MedCrave
Step into the World of Research

Journal of Cancer Prevention & Current Research

Research Article

Open Access
CrossMark

Adjuvant systemic therapy in early breast cancer: from CMF to precision risk-adapted treatment

Abstract

Background: Adjuvant systemic therapy has fundamentally altered the natural history of early breast cancer. Beginning with Bonadonna's CMF program, the curative principle of micrometastatic eradication became clinically proven, and subsequent EBCTCG meta-analyses quantified durable reductions in recurrence and mortality with polychemotherapy.[1–6]

Methods: Evidence-based narrative review of biological foundations (tumor kinetics and resistance), landmark randomized trials, meta-analyses, and contemporary subtype-driven strategies integrating chemotherapy, endocrine therapy, and modern biologic/targeted agents.

Results: Anthracycline and taxane-based regimens improved outcomes over earlier approaches, with additional gains from dose-dense scheduling (validated by randomized trials). HER2-directed therapy (trastuzumab ± pertuzumab) produced major reductions in recurrence; response-adapted escalation with antibody–drug conjugates further improved outcomes in residual disease. In HR-positive disease, endocrine therapy is foundational and long-horizon, while genomic assays refine chemotherapy selection. In TNBC, post-neoadjuvant capecitabine and perioperative immunotherapy improve event-free outcomes. In selected high-risk HR+/HER2− disease, CDK4/6 inhibition improves invasive disease-free survival; and in germline BRCA1/2-mutated high-risk HER2− disease, adjuvant PARP inhibition improves invasive DFS and overall survival.[4–12,14–30]

Conclusions: Modern adjuvant care is biology-driven and risk-adapted. Integrating subtype, nodal burden, genomic risk, and response to preoperative therapy maximizes cure while minimizing toxicity and overtreatment. Future directions include ctDNA-based minimal residual disease (MRD) strategies and adaptive escalation/de-escalation trials.[31–36]

Volume 17 Issue 1 - 2026

Adrian Hunis MD
Emeritus member of ASCO, ESMO, Honorary member of AMA, Argentina

Correspondence: Adrian Hunis MD, Emeritus member of ASCO, ESMO, Honorary member of AMA, Department of Oncology, Buenos Aires, Argentina

Received: March 02, 2026 | **Published:** March 10, 2026

Introduction and objectives

Early breast cancer is frequently curable, yet historical relapse rates remained substantial with local therapy alone, especially in node-positive disease. Bonadonna's randomized CMF trials established that postoperative systemic therapy can eradicate occult micrometastatic disease and improve long-term survival.[1,2]

The EBCTCG overviews provided robust population-level estimates of benefit, confirming that polychemotherapy reduces recurrence and breast cancer mortality over 15 years and beyond.[3–6]

Objectives of this review are to:

- Summarize biological principles supporting adjuvant systemic therapy (micrometastases, log-kill, tumor kinetics, resistance).
- Trace historical evolution from CMF to anthracyclines, taxanes, and dose-dense strategies.
- Integrate endocrine therapy as the cornerstone of HR-positive disease and clarify its interaction with chemotherapy.
- Review the impact of HER2-directed therapy, response-adapted escalation, and modern targeted/biologic treatments (CDK4/6, PARP, immunotherapy).
- Provide a practical, subtype-driven contemporary framework and future directions (ctDNA/MRD).

Biological foundations: Skipper, Norton–Simon, Goldie–Coldman Limitations of Skipper's model in solid tumors.

Although Skipper's log-kill hypothesis provided a foundational conceptual framework for cytotoxic chemotherapy, it was originally derived from rapidly proliferating leukemia models and therefore has limitations when extrapolated to solid tumors such as breast cancer. Solid tumors display significant spatial heterogeneity, variable vascularization, and regions of hypoxia that may limit uniform drug delivery. In addition, breast cancers often have lower proliferative fractions and complex tumor–microenvironment interactions not represented in leukemia systems. These biological characteristics reduce the predictability of constant fractional cell kill and help explain the heterogeneous therapeutic responses observed in solid tumors.

Skipper's log-kill hypothesis posits that cytotoxic therapy kills a constant fraction of tumor cells per cycle, supporting combination therapy and adequate dose intensity to drive cell burden below a regrowth threshold (Figure 1).

