

Systemic Treatment of HR+/HER2-Metastatic Breast Cancer

A Visual Blueprint of the 2025 REAL Alliance
National Consensus Recommendations



Target Audience: Medical Oncologists & Clinical Pharmacists

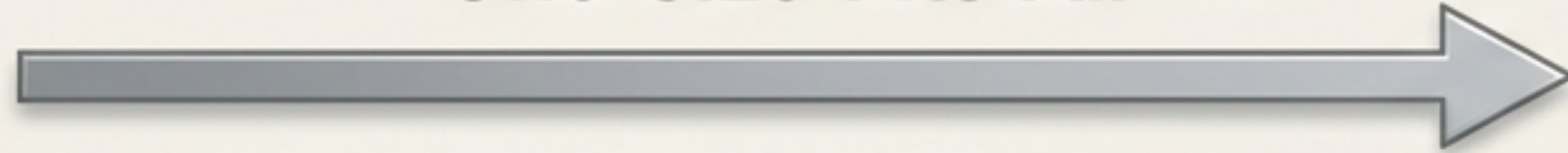
Source Data: Current Oncology (2026), Sunnybrook Odette
Cancer Centre, University of Toronto.

The Precision Pathway

The Clinical Reality

64–76% of all breast cancers are HR+/HER2–

One-Size-Fits-All

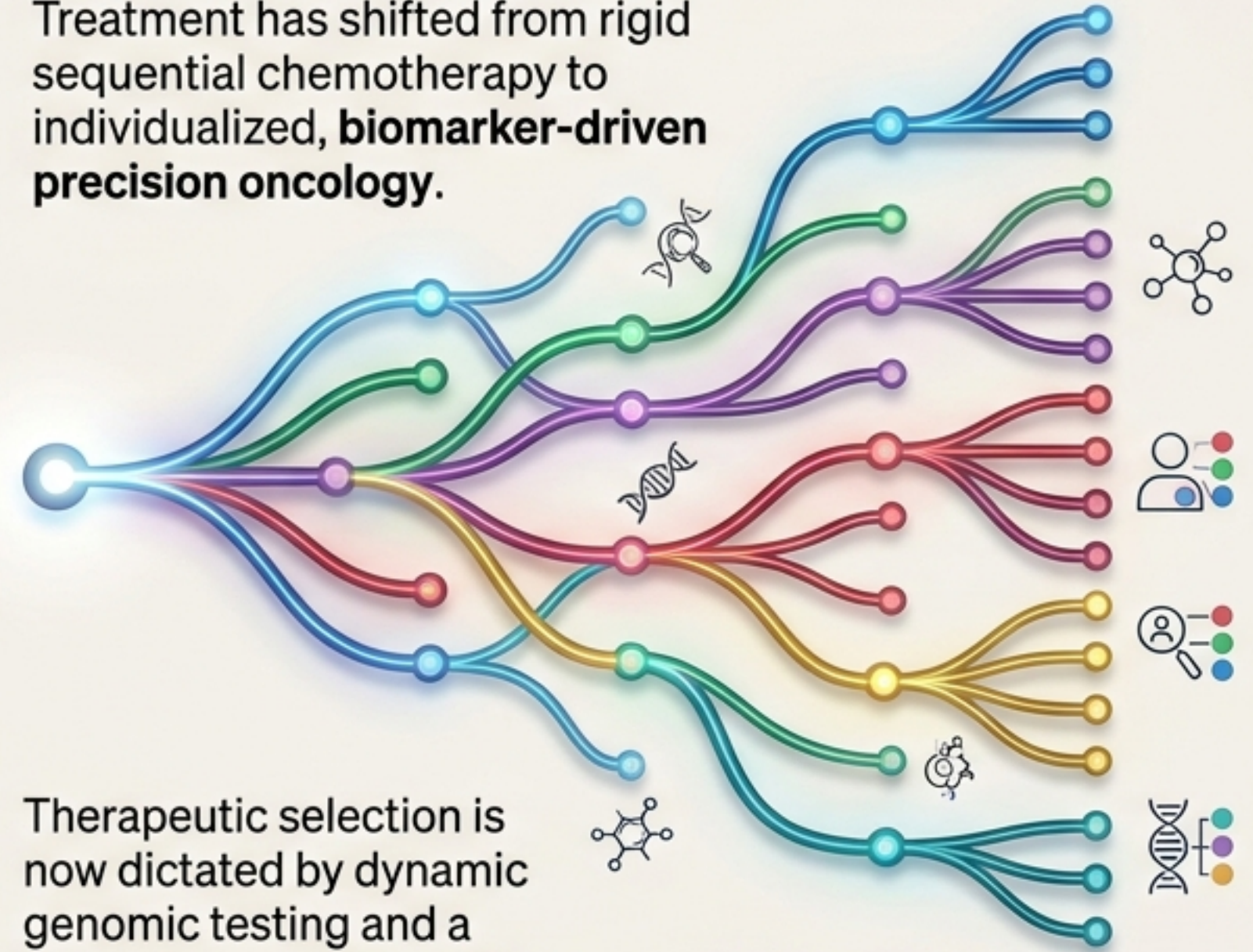


Goal of systemic treatment:

- ✓ Stabilize disease,
- 🕒 delay progression,
- ♥ improve quality of life,
- ♾️ prolong Overall Survival (OS)

The Modern Paradigm

Treatment has shifted from rigid sequential chemotherapy to individualized, **biomarker-driven precision oncology**.



