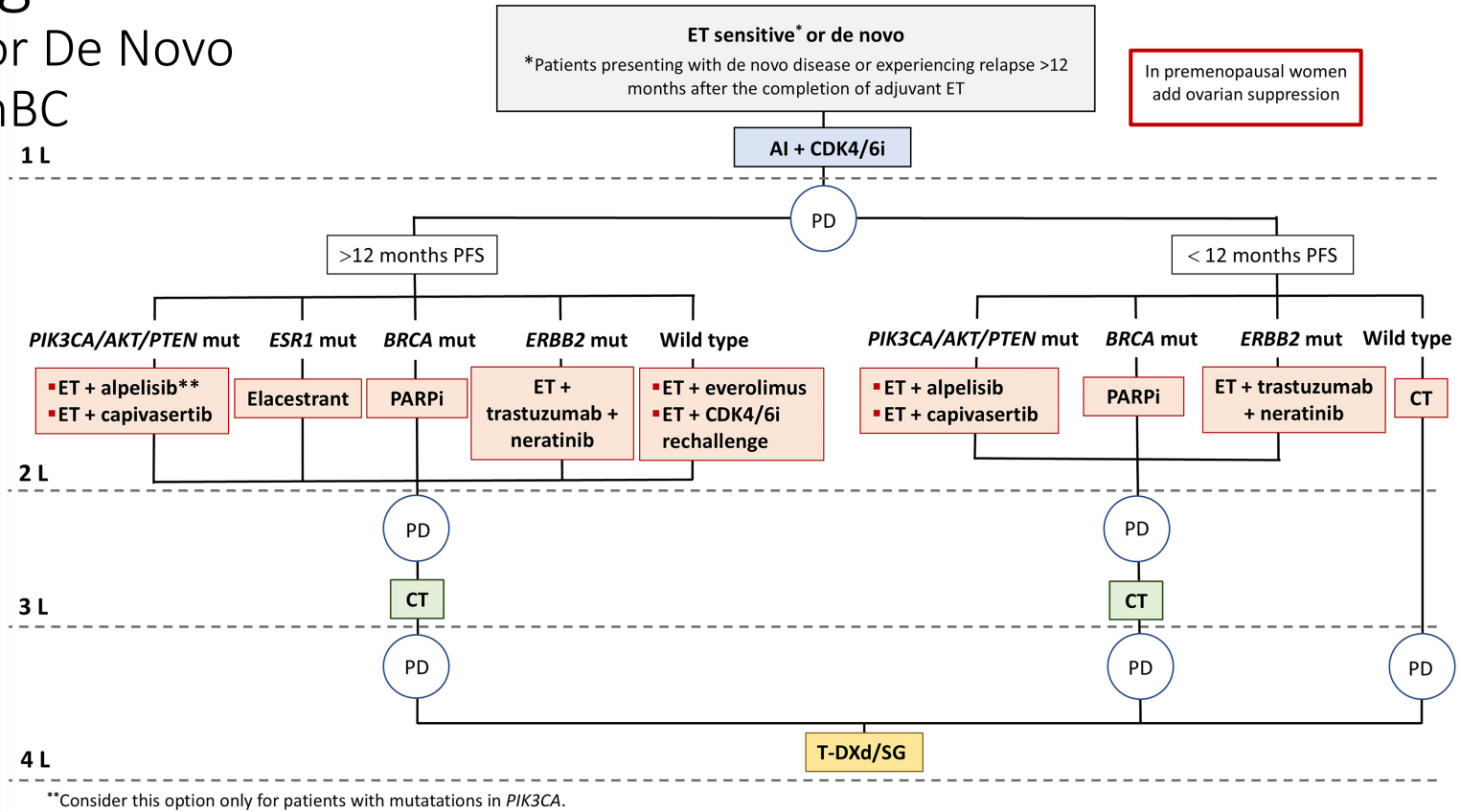
FDA approved January 2023 for postmenopausal men and women with HR+/HER2-, *ESR1* mutated advanced or metastatic breast cancer following disease progression on ≥1 ET

ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mPFS, median progression free survival; SERD, selective estrogen receptor down regulator

Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256.

