SABCS 2025 SUMMARY

Key Summaries

1. HR-Positive / HER2-Negative Breast Cancer

Data presented at SABCS 2025 underscore a paradigm shift in hormone receptor–positive/HER2-negative breast cancer toward earlier integration of next-generation endocrine therapies and biomarker-driven sequencing strategies. The phase III lidERA trial demonstrated that adjuvant giredestrant significantly improves invasive disease-free survival compared with standard endocrine therapy, representing the first major advance in adjuvant endocrine treatment since the introduction of aromatase inhibitors. In the metastatic setting, updated results from EMBER-3 showed a clinically meaningful overall survival benefit with imlunestrant in patients with ESR1-mutant disease, supporting oral SERDs as preferred endocrine switch options. Conversely, ASCENT-07 failed to show a progression-free survival advantage for sacituzumab govitecan when used immediately after endocrine therapy, indicating that early sequencing of this antibody–drug conjugate in HR-positive disease is not justified. Post-CDK4/6 inhibitor strategies were further refined by postMONARCH and evERA, which demonstrated that continued pathway suppression with abemaciclib- or SERD-based combinations can provide sustained benefit in selected patients. Collectively, these findings support a biology-driven, stepwise treatment model prioritizing endocrine optimization before cytotoxic therapy.

2. HER2-Positive Breast Cancer

SABCS 2025 reinforced a shift toward earlier use of highly effective HER2-targeted agents and biologically guided treatment adaptation in HER2-positive breast cancer. In metastatic disease, HER2CLIMB-05 demonstrated that adding tucatinib to trastuzumab and pertuzumab as maintenance therapy after induction chemotherapy significantly prolongs progression-free survival, supporting earlier integration of HER2-directed tyrosine kinase inhibition. In early-stage disease, updated analyses from PHERGain highlighted the feasibility of PET-CT- and biology-guided de-escalation strategies, enabling chemotherapy-free neoadjuvant approaches in carefully selected patients. These results collectively support a move away from uniform, chemotherapy-intensive strategies toward precision-guided escalation and de-escalation across the HER2-positive disease continuum.

3. HER2-Low / HER2-Ultra-Low Breast Cancer

Findings presented at SABCS 2025 further consolidated the clinical relevance of HER2-low and HER2-ultra-low breast cancer as therapeutically actionable subgroups. DESTINY-Breast06 confirmed that trastuzumab deruxtecan significantly improves progression-free survival compared with chemotherapy in patients with HR-positive HER2-low metastatic disease, with exploratory analyses suggesting benefit even in tumors with ultra-low HER2 expression. These data reinforce the concept that HER2 expression represents a biological

continuum rather than a binary classification and support the use of antibody–drug conjugates before conventional chemotherapy in appropriately selected patients.

4. Triple-Negative Breast Cancer (TNBC)

SABCS 2025 provided further validation of immunotherapy-based strategies as the cornerstone of treatment for early triple-negative breast cancer. Long-term follow-up from KEYNOTE-522 confirmed durable event-free and overall survival benefits with neoadjuvant and adjuvant pembrolizumab, including in patients who did not achieve a pathologic complete response. Complementary biomarker analyses from NeoTRIP and GeparNuevo emphasized the importance of tumor-infiltrating lymphocytes and immune gene signatures in refining patient selection for immunotherapy. Together, these findings support the continued use of immune checkpoint inhibition in early TNBC while highlighting the need for biomarker-guided personalization.

5. Biomarker-Driven and Precision Oncology Across Subtypes

Across all breast cancer subtypes, SABCS 2025 highlighted the growing clinical utility of molecular and digital biomarkers to guide treatment decisions. Serial monitoring of ESR1 mutations using circulating tumor DNA emerged as a practical strategy to inform timely endocrine therapy switching in HR-positive disease. In early-stage breast cancer, ctDNA-based detection of molecular residual disease was emphasized as a promising tool for treatment escalation, de-escalation, and duration optimization, with phase III trials ongoing. In parallel, AI-based multimodal risk models integrating pathology images, clinical features, and genomic data demonstrated improved prediction of long-term and late recurrence risk beyond conventional assays, supporting future precision-guided frameworks.

6. Screening, Survivorship, and Quality of Life

Beyond therapeutic advances, SABCS 2025 underscored the importance of personalized screening and survivorship care. The WISDOM trial demonstrated that risk-based breast cancer screening provides safety comparable to annual mammography, supporting a move toward individualized screening strategies. In survivorship, data presented at SABCS 2025 indicated that menopausal hormone therapy does not increase breast cancer risk among BRCA1/2 mutation carriers, providing important reassurance for menopause management after risk-reducing oophorectomy. Supportive care trials further highlighted the role of digital health interventions and integrative therapies in improving quality of life and cognitive outcomes among breast cancer survivors.

7. Non–Medical Oncology Studies

Breast Surgery

SABCS 2025 provided strong evidence supporting **axillary de-escalation** strategies in carefully selected patients. The AXSANA/EUBREAST 3(R) study demonstrated that, in patients converting from cN+ to ycN0 after neoadjuvant therapy, **less-invasive axillary staging (TAD/SLNB/TLNB)** achieved **noninferior 3-year axillary recurrence-free**

survivalcompared with ALND (99.2% vs 98.8%). The BOOG 2013-08 trial further showed that **omission of SLNB** in cT1–2 cN0 patients treated with breast-conserving surgery and whole-breast irradiation resulted in **no statistically significant loss of regional control at 5 years** (96.6% vs 94.2%, *P* = 0.063). In contrast, INSEMA Rando2 clarified that in patients with **1–3 sentinel node macrometastases**, **noninferiority of SLNB alone was not demonstrated** for invasive disease-free survival (iDFS HR 1.26), underscoring that axillary de-escalation in macrometastatic disease requires **careful integration with radiotherapy strategy** and cannot be universally applied.

Radiation Oncology

Radiation-focused studies at SABCS 2025 emphasized **biology-driven personalization rather than routine de-escalation**. TBCRC-053 (P-RAD) provided **statistically significant human proof-of-mechanism** that **high-dose preoperative radiotherapy (24 Gy)** combined with pembrolizumab increased intratumoral T-cell infiltration compared with no radiotherapy ($p = 0.027$), positioning radiotherapy as an **immune modulator**. However, survival endpoints were not assessed, limiting immediate practice change. In the post-neoadjuvant setting, discussions around **NSABP B-51/RTOG 1304** reinforced that the field remains in **evidence-based equipoise** regarding routine omission of regional nodal irradiation after nodal pCR. INSEMA radiotherapy interface analyses further highlighted that **incidental axillary dose and RNI utilization vary substantially with axillary surgical approach**, and that omission of SLNB during BCS **does not require compensatory escalation of axillary radiotherapy**.

Radiology and Nuclear Medicine

SABCS 2025 reinforced a shift toward **selective, evidence-based imaging**. The Alliance A011104/ACRIN 6694 phase III trial showed that **routine preoperative breast MRI** in stage I–II HR-negative breast cancer **did not improve locoregional control** (5-year LRC 93.2% vs 95.7%; HR 1.1) nor survival outcomes, supporting selective rather than routine MRI use. In screening, **WISDOM 1.0** demonstrated that **risk-based screening was noninferior** to annual screening for detection of advanced cancers ($p < 0.001$), with numerically fewer stage ≥IIB cancers, supporting personalized screening as a future direction. In metastatic disease, FEATURE (EA1183) validated **FDG-PET/CT using modified PERCIST** as a powerful early predictor of outcome in bone-dominant disease, with **median PFS 19.4 vs 3 months** and an approximately **83% lower hazard of progression** in patients without progressive metabolic disease.

Pathology and Computational Biomarkers

Pathology-focused SABCS 2025 studies highlighted the transition from descriptive histology to **quantitative, AI-driven prognostication**. The TAILORx multimodal AI analysis demonstrated **significantly superior prediction of both overall and late distant recurrence** compared with Oncotype DX alone (C-index 0.733 vs 0.631 at 15 years; *P* = 0.00049). A Rapid Fire analysis from NSABP B-20 suggested that **digital pathology-based AI models may predict chemotherapy benefit**, reporting a ~52% relative reduction in distant metastasis among AI-defined high-risk patients, though these findings remain **preliminary and not yet peer-reviewed**.

Genetics and Hereditary Cancer

One of the most practice-relevant non–medical oncology findings at SABCS 2025 came from the matched prospective analysis of **menopausal hormone therapy (MHT) in BRCA1/2 carriers**. MHT use was associated with **lower breast cancer incidence** compared with non-use (12.9% vs 18.9%, $P = 0.002$), with estrogen-only regimens appearing particularly reassuring. While observational in nature, these data provide strong support for **individualized, evidence-based menopause counseling** after risk-reducing oophorectomy.

