Keynote presentation

LIVING BEYOND
BREAST CANCER®

Updates by subtype

HER2-positive, hormone receptor-positive, and triple-negative MBC

Speaker: Virginia Borges, MD, MMSc

2026 Conference on Metastatic Breast Cancer

Updates on HR+ MBC

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University of Colorado Cancer Center

University of Colorado Cancer Center

Young Women's Breast Cancer Translational Program

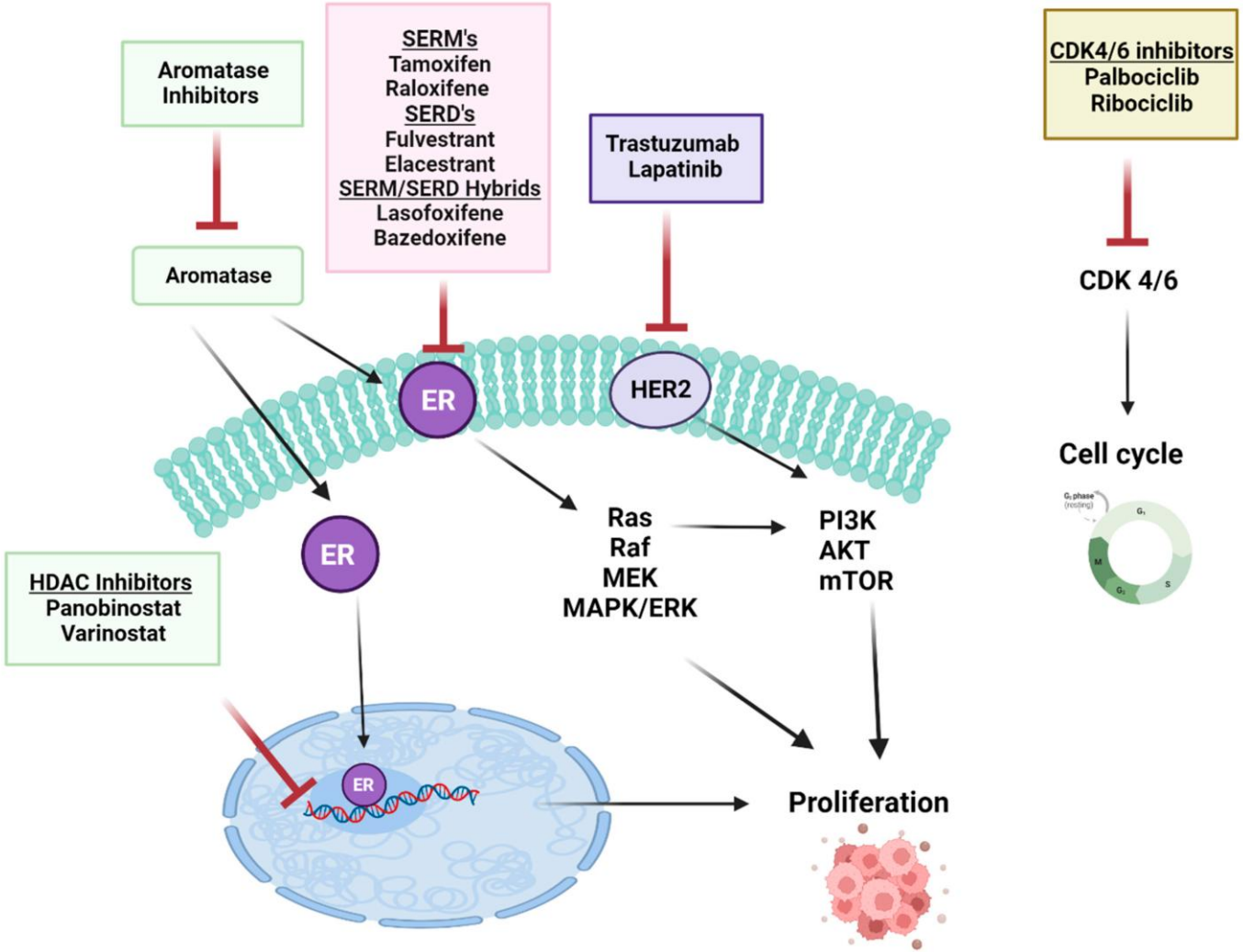
EVERY MOMENT COUNTS

MBC basics

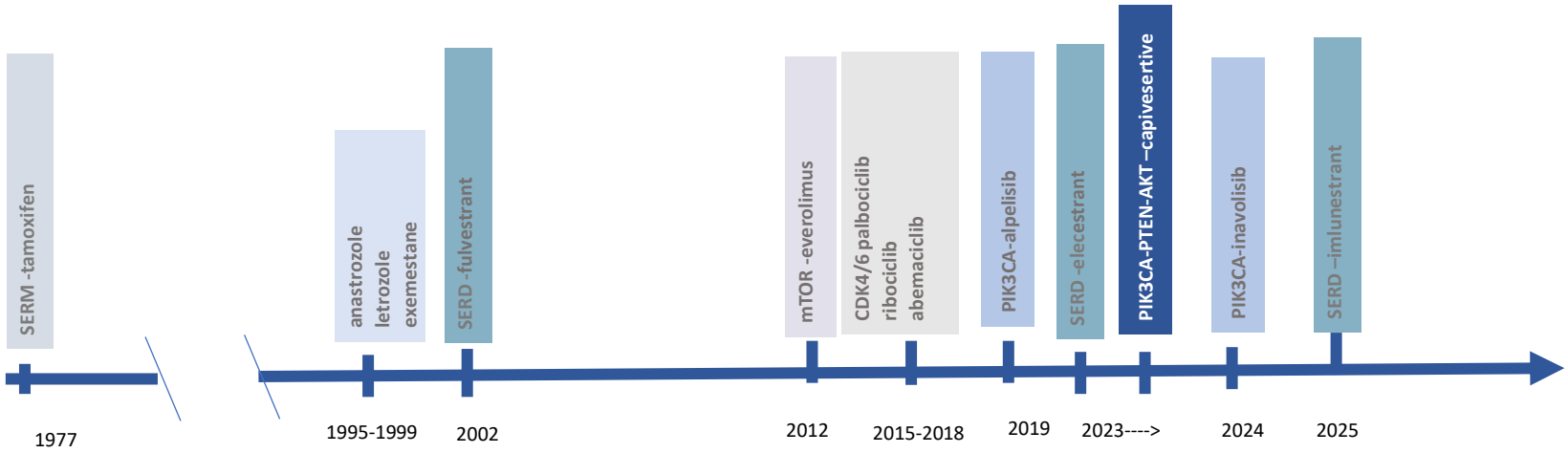
De Novo disease
Oligometastatic
Bone only
Visceral disease
Sites of Metastasis
Tumor markers
ctDNA testing
NGS/genomic testing
Evidenced based medicine
Real World Evidence
No evidence of disease
Scan results, “scanxiety”, and accuracy
What a care team looks like 2026

Patient focused care

Performance status
Genetic testing
Goals of Care
The Captain and the Navigator
The importance of exercise
The importance of diet
The role of supplements
Proven Eastern, Complementary &
Alternative medicine interventions
Sexual Wellness
Mental healing and resiliency


Aromatase Inhibitors
Aromatase
SERM's
Tamoxifen
Raloxifene
SERD's
Fulvestrant
Elacestrant
SERM/SERD Hybrids
Lasofoxifene
Bazedoxifene
Trastuzumab
Lapatinib
CDK4/6 inhibitors
Palbociclib
Ribociclib
CDK 4/6
Cell cycle
ER
HER2
ER
HDAC Inhibitors
Panobinostat
Varinostat
Ras
Raf
MEK
MAPK/ERK
PI3K
AKT
mTOR
ER
Proliferation

Timeline of initial novel drug approvals for HR+ HER 2- metastatic breast cancer



Borges, JCO, Dec 2021- updated March 2026