Optimizing Treatment

ET Sensitive or De Novo HR+/HER2- mBC

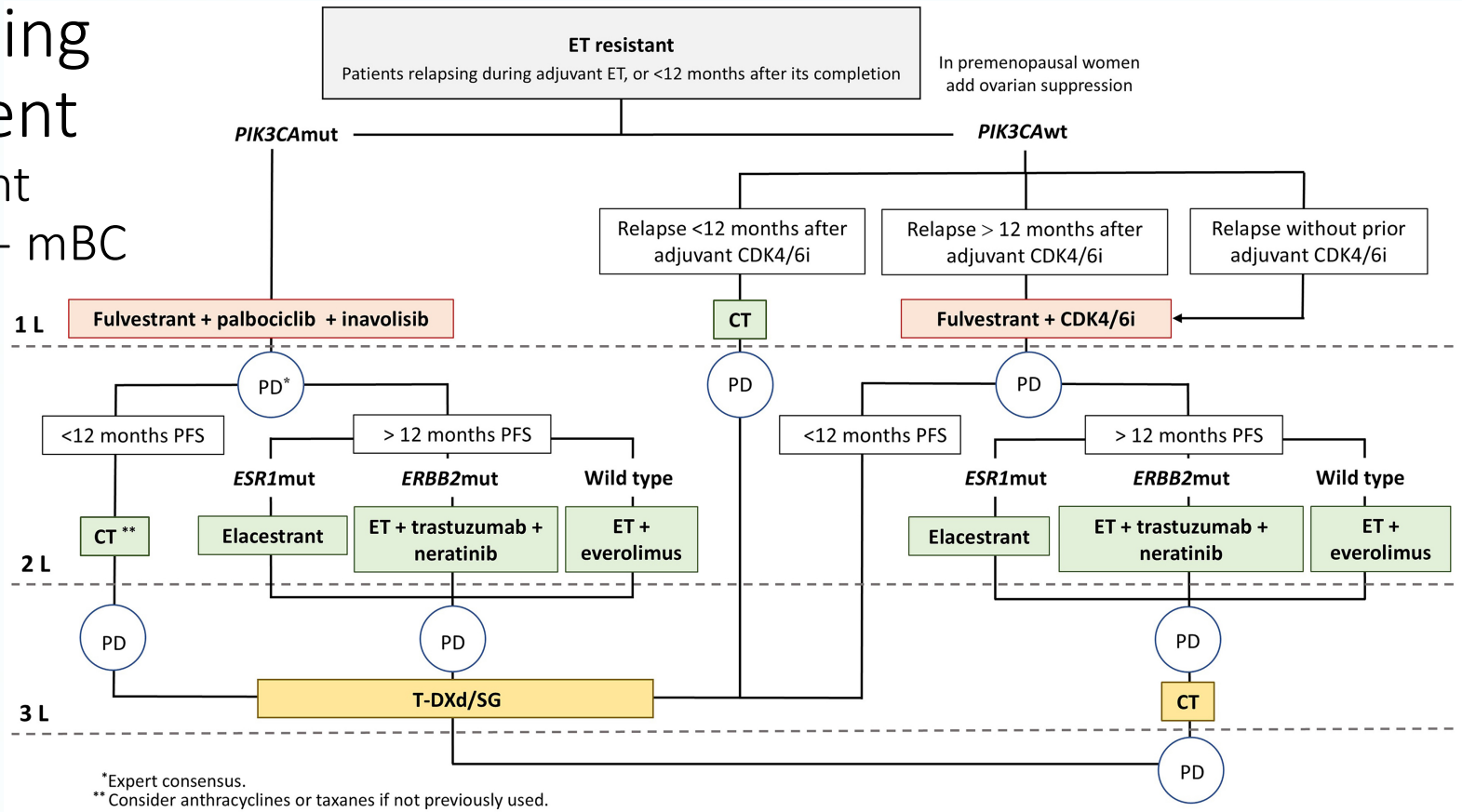


AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase inhibitors; ERS1 mut, estrogen receptor 1 mutation; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PD, progressive disease

**Consider this option only for patients with mutatations in *PIK3CA*.

Optimizing Treatment

ET Resistant HR+/HER2- mBC



AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase inhibitor; ERS1 mut, estrogen receptor 1 mutation; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PD, progressive disease; wt, wild type

Key Concepts

- Implement evidence-based guidelines and recommendations for the treatment of patients with HR+/HER2- mBC
  - Mitigate the risk of ET resistance
  - Consider patient goals- shared decision-making