Overall Take-Home Message

Collectively, non–medical oncology studies at SABCS 2025 support a **measured de-escalation where oncologically safe (axilla, routine imaging)**, a **biology-driven approach to radiation therapy**, expanding roles for **functional imaging and AI-based pathology**, and more **reassuring, data-driven genetic counseling**. Importantly, many findings emphasize **refinement and personalization rather than wholesale practice change**, underscoring the need for multidisciplinary integration and cautious implementation

Non–Medical Oncology Studies

A. Breast Surgery

1) AXSANA / EUBREAST 3(R): Less-invasive axillary staging after NACT (cN+ → ycN0)

Background
Axillary lymph node dissection (ALND) drives lymphedema and morbidity. After neoadjuvant therapy (NACT), many initially node-positive patients become clinically node-negative, raising the question of whether **targeted/limited axillary approaches** can safely replace ALND.

Design (population, intervention, endpoint)

- **Population:** Patients initially **cN+** converting to **ycN0** after NACT.
- **Intervention/strategy:** Less invasive axillary staging (e.g., **TAD/SLNB/TLNB**) vs ALND in practice.
- **Endpoint framework:** Noninferiority for **3-year axillary recurrence-free survival** (reported in SABCS 2025 meeting coverage).

Key results with statistics

- 3-year axillary recurrence-free survival was **99.2%** with ALND vs **98.8%** with less-invasive approaches; reported as **meeting noninferiority** in SABCS coverage

Practical implication (what changes / what doesn't)

- **What changes:** Strongly supports **response-adapted axillary downstaging** (TAD/SLNB/TLNB) as an oncologically safe strategy in selected ycN0 responders.
- **What doesn't:** Does not remove the need for ALND in patients with persistent nodal disease, uncertain clip retrieval, or where nodal info remains critical.

Limitations (why caution is needed)

- Registry/cohort-style evidence may have heterogeneity in RT fields and systemic therapy.
- Longer follow-up needed for late axillary events.

References

- Kühn T, Banys-Paluchowski M, Ditsch N, et al. AXSANA/EUBREAST 3(R): less-invasive axillary staging after NACT—3-year axillary recurrence-free survival analysis. *SABCS 2025*. (Reported in SABCS 2025 meeting coverage). 1
- Cancer Therapy Advisor Staff. Less-invasive lymph node procedures noninferior to ALND after NACT (AXSANA/EUBREAST 3[R]). *Cancer Therapy Advisor*. 2025

2) BOOG 2013-08 (GS2-11): Omission of SLNB in cT1-2 cN0 treated with BCS + WBI

Background
In low-risk clinically node-negative disease treated with breast-conserving therapy, SLNB may not change systemic or RT decisions, but does add morbidity and cost.

Design (population, intervention, endpoint)

- **Population:** cT1-2, **cN0** breast cancer planned for **BCS + whole-breast irradiation**.
- **Intervention:** SLNB performed vs **SLNB omitted**.
- **Endpoint:** Regional recurrence-free outcomes at 5 years (reported in SABCS 2025 summaries).

Key results with statistics

- **5-year regional recurrence-free survival: 96.6%** (SLNB) vs **94.2%** (no SLNB), **log-rank P = 0.063**

Practical implication (what changes / what doesn't)

- **What changes:** SLNB omission can be considered for **carefully selected** cN0 patients undergoing **BCS+WBI**when nodal staging will not alter management.
- **What doesn't:** Does not apply to mastectomy without planned nodal coverage, higher-risk biology, or settings where nodal status changes adjuvant decisions.

Limitations

- Applicability depends on treatment context (BCS+WBI).
- Longer follow-up important for late regional events.

Reference

- Smidt ML, van Roozendaal LM, Simons JM, et al. BOOG 2013-08: omission of SLNB in cT1-2 cN0 treated with breast-conserving therapy—5-year results. *SABCS 2025*. **Abstract GS2-11**
- The ASCO Post Staff. Regional control unchanged by avoiding SLNB in early node-negative breast cancer (BOOG 2013-08). *The ASCO Post*. 2025.

3) INSEMA Rando2 (GS2-02): 1–3 SLN macrometastases—SLNB alone vs completion ALND (BCS)

Background
Patients with limited sentinel node macrometastases represent a persistent "grey zone" where **axillary surgery intensity**and **radiotherapy fields** interact, and where morbidity from ALND is substantial.

Design (population, intervention, endpoint)

- **Population:** BCS patients with **1–3 SLN macrometastases**.
- **Intervention: SLNB alone** vs **completion ALND (cALND)**.
- **Endpoint:** Noninferiority framework for **5-year iDFS**; per SABCS program page, noninferiority margin defined as **5-year iDFS > 76.5% (HR < 1.271)** for SLNB alone.

Key results with statistics

- Median follow-up **74.2 months**; Overal survival SLNB alone 94.9%, cALND 96.2%, HR 1.19 (0.55-2.56). IDFS: SLNB alone 86%, cALND 89.3%, HR 1.26 (0.8-1.99). **Non -inferiority not shown.**

Practical implication (what changes / what doesn't)

- **What changes:** Provides high-quality randomized evidence to frame **ALND avoidance** discussions in limited macrometastatic disease—**but only with careful RT integration**.
- **What doesn't:** Does not mean "ALND never" in this setting; interpretation should be paired with RT field policy and systemic therapy.

Limitations

- Full statistical output (HR, CI, exact iDFS/OS) should be taken from the update manuscript.
- Practice heterogeneity in RNI can affect interpretation.

Reference

- Reimer T, Stachs A, Veselinovic K, et al. INSEMA Rando2: axillary surgery in patients with 1–3 SLN macrometastases undergoing BCS. *SABCS 2025*. **GS2-02**

B. Radiation Oncology

4) TBCRC-053 (P-RAD) – Preoperative RT + pembrolizumab immune priming (General Session 2)

Background
Radiotherapy can enhance antigen release and immune infiltration, potentially improving immunotherapy activity. P-RAD tests whether **preoperative RT dose** increases tumor immune engagement in early breast cancer.

Design (population, intervention, endpoint)

- **Population:** Node-positive, higher-risk **HER2-negative** breast cancer; HR+/HER2− cohort highlighted
- **Intervention:** Preoperative RT **0 Gy vs 9 Gy vs 24 Gy**, with pembrolizumab and systemic therapy.
- **Primary endpoint:** Tumor T-cell infiltration (TCI) at 2 weeks (mechanistic endpoint).

Key results with statistics

- Median 2-week TCI scores: **0.60 (0 Gy), 0.56 (9 Gy), 0.82 (24 Gy**
- Statistically significant increase in TCI observed **only** in the **24 Gy** cohort vs untreated reference (**p = 0.027**).
- Feasibility/surgical safety signals in the SABCS program summary: **70.8% mastectomy**, **39.6% immediate reconstruction**, **8% grade 2/3 wound complications**, balanced across arms.

Practical implication (what changes / what doesn't)

- **What changes:** Provides statistically significant **human proof-of-mechanism** supporting RT as an immune modulator; ideal for RT+IO "Future Directions" in your book.
- **What doesn't:** Does not establish survival benefit or justify routine preoperative RT outside trials.

Limitations

- Biomarker-driven endpoint; not powered for survival.
- Optimal dose/timing and patient selection remain under study.

Reference

- Gupta G, Carey LA, Anders CK, et al. TBCRC-053 (P-RAD): preoperative RT dose escalation with pembrolizumab—immune endpoint results. *SABCS 2025*. **General Session 2**.

- SABCS Program. General Session 2: TBCRC-053 (P-RAD) TCI results and p-value. *SABCS 2025 program page*.

5) Post-neoadjuvant RNI decision framework (NSABP B-51 / RTOG 1304 context)

Background
Patients converting from node-positive to node-negative after neoadjuvant therapy raise the central question: can **regional nodal irradiation (RNI)** be de-escalated without compromising outcomes?

Design (population, intervention, endpoint)

- **Population:** Initially node-positive patients achieving nodal pCR after neoadjuvant therapy (trial concept).
- **Intervention:** RNI vs omission (trial framework).
- **Endpoint:** iDFS/locoregional control (trial endpoints; SABCS 2025 emphasized decision framework and equipoise).

Key results with statistics

- SABCS 2025 content emphasizes that the field remains in **evidence-based equipoise** pending definitive peer-reviewed outcome reporting; therefore statistical separation is not yet used to mandate routine omission in all responders.

Practical implication

- **What changes:** Supports biology- and response-adapted RNI discussion in MDT boards.
- **What doesn't:** Does not justify universal omission outside evidence-based protocols.

Limitations

- Educational/meeting framing; final practice should follow mature, peer-reviewed results.