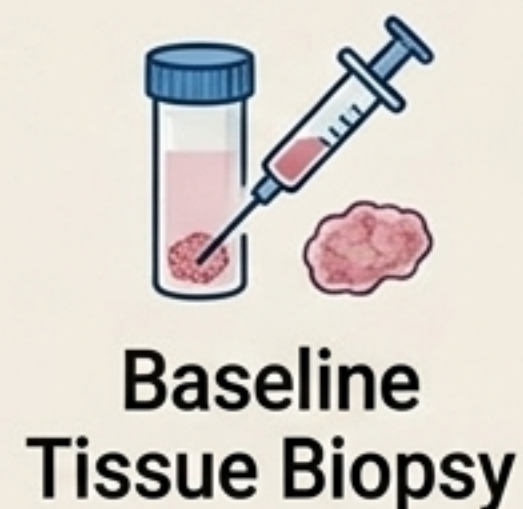
Therapeutic selection is now dictated by dynamic genomic testing and a patient's evolving sensitivity to endocrine therapy

The Precision Pathway

	Endocrine-Sensitive	Endocrine-Eligible	Endocrine-Ineligible
Clinical Definition	No prior/recent ET, or recurrence >12 months post-adjuvant ET. (De novo or late relapse).	Relapse on or ≤ 12 months post-adjuvant ET, or progression on metastatic ET. Retains partial estrogen responsiveness.	Extensive prior ET exposure with documented progression. Refractory biology.
Disease Characteristics	Hormone-driven, highly responsive to foundational backbone.	Emerging resistance, accumulation of targetable somatic pathway alterations.	Rapidly progressive, high visceral burden, loss of endocrine dependence.
Treatment Philosophy	Establish stable foundation (AI + CDK4/6i).	Manage resistance via targeted mutational rescue (SERDs + Pathway Inhibitors).	Cytotoxic escalation (Chemotherapy & ADCs).

The Precision Pathway

Phase 1



The Keys: ER, PR,
HER2-low/ultralow status.



The Locks (Unlocks):
Endocrine backbone
eligibility, eventual T-DXd
eligibility (if HER2-low).

Phase 2



**Progression
Liquid/ctDNA Biopsy**



**The Keys (Actionable
Alterations):**
PIK3CA, *ESR1*,
PI3K/AKT/PTEN,
germline *BRCA1/2*.



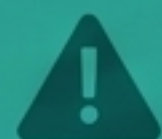
<i>PIK3CA</i>	→	Inavolisib / Alpelisib
<i>ESR1</i>	→	Oral SERDs
<i>PI3K/AKT/PTEN</i>	→	Capivasertib
g <i>BRCA1/2</i>	→	PARP Inhibitors (Olaparib/Talazoparib)

***ESR1* mutations are dynamic. Repeat testing via ctDNA at progression is essential to detect emerging resistance before clinical deterioration.**

The Precision Pathway: Endocrine-Sensitive 1L Therapy

[Aromatase Inhibitor (AI)] + [CDK4/6 Inhibitor] = 1L Standard of Care

For de novo metastatic disease or relapse >12 months post-adjuvant AI, first-line treatment is CDK4/6i + AI.



Clinical Note: Tamoxifen is generally avoided in combination with Ribociclib due to compounded QTc prolongation risk, and used with caution with Abemaciclib (VTE risk).

The Precision Pathway: CDK4/6 Inhibitor Class Comparison

	Ribociclib	Abemaciclib	Palbociclib
Landmark Trials	MONALEESA-2, -3, -7 (Only 1L trial dedicated to premenopausal)	MONARCH-2, -3	PALOMA-2, -3
Efficacy (OS Benefit)	Statistically significant OS benefit across populations (ESMO-MCBS: 4)	Strong OS trend; highly clinically meaningful 13.1-month difference (ESMO-MCBS: 1)	No OS benefit observed (ESMO-MCBS: 2)
Dosing Schedule	Intermittent (21 days on, 7 days off)	Continuous (Twice daily)	Intermittent (21 days on, 7 days off)
Signature Toxicities	QTc prolongation (requires ECG monitoring), hepatobiliary toxicity	Diarrhea (frequent, requires management), VTE risk. No antidepressant drug interactions	Neutropenia

Ribociclib or Abemaciclib are preferred. **Palbociclib** is reserved for contraindications/intolerance to others.

The Precision Pathway: CDK4/6i + ET in the Absence of Visceral Crisis



- **The Clinical Scenario:** Aggressive HR+/HER2- metastatic disease with symptomatic visceral metastases but NO true visceral crisis (severe organ dysfunction/rapid impending failure).
- **The Guideline:** Ribociclib + ET or Abemaciclib + ET is the standard of care over upfront chemotherapy.

RIGHT Choice Trial: Ribo + ET vs. Combo Chemo

Superior PFS (21.8 vs 12.8 mos), similar response rates (~66%), better tolerability.

ABIGAIL Trial: Abema + ET vs. Paclitaxel

Superior 12-week early response (59% vs 40%).

Key Takeaway: Trust the targeted backbone. Reserve cytotoxic chemo for true visceral crisis.

The Precision Pathway: The Pivot to SERD Therapy



Context:

Disease relapsing on or ≤ 12 months after adjuvant AI, or **non-**gresting or progressing on 1L metastatic therapy. The tumor remains partially sensitive to estrogen.