How Has This Cancer Been Treated?

The foundation that recent advances have built upon

1

Hormone Therapy (Endocrine Therapy)

Pills or injections that block estrogen from fueling cancer cells. First-line standard treatment.

2

CDK4/6 Inhibitors

Drugs (ribociclib, palbociclib, abemaciclib) that stop cancer cells from dividing. Combined with hormone therapy.

3

Resistance Develops

Over time most cancers find ways to grow despite treatment — this is the key challenge doctors are working to overcome.

4

Next Steps

After resistance: new targeted drugs, antibody-drug conjugates, or chemotherapy. This is where the newest advances shine.

Recent advances have dramatically expanded what happens at Steps 3 and 4 — giving patients more effective, better-tolerated options.

Precision Medicine: Knowing Your Tumor's 'Fingerprint'

Genetic testing of the person and genomic tests of tumor help doctors pick the right treatment for each patient

Before choosing a treatment, doctors now test tumors for specific genetic changes. Think of it like a blueprint that tells doctors which drugs will work best.

PIK3CA Mutation (~40% of patients)

Found in about 40% of HR+/HER2- breast cancers. Signals a growth pathway gone haywire. Targeted by inavolisib — a newly approved drug.

ESR1 Mutation (~40–50% of patients)

Develops after hormone therapy. The estrogen receptor changes shape so it's always 'on.' New drugs like elacestrant, imlunestrant and vepdegestrant and many others specifically target this.