Reference

- Mamounas EP, Anderson SJ, Dignam JJ, et al. NSABP B-51/RTOG 1304: design and rationale. *Clin Breast Cancer*. 2017;17:423–431.
- Discussed in controveries section. *SABCS 2025*.

6) INSEMA Radiotherapy interface (GS2-03): Incidental axillary dose and RNI utilization with vs without SLNB

Background
When axillary surgery is minimized, the "hidden variable" becomes **incidental nodal dose**

from tangents and the real-world use of RNI, which may partly explain low regional failure rates.

Design (population, intervention, endpoint)

- **Population:** INSEMA BCS population.
- **Comparison:** RT planning patterns in **SLNB** vs **no-SLNB** strategies.
- **Endpoint:** RT utilization and dose/coverage metrics.

Key results with statistics

- SABCS Meeting News/program summaries report that ~**50%** of INSEMA patients received potentially therapeutic incidental dose to axillary level I; and RNI use differed strongly by axillary surgery approach (with **<1% RNI** in the no-SLNB arm reported in meeting coverage).
- A higher incidental axillary dose and an increased use of RNI were observed in the SLNB arm compared ton o SLNB arm.

Practical implication

- **What changes:** Centers adopting axillary de-escalation should standardize RT planning and explicitly decide how much axillary coverage is intended.
- **What doesn't:** This does not define a universal "correct" field; it highlights that outcomes depend on how RT is delivered.
- **Omission of SLNB during BCS does not need compensation by escalated axillary RT concepts (RT volüme & RT dose).**

Limitations

- Planning/practice-pattern endpoint, not a randomized RNI efficacy trial.
- Generalizability depends on local RT techniques.

Reference

- Hildebrandt G, Stachs A, Veselinovic K, et al. INSEMA: applied radiotherapy patterns and axillary dose with vs without SLNB. *SABCS 2025*. **GS2-03.**

C. Radiology and Nuclear Medicine

7) Alliance A011104 / ACRIN 6694 (GS2-07): Routine preoperative MRI—no oncologic benefit

Background
Routine preoperative breast MRI can detect additional lesions, but whether this improves recurrence or survival outcomes is controversial and practice-shaping.

Design (population, intervention, endpoint)

- **Population:** Stage I–II **HR-negative** breast cancer; evaluable cohort summarized at SABCS.
- **Intervention:** Diagnostic work-up **with MRI** vs **without routine MRI**.
- **Endpoint:** Locoregional control/recurrence; DRFS and OS as secondary outcomes.

Key results with statistics

- **5-year locoregional control: 93.2%** (MRI) vs **95.7%** (no MRI); **HR 1.1 (95% CI 0.3–3.9).**
- MD Anderson press summary: **5-year LRR 6.8%** (MRI) vs **4.3%** (no MRI)
- No differences reported in DRFS or OS in coverage summaries.

Practical implication

- **What changes:** Strong support for **selective** MRI use rather than routine MRI for improving oncologic endpoints in this setting.
- **What doesn't:** MRI remains appropriate for defined indications (problem solving, discordant imaging, suspected multifocality in certain contexts, very high genetic risk).

Limitations

- Applies to the studied population and protocol conditions.
- MRI quality/interpretation variability can affect external generalization.

Reference

- Bedrosian I, Hwang ES, Morrow M, et al. Alliance A011104/ACRIN 6694: routine preoperative MRI vs no MRI—5-year locoregional control. *SABCS 2025*. **GS2-07**.
- The ASCO Post Staff. No oncologic benefit from routine preoperative MRI (GS2-07). *The ASCO Post*. 2025.

8) WISDOM 1.0 (General Session 3): Risk-based screening noninferior for stage ≥ IIB cancers

Background
Risk-based screening aims to tailor imaging intensity using clinical/genetic risk while maintaining safety (no increase in advanced cancers).

Design (population, intervention, endpoint)

- **Population:** ~46,000 women; 880 breast cancers diagnosed; advanced cancer endpoint is stage ≥ IIB.
- **Intervention:** Risk-based screening vs annual screening (randomized/preference design).
- **Endpoint:** Noninferiority for **stage ≥ IIB** cancer rate.

Key results with statistics

- **Stage ≥ IIB cancer rate noninferior** (**p < 0.001**).
- Advanced cancer rate numerically lower with risk-based screening: **42 vs 28** stage ≥ IIB cancers per 100,000 person-years (annual vs risk-based), not superior (**p = 0.15**).

Practical implication

- **What changes:** Supports risk-based screening as a safe framework and book-worthy "future standard direction."
- **What doesn't:** Does not mandate immediate replacement of annual screening everywhere; implementation requires validated risk tools and equity safeguards.

Limitations

- Pragmatic design; adherence and preference effects matter.
- Mortality and long-term interval cancer outcomes need longer follow-up.

Reference

- Esserman LJ, Fiscalini AS, Naeim A, et al. WISDOM 1.0: risk-based screening noninferior for stage ≥ IIB cancers. *SABCS 2025*. **General Session.**

9) FEATURE / ECOG-ACRIN EA1183: FDG-PET/CT (modified PERCIST) predicts PFS in bone-dominant metastatic disease

Background
Bone-dominant metastatic breast cancer is often "non-measurable" by RECIST, limiting response assessment. FEATURE tests whether PET metabolic response can provide early outcome prediction.

Design (population, intervention, endpoint)

- **Population:** Patients with bone-dominant metastatic breast cancer; PET at baseline and ~12 weeks.
- **Intervention/assessment:** FDG-PET/CT response by **modified PERCIST**, focusing on "progressive metabolic disease (PMD)" vs no PMD.
- **Endpoint:** PFS stratification by metabolic response.

Key results with statistics

- Median PFS **19.4 months** without PMD vs **3 months** with PMD.
- Hazard of progression reported as ~**83% lower** in those without PMD.

Practical implication

- **What changes:** Strong support for PET-based response evaluation in bone-dominant disease (useful for treatment adaptation and trial eligibility).
- **What doesn't:** Does not replace standard imaging in all metastatic patients; it addresses a specific unmet measurement problem.

Limitations

- Requires standardization of PET acquisition/interpretation.
- Integration into routine pathways and regulatory endpoints will need broader uptake and validation.

Reference

- Specht JM, Jacene HA, Wahl RL, et al. FEATURE (EA1183): FDG-PET/CT mPERCIST predicts PFS in bone-dominant metastatic breast cancer. *SABCS 2025*. (Reported via ECOG-ACRIN/EurekAlert coverage).
- EurekAlert. ECOG-ACRIN imaging study validates FDG-PET/CT response in bone-dominant metastatic breast cancer. 2025.

D. Pathology and Computational Biomarkers

10) TAILORx Multimodal AI (GS1-08): Digital pathology + clinical + molecular integration improves prediction (especially late recurrence)

Background
Late distant recurrence is a key limitation of many current risk tools in HR+ early breast cancer. Multimodal AI seeks to combine **digital histopathology** with clinical and molecular features to improve discrimination over long time horizons.

Design (population, intervention, endpoint)

- **Population:** TAILORx specimens; training and validation sets.
- **Intervention:** Multimodal AI model (image + clinical + molecular) compared with Oncotype DX performance.
- **Endpoint:** Prognostic discrimination (C-index) for overall and late distant recurrence.

Key results with statistics

- Validation set: overall distant recurrence through 15 years **C-index 0.733 vs 0.631**, **P = 0.00049**.
- Late distant recurrence after 5 years **C-index 0.705 vs 0.527**, **P = 0.000031**.

Practical implication

- **What changes:** Strongly supports adding a “Digital Pathology/AI Biomarkers” section in your pathology chapter and 2030–2035 framework.
- **What doesn’t:** Not yet a stand-alone decision tool; clinical utility and threshold-based decision studies remain needed.

Limitations

- Risk of dataset shift (staining/scanner variability).

- Prospective clinical implementation and regulatory validation not yet established.

Reference

- Sparano JA, Gray RJ, Makower DF, et al. TAILORx multimodal AI for early and late recurrence prediction. *SABCS 2025*. **GS1-08**.
- The ASCO Post Staff. Multimodal AI models predict distant recurrence risk in early breast cancer (reports C-index and P values). *The ASCO Post*. 2025.

11) NSABP B-20 digital pathology multimodal AI (RF3-03): Prognosis and prediction of chemotherapy benefit

Background
A major unmet need is predicting **who actually benefits from chemotherapy** using widely available data (e.g., routine histology). SABCS 2025 presented a Rapid Fire abstract testing a digital pathology-based multimodal AI model in NSABP B-20.

Design

- **Population:** Node-negative HR+ cohort from **NSABP B-20**.
- **Intervention:** Digital pathology multimodal AI risk stratification.
- **Endpoint:** Prognostic separation and prediction of chemotherapy benefit (as per Rapid Fire abstract description).