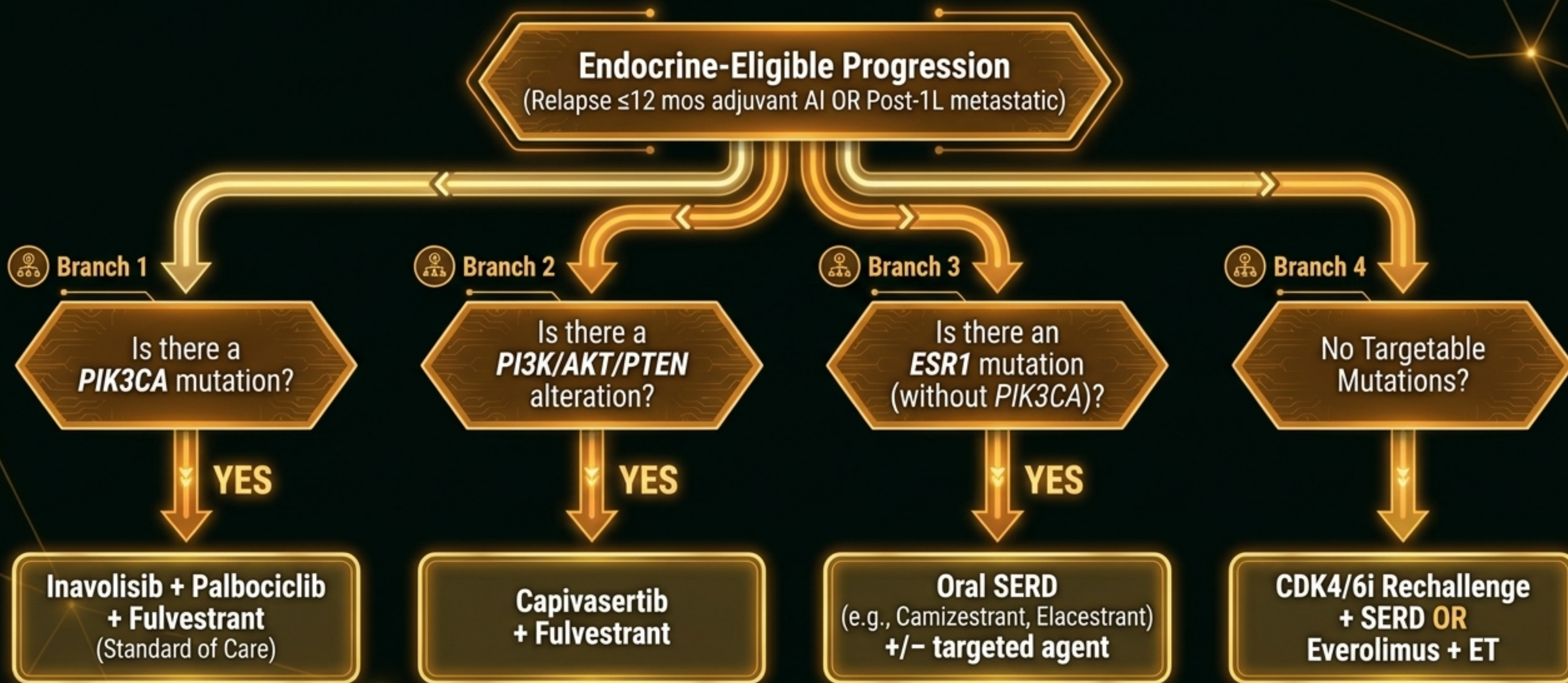
The ET Shift:

The standard of care Endocrine Therapy backbone shifts from an Aromatase Inhibitor to Aromatase Inhibitor to a Selective Estrogen Receptor Degradar (SERD) (e.g., Fulvestrant).

The Biomarker Imperative:

This inflection point mandates **precision genomic testing** to identify the specific mechanism of acquired resistance.

The Precision Pathway: Navigating Endocrine-Eligible Progression



The next four slides will drill down into each of these specific pathways.

The Precision Pathway: Branch 1 - *PIK3CA* Mutation Positive



Clinical Profile:

PIK3CA mutations occur in ~40% of patients and are associated with worse prognosis/aggressive biology.

The Evidence (INAVO120 Trial):