BRCA1/2 Mutation (~5–10% of patients)

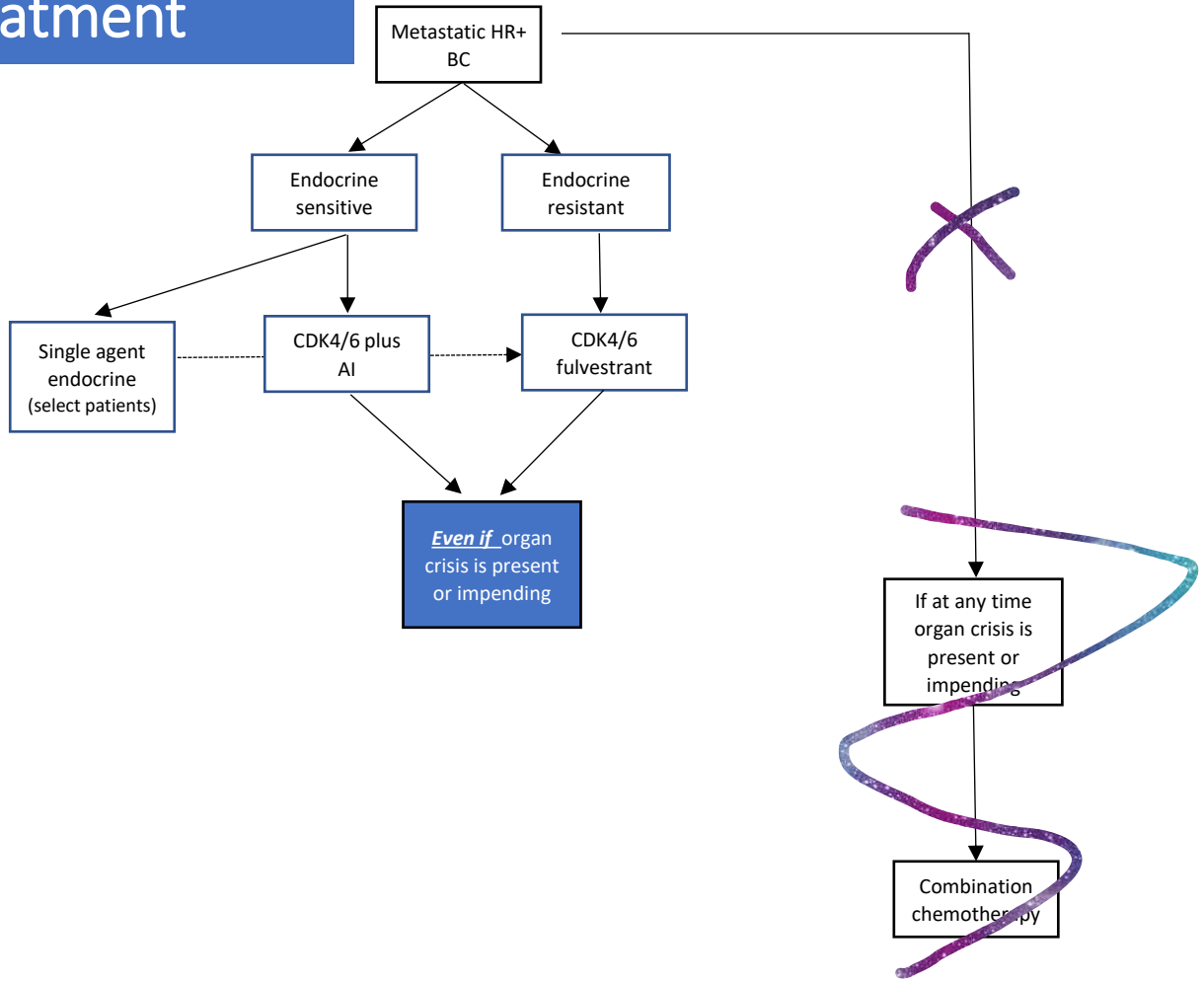
Inherited gene changes that affect DNA repair. Olaparib (PARP inhibitor) can significantly improve outcomes in these patients.

HER2-Low / Ultra-Low (~60% of patients)

Some HER2- tumors still have small amounts of HER2. New antibody-drug conjugates can now target even these low levels.

Sequencing of Treatment

First line therapy



Major FDA Approvals: 2024–2025

New treatments that have officially cleared for patient use

Inavolisib (Itovebi)

Oct 2024

+ palbociclib + fulvestrant

For: PIK3CA-mutated HR+/HER2- MBC

✓ First-ever survival benefit in PIK3CA-mutated patients: median survival 34 vs. 27 months

Datopotamab deruxtecan (Datroway)

Jan 2025

Trop-2 directed antibody-drug conjugate

For: Previously treated HR+/HER2- MBC

✓ 37% reduction in risk of cancer growing vs. chemotherapy

Trastuzumab deruxtecan (Enhertu)

Jan 2025

HER2-directed antibody-drug conjugate

For: HER2-low & HER2 ultra-low HR+ MBC after endocrine therapy

✓ 36% reduction in risk of cancer growing vs. chemotherapy — expanded eligibility dramatically