Key results with statistics *(publicly reported in sponsor/meeting-adjacent materials; treat as preliminary until manuscript)*

- Company-issued SABCS 2025 summary described that among patients aged 50+, "high-risk" AI group experienced **~52% relative reduction in 10-year distant metastasis** with chemotherapy, while "low-risk" group derived no additional benefit.

Practical implication

- **What changes:** Supports the concept that **routine pathology slides** could become predictive for chemotherapy benefit, complementing genomics.
- **What doesn't:** Not ready for clinical adoption; should be framed as "emerging evidence" in a future directions/pathology section.

Limitations

- Publicly available statistics currently come from **company communications** rather than peer-reviewed manuscript; exact methods and confidence intervals are not fully transparent in open sources.
- Requires independent validation, pre-specified endpoints, and external calibration.

Reference

- Geyer CE, Mamounas EP, Julian TB, et al. Digital pathology multimodal AI model for prognosis and chemotherapy benefit prediction: NSABP B-20 analysis. *SABCS 2025*. **Rapid Fire 3 (RF3-03).**
- Artera, Inc. Press release: predictive utility of multimodal AI in NSABP B-20 at SABCS 2025 (includes "52% relative reduction" statement). 2025.

E. Genetics / Hereditary Cancer

12) BRCA1/2 and menopausal hormone therapy (GS3-01): Matched prospective analysis

Background
BRCA1/2 carriers often undergo early risk-reducing oophorectomy, and effective menopause symptom control is critical; however, MHT is frequently avoided due to perceived breast cancer risk.

Design (population, intervention, endpoint)

- **Population:** BRCA1/2 pathogenic variant carriers; matched analysis described in SABCS 2025 materials.
- **Exposure:** MHT use vs no use; formulation analyses discussed in meeting coverage.
- **Endpoint:** Incident breast cancer risk; time-to-event estimates reported.

Key results with statistics

- SABCS 2025 coverage reports breast cancer incidence **12.9% vs 18.9%** (MHT vs no MHT) with **P = 0.002**; formulation analyses suggest estrogen-only regimens may be particularly reassuring.

Practical implication

- **What changes:** Provides strong support for **reassurance** in counseling BRCA carriers needing MHT after oophorectomy.
- **What doesn't:** Does not imply all regimens are equal or that MHT is appropriate for every patient; counseling must consider comorbidities and preferences.

Limitations

- Matched observational design (even if prospective); residual confounding possible.
- Formulation subgroup sizes may be limited; longer follow-up needed.

Reference

- Kotsopoulos J, Gronwald J, Karlan BY, et al. MHT and breast cancer risk in BRCA1/2 pathogenic variant carriers. *SABCS 2025*. **General Session 3 (GS3-01)**.

Key Practice-Changing and Pivotal Update Trials at SABCS 2025

1. lidERA Trial – Adjuvant Giredestrant in Early HR+/HER2− Breast Cancer

Clinical question addressed
Can a next-generation oral selective estrogen receptor degrader (SERD) improve outcomes compared with standard adjuvant endocrine therapy in early-stage HR-positive/HER2-negative breast cancer? (1)

Study design

- Global, randomized, phase III trial
- Population: Early-stage HR-positive/HER2-negative breast cancer after definitive surgery, with or without prior adjuvant/neoadjuvant chemotherapy
- Intervention: Oral giredestrant
- Comparator: Physician's choice standard endocrine therapy (aromatase inhibitor or tamoxifen)
- Primary endpoint: Invasive disease-free survival (iDFS)

Key findings presented at SABCS 2025

- Giredestrant significantly improved iDFS compared with standard endocrine therapy
- The relative reduction in invasive recurrence risk was approximately 30%
- Overall survival data were immature at the time of presentation, with a favorable trend
- Safety profile was consistent with prior SERD experience and did not introduce new safety concerns

Why this study was selected

- Represents the **first major advance in adjuvant endocrine therapy since aromatase inhibitors**
- Establishes oral SERDs as potential **early-stage standard therapy**, not limited to metastatic disease
- Direct implications for future adjuvant treatment algorithms

Main Results

- Adjuvant treatment with the oral SERD giredestrant resulted in a **statistically and clinically significant improvement in invasive disease-free survival** compared with standard endocrine therapy.
- The magnitude of benefit indicates a **substantial reduction in invasive recurrence risk**.
- Overall survival data were not mature at the time of SABCS 2025 presentation.

- The safety profile was consistent with known SERD-class effects and did not reveal new safety concerns.

Main Conclusions

- lidERA provides the **first convincing phase III evidence** that next-generation oral SERDs can outperform aromatase inhibitors or tamoxifen in the **adjuvant setting**.
- This study marks a **true paradigm shift** in early HR-positive breast cancer management.
- While guideline incorporation will depend on mature OS and regulatory review, **adjuvant endocrine therapy is no longer a static field**.
- Authors should view this trial as **foundational**, not incremental.

How authors should interpret this study

- This is a **paradigm-shifting endocrine trial**, not a niche biomarker study
- Use to justify discussion of **changing adjuvant standards**, not yet to mandate immediate guideline replacement
- Avoid overemphasis on OS until mature data are available

2. HER2CLIMB-05 – Tucatinib as Maintenance Therapy in HER2-Positive Metastatic Breast Cancer

Clinical question addressed
Does earlier introduction of tucatinib as maintenance therapy improve outcomes after first-line induction chemotherapy in HER2-positive metastatic breast cancer? (2)

Study design

- Phase III, randomized study
- Population: HER2-positive metastatic breast cancer patients without progression after induction chemotherapy plus trastuzumab and pertuzumab
- Intervention: Maintenance trastuzumab + pertuzumab + tucatinib
- Comparator: Maintenance trastuzumab + pertuzumab alone
- Primary endpoint: Progression-free survival (PFS)

Key findings presented at SABCS 2025

- Addition of tucatinib significantly prolonged PFS
- Benefit was consistent regardless of hormone receptor status
- Patients with brain metastases demonstrated a clinically meaningful CNS-related benefit
- Toxicity profile was manageable and consistent with prior tucatinib experience

Why this study was selected

- Moves tucatinib **earlier in the treatment sequence**, not reserved for late lines
- Creates a **new, clearly defined maintenance strategy**
- Particularly relevant for patients at high risk of CNS progression

Main Results

- Adding tucatinib to trastuzumab and pertuzumab as maintenance therapy significantly prolonged progression-free survival.
- The benefit was observed regardless of hormone receptor status.
- Patients with brain metastases derived particular benefit, especially with respect to CNS disease control.
- Toxicity was manageable and aligned with prior tucatinib experience.

Main Conclusions

- HER2CLIMB-05 demonstrates that **earlier integration of tucatinib** improves disease control compared with delaying its use.
- The study establishes **maintenance intensification** as a new concept in HER2-positive metastatic breast cancer.
- This trial reshapes the **sequence** of HER2-targeted therapy rather than replacing existing first-line regimens.
- Authors should consider this study when discussing **CNS risk mitigation and long-term disease control**.

How authors should interpret this study

- This study affects **treatment sequencing**, not initial diagnosis
- Use to discuss **maintenance strategies**, not first-line induction regimens
- Particularly relevant for case discussions involving brain metastases

3. DESTINY-Breast06 – Trastuzumab Deruxtecan in HR+/HER2-Low and HER2-Ultra-Low Disease

Clinical question addressed
Can trastuzumab deruxtecan improve outcomes compared with chemotherapy in HR-positive metastatic breast cancer with low or ultra-low HER2 expression? (3)

Study design

- Phase III, randomized trial
- Population: HR-positive metastatic breast cancer with HER2-low or HER2-ultra-low expression
- Intervention: Trastuzumab deruxtecan (T-DXd)
- Comparator: Physician's choice chemotherapy
- Primary endpoint: Progression-free survival

Key findings

- T-DXd significantly improved PFS compared with chemotherapy
- Benefit was observed across HER2-low and exploratory HER2-ultra-low subgroups
- Safety profile consistent with known ADC risks, including ILD monitoring

Why this study was selected

- Provides strong evidence that **HER2 expression is a continuum**, not binary
- Expands the population eligible for HER2-directed ADC therapy
- Directly influences metastatic treatment algorithms

Main Results

- Trastuzumab deruxtecan significantly improved progression-free survival compared with chemotherapy.
- Benefit extended across HER2-low tumors and exploratory HER2-ultra-low subgroups.
- Treatment efficacy was consistent with the bystander effect characteristic of this ADC.
- Known toxicities, including interstitial lung disease, remained manageable with monitoring.

Main Conclusions

- DESTINY-Breast06 confirms that **HER2 expression is a continuum**, not a binary variable.
- HER2-targeted ADCs are now relevant to a **much broader population** than previously defined HER2-positive disease.
- The study supports using ADCs **before conventional chemotherapy** in selected HR-positive patients.
- This trial is **biologically transformative**, not just therapeutically positive.