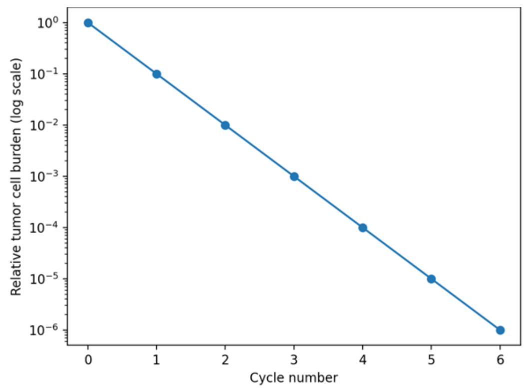

Figure 1 Skipper log-kill concept (schematic).

The Norton–Simon hypothesis proposes that tumor regression under therapy is proportional to intrinsic tumor growth rate; reducing inter-cycle intervals limits regrowth and can increase efficacy. This concept underpins dose-dense therapy, validated clinically in randomized trials [7]

(Figure 2) The Goldie–Coldman hypothesis emphasizes that resistant subclones arise stochastically as tumors grow; early multi-agent therapy reduces the probability that resistant clones dominate and supports combination regimens in curative settings.

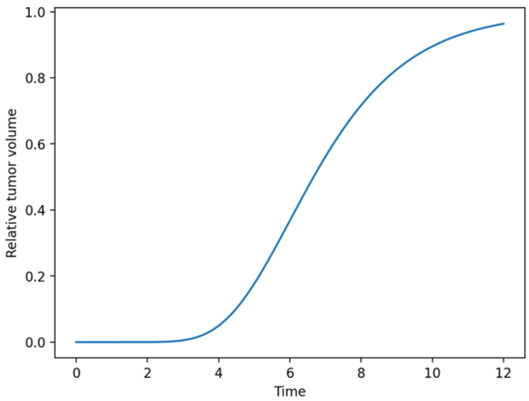

Figure 2 Norton-Simon tumor growth kinetics (schematic).

History of adjuvant chemotherapy

The modern era began with Bonadonna's CMF program, demonstrating durable DFS and OS benefits in operable node-positive disease, including 20-year follow-up data.[1,2]

EBCTCG meta-analyses subsequently confirmed long-term reductions in recurrence and breast cancer mortality with polychemotherapy, providing the statistical foundation for global adoption of ACT.[3–6]

Development of adjuvant chemotherapy protocols

Anthracyclines replaced CMF in many settings after meta-analytic evidence of superior recurrence reduction. Subsequent taxane incorporation provided additional benefit, and randomized trials established dose-dense schedules as a high-risk standard when tolerated.[4–7]

Common historical and contemporary backbones include CMF; AC/FAC/FEC; sequential or combined anthracycline–taxane regimens; and non-anthracycline options (e.g., TC) in selected patients to limit cardiotoxicity.[4,8,37]

Long-term outcomes: 5, 10, 20 Years

Long-term follow-up is essential because benefits accrue over years and late events are common in HR-positive disease. EBCTCG analyses demonstrate that early recurrence reductions translate into sustained mortality reductions at 10–15 years and beyond.[4–6,20]

Bonadonna's 20-year CMF follow-up confirmed durability of benefit and established ACT as a curative-intent intervention rather than transient delay.[2]

Current state of adjuvant chemotherapy

Contemporary adjuvant therapy is subtype-driven and increasingly risk-adapted. Chemotherapy remains essential for biologically high-risk disease, while endocrine therapy is foundational in HR-positive tumors and genomic assays refine chemotherapy selection. Targeted agents and immunotherapy deliver additional benefits in selected populations.[15–19,20–30]

Indications

Adjuvant chemotherapy is generally indicated for node-positive disease, most TNBC ≥T1c, and many HER2-positive tumors requiring systemic therapy. In HR+/HER2− disease, chemotherapy is recommended for higher clinical risk and/or high genomic risk, while many low genomic-risk patients can safely omit ACT.[4–6,15–19,38–40]

Current Protocols (Table 1).

Table 1 Contemporary systemic therapy framework (illustrative).

Subtype / setting	Backbone	Key additions	Notes
HR+/HER2− (low genomic risk)	Endocrine therapy	—	Avoid chemotherapy when validated low risk.
HR+/HER2− (high clinical/ genomic risk)	Anthracycline-taxane or TC	± abemaciclib (selected high-risk)	Balance benefit vs toxicity; consider menopausal status.
HER2+ (node+ or high risk)	Taxane-based chemo	trastuzumab ± pertuzumab; consider T-DM1 if residual disease	Response-adapted escalation after neoadjuvant therapy.
TNBC stage II–III	Anthracycline-taxane (± platinum per context)	pembrolizumab perioperative; capecitabine if residual disease	Immunotherapy for eligible stage II–III; post-neoadjuvant escalation if residual.