Elacestrant (Orserdu)

2023

Oral SERD (estrogen receptor degrader)

For: ESR1-mutated HR+/HER2- MBC

✓ First oral SERD approved in 20+ years; now being combined with other drugs with even better results

Spotlight: Inavolisib — A Triple-Threat Approach

First-ever survival improvement for patients with PIK3CA mutation

How It Works

THREE drugs work together:

Inavolisib
Blocks the PI3K pathway — a cell growth highway that's sped up by the PIK3CA mutation

Palbociclib
Stops cancer cells from dividing

Fulvestrant
Blocks estrogen receptors on cancer cells

The Results (INAVO120 Trial)

Median Overall Survival

34 months (with inavolisib) vs. 27 months (without)

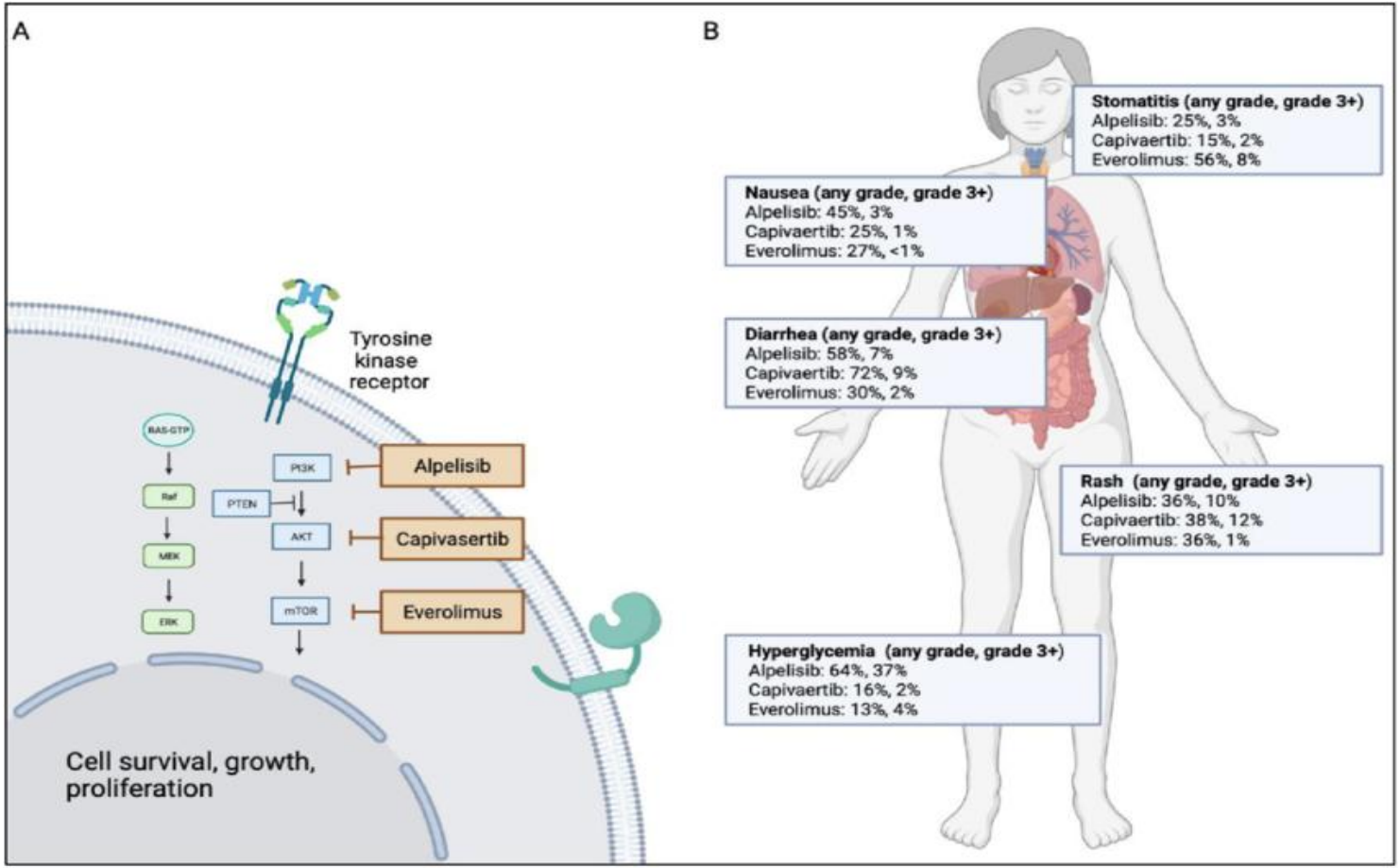
✓ **+7 months survival**

Progression-Free Survival

15 months (with inavolisib) vs. 7 months (without)

✓ **2× as long without cancer growing**

FDA approved October 2024. Who qualifies- patients whose tumor has a PIK3CA mutation, detected by a blood or tumor test.