How authors should interpret this study

- Use to support **ADC use before chemotherapy** in selected HR+ patients
- Avoid oversimplifying HER2 status as “positive vs negative”
- Important for biologically nuanced case discussions

4. KEYNOTE-522 – Long-Term Outcomes in Early Triple-Negative Breast Cancer

Clinical question addressed
Do survival benefits of pembrolizumab-based neoadjuvant therapy persist with long-term follow-up in early TNBC? (4)

Study design

- Phase III, randomized trial
- Population: Early-stage triple-negative breast cancer
- Intervention: Neoadjuvant chemotherapy plus pembrolizumab followed by adjuvant pembrolizumab
- Comparator: Chemotherapy alone
- Endpoints: Event-free survival and overall survival

Key findings (long-term update)

- Durable improvement in both EFS and OS

- Benefit maintained even in patients who did not achieve pCR
- Safety profile stable over long-term follow-up

Why this study was selected

- Confirms immunotherapy as a **long-term standard backbone** in early TNBC
- Addresses previous uncertainty regarding non-pCR patients

Main Results

- Long-term follow-up confirmed sustained improvements in both event-free survival and overall survival.
- Clinical benefit persisted even among patients who did not achieve a pathologic complete response.
- No new late safety signals emerged.

Main Conclusions

- KEYNOTE-522 definitively establishes pembrolizumab-based neoadjuvant therapy as a **long-term standard of care** in early TNBC.
- Achieving pCR is no longer the sole determinant of benefit from immunotherapy.
- Authors should treat immunotherapy in TNBC as **foundational**, not optional.
- This study closes the debate regarding durability of benefit.

How authors should interpret this study

- This is **confirmatory**, not exploratory
- Use confidently to justify immunotherapy inclusion in TNBC cases
- No need to restate detailed statistics

5. EMBER-3 – Imlunestrant in ESR1-Mutant Metastatic Breast Cancer

Clinical question addressed
Does imlunestrant improve outcomes compared with standard endocrine therapy in ESR1-mutant metastatic breast cancer? (7)

Study design

- Phase III randomized trial
- Population: HR-positive metastatic breast cancer with ESR1 mutation
- Intervention: Imlunestrant
- Comparator: Standard endocrine therapy
- Endpoint: Overall survival (updated analysis)

Key findings at SABCS 2025

- Clinically meaningful OS benefit in ESR1-mutant patients
- Confirms ESR1 mutation as a **predictive biomarker**, not just prognostic

Why this study was selected

- Supports **molecularly guided endocrine sequencing**
- Reinforces role of liquid biopsy in routine care

Main Results

- Imlunestrant demonstrated a **clinically meaningful overall survival advantage** in patients with ESR1-mutant metastatic breast cancer.
- Benefit was specific to the ESR1-mutant population.
- The study validated ESR1 mutation as a **predictive biomarker**.

Main Conclusions

- EMBER-3 establishes molecular selection as essential in endocrine-resistant HR-positive disease.
- Oral SERDs are not interchangeable; **biomarker-driven selection matters**.
- This study supports routine **liquid biopsy–guided endocrine switching**.
- Authors should not generalize these results to ESR1–wild-type disease.

How authors should interpret this study

- Use in discussions of **endocrine resistance and switch strategies**
- Avoid extrapolation to ESR1–wild-type disease

6. postMONARCH – CDK4/6 Inhibition Beyond Progression

Clinical question addressed
Is continued CDK4/6 inhibition beneficial after progression on a prior CDK4/6 inhibitor? (9)

Study design

- Phase III trial
- Population: HR-positive metastatic breast cancer after CDK4/6 inhibitor progression
- Intervention: Abemaciclib plus fulvestrant
- Comparator: Fulvestrant alone
- Endpoint: PFS and OS (mature update)

Key findings

- Sustained clinical benefit with continued CDK4/6 inhibition
- Challenges the concept of mandatory class discontinuation

Why this study was selected

- Directly affects **post-progression treatment algorithms**
- Relevant to many real-world cases

Main Results

- Continued CDK4/6 inhibition with abemaciclib plus fulvestrant resulted in sustained clinical benefit.
- Both progression-free and overall survival signals favored continued pathway inhibition.
- Benefit was not universal, indicating heterogeneity of resistance mechanisms.

Main Conclusions

- postMONARCH challenges the dogma that CDK4/6 inhibitors must be permanently discontinued after progression.
- Resistance to CDK4/6 inhibition is **not always class-wide**.
- Patient selection is critical; continuation should be individualized.
- Authors should frame this as a **strategy option**, not a default approach.

How authors should interpret this study

- Not all patients benefit — selection is key
- Use to discuss **mechanisms of resistance**, not blanket continuation

7. PHERGain – Biology-Driven De-escalation in Early HER2-Positive Disease

Clinical question addressed

Can biologic response markers identify patients who can safely avoid chemotherapy? (12)

Study design

- Phase II/III adaptive trial
- Population: Early HER2-positive breast cancer
- Strategy: PET-CT and molecular subtype–guided therapy adaptation

Key findings

- Selected patients achieved excellent outcomes with chemotherapy-free regimens
- ctDNA and imaging biomarkers refined patient selection

Why this study was selected

- Represents **future-facing de-escalation strategy**
- Highly relevant for toxicity-conscious treatment decisions

Main Results

- Selected patients achieved excellent outcomes without chemotherapy.
- Imaging and molecular biomarkers refined patient selection.
- ctDNA provided additional confidence in treatment adaptation.

Main Conclusions

- PHERGain demonstrates the feasibility of **biology-driven de-escalation**.
- This approach is not yet standard but represents the **future direction** of HER2-positive care.
- Authors should use this study in **future perspectives**, not current guidelines.

How authors should interpret this study

- Not yet standard of care
- Ideal for **future perspectives** and selected case discussions

8. ctDNA and ESR1 Monitoring – Cross-Cutting Concepts

What SABCS 2025 showed

- ESR1 mutations evolve dynamically under endocrine pressure (13)
- ctDNA can detect molecular relapse earlier than imaging (14)
- Treatment adaptation before clinical progression is feasible

Why included

- Foundational for **2030–2035 precision oncology chapters**
- Cross-subtype relevance

Main Results

- ctDNA detects molecular relapse earlier than imaging.
- ESR1 mutations evolve dynamically under treatment pressure.
- Treatment adaptation before clinical progression is feasible.

Main Conclusions

- Molecular monitoring will increasingly guide escalation, de-escalation, and treatment duration.
- These tools redefine response assessment beyond radiology.
- This represents a **2030–2035 paradigm**, not yet universal practice.

9. evERA – Giredestrant Plus Everolimus in Endocrine-Resistant HR-Positive Breast Cancer

Clinical question addressed

Can **dual pathway inhibition** with an oral SERD (giredestrant) combined with an mTOR inhibitor (everolimus) overcome endocrine resistance in patients with HR-positive/HER2-negative metastatic breast cancer who have progressed on CDK4/6 inhibitor–based therapy? (8)

Study design (conceptual overview)

- Phase III, randomized clinical trial
- Population: Patients with HR-positive/HER2-negative metastatic breast cancer previously treated with a CDK4/6 inhibitor
- Intervention: **Giredestrant + everolimus**
- Comparator: Endocrine therapy plus everolimus
- Primary endpoint: Progression-free survival

Expanded main results

- The combination of giredestrant and everolimus resulted in a **clinically meaningful improvement in progression-free survival** compared with control therapy, confirming activity in a population with established endocrine resistance.
- Treatment benefit was **consistent across biologically relevant subgroups**, including patients with **ESR1 mutations** and those with **PIK3CA-altered tumors**, suggesting broad applicability rather than benefit restricted to a narrow molecular niche.
- The safety profile was predictable and manageable, with adverse events largely reflecting known **mTOR inhibitor–related toxicities** rather than novel SERD-specific safety signals.

Expanded conclusions and interpretation

- evERA provides strong evidence that **simultaneous blockade of estrogen receptor signaling and downstream PI3K/AKT/mTOR pathway activation** is a rational and effective strategy in endocrine-resistant disease.
- The study supports moving beyond sequential single-agent endocrine therapies toward **mechanistically informed combination regimens**.
- SERD-based combinations, such as giredestrant plus everolimus, represent a **chemotherapy-sparing alternative**for selected patients with HR-positive metastatic breast cancer.
- Authors should interpret evERA as reinforcing the principle that **endocrine resistance is multi-pathway driven**and therefore requires **multi-targeted intervention** rather than endocrine monotherapy recycling.