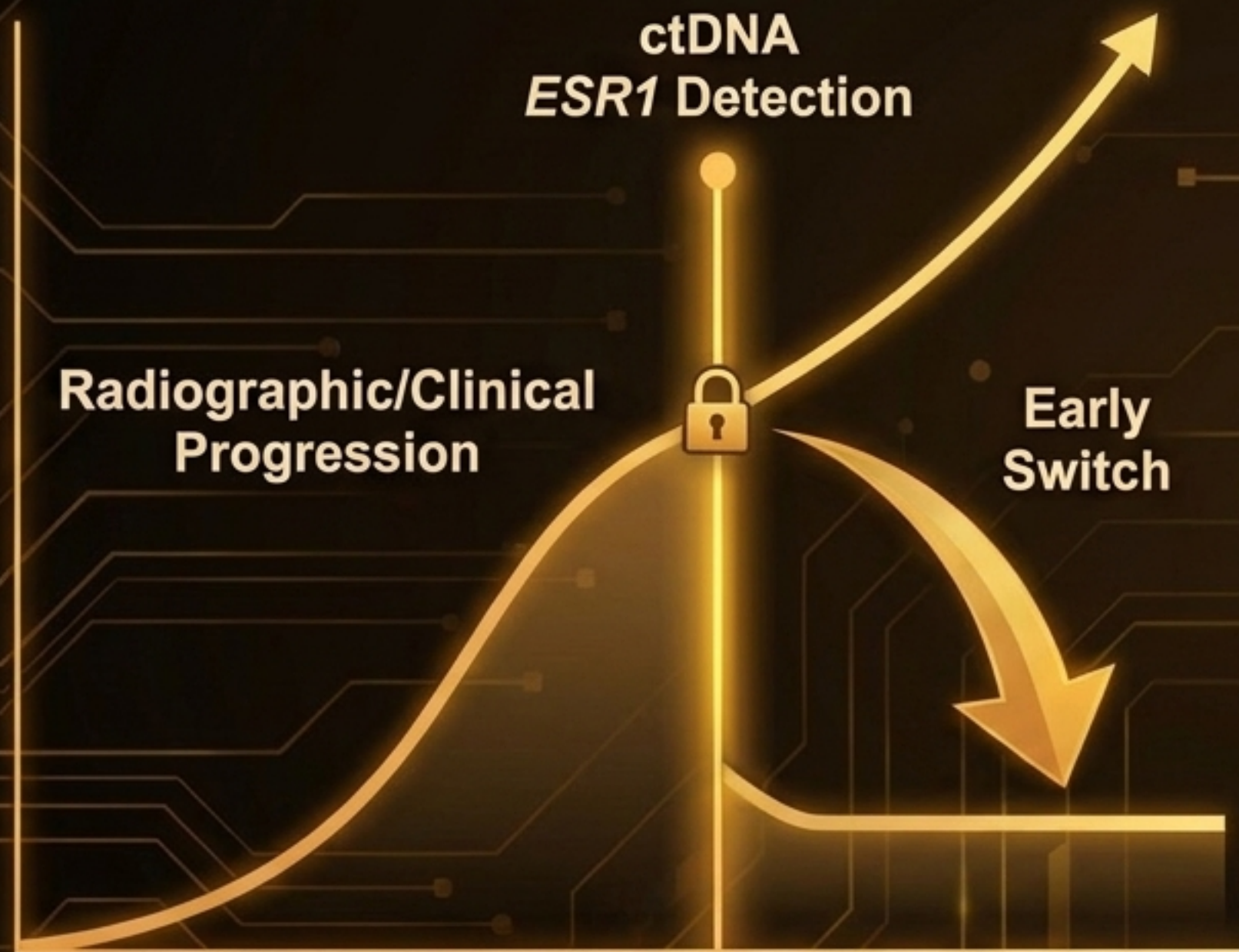
- Statistically significant PFS improvement (15.0 vs 7.3 months).
- Prolonged OS (34.0 vs 27.0 months).
- 33% reduction in risk of death.

⚠️ Hyperglycemia

Occurred in 63.4% of patients (6.8% Grade 3/4).

Actionable step: Requires baseline/routine blood glucose monitoring. Prophylactic metformin recommended for high-risk patients (pre-diabetes, BMI ≥ 30).

The Precision Pathway: Branch 3 - *ESR1* Mutation Positive



Clinical Profile:

ESR1 mutations drive AI resistance, emerging in 20-40% of metastatic patients.

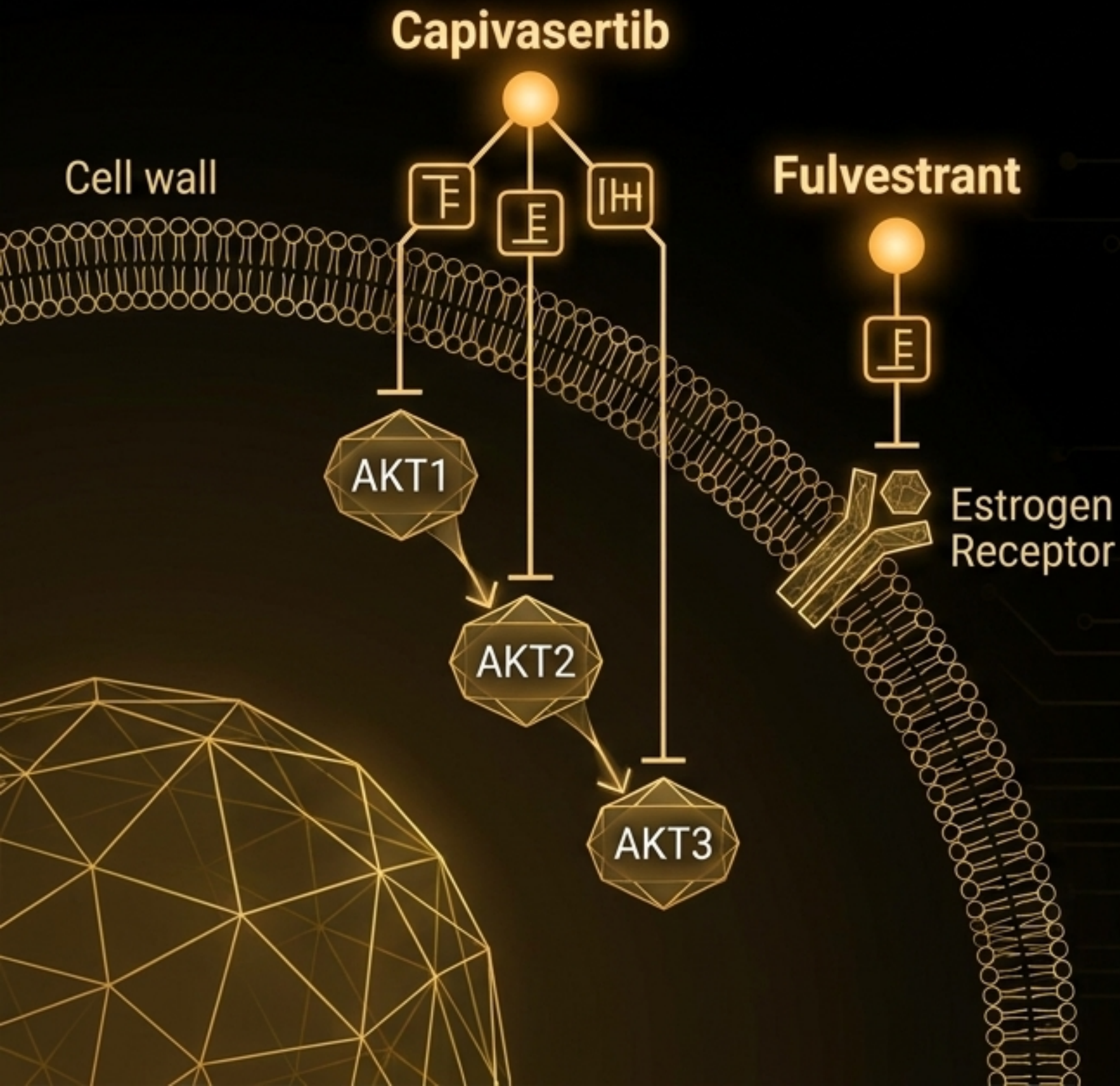
The Treatment Shift:

Oral SERDs (Elacestrant, Imlunestrant, Camizestrant) and PROTAC agents (Vepdegestrant) significantly outperform standard ET (fulvestrant/AI) in PFS and preserve quality of life via oral administration.

The SERENA-6 Paradigm:

Early detection of *ESR1* via ctDNA allows for switching the ET backbone from an AI to an oral SERD (Camizestrant) prior to clinical progression while maintaining the same 1L CDK4/6i. Result: 66% risk reduction in disease progression (PFS 16.0 vs 9.2 mos).

The Precision Pathway: Branch 2 - PI3K/AKT/PTEN Alterations



Clinical Profile:

Capivasertib + Fulvestrant is the standard of care for patients with PI3K/AKT/PTEN alterations and no prior pathway-directed therapy.

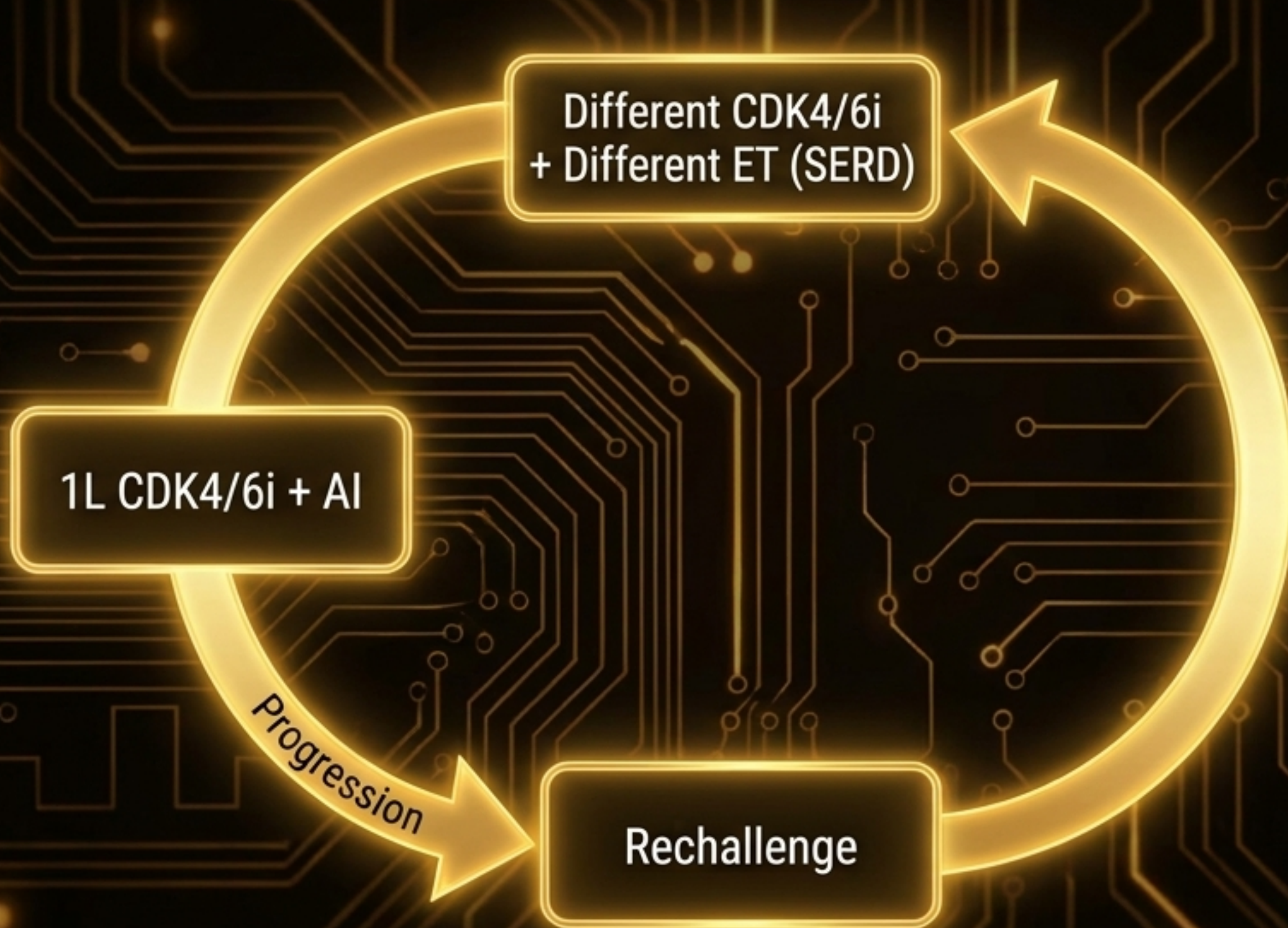
The Evidence (CAPItello-291 Trial):