A.) Mechanism of action of everolimus, alpelisib, capivasertib.
B.) Selected side effects of interest of everolimus, alpelisib, capivasertib (*Created with BioRender.com, 2023*)

Schlam & Chavez-McGregor, Feb 2024

Outsmarting Resistance: New Hormone-Blocking Drugs

When cancer learns to dodge standard hormone therapy, these new drugs fight back

The estrogen receptor can mutate under the pressure of treatment. **ESR1 mutations** cause up to 50% of cases where HR+ cancer stops responding to hormone therapy. New drug classes specifically designed to overcome this:

Oral SERDs — Selective Estrogen Receptor Degraders

Instead of just blocking the estrogen receptor, SERDs destroy it entirely — the cancer can't use something that no longer exists.

Elacestrant (Orserdu) *[FDA approved 2023]*

Now being combined with abemaciclib — showing 14.3 months without cancer progression (vs. 8.3 with other combos)

Imlunestrant (Inluriyo) *[Recently approved 2025]*

Penetrates the brain — important for patients with brain metastases. Shown to work alone or with abemaciclib.

Camizestrant *[Phase 3 trials ongoing]*

Can detect ESR1 mutations in blood (ctDNA) and switch therapy early — before the cancer has a chance to grow significantly.

PROTACs — Proteolysis Targeting Chimeras

A brand-new technology that tags the estrogen receptor for destruction by the cell's own waste-disposal system. Think of it as putting a 'demolish this' sticker on the problem protein.

Vepdegestrant *[NDA filed mid-2025; decision pending]*

First-ever PROTAC in breast cancer. Breakthrough Therapy designation from FDA. Showed superior progression-free survival in ESR1-mutated patients.

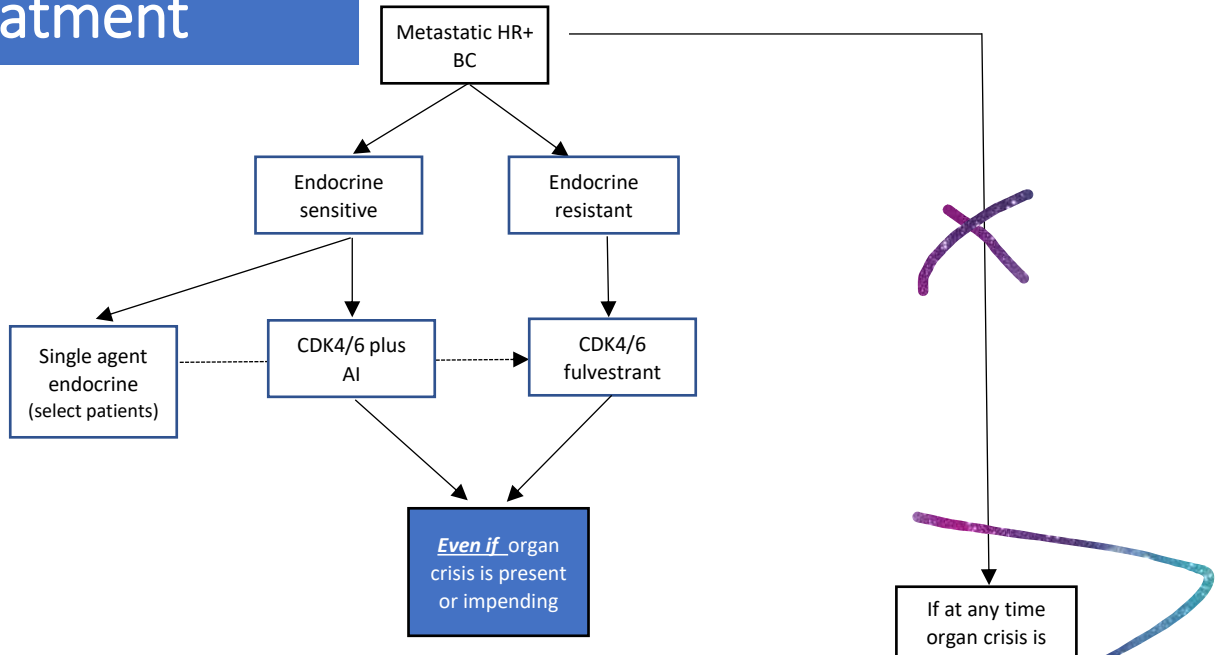
CERANs –Complete Estrogen Receptor Antagonists

An extended dual targeting and blocking at the estrogen receptor. It destroys it like a SERD and blocks the ability of the ER to signal.