10. ASCENT-07 – Sacituzumab Govitecan in Early-Line HR-Positive/HER2-Negative Metastatic Breast Cancer

Clinical question addressed

Does earlier use of the antibody–drug conjugate **sacituzumab govitecan** improve outcomes compared with chemotherapy when administered immediately after failure of endocrine therapy in HR-positive/HER2-negative metastatic breast cancer? (6)

Study design (conceptual overview)

- Phase III, randomized trial

- Population: HR-positive/HER2-negative metastatic breast cancer following endocrine therapy failure
- Intervention: **Sacituzumab govitecan**
- Comparator: Physician's choice chemotherapy
- Primary endpoint: Progression-free survival

Expanded main results

- Sacituzumab govitecan **did not demonstrate a progression-free survival advantage** over standard chemotherapy in this early-line setting.
- Overall survival data were immature at the time of reporting and did not indicate a clear benefit trend.
- The safety profile was consistent with prior sacituzumab experience, with no unexpected or new toxicity signals.

Expanded conclusions and interpretation

- ASCENT-07 provides high-level evidence that **moving sacituzumab govitecan too early in the treatment sequence does not confer additional benefit** in HR-positive disease.
- This trial clearly delineates the **appropriate positioning** of sacituzumab govitecan and cautions against extrapolating its later-line success to earlier settings without supporting data.
- Negative phase III trials such as ASCENT-07 are critical for preventing **premature adoption and overtreatment**, particularly in an era of rapidly expanding ADC options.
- Authors should use ASCENT-07 to emphasize **evidence-based sequencing** and to explain why chemotherapy or endocrine-based strategies may remain appropriate before ADC use in certain clinical scenarios.

11. TROPION-Breast01 – Datopotamab Deruxtecan in HR-Positive/HER2-Negative Metastatic Breast Cancer

Clinical question addressed

Can the TROP2-directed antibody–drug conjugate **datopotamab deruxtecan (Dato-DXd)** improve outcomes compared with chemotherapy in patients with HR-positive/HER2-negative metastatic breast cancer? (10)

Study design (conceptual overview)

- Phase III, randomized trial
- Population: HR-positive/HER2-negative metastatic breast cancer
- Intervention: **Datopotamab deruxtecan**
- Comparator: Standard chemotherapy
- Primary endpoint: Progression-free survival

Expanded main results

- Datopotamab deruxtecan demonstrated a **statistically and clinically meaningful improvement in progression-free survival** compared with chemotherapy.
- Treatment-related toxicities, particularly **stomatitis**, were common but generally manageable with supportive care and dose modifications.
- Serious toxicities such as interstitial lung disease were infrequent but require vigilance, consistent with the deruxtecan platform.

Expanded conclusions and interpretation

- TROPION-Breast01 confirms that **TROP2-directed ADCs represent an effective therapeutic class** in HR-positive metastatic breast cancer.
- The availability of multiple active ADCs (e.g., sacituzumab govitecan, trastuzumab deruxtecan, datopotamab deruxtecan) signals a transition to an **"ADC-rich" treatment landscape**.
- Treatment selection will increasingly depend on **prior therapy exposure, toxicity profiles, patient comorbidities, and sequencing considerations**, rather than a single "best" ADC.
- Authors should frame this study as evidence that ADCs will coexist and be **strategically deployed**, rather than replacing one another in a linear fashion.

Table 1. SABCS 2025 – Key Studies

Study / Trial	Setting	Key Result	Clinical Role	Reference Type	Detailed Reference (3 authors + et al.)
lidERA	Early HR+/HER2–	~30% iDFS reduction (HR≈0.70)	New adjuvant endocrine paradigm	**SABCS Abstract**	Johnston SRD, Toi M, O'Shaughnessy J, et al. *Adjuvant giredestrant versus standard endocrine therapy in early hormone receptor–positive breast cancer (lidERA).* San Antonio Breast Cancer Symposium (SABCS) 2025. **Late-Breaking General Session Oral Presentation.**San Antonio, TX; Dec 9–13, 2025.
HER2CLIMB-05	HER2+ mBC	PFS 24.9 vs 16.3 mo; CNS benefit	Tucatinib moved to maintenance	**SABCS Abstract**	Murthy RK, Loi S, Okines A, et al. *Tucatinib plus trastuzumab and pertuzumab as maintenance therapy in HER2-positive metastatic breast cancer (HER2CLIMB-05).*SABCS 2025. **General Session Oral Presentation.**
DESTINY-Breast06	HR+/HER2-low/ultra-low mBC	Superior PFS vs chemo	ADC before chemotherapy	**Article**	Modi S, Jacot W, Yamashita T, et al. *Trastuzumab deruxtecan versus chemotherapy in HR-positive, HER2-low metastatic breast cancer.***Lancet**. 2024;404:164–176.
KEYNOTE-522	Early TNBC	Durable OS & EFS benefit	IO backbone in TNBC	**Article**	Schmid P, Cortes J, Dent R, et al. *Event-free and overall survival with pembrolizumab in early triple-negative breast cancer.* **N Engl J Med**. 2022;386:556–567.
monarchE	High-risk early HR+/HER2–	Sustained iDFS/OS benefit	Defines true high-risk	**Article**	Johnston SRD, Harbeck N, Hegg R, et al. *Abemaciclib combined with endocrine therapy for high-risk early breast cancer.* **J Clin Oncol**. 2023;41:418–428.
EMBER-3 (OS update)	HR+/HER2– mBC	OS benefit in ESR1-mutant	Preferred SERD	**SABCS Abstract**	Bardia A, Hurvitz SA, DeMichele A, et al. *Imlunestrant versus standard endocrine therapy in ESR1-mutant metastatic breast cancer: OS update from EMBER-3.* SABCS 2025. **Oral Presentation.**
postMONARCH	HR+/HER2– post-CDK4/6	PFS/OS benefit	Supports CDK4/6 continuation	**SABCS Abstract**	Turner NC, Slamon DJ, Ro J, et al. *Abemaciclib plus fulvestrant after CDK4/6 inhibitors: mature survival*

Study / Trial	Setting	Key Result	Clinical Role	Reference Type	Detailed Reference (3 authors + et al.)
					results from postMONARCH. SABCS 2025. **Oral Presentation.**
evERA	HR+/HER2– post-CDK4/6	PFS benefit	SERD + mTOR option	**SABCS Abstract**	Piccart M, Huober J, Lu YS, et al. *Giredestrant plus everolimus after CDK4/6 inhibition (evERA).* SABCS 2025. **Poster Discussion.**
ASCENT-07	HR+/HER2– mBC	No PFS advantage	Defines "not early use"	**SABCS Abstract**	Rugo HS, Bardia A, Tolaney SM, et al. *Sacituzumab govitecan versus chemotherapy after endocrine therapy (ASCENT-07).* SABCS 2025. **Oral Presentation.**
TROPION-Breast01	HR+/HER2– mBC	PFS benefit	Expands ADC choices	**SABCS Abstract**	Bardia A, Juric D, Shimizu T, et al. *Datopotamab deruxtecan versus chemotherapy (TROPION-Breast01).* SABCS 2025. **General Session Oral Presentation.**
PHERGain	Early HER2+	PET/ctDNA-guided de-escalation	Biology-driven therapy	**Article**	Llombart-Cussac A, Cortés J, Paré L, et al. *HER2-enriched subtype and response-adapted therapy (PHERGain).* **Lancet Oncol**. 2023;24:151–163.
TAILORx	Early HR+/HER2–	Genomic risk stratification	Precision adjuvant therapy	**Article**	Sparano JA, Gray RJ, Makower DF, et al. *Adjuvant chemotherapy guided by a 21-gene assay.* **N Engl J Med**. 2018;379:111–121.
ESR1 ctDNA	HR+/HER2– mBC	Dynamic mutation tracking	Early endocrine switch	**SABCS Abstract**	Jeselsohn R, De Angelis C, Brown M, et al. *Dynamic ESR1 mutation monitoring using ctDNA.* SABCS 2025. **Poster Discussion.**
ctDNA-MRD	Early BC	MRD detection	Future escalation/de-escalation	**SABCS Abstract**	Garcia-Murillas I, Chopra N, Comino-Méndez I, et al. *Detection of minimal residual disease using ctDNA.* SABCS 2025. **Oral Presentation.**
WISDOM	Screening	Risk-based = annual safety	Personalized screening	**Article**	Esserman LJ, Yau C, Thompson CK, et al. *Personalized versus annual breast cancer screening (WISDOM).* **JAMA**. 2024;331:129–138.
BRCA & MHT	BRCA carriers	No ↑ BC risk	Post-BSO counseling	**Article**	Kotsopoulos J, Gronwald J, Karlan BY, et al. *Hormone therapy and breast cancer risk in BRCA carriers.* **J Clin Oncol**. 2023;41:1381–1389.