- Evaluated patients progressing on/after AI (69% had prior CDK4/6i).
- PFS more than doubled (7.3 vs 3.1 months).
- Quality of life/global health status maintained twice as long.

Alternative Option:

Alpelisib + Fulvestrant can be considered for confirmed PIK3CA mutations, though hyperglycemia toxicity is notably severe and requires strict patient selection based on metabolic comorbidities.

The Precision Pathway: Rechallenge & CDK4/6i Maintenance



The Clinical Question:

Does maintaining CDK4/6 inhibition work after progression?

The Evidence (MAINTAIN & postMONARCH):

- Rechallenge with ET + Ribociclib (MAINTAIN) or Abemaciclib (postMONARCH) provides modest but real clinical benefit (e.g., doubling median PFS from ~2.7 to ~5.3 months).
- **Crucial Caveat:** Benefits were most notable in patients who received Palbociclib in the 1L setting. Extrapolating this to patients progressing on adjuvant/1L Ribo/Abema is uncertain.

Clinical Consensus (Moderate Recommendation):

Consider rechallenge depending on the clinical scenario. Switch the ET backbone (e.g., AI to Fulvestrant/Imlunestrant).

Not recommended if disease progression is rapid or visceral burden is high.

The Precision Pathway: Transition to Cytotoxic & ADC Therapy

Endocrine Depletion

Defining Ineligibility: Disease has progressed on prior ET + CDK4/6i and demonstrates endocrine-refractory biology. Further ET is futile.

Cytotoxic & ADC Escalation

The New Standard: Non-ET-based chemotherapy or Antibody-Drug Conjugates (ADCs).

Chemotherapy Principles:

- Single-agent chemotherapy (Capecitabine, taxanes, eribulin) is generally preferred to minimize toxicity.
- Doublet regimens are reserved for aggressive disease or visceral crisis demanding rapid response.



Safety Note: Germline testing for DPD deficiency is required before initiating Capecitabine to prevent fatal fluorouracil reactions.

The Precision Pathway: The HER2-Low Revolution with T-DXd

HER2 receptors

IHC 1+, 2+, or ≥0 to <1+

T-DXd

Bystander Effect

The HER2-Low Revolution:

~65% of traditionally HR+/HER2- breast cancers actually express low or ultralow levels of HER2, making them targetable by Trastuzumab deruxtecan (T-DXd).

Positioning T-DXd:

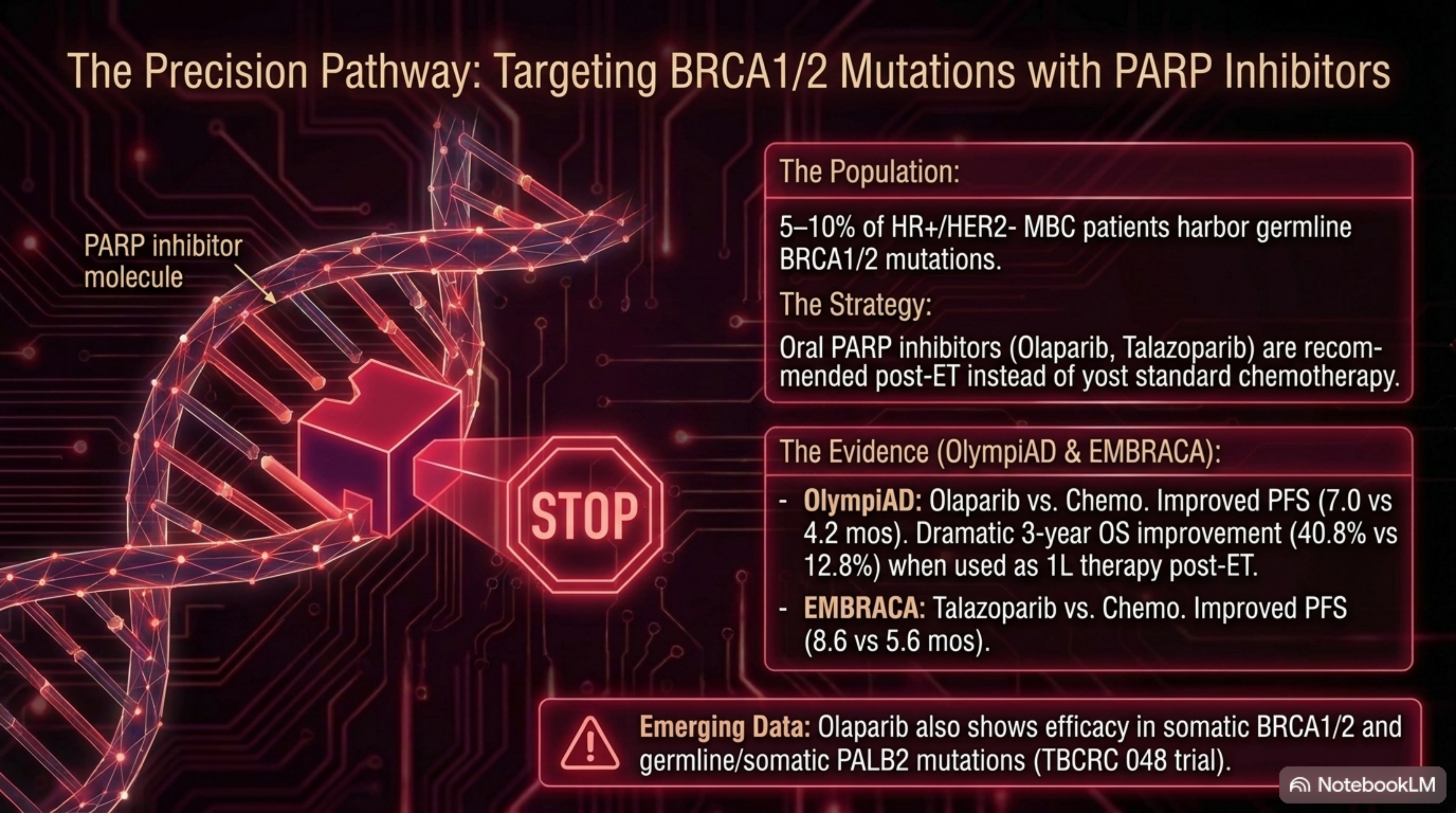
- **DESTINY-Breast06:** T-DXd is now an option as the first line of systemic chemotherapy (post-ET + CDK4/6i), significantly outperforming physician's choice chemo (PFS 13.2 vs 8.1 mos) with superior QoL and pain control.
- **DESTINY-Breast04:** Unquestioned standard of care for HER2-low patients who have already received at least one prior line of chemotherapy (OS 23.9 vs 17.5 mos).



Toxicity Warning: Interstitial Lung Disease (ILD) / Pneumonitis. Proactive monitoring and prompt management are mandatory.

The Precision Pathway: Targeting BRCA1/2 Mutations with PARP Inhibitors

PARP inhibitor molecule



The Population:

5–10% of HR+/HER2- MBC patients harbor germline BRCA1/2 mutations.

The Strategy:

Oral PARP inhibitors (Olaparib, Talazoparib) are recommended post-ET instead of yost standard chemotherapy.

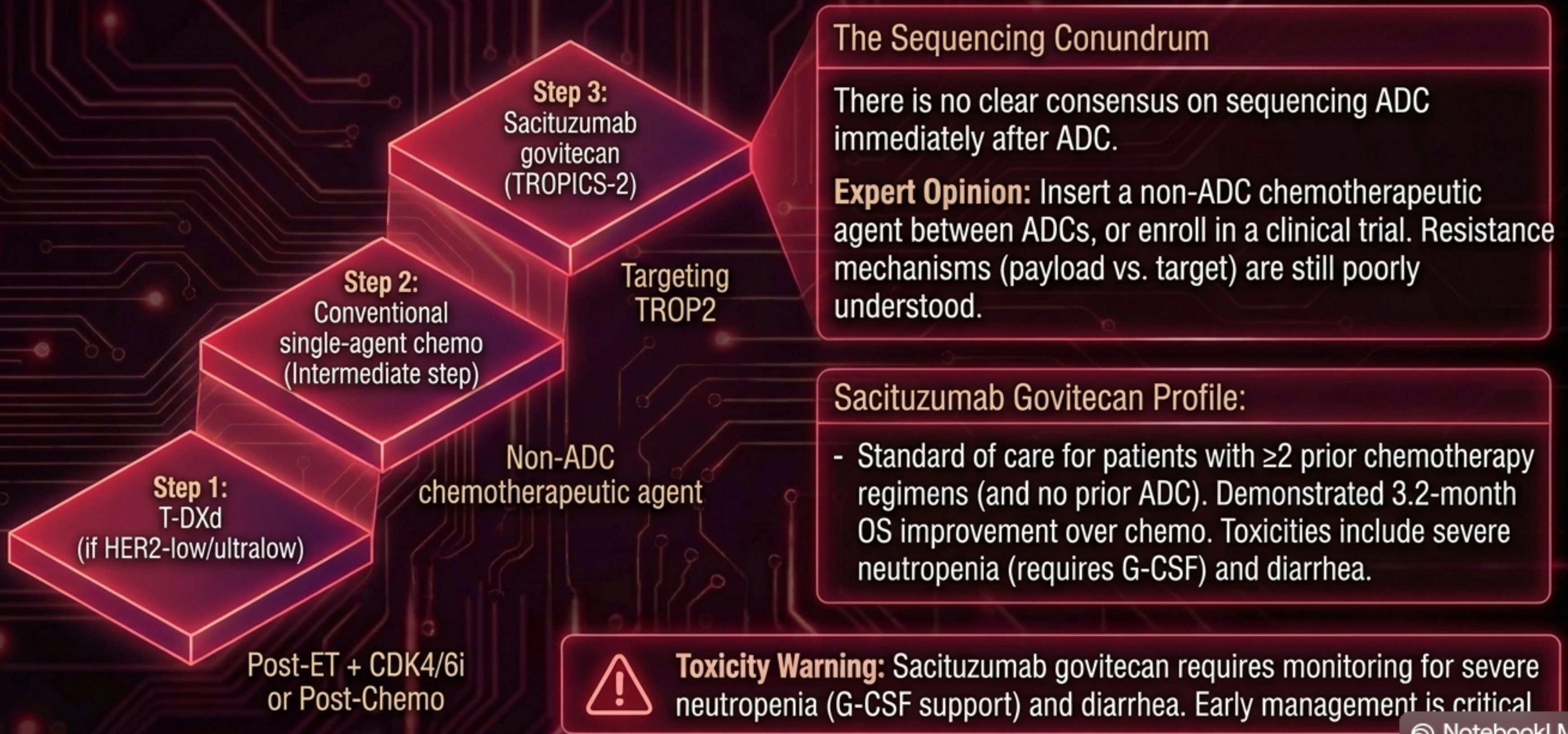
The Evidence (OlympiAD & EMBRACA):