Palezestrant *[phase 3 trials ongoing]*

Sequencing of Treatment

First line therapy

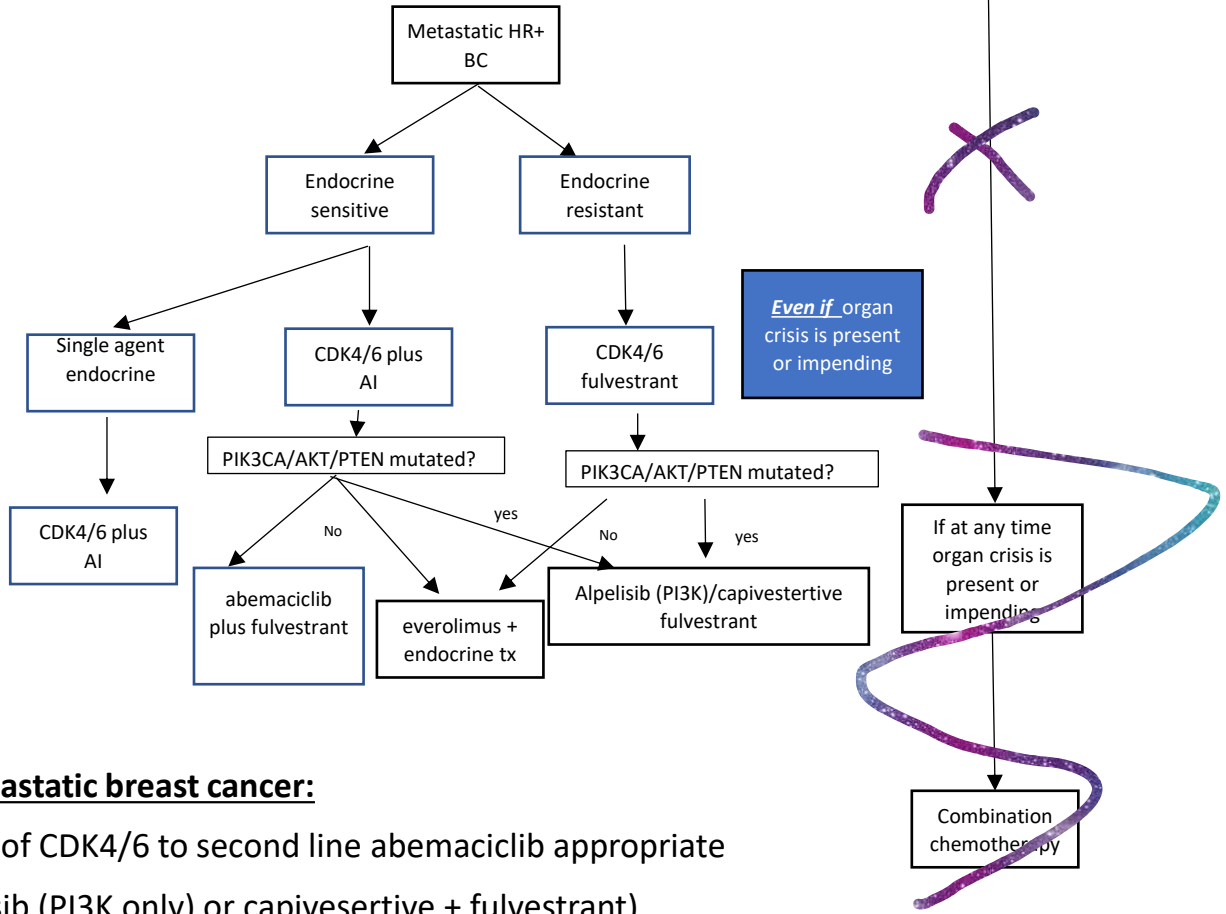


What about after a CDK4/6 inhibitor?

chemotherapy

Sequencing of CDK4/6 inhibitor data in context

Second line therapy



Second line therapy for HR+ metastatic breast cancer:

SERD + CDK 4/6 and sequencing of CDK4/6 to second line abemaciclib appropriate

PI3K/AKT/PTEN + consider alpelisib (PI3K only) or capivesertive + fulvestrant)

Smart Missiles: Antibody-Drug Conjugates (ADCs)

Powerful chemotherapy guided precisely to cancer cells

💡 Think of ADCs as "smart missiles": an antibody finds the target on the cancer cell surface, locks on, then delivers a powerful cancer-killing drug directly inside the cell — sparing healthy tissue.

Enhertu (trastuzumab deruxtecan / T-DXd)

FDA approved Jan 2025

Target: HER2 — even at very low levels (HER2-low & HER2 ultra-low)

Results: 36% reduction in risk of disease progression vs. chemotherapy. Now eligible: ~60% of HR+/HER2- patients who were previously excluded.

★ Game-changer: expands who qualifies for HER2-directed therapy

Datroway (datopotamab deruxtecan / Dato-DXd)

FDA approved Jan 2025

Target: TROP2 — a protein found on the surface of many breast cancer cells

Results: 37% reduction in risk of disease progression vs. chemotherapy. All-comers eligible regardless of HER2 or mutation status.