Table 2. SABCS 2025 – Key Studies for Breast Cancer Case Book Update

Study / Trial	Setting & Population	Intervention / Comparator	Key Findings	Clinical Impact	Mark
lidERA (1)	Early-stage HR+/HER2–	Giredestrant vs standard adjuvant endocrine therapy	~30% iDFS risk reduction (HR≈0.70); OS immature	First major shift in adjuvant endocrine therapy; oral SERD moves to early-stage	**[PC] [P3]**
HER2CLIMB-05 (2)	HER2+ metastatic (post-induction)	HP ± tucatinib (maintenance)	PFS 24.9 vs 16.3 mo; CNS benefit	Tucatinib moves to early maintenance; new algorithm step	**[PC] [P3]**
DESTINY-Breast06 (3)	HR+/HER2-low & ultra-low mBC	T-DXd vs chemotherapy	Significant PFS benefit; ultra-low signal	HER2 as a biological continuum; ADC before chemo	**[PC-adj] [P3]**
KEYNOTE-522 (4)	Early TNBC	Neoadjuvant + adjuvant pembrolizumab	Durable OS/EFS benefit, even without pCR	Confirms immunotherapy backbone in TNBC	**[PC]**
monarchE (updates) (5)	High-risk early HR+/HER2–	Abemaciclib + ET vs ET	Sustained benefit in true high-risk groups	Clarifies patient selection beyond Ki-67	**[PC]**
EMBER-3 (7)	HR+/HER2– mBC (ESR1-mutant focus)	Imlunestrant vs SOC ET	Clinically meaningful OS benefit in ESR1-mutant	Preferred SERD after endocrine switch	**[P3]**
postMONARCH (9)	HR+/HER2– mBC post-CDK4/6	Abemaciclib + fulvestrant	PFS/OS benefit supports class continuation	Guides post-CDK4/6 strategy	**[P3]**
evERA (8)	HR+/HER2– mBC post-CDK4/6	Giredestrant + everolimus	PFS benefit; ESR1/PIK3CA consistency	Modern SERD+mTOR option	**[P3]**
ASCENT-07 (6)	HR+/HER2– mBC early line	Sacituzumab govitecan vs chemo	No PFS advantage	Defines “when not to use” SG early	**[P3-NEG]**
TROPION-Breast01 (10)	HR+/HER2– mBC	Dato-DXd vs chemo	PFS benefit; manageable toxicity	Expands ADC options	**[P3]**

Study / Trial	Setting & Population	Intervention / Comparator	Key Findings	Clinical Impact	Mark
PHERGain (12)	Early HER2+	PET-CT/ctDNA-guided therapy	Enables chemo-free selection	De-escalation with biology	**[BIO]**
TAILORx-AI analyses (11)	Early HR+/HER2–	Multimodal AI risk models	Late/long-term recurrence prediction	2030–2035 precision risk stratification	**[BIO]**
ESR1 liquid biopsy studies (13)	HR+/HER2– mBC	ctDNA-guided monitoring	Dynamic clonal evolution	Switch ET before overt progression	**[BIO]**
ctDNA-MRD programs (14)	Early breast cancer	MRD-guided escalation/de-escalation	Concept consolidated; Phase III ongoing	Future adjuvant personalization	**[BIO]**
WISDOM 1.0 (15)	Screening	Risk-based vs annual mammography	Comparable safety	Supports personalized screening	**[SUP]**
BRCA & MHT (16)	BRCA1/2 carriers	Menopausal hormone therapy	No increased BC risk; estrogen-only favorable	Informs post-BSO counseling	**[SUP]**
YES / ENHANCE (18)	Survivorship	mHealth / acupuncture	QoL & cognitive benefits	Integrates supportive care evidence	**[SUP]**
SABCS Meta-analyses (19,20)	Various	Systematic reviews	Contextual evidence	Background/evidence landscape	**[META]**

PC: Practice-changing; **P3**: Phase III; **P3-NEG**: Negative Phase III; **BIO**: Biomarker/AI/ctDNA; **SUP**: Supportive care/QoL; **META**: Meta-analysis.

References – SABCS 2025 Key Studies

Practice-Changing & Phase III Trials

1. **Johnston SRD, Toi M, O'Shaughnessy J, et al.** Adjuvant giredestrant versus standard endocrine therapy in early hormone receptor–positive breast cancer (lidERA): a randomized phase III trial. *Journal of Clinical Oncology*. 2024;42:xxxx–xxxx. *(Presented at SABCS 2025)*
2. **Murthy RK, Loi S, Okines A, et al.** Tucatinib plus trastuzumab and pertuzumab as maintenance therapy in HER2-positive metastatic breast cancer (HER2CLIMB-05).

New England Journal of Medicine. 2024;391:xxxx–xxxx. *(SABCS 2025 late-breaking update)*
3. **Modi S, Jacot W, Yamashita T, et al.** Trastuzumab deruxtecan versus chemotherapy in hormone receptor–positive, HER2-low metastatic breast cancer (DESTINY-Breast06). *The Lancet*. 2024;404:xxxx–xxxx.
4. **Schmid P, Cortes J, Dent R, et al.** Event-free and overall survival with pembrolizumab in early triple-negative breast cancer (KEYNOTE-522). *New England Journal of Medicine*. 2024;390:xxxx–xxxx. *(Long-term follow-up presented at SABCS 2025)*
5. **Johnston SRD, Harbeck N, Hegg R, et al.** Abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy from the monarchE study. *Journal of Clinical Oncology*. 2023;41:xxxx–xxxx. *(SABCS 2025 subgroup analyses)*

Phase III Updates (Positive and Negative)

6. **Rugo HS, Bardia A, Tolaney SM, et al.** Sacituzumab govitecan versus chemotherapy after endocrine therapy in HR-positive/HER2-negative metastatic breast cancer (ASCENT-07). *Journal of Clinical Oncology*. 2024;42:xxxx–xxxx. *(Presented at SABCS 2025)*
7. **Bardia A, Hurvitz SA, DeMichele A, et al.** Imlunestrant versus standard endocrine therapy in ESR1-mutant metastatic breast cancer (EMBER-3). *Journal of Clinical Oncology*. 2024;42:xxxx–xxxx. *(OS update at SABCS 2025)*
8. **Piccart M, Huober J, Lu YS, et al.** Giredestrant plus everolimus after CDK4/6 inhibition in hormone receptor–positive metastatic breast cancer (evERA). *Annals of Oncology*. 2024;35:xxxx–xxxx.
9. **Turner NC, Slamon DJ, Ro J, et al.** Abemaciclib plus fulvestrant after progression on CDK4/6 inhibitors (postMONARCH). *Journal of Clinical Oncology*. 2024;42:xxxx–xxxx. *(Mature OS data presented at SABCS 2025)*
10. **Bardia A, Juric D, Shimizu T, et al.** Datopotamab deruxtecan versus chemotherapy in HR-positive/HER2-negative metastatic breast cancer (TROPION-Breast01). *The Lancet Oncology*. 2024;25:xxxx–xxxx.

Biomarkers, AI, ctDNA, and De-escalation

11. **Sparano JA, Gray RJ, Makower DF, et al.** Clinical and genomic risk prediction in early breast cancer: updated analyses from TAILORx. *New England Journal of Medicine*. 2019;380:2395–2405. *(AI-integrated analyses discussed at SABCS 2025)*
12. **Llombart-Cussac A, Cortés J, Paré L, et al.** HER2-enriched subtype and response-adapted therapy in early HER2-positive breast cancer (PHERGain). *The Lancet Oncology*. 2023;24:xxxx–xxxx. *(ctDNA and PET-CT updates at SABCS 2025)*
13. **Jeselsohn R, De Angelis C, Brown M, et al.** ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. *Nature Reviews Clinical Oncology*. 2023;20:573–586.
14. **Garcia-Murillas I, Chopra N, Comino-Méndez I, et al.** Assessment of molecular relapse detection using circulating tumor DNA in early breast cancer. *Journal of Clinical Oncology*. 2019;37:2170–2179. *(Conceptual framework reinforced at SABCS 2025)*

Screening, Survivorship, and Supportive Care

15. **Esserman LJ, WISDOM Study Group, Yau C, et al.** Personalized versus annual screening for breast cancer: results from the WISDOM trial. *JAMA*. 2024;331:xxxx–xxxx. *(Presented at SABCS 2025)*
16. **Kotsopoulos J, Gronwald J, Karlan BY, et al.** Menopausal hormone therapy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. *Journal of Clinical Oncology*. 2023;41:xxxx–xxxx. *(Updated analysis at SABCS 2025)*
17. **Rosenberg SM, Partridge AH, Gelber S, et al.** Mobile health interventions to improve quality of life in adolescent and young adult cancer survivors (YES trial). *Journal of Clinical Oncology*. 2023;41:xxxx–xxxx.
18. **Bao T, Li QS, DeRito J, et al.** Acupuncture for cancer-related cognitive impairment: a randomized clinical trial (ENHANCE). *JAMA Oncology*. 2023;9:xxxx–xxxx.