- **OlympiAD:** Olaparib vs. Chemo. Improved PFS (7.0 vs 4.2 mos). Dramatic 3-year OS improvement (40.8% vs 12.8%) when used as 1L therapy post-ET.
- **EMBRACA:** Talazoparib vs. Chemo. Improved PFS (8.6 vs 5.6 mos).



Emerging Data: Olaparib also shows efficacy in somatic BRCA1/2 and germline/somatic PALB2 mutations (TBCRC 048 trial).

The Precision Pathway: Sequencing ADCs – The Challenge of T-DXd and Sacituzumab Govitecan



The Precision Pathway: Foundational Principles for Special Populations



The Elderly (≥ 75 years)

Guideline: Standard of care and standard recommended starting doses remain exactly the same as for younger patients.

Rationale: AMALEE trial proved lower starting doses of Ribociclib were inferior. Efficacy is maintained despite subsequent dose reductions for adverse events. Treat the physiological status, not the chronological age.



Limited Life Expectancy / Quality of Life Prioritization

Guideline: Endocrine Therapy (ET) alone is a highly reasonable option.

Rationale: SONIA trial showed that delaying CDK4/6i to the second line did not hurt overall survival but significantly reduced Grade ≥ 3 adverse events and extended time free from toxicity. Shared decision-making is paramount.

The Precision Pathway: Frameworks for Metastasis Management (Skeletal & CNS)



Skeletal Framework (Bone)

- Affects up to 70% of HR+/HER2-MBC patients.

Action: Bone-modifying agents (bisphosphonates or denosumab) are mandatory to delay skeletal-related events (SREs), even if asymptomatic.

Management: Denosumab highly effective but higher osteonecrosis of the jaw risk. De-escalate dosing to every 24 weeks after 2 years of stability (REaCT-Hold BMA trial).



Neurological Framework (CNS)

Reality: Unlike HER2+ disease, effective systemic-only therapies for HR+/HER2-CNS metastases are lacking.

Action: Multidisciplinary Team (MDT) involvement is critical. Local therapy (radiation/surgery) remains the cornerstone. Abemaciclib and ADCs show early intracranial promise, but not enough to replace local intervention.

The Precision Pathway: Master Algorithm Flowchart



HR+/HER2- MBC Diagnosis

Emerald Zone



Endocrine-Sensitive -> 1L AI + CDK4/6i (Ribo/Abema)

Amber Zone



Endocrine-Eligible Progression

Biomarker Split



PIK3CA ->
(Inavolisib + Palbo + Fulv)



AKT/PTEN ->
(Capivasertib + Fulv)



ESR1 ->
(Oral SERD +/- target)



Wildtype ->
(CDK4/6i Rechallenge or
Everolimus + ET)

Crimson Zone

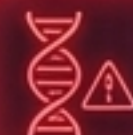


Endocrine-Ineligible Progression

Biomarker Split



HER2-Low ->
(T-DXd)



gBRCA ->
(PARP Inhibitor)



HER2-Zero/Wildtype ->
(Capecitabine/Single
Agent Chemo)



Post-Chemo ->
(Sacituzumab govitecan)

Takeaway 1: Endocrine Sensitivity is a Continuum

The rigid binary of sensitive vs. resistant is obsolete. Treatment is about dynamically maximizing the endocrine window.

Takeaway 2: Biomarkers Dictate the Path

Routine tissue and longitudinal ctDNA testing (PIK3CA, ESR1, AKT, HER2-low) are no longer optional—they are the architectural pillars of standard care.

Takeaway 3: The ADC Era Requires Strategic Sequencing

As ADCs move earlier into the treatment algorithm, protecting patient quality of life and understanding cross-resistance will define the next decade of oncology.

REAL Alliance 2025:

Evidence-informed guidance for equitable, precision breast cancer care across Canada.