★ Offers a chemo-free-feeling option for patients who've already had hormone therapy

What's Coming Next: Promising Results from Recent Trials

Treatments approaching FDA approval or showing exciting early data

Post-CDK4/6: Abemaciclib Continues After Progression

Phase 3 data 2024

The postMONARCH trial showed that continuing abemaciclib (Verzenio®) with fulvestrant after disease progresses on a different CDK4/6 inhibitor can still extend time without cancer growing.

Giredestrant + Everolimus (evERA Trial)

Potential FDA submission

Combines a new oral SERD with an mTOR blocker for patients who progressed on CDK4/6 inhibitors. This is an all-oral regimen — no IV required. Phase 3 results presented at ESMO 2025.

Sacituzumab Tirumotecan (Sac-TMT)

Phase 3 data 2025

A next-generation Trop-2 ADC (the same target as Datroway, but with a different payload). Phase 3 OptiTROP trial data presented at ESMO 2025 showed significant improvement vs. chemotherapy in HR+/HER2- MBC.

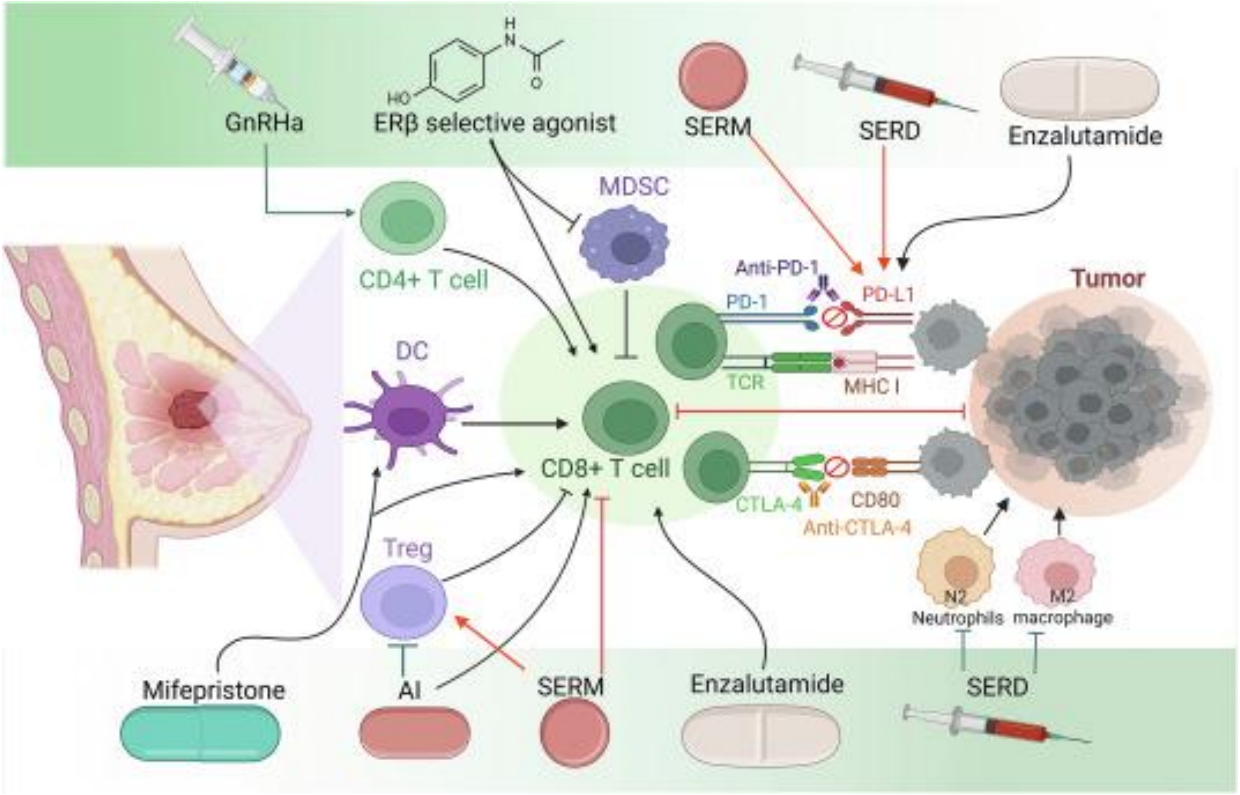
AI-Powered Recurrence Prediction

Published research 2025

A new AI model combining pathology slide images with molecular and clinical data can now predict recurrence risk out to 15 years — far beyond the Oncotype DX test's 5-year window. May help doctors tailor long-term treatment plans.

For educational purposes only. Talk to your oncologist about what options are right for you.