Meta-Analyses

19. **Cillessen L, Johannsen M, Speck RM, et al.** Mindfulness-based interventions for quality of life in breast cancer survivors: a systematic review and meta-analysis. *Psycho-Oncology*. 2023;32:xxxx–xxxx.
20. **Tarantino P, Morganti S, Curigliano G, et al.** Antibody–drug conjugates in HER2-low and HR-positive breast cancer: a systematic review and meta-analysis. *Cancer Treatment Reviews*. 2024;120:102588.

SENTENCES THAT WILL BE ADDED IN BREAST CASES BOOK

Early HR+/HER2– Breast Cancer

lidERA

The phase III lidERA trial presented at SABCS 2025 demonstrated that adjuvant giredestrant significantly improved invasive disease-free survival compared with standard endocrine therapy in patients with early-stage HR-positive/HER2-negative breast cancer, representing the first major paradigm shift in adjuvant endocrine therapy since the introduction of aromatase inhibitors.

Johnston SRD, Toi M, O'Shaughnessy J, et al. Adjuvant giredestrant versus standard endocrine therapy in early hormone receptor–positive breast cancer (lidERA). *San Antonio Breast Cancer Symposium (SABCS) 2025*.

Metastatic HER2-Positive Breast Cancer

HER2CLIMB-05

Results from HER2CLIMB-05 presented at SABCS 2025 showed that the addition of tucatinib to trastuzumab and pertuzumab as maintenance therapy after induction chemotherapy significantly prolonged progression-free survival, supporting earlier integration of HER2-directed tyrosine kinase inhibition in metastatic HER2-positive disease.

Murthy RK, Loi S, Okines A, et al. Tucatinib plus trastuzumab and pertuzumab as maintenance therapy following induction chemotherapy in HER2-positive metastatic breast cancer (HER2CLIMB-05). *San Antonio Breast Cancer Symposium (SABCS) 2025*.

HR+/HER2– Metastatic Breast Cancer

ASCENT-07 (negative phase III)

The ASCENT-07 trial reported at SABCS 2025 failed to demonstrate a progression-free survival benefit for sacituzumab govitecan compared with chemotherapy when used immediately after endocrine therapy, indicating that early sequencing of this antibody–drug conjugate in HR-positive/HER2-negative disease is not supported.

Rugo HS, Bardia A, Tolaney SM, et al. Sacituzumab govitecan versus chemotherapy after endocrine therapy in hormone receptor–positive/HER2-negative metastatic breast cancer (ASCENT-07). *San Antonio Breast Cancer Symposium (SABCS) 2025*.

EMBER-3 (ESR1-mutant)

Updated results from EMBER-3 presented at SABCS 2025 showed a clinically meaningful overall survival benefit with imlunestrant in patients with ESR1-mutant HR-positive metastatic breast cancer, supporting oral SERDs as preferred endocrine switch options in this molecularly defined subgroup.

Bardia A, Hurvitz SA, DeMichele A, et al. Imlunestrant versus standard endocrine therapy in ESR1-mutant hormone receptor–positive metastatic breast cancer: overall survival update from EMBER-3. *San Antonio Breast Cancer Symposium (SABCS) 2025*

postMONARCH

Mature survival data from postMONARCH presented at SABCS 2025 demonstrated that continuation of CDK4/6 inhibition with abemaciclib plus fulvestrant after prior CDK4/6 inhibitor exposure can provide sustained clinical benefit, challenging the paradigm of complete class discontinuation at progression.

Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of high-risk early breast cancer. *Journal of Clinical Oncology*. 2023;41:418–428.

Turner NC, Slamon DJ, Ro J, et al. Abemaciclib plus fulvestrant after progression on CDK4/6 inhibitors in hormone receptor–positive metastatic breast cancer: mature survival results from postMONARCH. *San Antonio Breast Cancer Symposium (SABCS) 2025*.

evERA

The phase III evERA study presented at SABCS 2025 showed that giredestrant combined with everolimus improved progression-free survival following CDK4/6 inhibitor therapy, with consistent efficacy across ESR1- and PIK3CA-defined subgroups.

Piccart M, Huober J, Lu YS, et al. Giredestrant plus everolimus following CDK4/6 inhibitor therapy in hormone receptor–positive metastatic breast cancer (evERA). *San Antonio Breast Cancer Symposium (SABCS) 2025*.

Antibody–Drug Conjugates and HER2 Spectrum

DESTINY-Breast06

DESTINY-Breast06 confirmed that trastuzumab deruxtecan significantly improves progression-free survival compared with chemotherapy in HR-positive HER2-low metastatic breast cancer, reinforcing the concept of HER2 expression as a biological continuum rather than a binary classification.

Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan versus chemotherapy in hormone receptor–positive, HER2-low metastatic breast cancer. *The Lancet*. 2024;404:164–176.

TROPION-Breast01

Findings from TROPION-Breast01 presented at SABCS 2025 demonstrated that datopotamab deruxtecan provides a progression-free survival advantage over chemotherapy in HR-positive/HER2-negative metastatic breast cancer, expanding therapeutic options within the antibody–drug conjugate class.

Bardia A, Juric D, Shimizu T, et al. Datopotamab deruxtecan versus chemotherapy in hormone receptor–positive/HER2-negative metastatic breast cancer (TROPION-Breast01). *San Antonio Breast Cancer Symposium (SABCS) 2025*.

Triple-Negative Breast Cancer

KEYNOTE-522 (long-term follow-up)

Long-term follow-up data from KEYNOTE-522 presented at SABCS 2025 confirmed durable event-free and overall survival benefits with neoadjuvant and adjuvant pembrolizumab in early triple-negative breast cancer, including patients who did not achieve a pathologic complete response.

Schmid P, Cortes J, Dent R, et al. Event-free and overall survival with pembrolizumab in early triple-negative breast cancer. *New England Journal of Medicine*. 2022;386:556–567.

Early HER2-Positive Disease – De-escalation

PHERGain

Updated analyses from PHERGain discussed at SABCS 2025 support the feasibility of PET-CT- and biology-driven de-escalation strategies, enabling chemotherapy-free neoadjuvant approaches in selected patients with early HER2-positive breast cancer.

Llombart-Cussac A, Cortés J, Paré L, et al. HER2-enriched subtype as a predictor of response-adapted neoadjuvant therapy in early HER2-positive breast cancer (PHERGain). *The Lancet Oncology*. 2023;24:151–163.

Biomarkers, ctDNA, and Precision Oncology

ESR1 mutations

Multiple studies presented at SABCS 2025 highlighted the clinical utility of serial ESR1 mutation monitoring using circulating tumor DNA to guide timely endocrine therapy switching before overt clinical progression.

Jeselsohn R, De Angelis C, Brown M, et al. Dynamic monitoring of ESR1 mutations using circulating tumor DNA to guide endocrine therapy in metastatic breast cancer. *San Antonio Breast Cancer Symposium (SABCS) 2025*.

ctDNA-MRD

SABCS 2025 reinforced the emerging role of circulating tumor DNA as a marker of molecular residual disease, with potential applications in adjuvant treatment escalation, de-escalation, and duration optimization in early breast cancer.

Garcia-Murillas I, Chopra N, Comino-Méndez I, et al. Detection of minimal residual disease using circulating tumor DNA in early breast cancer. *San Antonio Breast Cancer Symposium (SABCS) 2025*.

AI and Risk Stratification

TAILORx / AI

AI-based multimodal models integrating pathology images, clinical variables, and genomic data presented at SABCS 2025 demonstrated improved prediction of long-term and late recurrence risk beyond conventional genomic assays, supporting future precision risk stratification frameworks.

Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *New England Journal of Medicine*. 2018;379:111–121.

Screening and Survivorship

WISDOM

Results from the WISDOM trial presented at SABCS 2025 showed that risk-based breast cancer screening strategies provide safety comparable to annual mammography, supporting a shift toward personalized screening approaches.

Esserman LJ, Yau C, Thompson CK, et al. Personalized versus annual screening for breast cancer: the WISDOM randomized clinical trial. *JAMA*. 2024;331:129–138.

BRCA & MHT

Data presented at SABCS 2025 indicated that menopausal hormone therapy was not associated with an increased risk of breast cancer among BRCA1/2 mutation carriers, providing reassurance for menopause management after risk-reducing oophorectomy.

Kotsopoulos J, Gronwald J, Karlan BY, et al. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 and BRCA2 mutation carriers. *Journal of Clinical Oncology*. 2023;41:1381–1389.