Which patients should receive adjuvant chemotherapy?

In HR+/HER2− disease, the key question is for whom chemotherapy adds clinically meaningful benefit beyond endocrine therapy. Prospective trials using genomic assays (TAILORx, MINDACT, RxPONDER) established that many patients—particularly postmenopausal with low recurrence scores—can avoid chemotherapy without compromising invasive or distant outcomes.[15–19]

In premenopausal HR-positive patients, apparent chemotherapy benefit may reflect both cytotoxic and endocrine (ovarian suppression) effects; treatment selection should integrate clinical risk, genomic risk, and endocrine strategy intensity.[19,27]

Standard for high-risk patients

High-risk early breast cancer typically includes ≥4 positive nodes, inflammatory breast cancer, large or high-grade tumors, aggressive subtypes (TNBC, HER2+), and/or high genomic risk. Standards include anthracycline-taxane backbones with dose-dense scheduling when feasible, dual HER2 blockade for selected HER2+ patients, and response-adapted escalation with T-DM1 after residual HER2+

Citation: Hunis A. Adjuvant systemic therapy in early breast cancer: from CMF to precision risk-adapted treatment. *J Cancer Prev Curr Res.* 2026;17(1):9–13. DOI: 10.15406/jcpcr.2026.17.00599

disease or capecitabine after residual HER2− disease (especially TNBC).[7,13,14,16]

In high-risk HR+/HER2− disease, adding CDK4/6 inhibition (abemaciclib) to endocrine therapy improves invasive DFS in selected patients; in germline BRCA1/2 mutations and high-risk HER2− disease, adjuvant olaparib improves invasive DFS and OS.[28,30]

Role of adjuvant endocrine therapy

Endocrine therapy is the cornerstone of adjuvant treatment for HR-positive disease and reduces both early and late recurrence. Tamoxifen for 5 years reduces recurrence and breast cancer mortality; extending to 10 years further reduces late events (ATLAS, aTTom). In postmenopausal patients, aromatase inhibitors reduce recurrence compared with tamoxifen. In premenopausal higher-risk patients, ovarian function suppression plus tamoxifen or an aromatase inhibitor improves outcomes (SOFT/TEXT).[20–27]

New biologic and targeted adjuvant therapies

HER2-directed therapy (trastuzumab) dramatically reduced recurrence, with incremental benefit from pertuzumab in selected high-risk patients and major benefit from T-DM1 in residual disease after neoadjuvant therapy. Beyond HER2, modern adjuvant therapy includes CDK4/6 inhibition for selected high-risk HR+/HER2− disease and PARP inhibition (olaparib) for germline BRCA1/2-mutated high-risk HER2− disease. In TNBC, perioperative pembrolizumab improves event-free outcomes.[8–16,28–30]

Future directions: ctDNA/MRD and adaptive escalation/de-escalation

Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for the detection of minimal residual disease after curative-intent surgery. Tumor-specific genomic alterations identified in the primary tumor can be tracked in plasma using highly sensitive sequencing technologies. Detection of ctDNA after surgery or after completion of adjuvant therapy strongly correlates with an increased risk of relapse and may precede radiologic recurrence by several months or even years. This approach offers the potential to identify patients with molecular residual disease who may benefit from treatment escalation or enrollment in clinical trials, while ctDNA-negative patients could be candidates for therapeutic de-escalation.[31-36]

Conclusions

From CMF to modern targeted therapy, adjuvant systemic treatment has progressively reduced recurrence and mortality in early breast cancer. Contemporary practice is biology-driven: endocrine therapy is foundational in HR-positive disease; chemotherapy remains essential for high-risk phenotypes; and targeted/biologic agents deliver additional absolute benefits in selected populations. The next wave of progress is likely to be defined by MRD-guided personalization and rational de-escalation strategies (Table 2 & Table 3).[1–6,20–30,31–60]