What's In the Pipeline of Science: Beyond ER, PR, PIK3CA/AKT/PTEN and BRCA



Androgen Receptor
HDAC inhbitors
Immunotherapy
Novel targets in BC

Questions to Ask Your Doctor

Being an informed partner in your care – YOU are the Captain. Your MD, the Navigator, needs to give you clear directions

1 **Has my tumor been tested for PIK3CA, ESR1 mutations, and HER2 levels?**

Why: These tests determine eligibility for several newly approved drugs.

2 **Am I a candidate for any of the new FDA-approved treatments like inavolisib, Datroway, or Enhertu?**

Why: New approvals in 2024–2025 may be right for you based on your tumor profile.

3 **What clinical trials are available to me?**

Why: Trials give access to tomorrow's therapies today — often at no extra cost.

4 **If my cancer is progressing, what is the next treatment plan?**

Why: Having a 'treatment roadmap' helps reduce anxiety and ensures no option is missed.

5 **Are there brain-penetrant options if I have or am at risk for brain metastases?**

Why: New oral SERDs like imlunestrant are designed to reach the brain.

6 **How will you monitor me for treatment resistance, and what's the plan if it happens?**

Why: Liquid biopsies can now detect ESR1 mutations early — before visible progression. These can be considered with careful discussion.

For educational purposes only. Talk to your oncologist about what options are right for you.

Reasons for Hope

The treatment landscape for HR+/HER2- metastatic breast cancer has never been more active or more hopeful.

More FDA approvals in 2024–2025 than in the prior decade combined for this cancer type

Precision medicine means treatment is increasingly tailored to your tumor's unique 'fingerprint' — not one-size-fits-all

Many new treatments are oral pills taken at home — not IV infusions requiring clinic visits

Blood tests (liquid biopsies) can now detect resistance early, allowing doctors to switch strategy before cancer visibly grows

Large survival benefit demonstrated for the first time in PIK3CA-mutated patients — a population of 40% of HR+ MBC

PROTACs and ADCs represent entirely new classes of drugs — meaning the pipeline for future treatments is robust

Your oncology team is your partner in navigating these advances — every patient deserves a conversation about what's new.

Reasons for Hope

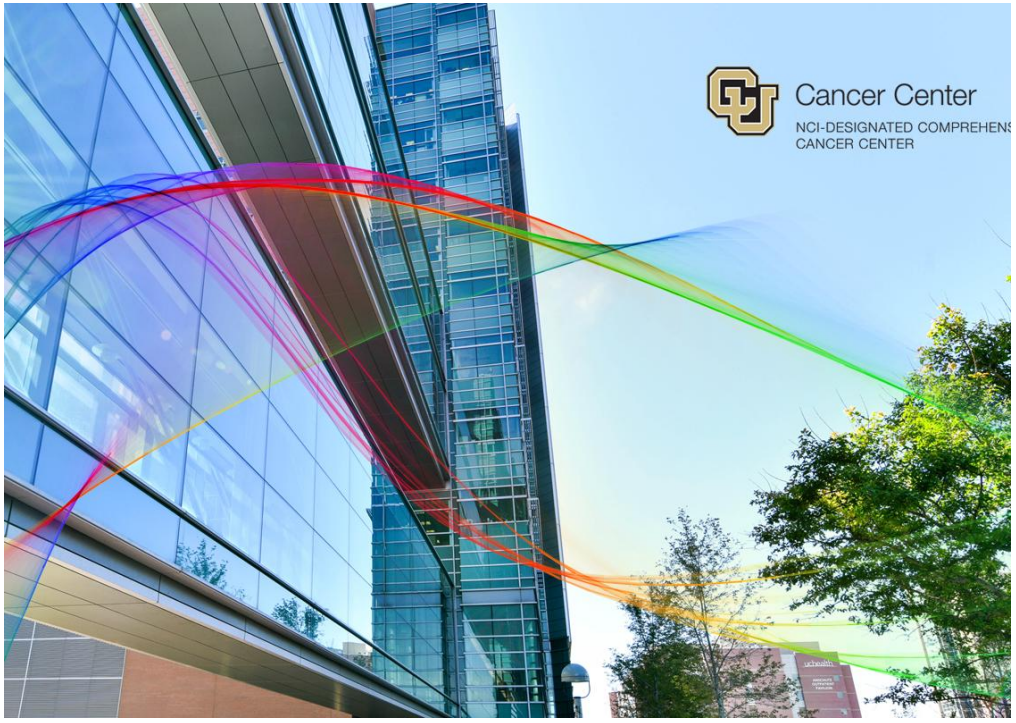
The treatment landscape for HR+/HER2- metastatic breast cancer has never been more active or more hopeful.

I CANNOT PREDICT HOW LONG MY PATIENTS ARE GOING TO LIVE ANYMORE – THE OUTER LIMIT IS TOO HARD TO PREDICT

Your oncology team is your partner in navigating these advances — every patient deserves a conversation about what's new.

Thank you!

Bring your questions during the panel session!



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