Table 2 Landmark trials informing contemporary adjuvant therapy

Trial	Population	Intervention	Key outcome (headline)
CMF program	Node-positive	CMF vs observation	Durable DFS/OS benefit
EBCTCG meta-analyses	Meta-analysis	Polychemotherapy comparisons	Sustained mortality reductions
CALGB 9741	High-risk/node+	Dose-dense vs q3w	OS improvement
NSABP B-31 / N9831	HER2+	Chemo + trastuzumab	~50% recurrence reduction
HERA	HER2+	Trastuzumab after chemo	DFS improvement
APHINITY	HER2+ high-risk	Pertuzumab + trastuzumab	iDFS benefit in node+
KATHERINE	Residual HER2+	T-DM1 vs trastuzumab	iDFS improvement
CREATE-X	Residual HER2−	Capecitabine vs none	Benefit in TNBC
KEYNOTE-522	Stage II–III TNBC	Pembrolizumab + chemo	EFS improvement
TAILORx / MINDACT / RxPONDER	HR+/HER2−	Genomic risk-guided	Chemo omission in low-risk subsets
monarchE	High-risk HR+/HER2−	Abemaciclib + ET	iDFS improvement
OlympiA	gBRCA, HER2− high-risk	Olaparib vs placebo	iDFS/OS improvement

Table 3 Practical high-risk features suggesting escalation

Category	Examples
Anatomic burden	≥4 positive nodes; bulky nodal disease; T3/T4 tumors
Aggressive biology	TNBC; HER2+; high grade; high Ki-67
Residual disease after neoadjuvant	Residual invasive disease in HER2+ (→ T-DM1); residual TNBC (→ capecitabine)
Genomics / host factors	High recurrence score: premenopausal with node+ and RS≤25 (consider endocrine intensity + systemic strategy)
Genetics	gBRCA1/2 with high-risk HER2− disease (→ olaparib)

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med.* 1976;294:405-410.

2. Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: 20 years of follow-up. *N Engl J Med*. 1995;332:901–906.
3. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet*. 1992;339:1–15.
4. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: overview. *Lancet*. 2005;365:1687–1717.
5. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses. *Lancet*. 2012; 379:432–444.
6. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview. Lancet. 1998; 352:930-942.
7. Citron ML, Berry DA, Cirrincione C, et al. Dose-dense versus conventionally scheduled adjuvant chemotherapy (CALGB 9741). *J Clin Oncol*. 2003; 21:1431-1439.
8. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005; 353:1673-1684.
9. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy: joint analysis of NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2011; 29:3366-3373.
10. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer (HERA). *N Engl J Med*. 2005;353:1659-1672.
11. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy (CREATE-X). *N Engl J Med*. 2017;376:2147-2159.
12. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer (KEYNOTE-522). *N Engl J Med*. 2020; 382:810-821.
13. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer (KATHERINE). *N Engl J Med*. 2019;380:617-628.
14. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer (TAILORx). *N Engl J Med*. 2018; 379:111-121.
15. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions (MINDACT). *N Engl J Med*. 2016; 375:717-729.
16. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer (APHINITY). *N Engl J Med*. 2017; 377:122-131.
17. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer (RxPONDER). *N Engl J Med*. 2021;385:2336-2347.
18. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated node-negative breast cancer. *N Engl J Med*. 2004;351:2817-2826.
19. Henderson IC, Berry DA, Demetri GD, et al. Sequential paclitaxel after AC in node-positive breast cancer (CALGB 9344). *J Clin Oncol*. 2003;21:976-983.
20. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors to the efficacy of adjuvant tamoxifen (EBCTCG). *Lancet*. 2011;378:771-784.
21. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis. *Lancet*. 2015; 386:1341-1352.
22. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years (ATLAS). *Lancet*. 2013;381:805-816.
23. Gray R, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years. *J Clin Oncol*. 2013;31(suppl): abstr 5.
24. Goss PE, Ingle JN, Martino S, et al. Letrozole after five years of tamoxifen (MA.17). *N Engl J Med*. 2003;349:1793-1802.
25. Mamounas EP, Jeong JH, Wickerham DL, et al. NSABP B-42: extended letrozole after endocrine therapy. *J Clin Oncol*. 2019; 37:1544-1551.
26. Blok EJ, van der Hoeven JJM, van der Wall E, et al. Optimal duration of extended adjuvant endocrine therapy (IDEAL). *J Natl Cancer Inst*. 2018;110:40-48.
27. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer (SOFT/TEXT). *N Engl J Med*. 2018; 379:122-137.
28. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib with endocrine therapy in high-risk early breast cancer (monarchE). *J Clin Oncol*. 2023;41:1-12.
29. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for BRCA1/2-mutated breast cancer (OlympiA). *N Engl J Med*. 2021;384:2394-2405.
30. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and docetaxel: efficacy/safety foundation (CLEOPATRA; metastatic). *N Engl J Med*. 2015;372:724-734.
31. Coombes RC, Page K, Salari R, et al. Circulating tumor DNA and residual disease detection in early breast cancer: foundational studies. *J Clin Oncol*. 2019;37:517-527.
32. Garcia-Murillas I, Chopra N, Comino-Méndez I, et al. Assessment of molecular relapse detection by ctDNA in early breast cancer. *Sci Transl Med*. 2015;7:302ra133.
33. Turner NC, Swift C, Kilburn L, et al. ctDNA/MRD-guided approaches in breast cancer: emerging trial frameworks. *Ann Oncol*. 2020; 31:1352-1361.
34. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease. *Nat Rev Clin Oncol*. 2019;16:409-424.
35. Nitz U, Gluz O, Christgen M, et al. De-escalation concepts guided by biology and response: review evidence. *Breast*. 2021; 59:1-10.
36. Sparano JA, et al. Clinical utility of genomic assays and risk-adapted adjuvant therapy: contemporary perspectives. *J Clin Oncol.* 2019; 37:1-10.
37. Jones SE, Savin MA, Holmes FA, et al. Docetaxel/cyclophosphamide (TC) compared with doxorubicin/cyclophosphamide (US Oncology 9735). *J Clin Oncol*. 2006;24:5381-5387.
38. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with HR-positive breast cancer: ASCO guideline update. *J Clin Oncol*. 2019;37:423-438.
39. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in postmenopausal breast cancer (ABCSG-18). *Lancet*. 2015; 386:433-443.
40. Coleman R, Cameron D, Dodwell D, et al. Adjuvant bisphosphonates and breast cancer outcomes (EBCTCG). *Lancet*. 2015; 386:1353-1361.
41. Slamon D, Eiermann W, Robert N, et al. BCIRG 006: trastuzumab-containing regimens in early HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273-1283.
42. Eiermann W, et al. BIG 1-98: letrozole vs tamoxifen in postmenopausal early breast cancer. *N Engl J Med*. 2005;353:2747-2757.
43. Howell A, Cuzick J, Baum M, et al. ATAC trial: anastrozole vs tamoxifen. *Lancet*. 2005;365:60-62.

44. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—St Gallen International Consensus. *Ann Oncol*. 2015; 26:1533-1546.

45. Goldhirsch A, Winer EP, Coates AS, et al. St Gallen 2013: strategies for subtype-based treatment. *Ann Oncol*. 2013; 24:2206-2223.

46. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2024.

47. Gnant M. ESMO Clinical Practice Guidelines for early breast cancer (update). *Ann Oncol*. 2021;32:1475-1495.

48. Burstein HJ. ESMO/ASCO guidance on early breast cancer systemic therapy: updates. *J Clin Oncol*. 2021;39:3959-3977.

49. Bear HD, Anderson S, Smith RE, et al. NSABP B-27: neoadjuvant docetaxel added to AC. *J Clin Oncol*. 2006; 24:2019-2027.

50. von Minckwitz G. GeparSepto: nab-paclitaxel effect on pCR in TNBC. *J Clin Oncol*. 2014;32:1-10.

51. Sikov WM, Berry DA, Perou CM, et al. CALGB 40603: carboplatin/bevacizumab in neoadjuvant TNBC. *J Clin Oncol*. 2015; 33:13-21.

52. Loibl S, O'Shaughnessy J, Untch M, et al. Meta-analysis of platinum in TNBC and implications. *J Clin Oncol*. 2018;36:1-10.

53. Wolmark N. NSABP B-28: paclitaxel after AC in node+ disease. *J Clin Oncol*. 2005;23:3686-3696.

54. Roché H, Fumoleau P, Spielmann M, et al. PACS 01: FEC followed by docetaxel. *J Clin Oncol*. 2006;24:5664-5671.

55. Martin M. TAC vs FAC (BCIRG 001) long-term outcomes. *J Clin Oncol*. 2008;26:1-9.

56. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumors. *Nature*. 2000;406:747-752.

57. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns and subtypes. *Proc Natl Acad Sci U S A*. 2001; 98:10869-10874.

58. Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. *Oncologist*. 2011;16(Suppl 1):1-11.

59. Baselga J. NeoSphere: pertuzumab + trastuzumab in neoadjuvant HER2+ disease. *Lancet Oncol*. 2012;13:25-32.

60. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: CTNeoBC pooled analysis. *Lancet*. 2014; 384:164-172.

Citation: Hunis A. Adjuvant systemic therapy in early breast cancer: from CMF to precision risk-adapted treatment. *J Cancer Prev Curr Res.* 2026;17(1):9–13. DOI: 10.15406/jcpcr.2026.17.00599